Randomised clinical trials in perinatal health care: a cost-effective investment

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The known Return on investment quantifies improvements in health and the cost savings to society relative to the amount expended to fund the underlying research.

The new For one-time investments in 23 trials totalling $20.3 million, the total potential cost savings, should the findings of the six trials reporting superior interventions be applied to all eligible patients, were estimated to be $262.8 million over 5 years.

The implications Trials in maternal and perinatal health care have the potential to provide a significant return on investment by informing clinical practice, improving patient outcomes and reducing health care costs.

Abstract

Objective: To compare the health and economic impacts of implementing efficacious treatment interventions with maintaining standard practice in maternal and perinatal health care.

Design and setting: We identified randomised clinical trials (RCTs) in the Perinatal Society of Australia and New Zealand trials database that commenced recruitment during 2008 and had completed recruitment by 2015. Data from clinical trial registries and publications were collated to calculate the potential cost savings achievable by implementing efficacious treatment interventions.

Main outcome measure: Projected net cost savings over 5 years.

Results: Twenty-three eligible RCTs covering a range of behavioural and clinical interventions were identified, of which six reported interventions superior to standard practice (four trials) or placebo (two). The outcomes (but not the costs) of 17 trials were excluded from analysis (no difference between intervention and comparator groups in seven trials, recruitment problems in six, findings not yet published in four). The total funding amount for the 23 trials was $20.3 million; the potential cost savings over 5 years if the findings of the six trials reporting superior interventions were implemented was estimated to be $26.3 million if 10% of the eligible populations received the effective interventions, and $262.8 million with 100% implementation.

Conclusions: Our retrospective analysis highlights the value of research in perinatal care and the importance of implementing positive findings for realising its value. Future trials in maternal and perinatal health care may provide significant returns on investment by informing clinical practice, improving patient outcomes and reducing health care costs.

As health care costs rise, cost-effective alternatives to unevaluated interventions with uncertain effectiveness are needed. In clinical research, return on investment compares the value of improvements in health and cost savings to society achieved by clinical trials with the amount invested to fund them.[1] Research into return on research investment in Australia,[2] the United States,[1] and the United Kingdom[3] has assessed health gains across a range of medical specialties from the perspective of research funders rather than the health services; Dutch researchers have examined the return on investment of obstetric trials, emphasising the effect of cost savings in promoting change in clinical practice.[4]

We applied the methods of the Dutch researchers to exploring the health outcomes and costs of treatment interventions in maternal and perinatal health that have been evaluated in randomised clinical trials (RCTs), and calculated the potential cost savings and improved patient outcomes achievable by implementing efficacious treatment interventions.

Methods

Study selection

We identified relevant RCTs in the Perinatal Society of Australia and New Zealand (PSANZ) trials database (https://archserver.adelaide.edu.au/PSANZ100Plus/Trials). The database, maintained by the WOMBAT Collaboration[5] since the early 2000s and now by PSANZ, includes completed, ongoing and scheduled trials in maternal and perinatal health care. All trials that commenced recruitment in 2008 and had completed recruitment by April 2015, when we undertook our search, were included in our study.

Data extraction and analysis

Data on each trial were collected from clinical trial registries and relevant publications. Registry data were obtained from the Australian New Zealand Clinical Trials Registry (ANZCTR), the ISRCTN Registry, and ClinicalTrials.gov. Published articles were identified in the PSANZ trials database listing for each trial and through supplementary searches of PubMed (December 2016) for the lead investigator's name and keywords from the trial name. Data on the following characteristics were extracted: disease or condition; intervention and control groups; primary outcome; rate of primary outcome events for treatment and control groups; funding source and amount.

The included trials were categorised according to their findings (intervention was superior to or comparable with control treatment) and the nature of the control group (placebo or standard practice). Judgements about the superiority of an intervention were based on the overall findings of the trial; all outcome measures were assessed, but the intervention did not need to be superior on all measures to be considered superior. Interventions were considered comparable with the control group if there were no significant differences in outcomes between the treatment and control groups. Trials that reported recruitment problems or had not yet published their findings were excluded from the analysis of potential health

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gains and cost savings, but their costs were included in the overall calculation of funding costs. For trials reporting multiple primary outcomes, only the first primary outcome associated with a health disease or condition was included in the economic analysis (to enable calculations of health gains) (Box 1).

Eligible populations

The numbers of children or women in Australia in 2012 eligible to be treated with each evaluated intervention were estimated from the most recent data available at the time of analysis. The proportion of the population affected by a disease or condition was determined from data published by the Australian Institute of Health and Welfare,[12,13] the Australian Bureau of Statistics,[14,15] Obesity Australia,[16] and the National Institute of Child Health and Human Development.[17]

Potential health gains

The expected gains in health in 2012 from applying in clinical practice the interventions found to be superior to current practice were calculated as the absolute difference in primary outcome events between the intervention and control groups multiplied by the number of eligible children or women for the respective treatment in Australia in 2012.

Cost savings associated with avoiding a primary outcome event

The minimum health care cost savings associated with positive outcome events were estimated from the literature and clinical consultation; Box 2 summarises the assumptions about saved resources and costs.

The Father Infant Feeding Initiative (FIFI) study encouraged breastfeeding, for which cost savings were based on reduced formula feeding for 6 weeks. The primary outcomes of two studies (the Infant Feeding Activity and Nutrition Trial [InFANT] and the Analgesia after caesarean surgery study) were surrogate outcome measures that were not directly associated with a disease or condition. It is unlikely that a reduction in a surrogate outcome measure would have a major effect on direct costs; for instance, reducing the morphine requirement of a pregnant woman saves little compared with the cost of an elective caesarean delivery (the Analgesia after caesarean surgery study). For these two studies, the absolute difference in the primary outcome between intervention and control groups is therefore reported (Box 2), but additional health gains and the costs savings have not been calculated. For the Healthier Lifestyles: Preventing excess weight gain (HeLP-her) study, we analysed the secondary outcome of gestational diabetes prevalence, as the primary outcome (mean gestational weight gain) was a surrogate outcome measure.

Ongoing costs of implementing an intervention

For trials in which the intervention was superior to the control group, the ongoing additional costs of delivering the intervention were estimated. The costs of translating evidence into clinical practice (eg, administration, organisation, training) and other downstream costs (eg, future health benefits) were excluded from this calculation.

Economic analysis

For the first stage of the economic analysis, all calculations were standardised to 2016 prices with consumer price index data. The additional number of children or women who could benefit from an effective intervention (potential health gains) was multiplied by the estimated cost savings associated with avoiding the primary outcome event; the ongoing implementation cost of the intervention were then deducted, yielding the potential cost savings

1 Characteristics of the six trials included in the economic analysis

Trial name or acronym	Population	Intervention	Control	Funding source	Funding amount*
Intervention superior to standard practice					
FIFI[6]	Initial breastfeeding mothers	2-hour antenatal education session; postnatal support for fathers (n = 385)	Usual care (n = 314)	Healthway (#16175)	$405 539 ($340 653)
HeLP-her[7]	Overweight or obese women	Four-session lifestyle program (n = 121)	Written health information only (n = 107)	Jack Brockhoff Foundation; NHMRC postgraduate scholarship (#519457)	$1 785 714 ($1 500 000; includes $57 343 NHMRC scholarship)
InFANT[8]	Primiparous women	Dietitian sessions (n = 271)	Usual care (n = 271)	NHMRC primary health care project grant (#425801)	$631 499 ($530 459)
MANGO[9]	Singleton pregnancies	Caseload midwifery care (n = 871)	Usual care (n = 877)	NHMRC project grant (#510207)	$718 073 ($603 181)
Intervention superior to placebo					
Analgesia after caesarean surgery[10]	Elective caesarean delivery	Analgesia with ropivacaine (n = 23)	Saline (n = 24)	ANZCA novice investigator grant; Astra Zeneca	ANZCA: $7143 ($6000); Astra Zeneca: $7024 ($5900)
Sugar Babies[11]	Neonates with hypoglycaemia	Dextrose gel (n = 118)	Placebo gel (n = 119)	Waikato Medical Research Foundation	$53 792 (NZ$50 000)

ANZCA = Australian and New Zealand College of Anaesthetists; NHMRC = National Health and Medical Research Council. The six trials described are: FIFI = Father Infant Feeding Initiative (improving breastfeeding initiation and duration with education and social support for fathers); HeLP-her = Healthier Lifestyles: Preventing excess weight gain and gestational diabetes in overweight and obese pregnancies; InFANT = Infant Feeding Activity and Nutrition Trial (early intervention to prevent childhood obesity); MANGO = Midwives @ New Group practice Options (randomised controlled trial of caseload midwifery); Analgesia after caesarean surgery (ultrasound-guided transversus abdominis plane block for analgesia after caesarean surgery); Sugar Babies (dextrose gel for neonatal hypoglycaemia). * Funding amount adjusted to 2016 Australian dollars, with original amount granted in parentheses. ◆

2 Population and cost parameters for the six trials in which intervention was superior to usual care or placebo

Trial name or acronym	Number of people affected (proportion of live births in 2012*)	Primary outcome	Difference in outcome (95% CI)	Additional number who could benefit per year	Cost indicator	Savings from avoiding primary outcome event
Intervention superior to standard practice						
FIFI[6]	295 175 (96.0%)[18]	Any breastfeeding at 6 weeks	6% (0.1 to 12%)	18 266	Cost of formula feeding for 6 weeks	$125[19]
HeLP-her[7]	145 128 (47.2%)[16]	Prevalence of gestational diabetes†	−11% (−22% to 1%)	15 088	Cost per woman for managing mild gestational diabetes	$6000[20]
InFANT[8]	130 369 (42.4%)[13]	Non-core drink intake (eg, fruit juice, soft drinks)	−4.5 g/day (−0.9 to −7.9 g/day	NC	NC	NC
MANGO[9]	302 862 (98.5%)[13]	Elective caesarean delivery	−3% (−0.1 to −5.0%)	8469	Cost of hospital stay for caesarean delivery	$9500[21]
Intervention superior to placebo						
Analgesia after caesarean surgery[10]	99 622 (32.4%)[13]	Morphine requirement over 24 hours	−13.5 mg (−2.7 to −24.3 mg)	NC	NC	NC
Sugar Babies[11]	46 121 (15.0%)[17]	Treatment failure (blood glucose concentration < 2.6 mmol/L after 2 gel doses)	−10% (−8% to −21%)	4986	Cost for 2-day stay in neonatal intensive care unit	$8000[22]

NC = The additional number who could benefit and cost savings could not be calculated because surrogate primary outcome measures were used. For full names of trials, see Box 1. * The number of live births in Australia in 2012 was 307 474.[13] † Secondary outcome reported, as primary outcome was mean gestational weight gain. ◆

associated with the trial. Potential annual cost savings were calculated for scenarios in which different proportions of the eligible population received the treatment intervention (10–100%).

The second stage of the analysis was undertaken from the perspective of a decision to invest in a trial in 2008. The projected cost savings over a 5-year period (2016–2020) were calculated, allowing sufficient time to publish trial findings (most of the included studies published their findings in 2013 or 2014) and a time lag for knowledge translation of 2–3 years. The 2016 standardised annual cost savings were adjusted and discounted to 2008 values, and 5-year projections estimated (with 95% confidence intervals [CIs]). A discount rate of 5% was applied.[23] All costs are reported in Australian dollars.

Ethics approval

This study was considered to be negligible risk research and exempt from formal ethics review by the Human Research Ethics Committee of the University of Adelaide.

Results

A total of 23 RCTs conducted in Australia and New Zealand were eligible, covering a range of behavioural (eg, diet and lifestyle changes) and clinical interventions (eg, cervical priming for induction of labour). Of the 23 trials (online Appendix, table 1), six were included in the economic analysis; four reported interventions that were superior to standard practice, and two described interventions that were superior to placebo (Box 1). Only the funding allocated to the other 17 trials was included in the economic analysis (online Appendix, table 2), as outcomes were similar for the intervention and control arms (seven trials) or incomplete because of recruitment problems (six trials), or the findings had not yet been published (four trials).

The total cost for the six trials in which the interventions were superior to standard treatment or placebo was $3.6 million (Box 1). The additional number of women or children who could benefit from implementing the study findings ranged from 5000 (the Sugar Babies study) to 18 000 (the FIFI study) (Box 2).

For the FIFI study, the savings achieved by avoiding the primary outcome event did not offset the ongoing costs of the 2-hour antenatal education sessions required. For the three other trials with financially estimable outcomes, the estimated net 5-year cost savings with 10% implementation ranged from $684 000 (the randomised controlled trial of caseload midwifery [MANGO] study) to $13.6 million (the HeLP-her study), and from $6.8 million (MANGO) to $135.6 million (HELP-her) with 100% implementation (Box 3).

For the seven trials in which the efficacy of the intervention was similar to standard practice, the total cost of funding was approximately $5.0 million. The ten trials excluded from further analysis because of recruitment problems or lack of published findings cost a total of approximately $11.7 million (online Appendix, table 2).

The total cost of continuing standard practice in areas examined by the six trials in which the intervention was superior to the standard or placebo would have been $2130 million over 5 years (Box 3).

Discussion

For one-time investments in 23 trials during 2008 totalling $20.3 million, the total potential cost savings were estimated to be $26.3 million over 5 years were the findings of the six trials reporting superior interventions implemented in 10% of the eligible populations, and $262.8 million over 5 years with 100% implementation. That is, the funding costs of $16.7 million for the 17 trials with uncertain effectiveness were outweighed by the potential cost savings made possible by the six trials reporting superior interventions.

Evidence that confirms standard practice to be cost-effective should also be viewed as a positive rather than a negative in

3 Estimates of the costs over 5 years of continuing standard practice, and of the potential savings achieved by implementing the findings of four trials with financially estimable outcomes that reported interventions superior to standard treatment or placebo

Trial name or acronym	Proportion of control group with primary outcome	Cost of continuing standard practice, $ millions*	Cost saving (95% CI), $ millions		
			10% implementation	50% implementation	100% implementation
Intervention superior to standard practice					
FIFI[6]	75%†	$28.2	−$0.1 (−$0.8 to $0.5)	−$0.7 (−$4.1 to $2.6)	−$1.3 (−$8.2 to $5.3)
HeLP-her[7]	33%	$876.4	$13.6 (−$17.0 to $44.7)	$67.8 (−$84.8 to $223.3)	$135.6 (−$169.7 to $589.4)
MANGO[9]	11%	$948.9	$0.7 (−$23.2 to $20.2)	$3.4 (−$115.9 to $101.0)	$6.8 (−$231.9 to $201.9)
Intervention superior to placebo					
Sugar Babies[11]	24%	$276.7	$12.2 ($9.0 to $23.7)	$60.8 ($44.9 to $118.6)	$121.6 ($89.7 to $237.3)
Total		*$2130.1*	*$26.3 (−$32.0 to $89.1)*	*$131.4 (−$160.0 to $445.5)*	*$262.8 (−$320.1 to $891.0)*

For full names of trials, see Box 1. * Based on the proportion of the control group experiencing the primary outcome event, this reflects the costs incurred by the primary outcome event had the trials not been conducted. † 25% were not breastfeeding at 6 weeks. ◆

health care. However, publication bias may have been a problem in our study, as none of the eligible trials reported that an intervention had negative effects. Four trials could not be included for further analysis as their findings had not yet been published, despite participant recruitment commencing in 2008. There could be a range of reasons for this, including lack of resources for analysing data and drafting manuscripts after grant funding had ended, but dissemination bias — the effect of the direction or nature of the study findings on decisions about publishing them — cannot be discounted.

We found that the net return in health benefits on each dollar invested in the 23 trials in maternal and perinatal health in 2008 would be $2.40 per year with 100% implementation of the positive findings. However, the true return is likely to be higher, as our estimate was based only on the savings achieved by avoiding direct health system costs, and the ongoing costs of implementation; that is, the value of the health benefits for the women and children treated are not represented in this estimate.

The main determinant of additional health benefits and potential cost savings is the ability to translate the evidence provided by the trials into clinical practice. In 2011, the National Health and Medical Research Council (NHMRC) reported the economic benefits to Australia of public investment in health and medical research for selected diseases.[2,24] It was estimated that for each dollar invested in health research and development, the average annual return in health benefits ranged from $0.77 ($0.70 in 2011) for muscular dystrophy to $6.51 ($5.91 in 2011) for cardiovascular diseases. These estimates calculated the total net benefits, including net improvements in wellbeing, gains to the health system, productivity and other indirect gains, and commercial returns. Similarly, a US study[1] reported an average annual return in health benefit of $7.95 (US$4.50 in 2004) for stroke research, a UK study[3] an average annual return in health benefit of $14.90 (£8.10 in 2012) for a range of health interventions, and a study in the Netherlands[4] an average annual return in health benefit of $4.70 (€3.10 in 2011) for obstetric interventions.

Uptake of an effective intervention into clinical practice and public health policy is required for the potential benefit to be realised, but standard treatments are often retained despite the availability of new, more cost-effective alternatives. For the trials in our study, three of the four efficacious interventions, or components of the interventions, are currently being translated into routine clinical practice (Professor Colin Binns, FIFI study; Professor Helena Teede, HeLP-her study; Associate Professor Karen Campbell, InFANT; personal communication, July 2016). The findings of the FIFI, InFANT and HeLP-her studies have been translated into practice in the states where they were conducted, and those of the HeLP-her study have also been heeded overseas, while the results of the FIFI study intervention have been incorporated into NHMRC infant feeding guidelines.[25]

Limitations of our study include the crude estimation of costs for avoiding a primary outcome event and for ongoing implementation; only direct costs (ie, resources associated with the primary outcome event) and the ongoing costs of delivering the efficacious intervention are represented. The costs of translating efficacious interventions into clinical practice were excluded, and the monetary value of the health benefits were not estimated. The funding amount for each trial is likely to underestimate the actual costs, as it does not include in-kind contributions and potential direct and indirect trial-related effects on the delivery of health care services. The magnitude of these additional costs is likely to be small compared with the estimated potential cost savings; had the funding costs for the 23 trials been twice as high, cost savings would still be achieved were 20% of the eligible populations to receive the effective interventions over 5 years.

Further, we did not include opportunity cost in our analysis. The $20.3 million allocated to funding the 23 trials may have generated benefits had it been allocated elsewhere. However, few investment options generate cost savings and health benefits, and even a low level of implementation of the findings of the six trials with positive findings would mean that, overall, the 23 trials were high value investments.

The process of implementing a new intervention is an important problem. It is increasingly recognised that publication and even inclusion of research findings in clinical guidelines is not sufficient for promoting the translation of positive research findings. Identifying barriers to and facilitators of uptake, and providing the support necessary for enabling health care providers to deliver the intervention are required. Some hospitals may not have the

organisational capacity or resources to provide this support, and external funding may be required.

Prospective analyses of proposed trials could better inform individual funding decisions. The health care consequences of currently funded research and trials should be assessed to determine their cost-effectiveness and value. As we found, not all research is cost-effective. The value of a clinical trial is affected by the impact of estimated treatment effects on costs and patient outcomes, and by the costs and likelihood of implementing its findings. A top–down systematic approach to assessing current and past research could inform the focus of future investigations. To estimate the expected health benefit of proposed interventions, budgetary impact analyses, applying the methods we have employed, could be included in future research proposals.

The Australian Clinical Trials Alliance (ACTA) has established clinical trial networks and registries for generating high quality evidence and promoting the uptake of cost-effective health care. In perinatal medicine, the Interdisciplinary Maternal and Perinatal Australasian Collaborative Trials (IMPACT) network provides a collaborative and supportive environment for promoting well designed RCTs, and for disseminating and applying findings to improve maternal and perinatal health.

Conclusion

Our retrospective analysis investigated the value of clinical research in perinatal care, and the general importance of implementing research findings to realise their value. Accordingly, future trials in maternal and perinatal health may provide a significant return on investment by informing clinical practice, improving patient outcomes and reducing health care costs. The impact of research could be further amplified by improving the study design of some trials, as well as by better recruitment and more rapid implementation of findings.

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