Maternal and perinatal research conducted in Australia: Generation, synthesis, translation, implementation and impact

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<tr>
<td>ACOG</td>
<td>American College of Obstetrics and Gynecology</td>
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<tr>
<td>aCSR</td>
<td>Australian Cochrane systematic review</td>
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<td>ACPR</td>
<td>Australian Cerebral Palsy Register</td>
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<td>ACTA</td>
<td>Australian Clinical Trials Alliance</td>
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<td>ADA</td>
<td>American Diabetes Association</td>
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<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
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<td>AMICABLE</td>
<td>The Antenatal Magnesium Individual participant data international Collaboration: Assessing the Benefits for babies using the best Level of Evidence</td>
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<td>AMSTAR</td>
<td>Assessment of the Methodological Quality of Systematic Reviews</td>
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<tr>
<td>ANZCTR</td>
<td>Australian and New Zealand Clinical Trials Registry</td>
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<tr>
<td>ANZNN</td>
<td>Australian and New Zealand Neonatal Network</td>
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<tr>
<td>aOR</td>
<td>adjusted odds ratio</td>
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<tr>
<td>ARC</td>
<td>Australian Research Council</td>
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<td>ARCH</td>
<td>Australian Research Centre for Health of Women and Babies</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>BCW</td>
<td>Behaviour Change Wheel</td>
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<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<tr>
<td>CPG</td>
<td>clinical practice guideline</td>
</tr>
<tr>
<td>CSR</td>
<td>Cochrane systematic review</td>
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<tr>
<td>CTG</td>
<td>cardiotocography</td>
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<td>DIAMIND</td>
<td>Diabetes Reminder</td>
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<td>ERA</td>
<td>Excellence in Research for Australia</td>
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<td>FENO</td>
<td>fraction of exhaled nitric oxide</td>
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<td>FORM</td>
<td>Formulating Optimal Recommendations Methodology</td>
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<td>g</td>
<td>gram</td>
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<td>GAP</td>
<td>Guideline Action Pack</td>
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<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>GDM</td>
<td>gestational diabetes mellitus</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<td>HbA1c</td>
<td>glycated haemoglobin</td>
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<td>HIC</td>
<td>high income country</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IADPSG</td>
<td>International Association of the Diabetes and Pregnancy Study Groups</td>
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<td>ILCOR</td>
<td>International Liaison Committee on Resuscitation</td>
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<tr>
<td>IMPACT Network</td>
<td>Interdisciplinary Maternal Perinatal Australasian Collaborative Trials Network</td>
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<tr>
<td>IPD</td>
<td>individual participant data</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<td>JAMA</td>
<td>Journal of the American Medical Association</td>
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<td>kg</td>
<td>kilogram</td>
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<td>LMIC</td>
<td>low-middle income country</td>
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<td>m</td>
<td>metre</td>
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<td>mmHg</td>
<td>millimetre mercury</td>
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<td>mmol</td>
<td>millimole</td>
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<tr>
<td>MOOSE</td>
<td>Meta-analysis of Observational Studies</td>
</tr>
<tr>
<td>NEJM</td>
<td>New England Journal of Medicine</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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Abstract

**Background:** There is an increasing expectation by governments and communities that health research will lead to health and health system improvements, yet developing the necessary science behind translation and implementation of research findings into policy and practice has been neglected and underfunded.

**Aims:**
- to investigate the contribution made by Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health to improvements in the health and wellbeing of women, babies and their families in Australia and internationally;
- to evaluate different ways of assessing impact and to identify the most effective methods for informing future strategies to improve generation, synthesis, translation and implementation of research into health impact.

**Methods:** I used mixed methods (bibliometric and social media analyses; survey of triallists (quantitative and qualitative); case studies; systematic reviews of observational studies; systematic reviews of interventions; an overview; cohort studies; a randomised controlled trial; clinical practice guidelines; and implementation studies). I used behaviour change theory to explore uptake and implementation of research and developed a research, translation and impact cycle to chart the flow from knowledge to impact.

For the cohort of Australian maternal and perinatal randomised controlled trials, I compiled a database of all known trials published between 1986 and 2014. For the survey of triallists I developed a questionnaire using the Behaviour Change Wheel to assess perceptions related to capability, opportunity and motivation and the influences of these on uptake and implementation.

**Results:** In a cohort of over 500 Australian maternal and perinatal randomised trials, multi-centre design, National Health and Medical Research Council or equivalent funding, and larger sample sizes were associated with higher citation rates, increased inclusion in syntheses and policy documents. More recent trials (published from 2011-2014) also showed improvements compared with trials from 1986-2010.

In the survey of triallists, fellow health professionals were thought to be aware of trial findings only 50% of the time, but skill deficits were not major barriers to implementation. When trial results were widely known, confidence in the findings was sometimes low. Trials with null results were difficult to interpret and there was some lack of clarity about who should be responsible for translation and implementation.

Emerging citation and social media systems such as Altmetric could increase visibility of research and change some of the ways that impact is currently measured.

In three case studies addressing different stages of translation, I have demonstrated how integrating a research, translation and impact cycle with behaviour change theory can explain, predict and shape practice and policy change. These case studies were: closing an important research gap (reminder systems for women with previous gestational diabetes); initiatives to highlight the importance of stillbirth and its prevention (including development of a tool to assess the impact of bibliographic citations); and the implementation of antenatal magnesium sulphate for fetal neuroprotection (a project exemplifying rapid and effective implementation).

**Conclusions:** Maternal and perinatal research in Australia has made a major contribution to better health and health systems. I have shown that this impact could be even greater with improved translation processes such as making research more implementation ready, strengthening networks and using coordinated approaches to accelerate uptake and impact.

**Declaration**
I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary university and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

In addition, I certify that no part of this work will in the future be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Philippa Middleton
February 2015
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Lastly I would to acknowledge the many colleagues who generously provided information and insight into the often mysterious processes of research translation, implementation and impact.
List of key publications authored/co-authored by Philippa Middleton

Chapter 4:
- Middleton P, Crowther CA. Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance. *Cochrane Database of Systematic Reviews* 2014, Issue 3 (Middleton 2014a).

Chapter 5: Stillbirth prevention

Chapter 6:
1.1 Introduction and review of the literature on research impact

We know surprisingly little about how investments in research lead to better health and wellbeing outcomes (Druss 2005) despite “the tacit understanding ... that biomedical research ... will lead to an improvement” (Grant 2000). Peter Provonost, a champion of quality and safety in health care has described three main components of medical science – understanding the biology of disease, finding effective treatments and ensuring treatments are delivered effectively. The latter is now increasingly called research translation or implementation science, defined as “the scientific study of methods to promote the systematic uptake of clinical research findings and other evidence-based practices into routine practice, and hence to improve the quality and effectiveness of health care” (cited in the information section of the journal Implementation Science). Provonost points out that for every dollar spent on biology and treatment evaluation only one cent is spent on implementation science (Laurance 2009).

Many individuals and groups are now articulating the need to pay more attention to effective delivery of research results and to foster “a culture of and expectation for impact within Australian universities and wider society” (RAND 2013). For example, the National Health and Medical Research Council (NHMRC) has used the ‘virtuous cycle’ for several years to depict the desired flow from research to knowledge creation and translation to healthier Australians, improved healthcare and national wealth generation (Health and Medical Research Strategic Review 2000). More recently the McKeon Report (a high level review of the health and medical research sector commissioned by the Australian Government) has recommended greater investment in health and medical research, including clinical trials and their translation, to improve health outcomes for Australians and to more firmly embed health and medical research in the health system (Commonwealth of Australia 2013).

The UK Research Excellence Framework has defined the impact of research as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life beyond academia (Research Excellence Framework (2011), p. 26). Ideally the impact of health research would be assessed by seeing direct improvements in health outcomes of individuals and populations, and of health systems. In reality measuring research impact is recognised to be “an inherently difficult task” (Anderson 2014a) and we are often forced to rely on measuring a number of proxies for impact, with varying degrees of directness and accuracy. This has led to more emphasis on the ‘science of science’ (RAND 2013) or ‘research on research’ to see how the effectiveness of, and investment in, research can be improved and not wasted (Chalmers 2014).

Australia makes an impressive contribution to global health and medical research (Khachigian 2006). In terms of return on investment, Access Economics have estimated that every dollar invested in health research and development in Australia yields an average return of $5 (Access Economics 2003). However these returns could be much higher in Australia – and the rest of the world – since it has been estimated that as much as 85% of research investment is wasted due to wrong questions, poor study designs and biased findings (Kleinert 2014; Chalmers 2009).

In this thesis, I specifically aim to link the ‘science of science’ with the impact of research (‘science of impact’) by analysing Australian randomised controlled trials (RCTs) and Cochrane systematic reviews related to maternal and perinatal health. I have chosen RCTs and Cochrane systematic reviews as they generate the most reliable evidence about health outcomes and potential impact (Glasziou 2011) and they form much of the foundation of implementation science which examines processes such as generation, synthesis and translation of knowledge.
1.2 Measuring the impact of research

The notion of research impact is a multi-dimensional construct that cannot be adequately measured by any single indicator (Bollen 2009). Other difficulties in measuring research and tracking research impacts include problems in identifying research inputs (since many research activities may contribute to each clinical advance); in accurately ascribing the impact of the research; and appropriately valuing the attributed economic impact (Buxton 2004).

Most research measurement systems rely on measuring quantity rather than tackling the more elusive aspects of research quality and impact (Shewan 2006; Dembe 2014). Part of this complexity arises from the often lengthy, complicated and seemingly unpredictable nature of the paths from research findings to use in health care, along with the need to reconcile new knowledge with existing views and practices (Genuis 2006). Failure to implement what we know costs lives, yet very little is being invested to ensure that useful knowledge generated from research makes its way into policy and practice (Eccles 2009). The time it takes for research to translate from academia into wider societal benefits is largely unknown, and where known, it is highly variable. In the biomedical and health sciences this time has been estimated across a number of studies to be, on average, 17 years (Slote Morris 2011).

Despite these difficulties, a number of countries have been developing national research evaluation and impact assessment systems over the past decade or so, and according to the RAND Corporation, Australia has been at the forefront (RAND 2013). The primary purpose of Excellence in Research for Australia is “to identify research quality and assure Australians their investment in research is being spent wisely” (ERA 2012). This is highly pertinent to the concept of impact and its assessment.

ERA uses a five point rating scale with 5 representing outstanding performance, well above world standard, with the unit of analysis being a particular discipline of research (ERA 2012). Metrics assessing research outputs, research income, esteem and applied measures are combined, and reviewed by national evaluation committees. The 2012 ERA indicators were:

i. **Indicators of research quality**: publishing profile, citation analysis, ERA peer review, and peer reviewed Australian and international research income;

ii. **Indicators of research volume and activity**: total research outputs, research income and other research items;

iii. **Indicators of research application**: research commercialisation income and other applied measures (e.g. NHMRC-endorsed guidelines);

iv. **Indicators of recognition**: esteem measures.

Future directions for ERA will be to:
- expand metrics (research application, knowledge exchange and collaboration);
- expand the range of applied outputs;
- focus on pathways to impact (ERA 2012).

Traditional bibliometric analysis has concentrated on numbers of publications, in which journals these are published and how many times the individual articles are cited. However there may be little correlation between ‘academic’ measures such as these and actual health outcomes (Buxton 2011).

While an individual’s or research centre’s publishing output is clearly important, journal impact factors have attracted particular criticism, as they relate to journal level citation rates, and not the number of times that a particular article has been cited (PLoS Medicine Editors 2006). Further, it is implicitly assumed that citation of an article implies use of that document by the citing author; citation reflects the merit (quality, significance, impact) of the article; references are made to the best possible works; and that an article is related in content to the one in which it is cited (Nieminen 2006). These assumptions may not always hold and citations may have little to do with impact or influence on health policy and practice (Middleton 2007a).
Systems such as Web of Science and Scopus show variation in how many and which citations they detect. For Australian maternal and perinatal randomised controlled trials and Cochrane systematic reviews, Scopus has been shown to capture more citations than Web of Science (Middleton 2012a). Increased electronic sophistication has spawned a number of enhanced collection methods, such as Google Scholar, which captures significantly more citations in the maternal and perinatal area than systems such as Scopus (see Chapter 5: Stillbirth).

Hybrid systems, such as Public Library of Science (PLoS), have begun to count and tabulate document views and downloads as well as citations. The Altmetric system adds several social media and demographic components to the mix, as well as providing links to news items, blogs and tweets. Altmetric defines its score of a document as a “measure of the quality & quantity of online attention that it has received” (www.altmetric.com). Some publishers such as Scopus and the Cochrane Library (Wiley) are adding Altmetric scores to recent documents. For example, a 2013 Cochrane review on umbilical cord clamping after birth (McDonald 2013) had a Altmetric score of 212 (as at 17/11/14), comprising mentions from 9 news outlets, 5 blogs, 1 policy source, 124 tweets, 51 Facebook users and one highlight/review. This is a very high score, placing this review in the top 5% of all articles tracked by Altmetric. The attention gathered by Altmetric is visible very soon after publication of an article and well before academic citations appear. As noted by Dinsmore 2014, much of the attention captured by Altmetric comes from “stakeholders whose engagement would usually remain invisible to conventional bibliometrics”.

Some of these measures may be proxies for impact in terms of actual improvement in health outcomes as there are still many gaps in our knowledge about the links between dissemination and outcome. Measures such as publications, citation rates and grant funding indicate some aspects of attention, activity and outputs, but these do not indicate whether the research has had an impact on health outcomes of individuals and populations, and outcomes on health systems. Recently Cohen and colleagues have developed a tool to assess what they term “real world” impact arising from health intervention research. This includes changes to practice, to services and to policies, but does not include scholarly outputs such as publications, research funding and capacity building (Cohen 2014).

While ‘research on research’ is still underdeveloped, it is clear that understanding behaviours and motivations of health professionals and health consumers is crucial to predicting and influencing impact. Recent work on behaviour change is influencing uptake and implementation of effective interventions, exemplified by the work of Michie and colleagues (Michie 2011; Michie 2014).

1.3 Translational science and the research cycle

In its broadest sense, translation is about “the process of discovery, its translation into potential solutions, and in its implementation of those potential solutions” (Horner 2013). Translation can be distinguished from dissemination since it transforms or amends knowledge findings in some way before or during the dissemination process. Translation is used to describe the steps from basic research to applied or clinical research reflected in the definition of ‘knowledge translation’ as a “dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the healthcare system” (Straus 2009).

Translation can also refer to the narrower process of adapting the presentation of clinical research findings in order to make them more understandable or acceptable to specific groups such as policy makers and health professionals. These ‘translations’ can be summaries or messages targeted and/or tailored to particular groups, such as those provided by the National Institute for Health and Care Excellence (NICE) to clinicians, consumers and policy makers (www.nice.org.uk).
Synthesis is a particularly powerful form of translation. Although the evidence from general medical journals indicates that there has been a continuing failure to integrate existing research with new findings, synthesis is a particularly powerful part of the translation process (Clarke 2010; Clarke 2013). Clinical practice or public health guidelines can also have substantial influence on policy and practice (Grimshaw 2006) and have been attributed a credibility that “comes from a combination of impartiality and deep clinical and scientific expertise” (Garber 2005).

Some of the tools used to translate research findings into health policy and practice are not captured by traditional bibliometric methods. For example, guidelines are not indexed in the mainstream systems, although Altmetric is beginning to capture a few policy sources.

Even with excellent dissemination and acceptance of the course of action, there may still be a ‘know-do gap’, for example knowing what to do, but not knowing how to do it – and perhaps in some cases knowing, but not wanting to adopt a particular practice. For example, an assessment of 430 recommendations for preventive, acute and chronic care showed that just over half (55%) of US patients received the recommended care (McGlynn 2003). Implementation refers to the process of actual change in practice and often follows identification of evidence-practice (know-do) gaps and/or variation in practice (which may reflect poor uptake of effective strategies in some organisations). Barriers to the uptake of evidence can operate at many levels – the innovation itself; individual professionals or consumers; and social, organisational, economic and political contexts (WHO 2006).

Models of translation attempt to explain how research is implemented and how and when it makes an impact. Such models are prolific, and fall into two main camps – pipeline (linear) and cyclical. Some models conceptualise translation science as a pipeline moving from ‘bench to bedside’ (Figure 1.1) and others describe the processes of translation as a cycle. While translation is clearly a “messy, iterative and complex process” (Slote Morris 2011), models do help to identify stages in the processes of translation and implementation, which are crucial to understanding, and improving, the impact of research.

**Fig 1.1: Pipeline (linear) model (Slote Morris 2011)**

![Pipeline (linear) model](image)

T1 = translation stage 1; T2 = translation stage 2
Cycle models have the advantage of showing translational processes as a series of iterative loops. Informed by two seminal papers (Henderson-Smart 2003 and Graham 2006) I have developed a research/translation cycle schema (Figure 1.2), showing the important steps needed to address, achieve and measure change.

**Fig 1.2: Research/translation cycle (informed by Henderson-Smart 2003 & Graham 2006)**

![Research/translation cycle](image)

1.4 Maternal and perinatal health research

Maternal and perinatal ill health is the largest contributor to the global burden of disease (even without the inclusion of stillbirths) (Lopez 2001) and for the first time in history, complications from preterm birth now outrank all other causes as the number one killer of children under five, claiming more than one million lives each year (Liu 2014). Although the World Health Organization (WHO) has identified maternal and perinatal health second only to infectious disease as a priority for global health research, there is worldwide underinvestment in maternal and perinatal health and health research (Fisk 2009). Our deepening understanding that events during pregnancy may influence long term health outcomes for both mother and baby are further justification to conduct high quality research in this area and to ensure that research findings are effectively translated into practice and beneficial health impacts (Bhutta 2014; ten Hoope-Bender 2014).

This requires reliable knowledge about what works to be generated. While the randomised controlled trial is described as the gold standard for assessing the effects of interventions (Schulz 2010), the most comprehensive and powerful tool for assessing what is known for a particular question is the systematic review. The role of systematic reviews have been eloquently summarised: “Those who say that systematic reviews and meta-analyses are not “proper research” are wrong; it is clinical trials done in the absence of such reviews and meta-analyses that are improper, scientifically and ethically. Investigators and organisations who undertake and coordinate reviews and meta-analyses now need the funding and recognition they deserve if public trust in biomedical research is
to be maintained and resources used in an effective way” (Young 2005). Thus it follows that in order for decisions about health care to be based on the totality of research addressing a particular question, the basic unit of knowledge translation should be up-to-date systematic reviews or other syntheses of research findings (Grimshaw 2012).

Maternal and perinatal health research has a substantial track record of quality and impact with an emphasis on intervention and synthesis research (Chalmers 1989). More recently, international and national efforts such as the Cochrane Collaboration (www.cochrane.org) and the WOMBAT Collaboration (Middleton 2006; Middleton 2014c) have added to this output. However there is still a need for a greater emphasis on dissemination and translation/implementation research to ensure that the many effective interventions in this area are used optimally to improve the health and wellbeing of mothers, babies and their families (Belizan 2009). Antenatal corticosteroid therapy is an illustrative example. Though benefits of reduced risk of neonatal death and serious neonatal morbidities such as respiratory distress syndrome and intraventricular haemorrhage were known from research synthesis of randomised trials in the 1980s (Crowley 1989), clinician behaviour change and concerted implementation was needed. With widespread uptake of this intervention, considerable financial savings could eventually be realised (for example a net economic benefit of $3000 USD for each neonate treated) (Leviton 1999; Mugford 1991; Mugford 1993; NICHD 1994).

1.5 Outline and aims for this thesis

My overarching aims in this thesis are to investigate the contribution made by Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health to improvements in the health and wellbeing of women, babies and their families in Australia and internationally; and to inform future strategies for improving generation, synthesis, translation and implementation of research into health impact.

AIM 1: Bibliometric and social network analysis
To assess the impact of the findings from Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health through measuring the impact of this body of research with methods such as bibliometric and social network analysis (Chapter 2).

AIM 2: Survey of triallists
To survey over a hundred Australian maternal and perinatal triallists to determine their views about what impact their research has made or is making; to relate this to behaviour change theory and to explore factors influencing behaviour change and impact (Chapter 3).

AIM 3: Case studies of knowledge generation, synthesis, translation and implementation
Through three case studies from different areas of maternal and perinatal health, I assess and follow how knowledge has been generated, synthesised and implemented; and comment on the interaction between these processes and their impact on clinical practice and on health outcomes. Each of the three areas, gestational diabetes mellitus, stillbirth and cerebral palsy, is a source of considerable health and societal burden in Australia.

- Gestational diabetes mellitus: I show how a particular research to practice gap (low rates of postpartum screening for women who have experienced gestational diabetes mellitus) can be closed (Chapter 4).
- Stillbirth: I outline the challenges of preventing stillbirth, what needs to be done to reduce the numbers of stillbirths in high income countries and present some findings about the impact of two papers from the 2011 Lancet Stillbirth series (Chapter 5).
- Antenatal magnesium sulphate for preventing cerebral palsy: I document the steps our team has used, and is continuing to use, for knowledge synthesis, guideline development and uptake of antenatal magnesium sulphate for fetal, neonatal and infant neuroprotection. This is an example where one complete revolution of the research/translation cycle has achieved rapid, substantial and, thus far, sustainable implementation (Chapter 6).
AIM 4: Model and future strategies for translation and health impact

Finally I will summarise my findings and use these to expand the above model and propose future strategies for improving the translation of new and synthesised knowledge to maximise health impact (Chapter 7).
2.1 Overview

I have selected randomised controlled trials and Cochrane systematic reviews as my study cohort as these are often further along the translation trajectory and thus more ‘implementation-ready’ than some other types of studies, as shown by the research/translation cycle described in Chapter 1. My overall aim for this chapter (and for Chapter 3) is to investigate how the body of this maternal and perinatal knowledge generated in Australia has translated into impacts on health and health systems, internationally and nationally. While the ultimate definition of impact is in terms of health outcomes, I will explore a number of ways of estimating impact in this chapter.

In an ideal world, impact in terms of improvement in health and other outcomes would be measurable through routine and real-time data collection. Although seen as a necessary part of many business and management endeavours, we are a long way from achieving comprehensive and timely data collection in health care (Dobbins 2009).

Even then, it would still be difficult to determine the reasons and attributions for changes in outcomes. So we are forced to use proxies of various sorts to assess impact. Many of these proxies measure ‘use’ in terms of dissemination (which can encompass scanning, reading, or downloading), tweeting, or citing, any of which may not necessarily translate to impact on health outcomes.

### 2.1.1 How impact can be measured

Impact of research, particularly impact on health outcomes, is difficult to measure and although a variety of methods have been used such as bibliometrics, document analysis, surveys and case studies, no single method has emerged as the best option (Bunn 2014). Educational materials such as medical journal articles are commonly used to disseminate knowledge and to indicate impact. While they may slightly improve healthcare professional practice, it is not clear if they have much impact on health outcomes (Giguère 2012).

The main components of bibliometric analysis are impact factors (and their variants) and citation rates. Journal impact factors have often been debunked as a way of measuring use of a particular paper, as they relate to journal level citation rates, and not the number of times that a particular article has been cited (PLoS Medicine Editors 2006). Citation rates do at least indicate the number of authors who have been sufficiently interested in a paper to cite it in their work. However citation rates do not tell us anything about the reason why an author has chosen to make a citation. Indeed individual citations may have little to do with encouraging uptake and impact (Middleton 2007a) but all citations are effectively given the same weight in the present bibliographic systems (see Chapter 5 for further coverage of this).

A plethora of systems to capture accesses to publications have appeared in the wake of widespread online provision of medical and health literature. Some of these are hybrid systems which track social media and more conventional bibliographic sources, one example being Altmetric (www.altmetric.com) which scores each article. As yet we have limited understanding of how the various components of these hybrid systems are related to research impact and how the components relate to each other, although this is becoming an active field of research in its own right (Lin 2013).
2.1.2 Why we need to measure impact of Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health

As discussed in Chapter 1, syntheses such as systematic reviews and overviews of generated research knowledge are the most appropriate unit of research translation (Grimshaw 2012) and clinical practice guidelines are important in translating knowledge into actionable recommendations. Thus investigating the degree and nature of translation from RCTs to Cochrane systematic reviews and clinical practice guidelines may help to better understand these parts of the translation process.

Along the trajectory from design of a study to integration in a clinical practice guideline, randomised controlled trials are subject to many influences that can positively or negatively affect the future use of their findings. Some factors may be intrinsic – for example, neonatal randomised controlled trials are frequently conducted in highly selected populations such as very preterm babies and thus may have smaller sample sizes than maternal trials. Other factors may be more amenable to change such as formulating answerable, relevant questions and thus reducing waste in research (Chalmers 2009; Chalmers 2014; Ioannidis 2014a). Whether or not a trial was subsequently funded by NHMRC, Australian Research Council (ARC) or their international equivalents, may reflect the value of robust peer review systems in identifying quality research questions and design. Funding also increases the ability of the investigators to successfully complete their trial. Higher citation rates may be linked with higher sample sizes of trials and perhaps with positive rather than null findings. Dissemination through the research/translation cycle by integration in systematic reviews and policy documents would be expected to increase implementation of trial findings.

It is important to have a better understanding of the relationships between different forms of dissemination, and use of findings. Why do authors cite particular articles and what do mentions in social media mean? Are traditional citations and social media mentions completely different systems with little overlap between audiences? Is citation in a Cochrane systematic review or a clinical practice guideline important for uptake and ultimate impact on health outcomes?

Undertaking a randomised controlled trial is usually a large undertaking. It represents a considerable investment by the trialists who are therefore likely to be highly interested in ensuring the knowledge that they have generated moves through the research/translation cycle towards implementation or informing further research. Consequently many will be wish to be involved in translation or at least wish to encourage translation of the knowledge they have generated and often synthesised.

As far as I am aware, assessing the impact of maternal and perinatal RCTs and Cochrane systematic reviews on such a scale and using a diversity of methods to measure impact and its proxies has not previously been done.

2.2 Aims and hypotheses for cohorts of Australian maternal and perinatal randomised controlled trials and Cochrane systematic reviews

<table>
<thead>
<tr>
<th>Aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) To explore characteristics of trials and the relationship of these characteristics with various forms of impact measures, including citation rates, and inclusion/citation in reviews and clinical practice guidelines.</td>
</tr>
<tr>
<td>2) To determine if key characteristics of Australian maternal and perinatal trials and their impact, have changed over time (1986-2010 compared with 2011-2014).</td>
</tr>
<tr>
<td>3) To assess the impact of Cochrane systematic reviews using social network scores.</td>
</tr>
</tbody>
</table>
Study hypotheses

1) Hypotheses related to: Citation rates of Australian maternal and perinatal randomised controlled trials and their integration into Cochrane systematic reviews and clinical practice guidelines

Nature and design features of Australian maternal and perinatal trials
a) Trials with a maternal focus will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with a neonatal focus.

b) Multicentre trials will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than single centre trials.

Funding source
c) Trials funded by NHMRC, ARC or international equivalents will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials funded from other sources.

Sample size
d) Trials with larger sample sizes will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with smaller sample sizes (sample size in intervals of hundreds: 0-99 …. 1000+).

Direction of effect of trial findings
e) Trials with positive findings will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with null or true negative findings.

Publication
f) Trials published in ‘high impact’ journals (defined here as BMJ, Journal of the American Medical Association, Lancet, New England Journal of Medicine, PLoS Medicine) will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials published in other journals.

Integration into syntheses
g) Trials included in Cochrane systematic reviews will be cited more often than trials not included in Cochrane systematic reviews (citations in intervals of 25: 0-24 … 150+).

Integration into policy documents
h) Trials cited in clinical practice guidelines will be cited more often (in Scopus) than trials not included in clinical practice guidelines.

2) Hypotheses related to: Differences over time

a) Trials published or ongoing from 2011-2014 will have increased numbers of multicentre trials, higher sample sizes, more trials funded by NHMRC (or equivalent) than trials published from 1986-2010.

3) Hypotheses related to: Social network analysis of Cochrane systematic reviews

a) Cochrane systematic reviews with at least one Australian author and/or including at least one Australian maternal and perinatal trial will have higher Altmetric scores if the review has been cited in a clinical practice guideline.
Summary of hypotheses for Chapter 2

1. Citation rates by:
   a) maternal/neonatal focus
   b) multicentre
   c) funding source
   d) sample size
   e) direction of effect of trial findings
   f) publication
   g) integration into syntheses
   h) integration into policy documents

2. Differences in trials over time (1986-2010) versus 2011-2014

3. Social network analysis (Altmetric scores) of Cochrane systematic reviews

2.3. Methods

2.3.1 Overview of methods

I analysed two cohorts of Australian maternal and perinatal randomised controlled trials (1986-2010 and 2011-2014) and explored associations between trial characteristics and measures of impact. I also compared the two trial cohorts to determine trends over time.

I measured associations between Altmetric scores and citation in clinical practice guidelines of Cochrane systematic reviews with Australian authorship and/or including Australian maternal and perinatal trials.

2.3.2 Australian maternal and perinatal randomised controlled trials: 1986-2010 cohort

Definition: Australian maternal and perinatal trials were defined as randomised controlled trials of interventions for pregnant or postpartum women (up to six weeks postnatally) and/or their babies. Interventions for babies needed to have been within the neonatal period (up to four weeks) with no limits placed on length of follow-up. Trials needed to recruit at least some participants in Australia.

Time period: Trials published as full papers or abstracts with results between 1986 and 2010 and fitting the above definition were eligible for inclusion. Unpublished trials with at least some results available were also eligible. The rationale for going back to 1986 was that the journey from trial completion to impact on practice may take several decades (Slote Morris 2011); and the rationale for stopping at 2010 was to allow some time for trial findings to be considered for products further through the translation cycle such as systematic reviews and clinical practice guidelines (CPGs). A cohort of 2011-2014 Australian maternal and perinatal trials were also analysed to compare changes over time – see below.

Searching/sources:
I searched:
- the Cochrane Central Register of Controlled Trials (last searched October 2011);
- MEDLINE (last searched October 2011); and
- the Perinatal Society of Australia and New Zealand (PSANZ) Trials database (last searched November 2014).

This was supplemented with:
- Google Scholar searches;
- searches by author of known triallists;
- pearlring and snowballing of relevant references;
scanning of included, excluded and ongoing studies cited in Cochrane reviews addressing maternal and perinatal topics.

The PSANZ trials database is derived from sources including the Australian and New Zealand Clinical Trials Register and other trials registers, bibliographic databases, health and medical research grant outcome lists, and conference and meeting abstracts. I originally developed this database as part of the WOMBAT Collaboration (funded by a NHMRC Enabling Grant) and now maintained for PSANZ by myself and other Australian Research Centre for Health of Women and Babies (ARCH) personnel at the University of Adelaide. The database contains entries for trials from 2005 (published from 2005 or still recruiting at that time), currently has over 400 entries and is updated weekly.

Search terms for the relevant sources included maternal, antenatal, perinatal, neonatal, mothers, babies, infants, pregnant, pregnancies, pregnancy.

**Cochrane systematic reviews:**

**Definition:** Cochrane maternal and perinatal systematic reviews were defined as reviews published in the Cochrane Database of Systematic Reviews (CDSR) of interventions for pregnant or postpartum women (up to six weeks postnatally) and/or their babies. Interventions for babies needed to have been within the neonatal period (up to four weeks) with no limits placed on length of follow-up. To be included, Australian Cochrane maternal and perinatal systematic reviews needed to have at least one author based in Australia and/or include at least one Australian maternal and perinatal trial (fitting the above definition). Withdrawn reviews or review protocols were not eligible.

**Source:** The entire Cochrane Database of Systematic Reviews was manually scanned to identify maternal and perinatal Cochrane systematic reviews (last scanned in November 2014).

**Clinical practice guidelines**

**Definition:** guidelines following accepted methods for evidence-based guidelines with graded recommendations, not consensus documents.

Over 120 clinical practice guidelines were manually scanned for citations of Australian maternal and perinatal randomised controlled trials or citations of maternal and perinatal Cochrane systematic reviews. If the clinical practice guideline cited a superseded Cochrane systematic review, the current version of the review was used.

**Descriptors and variables:**

I selected trial characteristics following the path in the research/translation cycle described in Chapter 1 - from trial design and results (‘knowledge creation’) to publication through to integration in syntheses (‘knowledge synthesis’) and policy documents and dialogue (‘making knowledge actionable’):

- Trial question with a maternal or neonatal focus;
- Whether trial design was multicentre or single centre;
- Funding source (NHMRC, ARC or international equivalents);
- Sample size achieved;
- Direction of effect of trial findings (positive: primary outcome(s) with a clear beneficial effect, negative: primary outcome(s) with a clearly harmful effect, null: no significant or important differences seen in primary outcome(s));
- Publication in a ‘high impact’ journal (defined here as BMJ, Journal of the American Medical Association, Lancet, New England Journal of Medicine, PLoS Medicine);
- Whether trial was included in a Cochrane systematic review;
- Whether trial was cited in a clinical practice guideline;
The citation rate for each trial was retrieved from Scopus in December 2013. The Scopus citation service was chosen on the basis of evidence of higher coverage than Web of Science (Middleton 2012a).

Sample size and citation rate were grouped into categories for analysis. For sample size, I chose intervals of 100, ranging from 0-99 to 1000 or more. For citation rates, I chose intervals of 25, ranging from 0-24 to 150 or more.

**Analysis:** For analyses involving categorical data, Fisher's exact test was used (Stata 10.0 – www.stata.com). Other associations were analysed using Chi² tests. Analyses were also presented graphically.

**Data management:** I used the Cochrane Collaboration’s Review Manager software, RevMan 5.3 (Review Manager 2014) and Excel to manage details of Australian maternal and perinatal trials and Cochrane systematic reviews.

### 2.3.3 Later cohort of Australian maternal and perinatal trials: 2011-2014

In order to determine whether key characteristics of Australian maternal and perinatal trials and their impact have changed over time, I compared my 1986-2010 sample with a comparable sample of trials with results published from 2011 to 2014 (from the PSANZ trials database: www.archserver.adelaide.edu.au/psanz100plus/). The PSANZ trials database is derived from sources including the ANZCTR and other trials registers, bibliographic databases, health and medical research grant outcome lists, and conference and meeting abstracts and is updated weekly.

I extracted details of trials publishing results from 2011 to November 2014 and trials still ongoing at November 2014 from the PSANZ trials database. For each trial I extracted the target sample size, whether funded by NHMRC or equivalent, whether multicentre or not and whether the trial evaluated, or was evaluating, a lifestyle topic.

I compared each of these variables in the two time periods using Chi² tests and presented some of the results graphically.

I did not attempt to retrieve citations made to these trials, as the trials were either not yet published or had only been published for a short time, leaving insufficient time for citations to have accrued.

### 2.3.4 Altmetric scores of Cochrane systematic reviews with Australian authorship and/or including Australian maternal and perinatal trials

I chose Altmetric (www.altmetric.com) for analysis of Cochrane systematic reviews, as it has the most comprehensive coverage of social media and more conventional bibliographic sources. To date, Altmetric has tracked nearly 3 million articles. (My cohort of RCTs, published between 1986 and 2010, was not able to be analysed for Altmetric scores as Altmetric generally only captures activity from 2011 onwards.) From the Cochrane Library (www.thecochranelibrary.com), I extracted the Altmetric score from the Altmetric button on the summary page of each of the 359 Cochrane systematic reviews including at least one Australian maternal or perinatal randomised trial and/or with at least one Australian review author. This extraction was last updated in November 2014.

I crossmatched Altmetric scores and Cochrane systematic reviews cited in clinical practice guidelines through the RevMan database of maternal and perinatal Cochrane systematic reviews I have compiled. I explored the association between citation of the review in clinical practice guidelines and high Altmetric scores (top 25% of attention) with a Chi² test.
2.4 Results

2.4.1 Characteristics of Australian maternal and perinatal randomised controlled trials published between 1986 and 2010

I was able to locate and retrieve 306 Australian maternal and perinatal randomised controlled trials with findings published between 1986 and 2010. Summary characteristics for the 306 trials are shown in Table 2.1.

Description of included trial characteristics

Focus: Of the 306 trials, 213 (70%) had a predominantly maternal focus (usually the intervention occurred during pregnancy and/or lactation, usually reported maternal, neonatal and often reported later child outcomes) and the remaining 93 (30%) had a predominantly neonatal focus (intervention occurred in the neonatal period and usually with neonatal and later outcomes reported). A small number of trials (<10) reported only physiological or biochemical outcomes.

Multicentre: Forty-three of the 306 trials (14%) were multi-centre trials. The main coordinating centre was located in Australia in all but seven of these 43 trials.

Funding sources: 69/306 (22%) of trials received NHMRC or ARC funding (and/or the international equivalent).

Table 2.1: Summary of characteristics of Australian maternal and perinatal randomised controlled trials published 1986-2010 (N = 306)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Maternal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOCUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus</td>
<td>213 (70%)</td>
<td>93 (30%)</td>
</tr>
<tr>
<td><strong>MULTICENTRE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentre</td>
<td>43 (14%)</td>
<td>263 (86%)</td>
</tr>
<tr>
<td>Single centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PUBLICATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>272 (89%)</td>
<td>34 (11%)</td>
</tr>
<tr>
<td>Partial</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FUNDING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHMRC or equivalent</td>
<td>69 (22%)</td>
<td>237 (78%)</td>
</tr>
<tr>
<td>Other/none</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAMPLE SIZE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100+</td>
<td>161 (53%)</td>
<td>145 (47%)</td>
</tr>
<tr>
<td>Less than 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DIRECTION OF FINDINGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>155 (52%)</td>
<td>141 (48%)</td>
</tr>
<tr>
<td>Positive/Negative^</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CITATIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-49^^</td>
<td>237 (77%)</td>
<td>69 (23%)</td>
</tr>
<tr>
<td>50 or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COCHRANE SYSTEMATIC REVIEWS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Included</td>
<td>148 (48%)</td>
<td>158 (52%)</td>
</tr>
<tr>
<td>Not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CPGs</strong></td>
<td>136 (44%)</td>
<td>170 (56%)</td>
</tr>
</tbody>
</table>

^results available for 296 trials; ^1 trial was negative; ^^includes 34 trials not found in Scopus

Sample size: Nearly half (47%; 145/306) of trials had sample sizes under 100. Nine percent of trials (28/306) had a sample size of 1000 or more. See Figure 2.1 for a more detailed breakdown.

Publication status: Of the 306 trials, 34 (11%) were not fully published. Most (24) of these 34 trials were reported as conference abstracts only, three were PhD dissertations, two were letters, two trials were abandoned after recruiting a few participants, and there was one example each of an...
unpublished report, a planned trial that did not start and a trial that was stopped due to a drug recall for safety reasons. See Figure 2.2 for a flow diagram of these trials.

**Fig 2.1: Sample sizes of Australian maternal and perinatal randomised controlled trials 1986-2010**

**Fig 2.2: Flow diagram of publication status of Australian maternal and perinatal RCTs**

**Direction of effect of trial findings:** I classified published trial findings as null (no significant difference seen in the main outcomes between groups) or as positive (significant difference in one or more primary outcomes) or true negative (significant chance of harm) findings. There was insufficient information to determine the direction of findings for 10 trials. A small majority of trials were judged to have null findings, 155/296 (52%).

**Citations:** There were 23% of trials with 50 or more citations as at December 2013 (69/306). Twenty of these trials had 150 or more Scopus citations. More than three-quarters of trials (77%: 237/306)
had fewer than 50 Scopus citations (with 34 (11%) of these trials not captured by Scopus). See Figure 2.3 for a more detailed breakdown.

**Fig 2.3: Citations of Australian maternal and perinatal trials 1986-2010 (Scopus Dec 2013); n = 306**

![Bar chart showing citations distribution](image)

NA = No record in Scopus (or Web of Science)

**150 or more citations:**
- Twenty (6.5%) of the 306 trials were cited 150 times or more in SCOPUS (as at December 2013). This group of trials shared many characteristics – most were multi-centre, had sample sizes greater than 100, had NHMRC funding or equivalent, most had positive findings and most were studies included in Cochrane reviews. See Table 2.2.
- Focus of the 20 trials was evenly divided with 11 having a maternal, and nine a neonatal focus.
- Half of the trials (n = 10) were cited in guidelines – nine out of the 11 trials with a maternal focus but only one out of the 9 trials with a neonatal focus.
- Of the 14 multicentre trials, eight had their coordinating centre located in Australia with the remaining coordinating centres located outside Australia.
- Of the 13 trials with 150 or more citations published in the ‘high impact’ journals, most (9; 69%) also had positive findings, perhaps indicative of publication bias occurring in these journals.
- Almost all the ‘top 20’ trials (17; 85%) were included in a Cochrane review.
- Altmetric scores were available for only eight of the 20 trials. One trial was in the top 5% of attention, two in the top 25%. Of the remaining five trials, Altmetric recorded that three trials had been included in F1000Prime (which publishes “recommendations of the best research articles in biology and medicine from a faculty of global experts” [www.f1000.com/prime]).

**Trials included in Cochrane systematic reviews:** Almost half of the trials (148/306; 48%) were included in at least one Cochrane systematic review.

**Trials included in clinical practice guidelines:** Nearly half of the trials (136/306; 44%) were cited in at least one clinical practice guideline. Of these 136 trials, over half (74; 54%) were directly cited. The remaining 62 trials were part of a guideline only via a Cochrane review (including that trial) being cited in the guideline.
**Intervention category:** I classified each of the 306 trials into the following broad categories:

- a) drugs and supplements 131 (43%)
- b) processes and procedures 112 (37%)
- c) behavioural interventions 63 (20%)

**Fig 2.4: Intervention category of Australian maternal and perinatal trials**

![Pie chart showing intervention categories]
Table 2.2: Australian maternal and perinatal randomised controlled trials with 150 or more citations (Scopus December 2013)

<table>
<thead>
<tr>
<th>Study</th>
<th>Scopus cites (#papers if &gt; 1)</th>
<th>Multicentre</th>
<th>Focus M or N*</th>
<th>Sample size</th>
<th>Funding NHMRC/ARC or Internat’l (I)</th>
<th>Positive finding</th>
<th>‘high impact’ journal^</th>
<th>Cochrane Review</th>
<th>CPG</th>
<th>Altmetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hannah 2000</td>
<td>1240 (8)</td>
<td>✓ (I)</td>
<td>M</td>
<td>2088</td>
<td>I</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>2. ACHOIS 2005</td>
<td>971 (5)</td>
<td>✓</td>
<td>M</td>
<td>1000</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>3. Dunstan 2004</td>
<td>711 (11)</td>
<td>-</td>
<td>M</td>
<td>83</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>4. TIPP 2007</td>
<td>697 (5)</td>
<td>✓ (I)</td>
<td>N</td>
<td>999</td>
<td>I</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>5. CLASP 1994</td>
<td>559</td>
<td>✓ (I)</td>
<td>M</td>
<td>9364</td>
<td>I</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>7. Makrides 1995</td>
<td>382 (2)</td>
<td>-</td>
<td>N</td>
<td>89</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>8. Newnham 1993</td>
<td>370 (5)</td>
<td>✓</td>
<td>M</td>
<td>2834</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>9. COIN 2008</td>
<td>369 (2)</td>
<td>✓</td>
<td>N</td>
<td>610</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>10. Taylor 2006</td>
<td>315 (3)</td>
<td>-</td>
<td>N</td>
<td>178</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>11. ACTORDS 2006</td>
<td>280 (5)</td>
<td>✓</td>
<td>M</td>
<td>982</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>12. Askie 2003</td>
<td>244</td>
<td>✓</td>
<td>N</td>
<td>358</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>13. French/Aust 2001</td>
<td>234 (2)</td>
<td>✓ (I)</td>
<td>M</td>
<td>241</td>
<td>I</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>14. ACTS 2006</td>
<td>225</td>
<td>✓</td>
<td>M</td>
<td>1877</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>15. Armstrong 1999</td>
<td>197 (3)</td>
<td>-</td>
<td>M</td>
<td>181</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>16. McDonald 1997</td>
<td>197 (3)</td>
<td>✓</td>
<td>M</td>
<td>879</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>17. PINT 2006</td>
<td>193 (3)</td>
<td>✓ (I)</td>
<td>N</td>
<td>451</td>
<td>I</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>18. ACTOMgS04 2003</td>
<td>192</td>
<td>✓</td>
<td>M</td>
<td>1047</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>19. DINO 2009</td>
<td>173 (6)</td>
<td>✓</td>
<td>N</td>
<td>657</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>20. Makrides 1999</td>
<td>159 (2)</td>
<td>-</td>
<td>N</td>
<td>83</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

TOTAL 13 13 10

Grey: Multicentre trials with international main coordinating base
### 2.4.2 Citation rates of Australian maternal and perinatal randomised controlled trials and their integration into Cochrane systematic reviews and clinical practice guidelines

#### Hypotheses

**Nature and design features of Australian maternal and perinatal trials**

Trials with a maternal focus will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with a neonatal focus.

Multicentre trials will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than single centre trials.

**Funding source**

Trials funded by NHMRC, ARC or international equivalents will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials funded from other sources.

**Sample size**

Trials with larger sample sizes will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with smaller sample sizes (sample size in intervals of hundreds: 0-99, 100-499, 500-999, 1000+).

**Direction of effect of trial findings**

Trials with positive findings will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials with null or true negative findings.

**Publication**

Trials published in 'high impact' journals (defined here as BMJ, Journal of the American Medical Association, Lancet, New England Journal of Medicine, PLoS Medicine) will be cited and integrated into Cochrane systematic reviews and clinical practice guidelines more often than trials published in other journals.

**Integration into syntheses**

Trials included in Cochrane systematic reviews will be cited more often than trials not included in Cochrane systematic reviews (citations in intervals of 25: 0-24, 25-49, 50-99, 100-149, 150+).

**Integration into policy documents**

Trials cited in clinical practice guidelines will be cited more often (in Scopus) than trials not included in clinical practice guidelines.

#### 2.4.2.1 Citation rates of Australian maternal and perinatal randomised controlled trials

There were many significant associations between citation rates and trial characteristics, and also between sample size and other trial characteristics (see Table 2.3).

**Nature and design features of trials**

- Those trials with a maternal focus, and with a multicentre design, were more likely to have larger sample sizes.
- While the relationship between maternal or neonatal focus and citation rates was not statistically significant, trials with a multicentre design were more likely to be highly cited e.g. 14 of the 20 trials (70%) with Scopus citations of 150 or more were multicentre trials.

**Funding source**

- Trials funded by NHMRC, ARC or international equivalents were more likely to have larger sample sizes and were also more likely to have higher citation rates.

**Direction of effect of findings**

- No association was found between sample size and whether a trial had a positive finding (compared with a null or negative finding). For example, in the 28 trials with 1000 or more participants, 14 trials had null findings and 14 trials had positive findings.
- In contrast, trials with positive findings were more likely to be highly cited e.g. 13 of the 20 trials (65%) with Scopus citations of 150 or more had positive findings.
Publication

- Trials with larger sample sizes were more likely to be published in ‘high impact’ journals. This was also the case for highly cited trials – see Table 2.3.

Table 2.3: Sample size and citation rate analysis (Fisher’s exact test)

<table>
<thead>
<tr>
<th>COMPARISON</th>
<th>FINDING</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nature and design features of trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus &amp; sample size</td>
<td>Maternal focus associated with increasing sample size</td>
<td>0.003</td>
</tr>
<tr>
<td>Multicentre &amp; sample size</td>
<td>Multicentre design associated with increasing sample size</td>
<td>0.0001</td>
</tr>
<tr>
<td>Focus &amp; citation rate</td>
<td>No association seen between maternal or neonatal focus and citation rate</td>
<td>0.082</td>
</tr>
<tr>
<td>Multicentre &amp; citation rate</td>
<td>Multicentre design associated with increasing citation rate</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding &amp; sample size</td>
<td>Increasing sample size associated with NHMRC or equivalent funding</td>
<td>0.0001</td>
</tr>
<tr>
<td>Funding &amp; citation rate</td>
<td>Increasing citation rate associated with NHMRC or equivalent funding</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Direction of trial findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size &amp; positive findings (n = 296)</td>
<td>No association seen between sample size and direction of findings (positive or null/negative)</td>
<td>0.945</td>
</tr>
<tr>
<td>Positive findings &amp; citation rate</td>
<td>Positive trial findings associated with higher citation rates</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Publication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size &amp; ‘high impact’ publication</td>
<td>Larger sample sizes associated with publication in a ‘high impact’ journal</td>
<td>0.0001</td>
</tr>
<tr>
<td>‘high impact’ publication and citation rate</td>
<td>Publication in a ‘high impact’ journal associated with higher citation rates</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Integration into syntheses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size &amp; included in a Cochrane review and citation rate</td>
<td>Larger sample sizes associated with inclusion in Cochrane reviews</td>
<td>0.0001</td>
</tr>
<tr>
<td>Included in a Cochrane review and citation rate</td>
<td>Inclusion in a Cochrane review associated with higher citation rates</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Integration into policy documents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size &amp; cited in a guideline and citation rate</td>
<td>Larger sample sizes associated with being cited in a guideline</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cited in a guideline and citation rate</td>
<td>Citation in a guideline associated with higher citation rates</td>
<td>0.002</td>
</tr>
</tbody>
</table>

^sample size categories: 0-99, 100-199, 200-299, 300-399, 400-499, 500-599, 600-699, 700-799, 800-899, 900-999, 1000+

^^citation rate categories (Scopus Dec 2013): 0-24, 25-49, 50-74, 75-99, 100-124, 125-149, 150+


2.4.2.2 Integration of Australian maternal and perinatal randomised controlled trials into syntheses

- Trials with larger sample sizes were more likely to be included in Cochrane systematic reviews. This was particularly evident at either end of the spectrum – 50/145 (34%) of trials with sample sizes under 100 participants were included in Cochrane reviews compared with 25/28 (89%) of trials recruiting 1000 or more participants.
- Highly cited trials were also more likely to be included in a Cochrane review e.g. 17 of the 20 trials (85%) with Scopus citations of 150 or more were included in at least one Cochrane review.
2.4.2.3 Integration into policy documents

Trials with larger sample sizes were more likely to be cited in a clinical practice guideline. Again this was particularly evident at either end of the spectrum – 37/145 (25%) of trials with sample sizes under 100 participants were included in guidelines compared with 21/28 (75%) of trials recruiting 1000 or more participants.

2.4.3 Differences in Australian maternal and perinatal randomised controlled trials over time: 1986-2010 versus 2011-2014

**Hypothesis:** Trials published or ongoing from 2011-2014 will have increased numbers of multicentre trials, higher sample sizes, more trials funded by NHMRC or equivalent than trials published from 1986-2010.

In the 2011-2014 period, 228 Australian maternal and perinatal randomised trials were listed in the PSANZ database; 128 trials were still ongoing and 100 trials had completed recruitment. Although not completely comparable (as not all trials completed in the later period have published their results yet), this does indicate a doubling of the publication rate during 2011-2014 compared with the earlier 1986-2010 period (25 per year versus 12 per year).

Twenty percent of recent trials (46/228) have, or are, evaluating lifestyle interventions. This compares with only 23 (7%) trials that assessed lifestyle interventions in the 1986-2010 period.

**Multicentre:** The proportion of multicentre trials more than doubled over time – 36% (82/228) in 2011-2014 compared with 14% (43/306) in the 1986-2010 period; \( p = 0.00001 \).

**Sample size:** Low sample sizes (trials with less than 100 participants) approximately halved in the 2011-2014 period compared with 1986-2010 (20% versus 47%; \( p < 0.05 \)). Conversely, trials with 1000 participants nearly doubled in the 2011-2014 period compared with 1986-2010 (16% versus 9%; \( p = 0.004 \)). See Figure 2.5.

**Funding source:** in the 2011-2014 period nearly a third of trials had received NHMRC or equivalent funding (72/228: 31%) compared with 22% (69/306) for 1986-2010, \( p = 0.02 \).
Fig 2.5: Sample sizes of Australian maternal and perinatal randomised controlled trials: 1986-2010 compared with 2011-2014

2.4.4 Social network (Altmetric) analysis of Australian maternal and perinatal Cochrane systematic reviews

I located 838 current maternal and perinatal Cochrane systematic reviews (Cochrane Database of Systematic Reviews last scanned and searched November 2014). This represents approximately 20% of all published Cochrane systematic reviews. The majority of these 838 maternal and perinatal Cochrane reviews have been published by the Cochrane Neonatal, and Cochrane Pregnancy and Childbirth groups although relevant reviews have been published by 25 other Cochrane review groups. Over half the Cochrane groups have published one or more reviews relating to maternal and perinatal health. See Table 2.4 for more detail.

Over four in 10 of the reviews (43%; 359/838) included at least one Australian maternal or perinatal trial and/or had at least one Australian review author.

Table 2.4: Maternal and perinatal Cochrane reviews by Cochrane Group (as at November 2014)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number CSR</th>
<th>Number Australian CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airways</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Acute Respiratory Infections</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Consumers &amp; Communication</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Cystic Fibrosis &amp; Genetic Disorders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depression, Anxiety &amp; Neurosis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Developmental, Psychosocial &amp; Learning</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Problems</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Drugs &amp; Alcohol</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Effective Practice &amp; Organisation of Care</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Over a quarter of Australian maternal and perinatal Cochrane systematic reviews have an Altmetric score within the top 25% of publications tracked (99/359: 28%). Of those 99 reviews, over a third (39) were in the top 5%. For example, a Cochrane systematic review on midwifery-led care (including 6 Australian randomised controlled trials out of 12) is in the top 1% of all articles tracked by Altmetric (Sandall 2013). However this was not reflected in citation rate, with the review attracting only 15 Scopus citations to date.

**Hypothesis:** Cochrane systematic reviews with at least one Australian author and/or including at least one Australian maternal and perinatal trial will have higher Altmetric scores if the review has been cited in a clinical practice guideline.

Of the 359 Australian maternal and perinatal Cochrane systematic reviews, over a third (128; 36%) have been cited in one or more clinical practice guidelines.

The reviews cited in a clinical practice guideline were significantly more likely to have an Altmetric score in the top 25% of scores (48/128; 38%) compared with the reviews not cited in a clinical practice guideline (51/231: 22%); p = 0.002. See Table 2.5.

**Table 2.5:** Altmetric scores of Australian maternal and perinatal Cochrane systematic reviews (n = 359) and citation in clinical practice guidelines

<table>
<thead>
<tr>
<th>Altmetric score band</th>
<th>aCSR cited in CPG</th>
<th>aCSR not cited in CPG</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N     (%)</td>
<td>N         (%)</td>
<td>N      (%)</td>
</tr>
<tr>
<td>In Top 5%</td>
<td>26 (20.3)</td>
<td>13 (5.6)</td>
<td>39 (10.9)</td>
</tr>
<tr>
<td>In Top 6-25%</td>
<td>22 (17.2)</td>
<td>38 (16.5)</td>
<td>60 (16.7)</td>
</tr>
<tr>
<td>Score but &lt; top 25%</td>
<td>39 (30.5)</td>
<td>52 (22.5)</td>
<td>91 (25.3)</td>
</tr>
<tr>
<td>Not captured by Altmetric</td>
<td>41 (32.0)</td>
<td>128 (55.4)</td>
<td>169 (47.1)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>128</strong></td>
<td><strong>231</strong></td>
<td><strong>359</strong></td>
</tr>
</tbody>
</table>

*aCSR: Australian Cochrane systematic review; CPG: Clinical Practice Guideline*
2.5 Discussion

Over 300 Australian maternal and perinatal randomised controlled trials were published between 1986 to 2010, with one in five trials funded by NHMRC or equivalent. Nearly a quarter of the trials have more than 50 Scopus citations and about a half are included in Cochrane systematic reviews or cited in clinical practice guidelines. Perhaps indicating that some investigators were gaining experience in trial design and conduct in the earlier period, then only one in seven trials were multicentre and half the trials had sample sizes of less than 100 participants. Very substantial improvements have been seen in the last four years (2011-2014), with the number of multicentre trials more than doubling and the number of trials with 1000 participants nearly doubling, compared with 1986-2010. The rate of publication and initiation has also increased in the later period.

In the later period, one in three trials had received NHMRC or equivalent funding, compared with one in five for the earlier period. Although figures are not directly comparable, this funding rate indicates that Australian maternal and perinatal randomised controlled trials are gaining funding at rates well above the 15% success rate for this year’s NHMRC project grants (Anderson 2014b). It may also reflect a contraction of alternative funding sources.

For the 1986-2010 cohort, most of my hypotheses about associations between trial characteristics and sample size, and citation rate, held true. Trials with a multicentre design, funded by NHMRC or equivalent, and being published in a ‘high impact’ journal were all strongly associated with both larger sample sizes and higher citation rates. Trials with a maternal focus (compared with a neonatal focus) were more likely to have larger sample sizes but there was not a significant association between focus and citation rates. While trials with positive findings were more likely to have higher citation rates, there was not a significant association between sample size and whether trials had positive or null findings. Just under half the trials (48%) in my cohort had positive findings. This is a little lower than seen in a Cochrane systematic review of 743 RCTs with nearly 300,000 participants (‘New treatments compared to established treatments in randomized trials’). This review found that new treatments are slightly better (50-60% of the time) than existing treatments (Djulbegovic 2012). Thus my trial cohort meets the ‘uncertainty requirement’ for the results of individual RCTs to be unpredictable – on scientific and ethical grounds (Djulbegovic 2013). My finding of a higher null rate may be due to the many trials in my cohort with low sample sizes (nearly half under 100 participants) with many of the trials likely to be underpowered to detect differences between interventions and controls. An alternative explanation may be that low sample size is a proxy for lower interest or less conviction that the trial findings are robust, thus resulting in lower impact as measured by use in publications, syntheses and policy documents.

In contrast to the lack of association seen between sample size and direction of effects in trials and sample size, my finding that the positive trials were significantly more likely to be highly cited and more likely to be published in a high impact journal suggests that publication bias may be operating.

I found significant associations for integration of trial findings into syntheses and policy documents. Trials with larger sample sizes and higher citation rates were more likely to be included in Cochrane reviews and to be cited in clinical practice guidelines. Cochrane systematic reviews cited in guidelines were significantly more likely to have attracted Altmetric scores in the top 25%. Clinical practice guidelines and other policy documents not published in conventional journal article format are rarely captured by citation, access and social media systems (Middleton 2014c). As a result, it was necessary to undertake time-consuming manual searches to establish which Australian maternal and perinatal randomised controlled trials and Cochrane systematic reviews (with one or more Australian authors) were cited in which guidelines for my analyses involving clinical practice guidelines. Altmetric is gradually adding policy sources, although the coverage is still quite low (Middleton 2014c).

Chapter 2
Agreement with other studies

After extensive searching, very few comparable studies were located. A recently presented abstract about the Australian and New Zealand Clinical Trial Registry (ANZCTR) shows steady growth in number of Australian trials, with 1028 trials registered on ANZCTR/Clinical Trials.gov in 2013 (Smith 2014), consistent with the increasing number of trials over time seen in my study. The authors note a large increase in the number of trials assessing lifestyle interventions from 26 in 2005 to 185 in 2013, a phenomenon also seen in my study, albeit on a smaller scale.

In Smith 2014, median sample size was reported to have decreased over time (from 150 in 2005 to 84 in 2013) for trials registered in ANZCTR/Clinical Trials.gov whereas in my study, the median sample size for Australian maternal and perinatal randomised controlled trials increased over time (100 for 1986-2010 and 200 for 2011-2014).

Bunn 2014 assessed the impact of over 1500 Cochrane systematic reviews produced by 20 review groups from 2007-2011 (including 228 reviews from the Cochrane Pregnancy and Childbirth Group). They found that the largest impact of systematic reviews was on policy documents, with 32% of Cochrane systematic reviews cited in clinical practice guidelines. In my study, 36% of Australian maternal and perinatal Cochrane systematic reviews were cited in clinical practice guidelines, and 38% of all 796 maternal and perinatal Cochrane systematic reviews (Middleton 2014). Our overall conclusions are also similar – that impacts of Cochrane systematic reviews are considerable, but difficult to measure.

Limitations

- Although comprehensive searching was done, I may not have been able to locate all eligible Australian maternal and perinatal randomised controlled trials. This may be more likely for older unregistered trials as registration of Australian trials has now become almost universal. However there may be unregistered and/or unpublished industry trials that are missing from my sample (although there are few industry trials in this field).
- I have not made direct comparisons with other countries to see if similar results apply. However a recent NHMRC report suggests that Australian maternal and perinatal research (not restricted to randomised controlled trials and Cochrane systematic reviews) has higher bibliometric impact than comparable research from other countries (NHMRC 2013).

Challenges and potential solutions

Overall, the cumulative nature of evidence and its maturation has been evident in my analyses of impact. The amplifying effects of including Australian maternal and perinatal randomised controlled trials in Cochrane systematic reviews are also clear. However one in two of these trials has not been included in one or more Cochrane systematic reviews. Wallace and colleagues have recently published a systematic review, finding that educational visits, short summaries of systematic reviews, and targeting messaging help to improve the uptake of systematic reviews (Wallace 2014). Uptake could also be improved through producing new Cochrane systematic reviews on topics not yet covered but for which trials exist and by updating Cochrane reviews in a more timely fashion. Similar considerations apply for increasing inclusion of Australian maternal and perinatal randomised controlled trials in clinical practice guidelines. For example the Cochrane Pregnancy and Childbirth Group continues to work closely with guideline development groups such as NICE and WHO to produce and update Cochrane systematic reviews needed for the evidence base of clinical practice guidelines. This degree of collaboration with guideline developers is not yet so evident in the neonatal field, although the ILCOR initiative involves the development and updating of guidelines related to neonatal resuscitation (www.ilcor.org).

For two decades, the Perinatal Society of Australia and New Zealand (PSANZ) has been fostering collaboration through its Interdisciplinary Maternal Perinatal Australasian Collaborative Trials Network (IMPACT). The IMPACT Network was formed in 1994 within the then Australian Perinatal
Society and in 1997 became a subcommittee of PSANZ dedicated to improvement of maternal and perinatal health by promoting well-designed RCTs, and dissemination and application of their results. Its mission is to enhance the conduct of high quality, collaborative, investigator-driven randomised controlled trials addressing priority questions in maternal and perinatal health, and to ensure timely dissemination of their results and incorporation into practice (www.psanz.com.au/special-interest/impact).

IMPACT members are key players in the emerging Australian Clinical Trials Alliance (ACTA), the national peak body to represent and support ‘public good’ clinical trial networks (ACTA 2014). PSANZ has established a consumer advisory panel whose members are active in developing trial networks and providing the perspectives of parents on RCTs. For example, Australian consumers and clinicians have jointly designed and are conducting an international multicentre RCT on ‘Improving Public Awareness of Clinical Trials through Online Questionnaires: the IMPACT online study’ (ACTRN12613001337763).

My study has demonstrated the importance of multicentre trials, both national and international in scope. Their substantial increase over time is likely to increase the chance of robust results and higher uptake and implementation. However a multicentre design is not always possible or appropriate. Prospective meta-analysis methodology is an alternative which “provides the same strengths as a single large-scale multicentre randomised study whilst allowing greater pragmatic flexibility” (Askie 2011). The NeOProM Collaboration protocol is an example of a prospective meta-analysis of randomised controlled trials assessing levels of oxygenation in extremely preterm neonates where hypotheses, inclusion criteria and outcome measures to be used in each trial have been pre-specified (Askie 2011).

There has been an assumption that citations ‘count’ more than mentions, such as those captured by Altmetric and downloads or accesses, but very little work has been done to support or refute this. Indeed some citations have no impact at all on health outcomes (see Chapter 5 for a further discussion of this). The fulltext of some Cochrane systematic reviews may be downloaded thousands of times yet be cited less than 50 times (Middleton 2012a). It is hard to imagine that none of the thousands of accesses or downloads will have any influence on impact. In a sample of over 80,000 papers recently published in PLoS, one in 70 PDF downloads resulted in a citation (Lin 2013), indicating some link between access and use (the latter represented by citation). The review depicted in the Cochrane logo (Roberts 2006) illustrates a reverse example where citations greatly outnumber usage as reflected by an Altmetric score (more than 600 Scopus citations yet a relatively modest Altmetric score of 9). Clearly substantial future work is required to understand the links between different metrics and impact.

While nearly one in three Australian maternal and perinatal randomised trials is currently funded by NHMRC or an equivalent funding source, this may be leading to unsuccessful NHMRC or other grant proposals never getting off the ground. Many such proposals are for RCTs that are now too large and complex to start, let alone complete, without substantial funding which is already scarce and fiercely contested. The opportunity costs of grant preparation are considerable with a recent study finding that lead researchers spent nearly two months (38 working days) to prepare each new grant proposal for NHMRC (Herbert 2013). It is therefore likely that in the future the growth in overall numbers of Australian maternal and perinatal trials may slow, but that sample sizes and numbers of multicentre trials will increase or at least be maintained. This would be in line with Doug Altman’s call of 20 years ago for “less research, better research and research done for the right reasons” (Altman 1994) with similar sentiments reiterated in the recent Lancet series on waste in research (Chalmers 2014). However small trials may have a role in proving feasibility, and help provide better sample size estimates for larger trials. In addition, avenues need to be available for early career development and opportunities for novices to gain experience in the conduct of randomised controlled trials (which may be single centre and small).
2.6 Conclusions

Across the trajectory from trial design, funding, publication, citation, use and integration into syntheses and policy documents, there were clear patterns related to impact of Australian maternal and perinatal randomised controlled trials and Cochrane systematic reviews. While these are correlations and do not prove cause and effect, they show the extensive reach of these trial findings. They also indicate areas where trial design, conduct and translation might be enhanced.

Higher sample sizes were associated with maternal focus, multicentre design, citation rates, NHMRC or similar funding, publication in high impact journals, inclusion in Cochrane systematic reviews and clinical practice guidelines, but were not associated with trials reporting positive findings. Higher citation rates closely, but not exactly, mirrored these associations, differing only in an association with positive trial findings but not maternal or neonatal focus.

My results clearly indicate the importance of ensuring randomised controlled trials have adequate sample sizes, often requiring multicentre designs and thus high levels of collaboration between investigators. The randomised controlled trial landscape, here and overseas, is changing with increased collaboration and numbers of collaborators per trial, as well as strengthening of trials networks such as the Australian Clinical Trials Alliance (ACTA 2014). These are likely to improve trial quality and efficiency but other factors such as increased competition for funding may erode these advances. It will be important for research collaborations such as ACTA and the IMPACT network to monitor the impact of these factors over time on trial characteristics and outputs.

Some trials do not reach their target sample size for a number of reasons including poor recruitment rates. Therefore in order to assess whether a trial is adequately powered, the sample size achieved is needed, as opposed to the planned sample which is the basis for the calculation of detecting an important difference between intervention and control groups. This will help to reduce ‘wastage’ by reducing uncertain findings due to underpowered trials.

Although I have shown that dissemination and reach of Australian maternal and perinatal randomised controlled trials is considerable, another source of potential wastage is the lack of inclusion of half of my 1986-2010 trial cohort in Cochrane systematic reviews (and consequently less integration into policy documents such as clinical practice guidelines). As noted above, this can be addressed by producing Cochrane systematic reviews on topics not yet covered and by updating out of date Cochrane systematic reviews, and by enhanced dissemination strategies. Although acknowledging that there are many other ways in which policy decisions are made, I chose to focus on clinical practice guidelines.

There has been a very encouraging improvement over time with substantially higher sample sizes, numbers of multicentre trials and funding success in 2011-2014 compared with 1986-2010. This may be an indication of greater collaboration and stronger trials network development.

Many Cochrane systematic reviews with one or more Australian authors are scoring well in emerging citation and social media systems such as Altmetric. One in nine of these reviews has a score in the top 5%, with one in four reviews in the top 25%. Altmetric score seems to be related to citation in clinical practice guidelines but not necessarily to citations in traditional bibliometric systems. Altmetric is tapping into diverse dissemination and translation sources and revealing the diversity of audiences interested in evidence-based material. These systems are likely to play an important role in increasingly the visibility and reach, and ultimately the impact, of health research (Dinsmore 2014).
Practice and policy implications arising directly from the above findings:

- Trialists should be encouraged to become authors and reviewers of Cochrane systematic reviews as part of the process of moving from the generation to the synthesis phases of the research/translation cycle.
- Trial networks need to be inclusive and offer supportive environments for as many trialists as possible to optimise trial quality and uptake of findings.
- Collaborations with guideline developers such as WHO need to continue and be expanded.
- Citation, access, and social media systems need to increase their coverage of clinical practice guidelines and other policy sources.

Research recommendations

- A comparison of planned versus achieved sample size would quantify how many and which completed randomised trials do not reach their target sample size and therefore are at risk of having inadequate power to detect important differences. As achieved sample sizes are not usually provided in trial registry entries, they will need to be extracted from the main trial publication. In the future, it would be helpful to add achieved sample size to trial registries.
- It is important for research collaborations to monitor trial characteristics, outputs and impact over time, ideally by collaborative research groups and networks, to better understand changes in factors that may be positively or negatively influencing impact, and to assess which of these factors are potentially modifiable.
- Benchmarking and tracking bibliometrics of Australian maternal and perinatal trials and Cochrane systematic reviews against other countries, using methods such as relative citation impact, would provide another measure of potential impact.
- Initial indications that hybrid systems are capturing use of evidence from different sources and audiences than those shown by traditional bibliometrics needs to be followed further and investigated to determine if and which uses are linked to impact on policy and on health outcomes.
3.1 Overview

As the penultimate stage in each orbit of the research/translational cycle, effective implementation is crucial to achieving uptake and impact on policy and practice, and on health and health systems outcomes. However translation and implementation of research are not straightforward processes, relying on the vagaries of individual perceptions, values and motivations. In a critique maintaining that these processes are often oversimplified, Greenhalgh 2011 describes translation as “knowledge obstinately refus[ing] to be driven unproblematically into practice”.

Lockwood and colleagues have observed that “practice change is as much about behavioural change as it is about the use of technology” (Lockwood 2014). Consequently, translation and implementation are highly dependent on human behaviours. A randomised controlled trial in UK neonatal intensive care units which compared active implementation ‘champions’ with passive dissemination provides an example where active implementation resulted in practice change, specifically in rates of surfactant given to sick babies on the labour ward (Acolet 2011). Theories of behaviour change may help us to frame and understand how health professionals can assess, embrace and integrate new and better ways of delivering care. Theories have been defined as generalisable understandings that describe observations, summarise current evidence, propose explanations and yield testable hypotheses. They can be used to describe, explain, predict or control phenomena e.g. aspects of clinical practice (ICEBeRG 2006).

Frameworks such as the Theoretical Domains Framework (TDF) harness behaviour change theories and help to explore implementation barriers and enablers in more detail (Cane 2009; Michie 2011; Michie 2014). The Behaviour Change Wheel (BCW), grounded in the TDF, has been developed and tested to design behavioural interventions and to explain reasons and motivations for behaviour of clinicians and individuals (e.g. to change lifestyle behaviours such as smoking) (Michie 2014). I have used the BCW components at a later stage to explore how clinician behaviour and beliefs may be related to eventual uptake and impact of trial findings. I surveyed the investigators of maternal and perinatal trials based on the assumption that those individuals are likely to be more aware than anyone else of how their health professional colleagues perceive the value and impact of their research findings and the barriers and enablers influencing implementation. These methods have been described as ‘insider accounts’, where the generators of knowledge are assumed to know how their research findings are being used (Bunn 2014) and are recommended for assessing research impact (Hanney 2007).

In addition I wished to explore implementation more intensively than the more standard barrier and enablers analyses that may not capture or reveal the depth of individual capabilities and motivations and their intersection with system and organisational factors. Greenhalgh 2011 has criticised some of the commentary around knowledge translation as being overly simplistic and suggests that a wider notion of knowledge (practical wisdom, tacit knowledge, ‘mindlines’) is required, as well as a deeper understanding of the complex relationships between knowledge and power.

My work, using the Behaviour Change Wheel to explain and refine implementation of antenatal magnesium sulphate for fetal, neonatal and infant neuroprotection, has demonstrated the feasibility and utility of a behaviour change approach to help implement a single intervention (see Chapter 6). I also wished to apply the BCW to a large body of work to see if there were generic patterns across
multiple interventions which could inform ways to improve translation and implementation of findings.

3.2 Aims and hypotheses

AIM 1: To assess trialists’ perceptions of knowledge, skills, belief in their trial findings and barriers to uptake.

Hypotheses:

a) Trialists will perceive that a large majority of their fellow health professionals will know about the findings of their trial, and will have the skills to implement those findings.
b) Trialists will perceive that a smaller number (but still a majority) will believe the findings of their trial.
c) Trialists will perceive that there are implementation barriers for the majority of trials.

AIM 2: To determine the influences of perceived knowledge, skills, belief, and barriers, on uptake and implementation of trial findings.

Hypotheses:

a) Trial findings judged by trialists to be known and believed by their fellow Australian health professionals will be rated by the trialists to have higher uptake and impact.
b) Where fellow health professionals are judged to have the skills to implement the findings and where there are judged to be no or few barriers to implementation, the trial will be rated by the trialists to have higher uptake and impact.

AIM 3: To explore interactions between trialists’ ratings of uptake and impact of trial findings and trial characteristics (citation rates in journals; inclusion in Cochrane systematic reviews; citation in clinical practice guidelines).

Hypotheses:

Nature and design features of trials

a) Trials with a maternal focus will have higher uptake and impact ratings than trials with a neonatal focus.
b) Multicentre trials will have higher uptake and impact ratings than single centre trials.

Funding sources

c) Trials funded by NHMRC, ARC or international equivalents will have higher uptake and impact ratings than trials funded from other sources.

Sample size

d) Trials with larger sample sizes will have higher uptake and impact ratings than trials with smaller sample sizes (100 or more versus < 100).

Direction of effect of trial findings

e) Trials with positive findings will have higher uptake and impact ratings than trials with null or true negative findings.

Publication

f) Trials published in ‘high impact’ journals will have higher uptake and impact ratings than trials published in other journals.

Citations

g) Trials with higher citation rates will have higher uptake and impact ratings than trials with lower citation rates (25 or more Scopus citations versus < 25).

Integration into syntheses

h) Trials included in Cochrane systematic reviews will have higher uptake and impact ratings than trials not included in Cochrane systematic reviews.

Integration into policy documents

i) Trials cited in clinical practice guidelines will have higher uptake and impact ratings than trials not included in clinical practice guidelines.
Summary of aims and hypotheses

1. Behaviour change theory related to trial findings:
   a. knowledge and skills of fellow health professionals
   b. belief of fellow health professionals
   c. implementation barriers

2. Behaviour change theory and triallists’ ratings of uptake/impact of their trial findings
   a. knowledge/belief
   b. skills/lack of barriers

3. Triallists’ ratings of uptake/impact of trial findings by:
   a. maternal/neonatal focus
   b. multicentre
   c. funding source
   d. sample size
   e. direction of effect of trial findings
   f. publication
   g. citations
   h. integration into syntheses
   i. integration into policy documents

3.3 Methods

I surveyed the investigators of the 1986-2010 cohort of trials to assess their views about influences on uptake and impact of their trial findings. The survey design was based on behaviour change theory (Michie 2011; Michie 2014) and contained questions requiring both categorical and narrative responses. I explored triallists’ views of knowledge, beliefs, skills and barriers related to implementation of trial findings and explored associations between triallists’ rating of uptake/implementation and trial characteristics.

Survey of Australian maternal and perinatal randomised controlled triallists and influences on uptake and impact of their trial findings

I designed a 10 question survey incorporating behaviour change theory and partly based on the theory of planned behaviour and the Behaviour Change Wheel (Cane 2012; Michie 2005; Michie 2011; Michie 2014).

The first seven survey questions directly relate to capability, opportunity and motivation – the sources of behaviour in the inner circle (shown in green) in Michie’s Behaviour Change Wheel (see Figure 3.1). As each of these components influences behaviour, they help determine whether a new course of action will be adopted, or if the existing pattern of behaviour will be retained.

Capability can be defined as
- physical (physical skill, strength, stamina) or
- psychological (knowledge or psychological skills, strength or stamina to engage in the necessary mental processes).

Opportunity covers
- physical (opportunity afforded by the environment involving time, resources, locations, cues, physical ‘affordance’) and
- social (opportunity afforded by interpersonal influences, social cues and cultural norms that influence the way that we think about things).

Motivation encompasses
- reflective processes involving plans (self-conscious intentions) and evaluations (beliefs about what is good and bad)
- automatic processes involving emotional reactions, desires (wants and needs), impulses, inhibitions, drive states and reflex responses.
The 10 questions for the survey were mapped on to the sources of behaviour components of the Behaviour Change Wheel (BCW) - see Table 3.1.

Questions 1-4 related to Opportunity and Capability and explored whether triallists thought their fellow health professionals knew about (Q1) or believed trial findings (Q2), whether clinicians had the requisite skills (Q3) and problems or barriers they might face when implementing those findings (Q4). Both categorical and narrative responses were allowed for Questions 1-4.

Questions 5-7 (positive and negative consequences for adopting or not adopting trial findings and the consequences of doing so) relate to the Motivation part of the Behaviour Change Wheel. Narrative responses were more appropriate here and so I did not formulate hypotheses for these three questions.

The final three questions (8-10) assessed impact and implementation. Questions 8 and 10 assessed the impact triallists felt that their trial(s) had in terms of the implementation or uptake of their trial findings into clinical practice (Q8), as well as actual and potential impact on health outcomes in Australia (Q10) and I asked for categorical responses. As knowledge of trial findings could be disseminated in several ways, I asked respondents to assess impact on health outcomes from the trial itself, and through the trial being included in a systematic review or in guidelines. Question 9 asked triallists to provide suggestions for improving the implementation/uptake of their trial findings in a narrative form.
Table 3.1: Map of survey questions

**SOURCES OF BEHAVIOUR CHANGE (inner BCW): QUESTIONS 1-7 (Hypotheses 1a-1c)**

<table>
<thead>
<tr>
<th>Opportunity</th>
<th>Know (Q1); Problems (Q4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Q1: Do you think that Australian clinicians caring for women and babies KNOW about the findings of the trial?</td>
</tr>
<tr>
<td>Social</td>
<td>Q4: Do you think that Australian clinicians caring for women and babies encounter PROBLEMS (individual, environmental, system, social) in implementing these findings?</td>
</tr>
<tr>
<td>Capability</td>
<td>Believe (Q2); Skills (Q3); Problems (Q4)</td>
</tr>
<tr>
<td>Physical</td>
<td>Q2: Do you think that Australian clinicians caring for women and babies BELIEVE that the trial findings will improve health outcomes</td>
</tr>
<tr>
<td>Psychological</td>
<td>Q3: Do you think that Australian clinicians caring for women and babies currently have the SKILLS to implement the findings of the trial?</td>
</tr>
<tr>
<td></td>
<td>Q4: as above</td>
</tr>
<tr>
<td>Motivation</td>
<td>Positive consequences (Q5); Negative consequences (Q6); Motivations (Q7)</td>
</tr>
<tr>
<td>Automatic</td>
<td>Q5: What do you think the clinicians regard as POSITIVE CONSEQUENCES for clinicians adopting the findings?</td>
</tr>
<tr>
<td>Reflective</td>
<td>Q6: What do you think the clinicians regard as NEGATIVE CONSEQUENCES for clinicians adopting the findings?</td>
</tr>
<tr>
<td></td>
<td>Q7: What do you think the clinicians regard as MOTIVATIONS for clinicians adopting the findings?</td>
</tr>
</tbody>
</table>

**QUESTIONS 8-10: RELATING TO UPTAKE, IMPLEMENTATION AND IMPACT (Hypotheses 2a-2b)**

<table>
<thead>
<tr>
<th>Impact of trial on uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8: How would describe the implementation/uptake of your trial findings into Australian practice?</td>
</tr>
<tr>
<td>Suggestions for improving implementation and uptake of trial</td>
</tr>
<tr>
<td>Q9: Do you have any suggestions for improving the implementation/uptake of your trial findings?</td>
</tr>
<tr>
<td>Impact of trial on outcomes – actual and potential</td>
</tr>
<tr>
<td>Q10: How would you describe the ACTUAL and POTENTIAL impact of your trial findings on health outcomes for women and babies?</td>
</tr>
</tbody>
</table>

The survey was approved by the Human Research Ethics Committee of the University of Adelaide in November 2011. Survey requests were sent to triallists from early 2012.

**Analysis of survey questions**

For all questions, narrative responses were transcribed and grouped into themes. For Questions 1-4, categorical responses were grouped into the following:

- yes/most
- some
- no/few
- unsure
- not applicable
- not completed

For Questions 8 (implementation) and 10 (impact), the categories were:

- very high
- high
- moderate
- low
- none
- unsure
- not applicable
- not completed
Associations between degree of knowledge, belief in trial findings, skills and barriers to implementation and very high or high responses to Question 8 (uptake of trial findings) and Question 10 (impact on health outcomes) were explored with Chi\(^2\) tests.

### 3.4 Results

#### 3.4.1 Survey responses

Survey responses were potentially available for 238 (78%) of the 306 trials. For the remaining 68 trials (22%), the triallist was known to be deceased, retired or to have moved, with no new contact details available or no contact details available for any co-investigators.

Responses for 177 (74%) of the 238 trials were received. For 61 of these 238 trials (26%), no response was received after the initial email and at least one further email or phone contact. See Figure 3.2.

**Fig 3.2: Flow diagram of survey response from triallists**

![Flow diagram](image)

**AIM 1: Hypotheses**

- **a)** Triallists will perceive that a large majority of their fellow health professionals will know about the findings of their trial, and will have the skills to implement those findings.
- **b)** Triallists will perceive that a smaller number (but still a majority) will believe the findings of their trial.
- **c)** Triallists will perceive that there are implementation barriers for the majority of trials.

Hypothesis a) did not hold, with triallists reporting that they thought their fellow health professionals knew about specific trial findings only 50% of the time; with a similar proportion (47%) having the skills to implement those findings.

Nor did Hypothesis b), with triallists reporting only a third of their fellow health professionals were likely to believe their trial findings.
Barriers to implementation were reported for a third of trials, a lower proportion than anticipated (Hypothesis c).

These results are outlined in more detail below (under Questions 1-4).

3.4.2 Responses to Question 1-10

**Question 1: Do you think that Australian clinicians caring for women and babies KNOW about the findings of the trial?**

*Categorical and narrative synthesis*

Respondents thought that their fellow health professionals knew about the findings of their trial about half of the time (89/177; 50%). See Figure 3.3.

This was more likely to be the case if the trial was completed and published, and less likely if published as a conference abstract only. Many respondents felt that knowledge of their trial results was considerably amplified through incorporation into the body of evidence through systematic reviews and clinical practice guidelines. This may happen even though the results of a specific trial may not be known, or even remembered with the passage of time. Some respondents felt that publication in a high impact journal increased knowledge. If a particular practice had already commenced use at a hospital, this early implementation meant that more health professionals were aware of that particular intervention.

Trials in the form of pilot studies were discussed several times as strategies to explore feasibility and acceptability. While it was acknowledged that often these pilot studies will not be well known, they are important in testing feasibility of recruitment, clinician support, dose finding and sometimes in helping to elucidate mechanisms of action.

‘Selective’ knowledge was discussed – the findings of a trial may be better known in the geographical area where it was conducted than in Australia more widely or internationally. Understandably knowledge, and interest, may be greater within particular fields or disciplines such as obstetric anaesthesia or neonatology. Some concerning issues were raised by several respondents who indicated that some trial evidence would be disregarded or rejected because it was not generated by the ‘right’ groups – for example “medical clinicians are only interested in medical studies”. This is indicative of a ‘chasm’ - for example between perinatal medicine and public health.

Some respondents felt that a null trial result limited dissemination and knowledge and others described difficulties in getting trials with null results published. Another thought that there were “more appropriate channels than just academic journals” and one remarked that “clinicians rarely read the literature”. Lack of resources to implement effective practices may have stifled ongoing knowledge transfer of some trial results.

A small number of respondents felt unable to judge the extent of knowledge of their trial findings, with one suggesting that large studies would be needed to determine this.

**Question 2: Do you think that Australian clinicians caring for women and babies BELIEVE that the trial findings will improve health outcomes?**

*Categorical and narrative synthesis*

Triallists perceived that just over a third of their fellow health professionals believed the findings of particular trials (68/177; 38%). See Figure 3.3.

Overall there were considerable differences in interpretation of trial findings. There were examples of both inconclusive and conclusive trial results regarded as unconvincing. Null findings (as opposed
to negative findings) were sometimes interpreted as a reason to continue the unproven practice on the grounds that this showed that the current practice was no worse. Conversely some positive findings were dismissed on the grounds that they did not offer enough benefit to change current practice (e.g. some refinements to anaesthetic procedures). Health professionals were more likely to believe the results of trials if they had been conducted locally, as was the case for knowledge.

For findings of some specific trials, fellow health professionals appeared to be divided between sceptics and believers. Sometimes there was no discernible reason for this divide, but in one example allied health professionals were more likely to believe in the effectiveness of a particular intervention and neonatologists showed varying levels of acceptance.

There were several examples where lack of positive findings (in appropriately powered trials) stopped several lines of unfruitful research.

While there was only one example of a true negative trial (in line with maternal and perinatal trials in general), this trial was an excellent illustration of the tensions between evidence, current practice and belief. The intervention had been adopted in other parts of the world on the basis of subgroup analysis of a randomised trial and when conclusively shown to be harmful in a larger Australian RCT, the integrity of this trial was challenged - for a time.

Other trialists reported that leadership changes within the institution had shifted beliefs at the corporate level – in one case towards a more medicalised approach and thus away from an effective low-tech intervention. Several respondents noted that evidence was not always the driving force behind practice and that politics and organisational attitudes could be a more powerful driver of change (or of keeping the status quo). One example was a parenting intervention which was not ‘in vogue’ at that particular place and time.

Disappointment in the results of a trial was a recurrent theme – mostly due to null/inconclusive findings which conflicted with their previous (and perhaps current) beliefs. One example was a breastfeeding intervention which midwives had hoped would be effective but the trial findings did not support this. Increased belief (in a null, but disappointing) result was sometimes reported once more supporting evidence was published.

In one instance, clinicians expressed disbelief in a trial which indicated that their screening performances for detecting an infection were not optimal. Eventually, the triallists were vindicated when the alternative option to screening was shown to be more effective.

If industry had been involved in the research, respondents reported that clinicians may suspect a lack of independence and be more sceptical about the trial results.

**Question 3: Do you think that Australian clinicians caring for women and babies currently have the SKILLS to implement the findings of the trial?**

**Categorical and narrative synthesis**

Nearly half the respondents (83/177; 47%) stated that their fellow health professionals had the requisite skills to implement trial findings. Although only 15 (9%) felt that fellow health professionals definitely lacked the skills, over a third (67; 38%) either said this question was not applicable or they did not answer - see Figure 3.3.

Thus lack of skills did not appear to be a major issue in implementing trial findings. Several respondents highlighted the need to extend multidisciplinary teams to ensure they included all relevant professional groups. It was mentioned that teams need to be collaborative in order to function well - referral was cited as an activity and skill that was underutilised.
Behaviour change techniques, such as motivational interviewing for women, were highlighted as areas needing more skill development in order to implement findings of ‘lifestyle’ trials. Shared decision making was also nominated as an area where health professionals needed to upskill.

One respondent called for more guidance and clearer recommendations instead of “leaving this to clinicians to use their individual ‘skills’ to interpret and implement the study findings”.

Others noted that while individual clinicians had most of the requisite skills, systems factors in hospitals and health systems could block implementation. In other words, lack of skills and inability to implement change was sometimes apparent at the corporate level.

**Question 4: Do you think that Australian clinicians caring for women and babies encounter PROBLEMS (individual, environmental, system, social) in implementing these findings?**

**Categorical and narrative synthesis**

Barriers to uptake and implementation were mentioned for a third of the trials (62/177; 35%) - see Figure 3.3.

Many problems influencing policy and practice change were described. At the systems level, implementation of interventions, such as models of care, were likely to need significant organisational change requiring commitment at all levels of the workforce. At the beginning of this century, there was limited experience as to how trial evidence could inform implementation of interventions, particularly complex ones. Despite clinician support and appropriate skill levels, some of these interventions were not implemented widely or were not implemented at all, due to organisational policies.

Other effective interventions were blocked as they did not fit the current organisational workflow (e.g. timing of admission) or because there were legal and risk management issues with the proposed intervention. Changes of organisational leadership could also scuttle implementation of interventions shown to improve outcomes. For a shared decision-making intervention, hospital culture and organisational policies precluded some women from being able to receive their choice of care.

Several respondents said that evidence was ignored or relegated in the face of institutional pressures such as workforce shortages and rising birth rates. One respondent thought that economic evaluations could help implementation by showing how cost-effective interventions may be.

Uncertainty from interim or null results or even lack of evidence in under-researched areas made it difficult to know how to respond in terms of changing practice and policy. Some respondents mentioned that this resolved over time as more evidence became available, as previous concerns about harms were addressed and occasionally because the intervention under question had now been superseded in favour of a newer, more effective, practice.

Some clinician barriers were attitudinal – including perceptions that the new intervention would take more time. For a pain relief intervention that hospitals and individual clinicians seemed reluctant to implement, it was suggested that if women advocated for the intervention, this may be successful. There were several examples where lack of clinician support had caused the failure of a trial or had severely compromised recruitment to the trial. In one case, community-based clinicians appeared not to engage with the trial and very few women were recruited. On the other hand, there were examples where early opposition to removing an ineffective practice had dissipated over time.
The amount of resource required (particularly staff time) hindered implementation of some interventions. Several examples involved home visits and one group was subsequently working on developing lower cost alternatives such as social media and text messaging. The need to find resources to expand the scope of multidisciplinary teams, for example to include dietitians, was mentioned several times. Access to resources may differ between city and regional services and the cost of adding specialist services and equipment into more ‘mainstream’ areas of health services was also raised. It was noted that training was often not a one-off commitment and that ongoing training programs would be required. A gap between evidence and implementation was illustrated by an effective tool (a decision aid) which was unable to be implemented as it required updating and there were no longer resources to do this.

The nature of the intervention may influence implementation. Some drugs or supplements shown to be effective may not be available through the current markets or a particular dosage or composition may not be commercially available. On the other hand, interventions that do not work may cease to be offered. In one example, a company withdrew equipment when it was shown to be ineffective.

**Fig 3.3:** Responses from Australian triallists relating to their fellow health professionals’ opportunity and capability to implement trial findings (Questions 1-4)

*Question 5: What do you think the clinicians regard as POSITIVE CONSEQUENCES for clinicians adopting the findings?*

**Narrative synthesis**

The most common response was that the trial findings would improve health and other outcomes for women, babies and families. Other respondents provided more detail on this theme, nominating greater satisfaction, choice and/or convenience for women, and specific health outcomes such as better pain relief, reduced harms such as risk of injury or need for surgery in babies, improved fetal growth and longer term outcomes such as cognitive and motor development as some of the positive outcomes.

A smaller number of respondents proposed positive consequences for staff including providing safe care, being able to intervene earlier, having more say in how care is provided, greater job satisfaction and having greater knowledge about how to help women make lifestyle changes.
Reduced health utilisation (e.g. reduced hospital stay) was mentioned, but mostly in the context of null trials where a more expensive alternative was not shown to be superior to current practice. In one example of a null finding, the timely conduct of a trial of a new device was proclaimed as having “immeasurable” positive consequences in contrast with trials done only many years after devices had been introduced into care. Other examples described being able to ‘move on’ from a research question where it was unlikely to generate evidence of improved outcomes.

Another set of generic responses centred around finding the ‘truth’; using the best evidence; delivering best practice; informing future studies, and being seen as centres of excellence and leaders in the field.

Several respondents did not answer this question directly, with one feeling unable to answer as this would depend on clinicians’ “current practice, knowledge of the evidence and willingness to change in light of the evidence”.

**Question 6: What do you think the clinicians regard as NEGATIVE CONSEQUENCES for clinicians adopting the findings?**

**Narrative synthesis**
Many trialists responded that their fellow health professionals would not perceive any negative consequences from trial findings, or if they did, those consequences would be very minor. Some respondents did mention possible negative consequences but dismissed them as incorrect perceptions of harms or need for extra resources. Others felt that there would be not be negative consequences as long as the intervention was used or implemented correctly.

Trade-offs between benefits and harms were mentioned frequently, which included anxiety while waiting for results of longer term follow-up. Resource implications of implementing trial findings, including increased workload, were commonly raised. Sometimes implementation would require clinicians to learn new skills and in one case, the new intervention may have led to deskilling.

New interventions might mean more costs are passed on to families, such as additional supplements. Adoption of some models of care may be less financially attractive to private obstetricians and reimbursements may be lower for older practices – each of these may constrain the use of more effective interventions.

If clinicians were not convinced or there was uncertainty in the trial results, several respondents mentioned that their fellow health professionals may continue or adopt practices not shown to be evidence-based. In the case of a partial finding leaving residual uncertainty, one respondent thought there would be variation in practice until the next trial(s) resolved the uncertainty.

There were several mentions of discomfort if the topic was a controversial one or the new practice was seen to be unconventional. Other respondents mentioned power shifts resulting from new interventions – towards more medicalisation or towards more decisions made by women (with which clinicians may not agree).

**Question 7: What do you think the clinicians regard as MOTIVATIONS for clinicians adopting the findings?**

**Narrative synthesis**
The overwhelming motivation expressed was a desire to improve health and other outcomes for women, babies and families, closely followed by a desire for clinicians to offer high quality and the best possible practices. One respondent described motivation for a particular intervention being that...
it was “simple, safe and better for women”. Another talked about an intervention which ticked all the motivational boxes by preventing mortality and serious morbidity, being inexpensive and being easy to use. A landmark study finally provided a definitive answer to a longstanding uncertainty which motivated widespread belief in and thus adoption of the intervention. Several respondents mentioned greater clinician satisfaction as another motivating factor.

At a systems level, the public sector is likely to be motivated to change when programs or models are shown to be more efficient and cost less. Some clinicians may think a new intervention is not worth the effort compared to longstanding conventional methods or they may not be sufficiently convinced by the evidence to change their practice. Conversely clinicians may want to do something to make a difference, although sometimes these actions are not supported by the evidence. Other responses to a null trial were that clinicians had ‘permission’ to carry on with their usual practice. Topics such as preventing preterm birth are regarded as high priority even when implementing an intervention that will result in small changes only.

Some motivations were research oriented - supporting clinically useful research to enable more options for pregnant women or to provide a springboard for more research and implementation. The importance of cumulative evidence to change motivation and behaviour was highlighted. This may be through a ‘convincing’ follow-up trial and incremental and synthesised evidence that accretes over time.

One respondent noted the tension between short term gains and long term uncertainty and others speculated that attitudes about change and professional boundaries may decrease motivation to implement something more effective.

**Question 8: How would you describe the implementation/uptake of your trial findings into Australian practice?**

For this question, respondents were asked to rate the uptake of their trial findings from very high to none for the trial itself, the trial as part of a systematic review and the trial as part of a guideline. Just over half thought that their trial findings had been taken up to some degree due to the trial itself (102/177; 58%) or as part of a guideline (95/177; 54%). Uptake from inclusion in a systematic review was rated somewhat more highly (112/177; 63%).

About one in four trials were judged to have had high or very high uptake and again inclusion in a systematic review was higher than for the trial itself or as part of a guideline (27%, 23% and 20% respectively) - see Figure 3.4.

A small number of respondents provided narrative comments. Many of these were explanatory comments giving reasons why uptake was less than expected or less than optimal. Some of these related to practice having already changed prior to completion of the trial. Several respondents commented on slow translation processes (e.g. incorporation into guidelines was often a lengthy process). Others noted that further work on the research question needed to be done, either through larger trials after pilot trials had been conducted or confirmatory trials followed by implementation studies.

Several individuals commented that failing to implement the intervention was the appropriate course of action, as it had not been shown to improve outcomes.

Two respondents mentioned that inclusion of their trial in a Cochrane review had positively influenced uptake of their trial findings (e.g. smoking cessation strategies in pregnancy) and another noted an important national policy change (which led to lower neonatal mortality) after their trial had been published in a high impact journal.
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Fig 3.4: Question 8: Triallists’ rating of implementation/uptake of trial findings into Australian practice

Question 9: Do you have any suggestions for improving the implementation/uptake of your trial findings?

Some respondents (about one in 20) said that further implementation was not required as the trial findings had now become routine practice or that the necessary policy change had occurred (on one occasion shortly after the trial was published in a high impact journal). Others mentioned that the intervention had been taken up and well integrated into models and hospital systems.

A further one in 10 replied ‘no’ without further elaboration on apparently effective interventions that did not appear to be optimally or routinely implemented.

About one in 10 respondents indicated that their trials were not conducted in order to change practice (e.g. pilots, or trials to provide important biochemical and physiological understanding).

A number of dissemination strategies were suggested such as publication (in the case of trial findings not yet fully published), presentations and dissemination more widely outside specialist areas and to other disciplines. For some interventions, distribution, development, updating and funding of the actual resource or device were mentioned as strategies to assist access and implementation.

Several respondents addressed implementation processes, saying that implementation plans were needed, as were dedicated implementation people at each site. Another discussed the long term nature of implementation, describing the need for “longitudinal motivation”. A small number replied that implementation was out of their scope or that they did not have the skills or desire to be involved in implementation.

Other respondents discussed the importance of ‘people processes’ such as leadership and engagement (e.g. of consumers) in ensuring change happens. This may require triallists to become advocates and political ‘movers’.

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Involving end users, such as hospital administrators and managers, at design and conduct stages of a trial, was seen to be helpful. While national trials may be perceived more favourably than local trials, actual implementation needed to be carried out by local and passionate leaders, according to several respondents. The importance of better inservice, professional and undergraduate education and training was also noted, as was the need for more incentives.

At a systems level, implementation could be enhanced by better understanding of differences between services and how to work around these differences. Systems improvements such as computerisation may also assist implementation, particularly for monitoring and measuring key performance indicators. National (and international) audits and monitoring of uptake were suggested as a way to enhance implementation.

Implementation was recognised to often be a difficult undertaking. A respondent described a ‘trade-off’ situation of an effective intervention where concerns about potential harms have curtailed implementation. Another respondent implored clinicians not to “write off highly effective interventions because they are too hard”.

The usefulness of null findings was often raised. They can help to stop ineffective practice or to prevent it from starting and thus lessen waste of resources. This extends to halting unfruitful avenues of research, including research sponsored by industry. However, as one respondent noted, journals need to be supportive of publishing studies which have the capacity to change the course of practice even if it is by showing clinicians what not to do.

There were many comments about the influences of uncertainty and timing on uptake and implementation. Sometimes the interventions assessed in some trials had been replaced by newer technology, but in other cases, the ‘jury is still out’ and further evidence needs to be generated. Several respondents addressed the incremental nature of knowledge and change and the dynamic nature of evidence. In one example, a trial helped refine the intervention for the next trial and in another, an earlier trial led to a larger definitive trial which has had considerable impact. Other respondents discussed the need to find and test simpler and cheaper options. The need for longer term follow-up was mentioned several times.

The importance of synthesis was also recognised with preceding trials needing to be considered as part of the current body of synthesised evidence. One respondent said that “the Cochrane review was pivotal for implementation”. The need for guidelines and policies from professional bodies to help clinical decision making was also expressed several times. However different guidelines with different recommendations (some not evidence-based) were barriers to implementation.

**Question 10: How would you describe the ACTUAL and POTENTIAL impact of your trial findings on health outcomes for women and babies?**

For this question, respondents were asked to rate the impact of their trial findings on health outcomes from very high to none for the trial itself, the trial as part of a systematic review and the trial as part of a guideline on health outcomes. They were asked to judge actual impact (what had happened to date) and potential impact as findings filter through the processes of translation and implementation.

Respondents were generally optimistic about the impact of their trial findings on health outcomes and even more so about future impact. About one in five trials were rated as having high or very high actual impact on health outcomes (18% for the trial itself, 21% if included in systematic review and 17% if cited in a guideline). When asked to estimate future impact on health outcomes the comparable rates rose to one in three trials having high or very high future impact (32%, 36% and 34% respectively).
For trials themselves, triallists responded that very high impact on health outcomes would double (108% increase) from the present to the future. The corresponding percentages were a 133% increase for the trial as part of a systematic review and 131% increase for the trial as part of a guideline. Respective present to future increases for high impact were 58%, 40% and 67% and respective decreases for having no impact on health outcomes were 69%, 45% and 68%. See Figure 3.5.

A small number of respondents provided narrative comments. Several respondents said that while their trial had not directly influenced health outcomes, the impact on dissuading people from implementing ineffective practices was important and freed up resources for other interventions that may be beneficial. Another took a somewhat different view, saying that continuing to use an ineffective practice by some clinicians was acceptable as it caused no harm. One respondent highlighted the incremental nature of scientific knowledge, noting that while a particular trial would have minimal impact on outcomes, it had provided a crucial stepping stone to the next research questions which were now being addressed in large multicentre trials.

**Fig 3.5: Question 10: CHANGE in triallists’ ratings of actual (current) outcome compared with perceived potential impact**

![Bar chart showing change in triallists' ratings](image)

### 3.4.3 Triallists’ ratings of uptake and impact of their trial findings and associations with behaviour change

**AIM 2: Hypotheses**

a) Trial findings judged by triallists to be known and believed by their Australian fellow health professionals will be rated by the triallists to have higher uptake and impact.

b) Where fellow health professionals are judged to have the skills to implement the findings and where there are judged to be no or few barriers to implementation, the trial will be rated by the triallists to have higher uptake and impact.

Triallists rated nearly 23% of maternal and perinatal RCTs to have very high or high uptake ratings (40/177); and 32/177 (18%) to have perceived very high or high impact on health outcomes.
Uptake: The hypothesis that trial findings judged by triallists to be known and believed by their fellow health professionals would be associated with high uptake ratings did not hold (p = 0.07 and p = 0.33 respectively for knowledge and belief). This was also the case for barriers, with presence or absence of barriers having no association with the trials rated as having high uptake (p = 0.99). There was a seemingly counterintuitive result for a link between colleagues having the skills to implement the finding and high uptake, with assumed possession of implementation skills linked to lower rates of uptake (p < 0.05).

Impact on health outcomes: The results for associations with high impact ratings were similar to those for high uptake, as triallists’ ratings for uptake largely, but not completely, mirrored their ratings for impact. There were no significant associations seen between knowledge, belief and presence of barriers and high impact ratings (p = 0.11, 0.97 and 0.11 respectively). As for uptake, assumed possession of implementation skills was linked to lower rates of impact (p = 0.047).

3.4.4 Triallists’ ratings of uptake of trial findings and impact on health outcomes and associations with trial characteristics

AIM 3: Hypotheses
Nature and design features of trials
Trials with a maternal focus will have higher uptake and impact ratings than trials with a neonatal focus; Multicentre trials will have higher uptake and impact ratings than single centre trials.

Funding sources
Trials funded by NHMRC, ARC or international equivalents will have higher uptake and impact ratings than trials funded from other sources.

Sample size
Trials with larger sample sizes will have higher uptake and impact ratings than trials with smaller sample sizes (100 or more versus < 100).

Direction of effect of trial findings
Trials with positive findings will have higher uptake and impact ratings than trials with null or true negative findings.

Publication
Trials published in ‘high impact’ journals will have higher uptake and impact ratings than trials published in other journals.

Citations
Trials with higher citation rates will have higher uptake and impact ratings than trials with lower citation rates (25 or more Scopus citations versus < 25).

Integration into syntheses
Trials included in Cochrane systematic reviews will have higher uptake and impact ratings than trials not included in Cochrane systematic reviews.

Integration into policy documents
Trials cited in clinical practice guidelines will have higher uptake and impact ratings than trials not included in clinical practice guidelines.

Focus: No significant differences were seen between neonatal or maternal triallists in their rating of very high/high uptake (p = 0.14); or in regard to perceived very high/high impact of their trial findings on health outcomes (p = 0.38).

Multicentre: Compared with single centre trials, multicentre trials were significantly associated with both very high/high uptake ratings and perceived very high/high impact on health outcomes (p = 0.0002 and p = 0.004 respectively).

Funding: Trials funded by NHMRC or equivalent bodies were significantly more likely to have very high/high uptake ratings compared with trials funded through other sources (p = 0.005). The
comparable comparison for funding sources and perceived very high/high impact on health outcomes did not reach statistical significance (p = 0.07).

**Sample size:** Compared with trials with less than 100 participants, trials with sample sizes of 100 or more were significantly associated with very high/high uptake ratings (p = 0.008). The comparable result for sample size and perceived very high/high impact on health outcomes did not reach statistical significance (p = 0.07).

**Direction of effect of trial findings:** Trials with positive findings were significantly more likely to be rated very high/high for uptake compared with trials showing null findings (p = 0.017). No significant differences were seen between trials with positive and null findings for ratings of very high/high impact on health outcomes (p = 0.17).

**Publication in ‘high impact’ journals:** Compared with publication in other journals, publication in a ‘high impact’ journal showed strong associations with both ratings of very high/high uptake (p = 0) and very high/high impact on health outcomes (p < 0.05).

**Citations:** Trials with Scopus citations above and below a threshold of 25 citations showed no significant differences for either very high/high uptake (p = 0.103) or for very high/high impact on health outcomes (p = 0.104).

**Integration into syntheses:** Trials included in Cochrane systematic reviews had significantly higher ratings for very high/high uptake (p = 0.037) but not for very high/high impact on health outcomes (p = 0.181).

**Integration into policy documents:** Trials cited in clinical practice guidelines were significantly associated with higher ratings for very high/high uptake (p = 0.004) and also with very high/high impact on health outcomes (p = 0.006), compared with trials not cited in clinical practice guidelines.

### 3.5 Discussion

In the survey of triallists, I used Michie’s Behaviour Change Wheel as a framework to see what might be positively or negatively influencing the behaviour of clinicians in translating and implementing trial findings. Survey results relating to knowledge and barriers (opportunity); and belief, skills, and barriers (capability) were somewhat unexpected. As outlined in the relevant hypotheses, I had anticipated knowledge of trial findings and belief in the findings to be high, with most trials likely to have implementation barriers. However blockages were apparent much earlier in the research/translation cycle with limited awareness of trial results and fairly low confidence in trial results when they were known. Lack of skills was not seen to be a significant issue, and fewer trials than expected were perceived to have implementation barriers (although one-third of respondents indicated this question was not applicable or did not complete this question).

**Opportunity** (defined as physical opportunity such as resources and social opportunity such as cultural norms) was limited - only half of the triallists’ fellow health professionals were judged to be aware of specific trial findings. This knowledge could be restricted by geographic or territorial boundaries and null results were sometimes reported to be difficult to publish. Inclusion in syntheses and clinical practice guidelines was often thought to amplify the translation of trial findings. Organisational attitudes and change, both in terms of resources such as workforce shortages and social influences such as policy and culture changes sometimes curtailed opportunity to implement new practices. Null findings could leave clinicians uncertain of which practices to adopt or drop.

**Capability** (defined as physical skill or psychological knowledge and strength) was limited by low belief in trial findings, with only a third of fellow health professionals thought to sufficiently believe in a trial’s findings to change their practice or policy. This could manifest both as dismissal of trials
with positive findings as well as continuation of practices not shown to be effective. Sometimes this was accompanied by disappointment that a favoured practice did not improve outcomes. Timing was important – lack of belief could arise from older trials where findings are no longer current. It may also take some time for individuals and organisations to incorporate new knowledge into their belief systems, even if this knowledge had been well disseminated. Lack of skills did not appear to be a significant issue although the need to extend multidisciplinary teams was mentioned several times, as was the need to offer ongoing training and education.

**Motivation** (defined as reflective processes involving plans and evaluations and automatic processes involving emotional reactions and impulses) was reported to be largely driven by reflective processes such as a desire to improve outcomes and to provide high quality care. Negative consequences were rarely reported.

There was not a strong connection between knowing about trial findings, believing them or having the necessary skills; and perceived uptake and implementation, indicating that the implementation process is indeed complex and seemingly haphazard. This may also have been influenced by the lower than expected rates of knowledge and belief in particular, and as noted above, the likelihood that translation and implementation blocks might be happening quite early.

There were some similarities between my quantitative findings and the findings from self-reports by trialists of high uptake and impact. The strongest correlations for the latter were for multicentre trials, and if the trial in question had been cited in a clinical practice guideline with perceived uptake and impact on health outcomes. Uptake (but not impact on health outcomes) was associated with trials having NHMRC funding, sample sizes greater than 100, positive findings and being included in a Cochrane review. No association was seen between maternal/neonatal focus, or citation rate, with uptake or impact on health outcome.

**Limitations**

- Interpretation of the impact of null findings varied with some survey respondents indicating trials with null results had no impact and other respondents suggesting impact from not adopting or continuing something not shown to be effective and this may have led to underestimation of impact for adequately powered trials. Null results may also be due to underpowered trials and it was not always possible to distinguish these from adequately powered trials. Perceived impact of ‘trade-off’ results varied according to individual views of the balance between benefits and harms. This issue also applies to systematic reviews - in a sample of 154 maternal and perinatal Cochrane systematic reviews, nearly two-thirds were assessed to have uncertain findings, reflecting lack of relevant trials and small sample sizes of the trials able to be included (Middleton 2007b).

- A higher response rate for the survey would have been helpful, but was adequate considering that it was not a typical ‘snapshot’ survey. For my survey, I needed to contact triallists who had conducted research over two decades ago in some cases and inevitably some triallists were not able to be found or contacted.

- Tighter question design and framing may have decreased some missing data in the survey e.g. by providing and requiring categorical drop down responses for Questions 1-4.

- Free-text responses are often difficult to analyse and therefore often used sparingly in surveys, but these responses did provide much richer material than categorical responses only.

- A few respondents reporting that they did not understand the question(s). Further explanatory material could have been provided but more text may have put off other triallists from responding.

- I used the Behaviour Change Wheel framework (Michie 2011; Michie 2014) rather than the later and more encompassing Theoretical Domains Framework (Cane 2012). However the inner components of the Behaviour Change Wheel are particularly relevant to the influences on
health professionals when deciding whether or not to adopt findings from randomised controlled trials (Crowther 2013b).

- For the survey component of my study, I restricted the number of questions to lessen the load for respondents. However there are other issues that could have been addressed such as cost effectiveness and training which are encompassed in models such as the Payback Framework (Donovan 2011; Donovan 2014).

Translation and implementation remains a messy and sometimes seemingly irrational process. Even in the face of clear evidence, random or one-off events can disrupt implementation and decrease uptake, as exemplified by the antenatal corticosteroid story (Hanney 2005). Further, as a reminder that evidence must be regarded as dynamic and contextual, a very recent trial has shown that antenatal corticosteroid may not save babies’ lives and may even increase mortality if given to women in low and middle income countries where accurate estimation of gestational age and risk of imminent birth is not able to be determined (Althabe 2014).

Just as there is a generic chasm in translation (Butler 2008), specific chasms were apparent in my study. They were chasms between different disciplines and sometimes between public health and more ‘medicalised’ groups. As numbers (and importance) of lifestyle interventions increase, requiring the involvement of several disciplines, it is vital to bridge such chasms and for researchers to collaborate rather than compete.

It is apparent that health professionals and researchers are grappling with how to interpret null findings. Although appropriate design and effective recruitment may reduce the number of trials with null findings, trials will continue to compare interventions with small differences between them. As noted by Glasziou 2011 citing Dixon-Woods 2011, now “few innovations represent a real advance”. A shared understanding of what constitutes ‘clear’ and ‘unclear’ evidence is needed to distinguish between effective interventions with small but important differences, null results from underpowered studies and adequately powered studies showing unimportant differences between interventions. Just as we have statistical standards such as those described in the Cochrane Handbook for Systematic Reviews of Intervention (Higgins 2011), Hackshaw and Kirkwood have suggested that we also need descriptive standards (consistently accepted by publishers) for reporting results which are not definitive (Hackshaw 2011). This may counter unwarranted belief in the efficacy of new therapies, termed optimism bias (Chalmers 2006). A better understanding of the reasons for null findings may also dispel some of the disappointment expressed by triallists and is also likely to be welcomed by policy makers.

3.6 Conclusions

There is lack of clarity about who is responsible for translation and implementation and how these should be funded. The maternal-perinatal community worldwide has a well-deserved reputation for excellence in evidence-based health care (doing the right things) but there is still much implementation work to complete (“doing the right things right” (Glasziou 2011)); and confusion and sometimes disagreement about whose role this is.

The survey data indicate that it is common for the research/translation cycle to be disrupted quite early, even from the knowledge creation stage. Thus early intervention is required to increase publication profiles and ‘believability’ of trials, well before implementation barriers are considered.

Impact can be assessed in several ways, none of which is yet optimal for detecting change in health outcomes and ultimately all, except audit and routine data collection, are fairly distal proxies so far. Translation and implementation is an intrinsically human endeavour with all the complexities, variations and inconsistencies of individual and group behaviour. Furthermore there is not agreement about who should be responsible for translating and implementing health research,
although stronger embedding of research into health services would aid implementation of effective care and this increase impact on health outcomes.

Practice and policy implications arising directly from the above findings:
- Better understanding of complex lifestyle interventions is required.
- Embedding research into health services is needed to bridge gaps between researchers and health professionals and to facilitate better audit and routine data collection processes.

Other practice and policy implications:
- Stronger trial networks, ideally with some centralised support for trial coordination, are required to improve trial quality and efficiency and therefore impact.
- Increased parent/consumer involvement is needed to improve understanding and quality of randomised controlled trials.

Research recommendations
- Factors such as increased collaborations, strengthening of trials networks, and increased competition for funding can all influence trial characteristics and the impact of their findings. It is therefore important to monitor trial characteristics, outputs and impact to better understand changes in these factors that may be influencing impact over time.
- There is a need to develop standards for describing and interpreting null trials.
- Other models of assessing the impact of Australian maternal and perinatal trials and Cochrane systematic reviews, such as the Payback Framework (Donovan 2011; Donovan 2014), should be applied and tested.
- There is a need for more qualitative research on the motivations of researchers and users of research, including more ‘insider accounts’.
Chapter 4: Reminder strategies for reducing risk of type 2 diabetes in women with a history of gestational diabetes: synthesis and generation of new knowledge

4.1 Introduction and overview:

Women who have experienced gestational diabetes mellitus (GDM) are at substantially increased risk of type 2 diabetes in the future (Conway 1999; Hunt 2008; Retnakaran 2008; Retnakaran 2011; Schaefer-Graf 2002). There is also an increased risk of recurrent GDM in subsequent pregnancies (Bottalico 2007). Therefore implementation of interventions able to interrupt the progression to type 2 diabetes or to prevent GDM in future pregnancies is of substantial public health significance.

In many high-income countries, generally only a minority of women with GDM are followed up after giving birth (Blatt 2011; Carson 2013; Ferrara 2012) despite evidence that lifestyle management can substantially reduce their future risk of type 2 diabetes (Herman 2011; Kitzmiller 2007; Ratner 2007; Ratner 2008). A crucial first step is therefore to test glucose status for these women in the early postpartum period and at regular intervals thereafter, strategies recommended by most relevant bodies (ACOG 2013; ADA 2015; Metzger 2007; Simmons 2002; WHO 2013). In a systematic review of 11 studies, Tovar 2011 found that from 34% to 73% of women with GDM completed postpartum glucose screening. Up to 44% of women with GDM exhibit either impaired glucose tolerance or type 2 diabetes on testing early in the postpartum period (Benhalima 2014), and would therefore benefit from early diet and exercise advice.

In 2011, 7.0% of South Australian women were diagnosed with GDM (Scheil 2013), compared with 4.9% in 2007 (Chan 2008). This increase is in line with rising obesity rates and the older average age at which women are becoming mothers (Ferrara 2007). Where the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations for diagnostic thresholds have been adopted, rates of diagnosis have been predicted to double or treble (Metzger 2010). This is, however, dependent on the setting. For example, a recent Canadian study reported only a 32% increase in GDM diagnoses from old to newer criteria (7.9% to 9.4%), with little change seen in health outcomes (Kong 2014).

A number of national evidence-based clinical practice guidelines recommend early postpartum glucose testing including the USA, UK and New Zealand (ADA 2015; NICE 2008; Ministry of Health 2014). The gap between these recommendations and the low completion rates for postpartum screening is a ‘classic’ know-do gap which needs to be addressed by finding ways to improve the uptake of testing for type 2 diabetes or impaired glucose tolerance early in the postpartum period. One particular implementation method showing promise in many areas of health care is that of reminder systems (Car 2012; Dexheimer 2008; Grimshaw 2006; Weingarten 2002). Could reminders also be effective in increasing uptake of postpartum glucose testing in women with a history of GDM?

I investigated this question by:

i) initially conducting a Cochrane review to synthesise the evidence for reminder systems to increase the uptake of testing for type 2 diabetes in women with previous GDM (Middleton 2012d; Middleton 2014a) - see 3.3; and

ii) from the research recommendations, designed a randomised controlled trial of mobile phone text messaging (short message service (SMS)) to remind women who have experienced GDM to undertake testing for type 2 diabetes or impaired glucose tolerance in the early postpartum period (Heatley 2013) – see 4.4.
4.2 Aim of chapter

To show, through a case study, how a research to practice gap (low rates of postpartum screening for women who have experienced gestational diabetes mellitus) can be closed through knowledge synthesis and further knowledge generation, moving through the translation/research cycle towards making this knowledge actionable.

4.3 ‘Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance’: a Cochrane systematic review (Middleton 2014a)

A summary of this Cochrane systematic review follows:

4.3.1 Background

The purpose of postpartum screening of women with previous GDM is to promptly identify those women who will subsequently develop type 2 diabetes. Early identification allows earlier management through preventative strategies such as diet modification, exercise and avoiding excessive weight gain (Nield 2008; Norris 2005; Orozco 2008). Sometimes oral glucose-lowering drugs or insulin may be added to such lifestyle changes. In a subgroup analysis of the Diabetes Prevention Program, both intensive lifestyle interventions and metformin were effective in delaying or preventing diabetes in women with impaired glucose tolerance and a history of GDM (Ratner 2008).

However, the beneficial effects of these preventive measures will not be realised unless women with previous GDM are screened postpartum, offered appropriate management and follow up, and then agree to make lifestyle changes. Clinicians and women regard reminder systems for postpartum type 2 diabetes screening as important and useful (Keely 2010), and so reminders are likely to be able to address some of the awareness and behavioural barriers that women face when making lifestyle changes after giving birth, leading to women with a history of GDM being able to avoid developing, or delaying, a diagnosis of type 2 diabetes in the future.

The early postpartum period is an important time in which to identify the risk of diabetes in women with a history of GDM or milder glucose intolerance in pregnancy (Retnakaran 2008) and to translate postpartum testing into practice (Oza-Frank 2013). In fact, some researchers posit that prevention of subsequent type 2 diabetes may be the most compelling reason to diagnose GDM (Keely 2012a). For a majority of women with a history of GDM, the opportunity to prevent subsequent type 2 diabetes is currently missed because of poor uptake of postpartum glucose testing. So is the chance to detect any problems and intervene to prevent future diabetic complications such as cardiovascular disease (Kitzmiller 2007; Shah 2008) and future metabolic dysfunction (Stuebe 2011), and also the chance to reduce the risk of diabetes in their children (Clausen 2008; Dabelea 2011).

Early detection may also reduce healthcare costs - in a Swedish longitudinal study, women diagnosed with diabetes after GDM had more than a 14-fold likelihood of healthcare utilisation than controls (Anderberg 2012).

4.3.2 Objectives and Methods

Objectives

To assess whether reminder systems increase the uptake of testing for type 2 diabetes or impaired glucose tolerance in women with a history of GDM.
Searching

We searched MEDLINE and EMBASE (last searched 1 June 2013) and The Cochrane Library (last searched April 2013).

Selection criteria

We included randomised trials of women who had experienced GDM in the index pregnancy and who were then sent any modality of reminder (or control) to complete a test for type 2 diabetes after giving birth.

Prespecified outcomes:

Primary outcomes
- Proportion of women having their first oral glucose tolerance test (OGTT) (> 6 weeks to ≤ 6 months, > 6 months to ≤ 12 months, > 12 months) after giving birth.
- Proportion of women having a blood glucose test other than an OGTT (> 6 weeks to ≤ 6 months, > 6 months to ≤ 12 months, > 12 months) after giving birth.
- Proportion of women diagnosed with type 2 diabetes or showing impaired glucose tolerance or impaired fasting glucose after giving birth.
- Health-related quality of life.

Secondary outcomes
- Diabetes-associated morbidity.
- Death from any cause.
- Adverse events.
- Blood glucose concentrations.
- HbA1c levels.
- Appropriate referral or management, or both.
- GDM recurrence in the next or any subsequent pregnancy.
- Depression or depressive symptoms, anxiety, distress (as reported by authors).
- Self-reported lifestyle changes (e.g. increase in exercise or physical activity, dietary modification, weight loss strategies).
- Body mass index (BMI) or body weight.
- Need for insulin or other glucose-lowering medications after giving birth.
- Breastfeeding.
- Women's views of the intervention.
- Health professionals' views of the intervention.

Data collection and analysis

Two authors independently screened titles and abstracts for relevance. One author extracted the data, carried out 'Risk of bias' assessments and evaluated the overall study quality according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria; the other author double-checked these procedures. Meta-analysis was not possible as only one study was eligible for inclusion.

4.3.3 Results of Cochrane systematic review

Only one trial of 256 women was able to be included (Clark 2009). The trial had unclear risk of bias in the majority of domains (for example, method of allocation concealment was not reported and attrition of participants was fairly high and the rate of losses differed between groups).

The trial had a factorial design; it compared three types of postal reminder strategies (in a total of 213 women) with usual care (no postal reminder, 43 women) and reported on the uptake of four possible types of glucose tests. The three strategies investigated were: reminders sent to both the
woman and the physician; reminder sent to the woman only; and reminder sent to the physician only, all issued approximately three months after the woman had given birth.

There was low-quality evidence (see Summary of Findings: Table 4.1) that all three reminder interventions increased uptake of oral glucose tolerance tests compared with usual care (no reminder system): reminders to the woman and the physician (uptake 60% versus 14%): risk ratio 4.23 (95% confidence interval (CI) 1.85 to 9.71); 116 participants); reminder to the woman only (uptake 55% versus 14%): RR 3.87 (95% CI 1.68 to 8.93); 111 participants); reminder to the physician only (uptake 52% versus 14%): RR 3.61 (95% CI 1.50 to 8.71); 66 participants). This represented an increase in uptake from 14% in the no reminder group to 57% across the three reminder groups (see Figure 4.1).

There was also an increase in uptake of fasting glucose tests in the reminder group compared with the usual care group: reminders to the woman and the physician versus no reminder (uptake 63% versus 40%): RR 1.57 (95% CI 1.01 to 2.44); reminder to the woman only (uptake 71% versus 40%); RR 1.78 (95% CI 1.16 to 2.73); reminder to the physician only (uptake 68% versus 40%): RR 1.69 (95% CI 1.06 to 2.72). Uptake of random glucose and glycated haemoglobin A1c tests was low, and no statistically significant differences were seen between the reminder and no reminder groups for these tests. Uptake of any test was higher in each of the reminder groups compared with the no reminder group (RR 1.65 (95% CI 1.12 to 2.41); 1.73 (95% CI 1.18 to 2.52); and 1.55 (95% CI 1.01 to 2.38) in the respective reminder groups.

The trial did not report this review’s other primary outcomes (proportion of women diagnosed with type 2 diabetes or showing impaired glucose tolerance or impaired fasting glucose after giving birth; or health-related quality of life). Nor did it report any secondary review outcomes such as diabetes-associated morbidity, lifestyle changes, need for insulin, GDM recurrence, or women’s and/or health professionals’ views of the intervention. No adverse events of the intervention were reported. Subgroup interaction tests gave no indication that dual reminders (to both women and physicians) were more successful than single reminders to either women or physicians alone. It was also not clear if test uptakes between women in the reminder and no reminder groups differed by type of glucose test undertaken.
### Table 4.1  Summary of findings for ‘Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance’

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
</table>
| Proportion of women having their first OGTT after giving birth (Follow-up: up to 1 year) | a) 604 per 1000 (264 to 1387)          | a) RR 4.23 (1.85 to 9.71) | a) 116 (1)                    | ⊕⊕⊕⊕ low
| a) Postal reminder to woman and physician                                | a) 143 per 1000                        | b) RR 3.87 (1.68 to 8.93)   | b) 111 (1)                    | low
| b) Postal reminder to woman                                              | b) 143 per 1000                        |                           |                               |                                |
| c) Postal reminder to physician                                          | c) 143 per 1000                        |                           |                               |                                |
| c) 516 per 1000 (214 to 1244)                                            |                                        |                           |                               |                                |
| Proportion of women having a blood glucose test other than an OGTT after giving birth: fasting blood glucose (Follow-up: up to 1 year) | a) 628 per 1000 (404 to 976)           | a) RR 1.57 (1.01 to 2.44)   | a) 116 (1)                    | ⊕⊕⊕⊕ low
| a) Postal reminder to woman and physician                                | a) 400 per 1000 (464 to 1092)          | b) RR 1.78 (1.16 to 2.73)   | b) 111 (1)                    | low
| b) Postal reminder to woman                                              | b) 400 per 1000                        |                           |                               |                                |
| c) Postal reminder to physician                                          | c) 400 per 1000                        |                           |                               |                                |
| c) 676 per 1000 (424 to 1088)                                            |                                        |                           |                               |                                |
| Proportion of women diagnosed with type 2 diabetes or showing impaired glucose tolerance/fasting glucose after giving birth; Health-related quality of life; Diabetes-associated morbidity; Costs or other measures of resources use were reported |

**Footnotes**

The basis for the assumed risk is the number of events in the comparator groups

*Number of participants: the same control group (no reminder) data were used for comparison with the three intervention groups in the four-arm study

*Downgraded by two levels owing to few participants and one included study only, with unclear risk of bias in most domains, and imprecise results (wide confidence intervals)*
4.3.4 Discussion

The evidence base is very incomplete regarding reminder systems for increasing the uptake of testing for type 2 diabetes or impaired glucose tolerance in women with a history of GDM, with only one relatively small RCT identified to date as addressing the question posed by this review. This RCT reported only the uptake of various glucose tests (our other pre-specified outcomes were not investigated) and utilised only postal reminders. In a later paper from the authors of the included RCT (Clark 2012), the need for other reminder methods such as SMS was emphasised and, in a subsequent survey administered to 51 women with GDM, the authors of this RCT found that most women with GDM said they wished to receive a reminder as a voice message on their home (landline) phone; and a majority (73%) wanted their primary care physician to receive a reminder (Keely 2012b).

As the ultimate aim of increasing postpartum testing is to identify women at risk and to prevent the subsequent development of type 2 diabetes, it is important to test preventive interventions such as lifestyle changes, ideally in RCTs. These interventions and any subsequent implementation require careful design as there are many barriers that women with previous GDM face when making lifestyle changes after giving birth, even when they are aware of their increased future risk of type 2 diabetes (Lie 2013). Numbers of women diagnosed with GDM are likely to continue to increase due to demographic changes (older mothers, increasing rates of obesity) as well as the proposed diagnostic threshold changes (Metzger 2010).

Although we did not identify any other completed RCTs assessing the effect of reminders in improving the uptake of glucose tests after birth in women with a history of GDM, one RCT, testing whether SMS reminders can increase test uptakes in such women, is underway (Heatley 2013). A number of cohort studies and reviews have found lower than optimal test uptake, in line with the findings of Clark 2009. A review by Tovar 2011 reported that 34% to 73% of women with a history of GDM completed postpartum glucose screening. In the Carson 2013 review, programmes where women with a history GDM were proactively contacted showed an increase of about one-third in postpartum glucose testing compared with usual care. A later study, not included in Carson 2013, compared telephone nurse management programmes and found that postpartum glucose testing was increased over 20-fold when referral proportions in centres were high (over 70%) (Ferrara 2012). Other follow-up studies from Clark and colleagues show an initial increase in postpartum diabetes screening after the Clark 2009 RCT (Vesco 2012), and Shea 2011 reported a higher likelihood of having an OGTT if a postal or phone reminder had been sent as routine practice (although at 28% for reminders and 14% for no reminders, test uptake was much lower in actual practice than in the Clark 2009 RCT).
4.3.5 Cochrane Systematic Review conclusions

Implications for practice
While only one trial fulfilled our inclusion criteria and the overall quality of evidence was low, it showed that postal reminders increased the uptake of testing for type 2 diabetes in women with previous GDM. Other forms of reminder systems (e.g. email and telephone reminders) could potentially be effective, although our review was not able to compare these approaches due to lack of studies. The number of women diagnosed with GDM is projected to rise due to expected increases in BMI and maternal age, as well as possible changes to diagnostic thresholds, so healthcare systems will require effective postpartum reminder and diabetes screening programmes.

Implications for research
The effects of other forms of reminder systems need to be assessed to see whether test uptake is also increased when email and telephone reminders are deployed. We also need a better understanding of why some women fail to take opportunities to be screened postpartum. As the ultimate aim of increasing postpartum testing is to prevent the subsequent development of type 2 diabetes, it is important to determine whether increased test uptake rates also increase women’s use of preventive strategies such as lifestyle modifications.

4.4 The DIAMIND (diabetes reminder) randomised controlled trial: study protocol

The Cochrane systematic review summarised above (Middleton 2014a) showed that only one randomised controlled trial (RCT) (Clark 2009) had so far assessed whether reminders can increase the uptake of postpartum glucose tests in women with previous GDM. To address this research gap, I designed a randomised trial using text (SMS) messaging as the reminder strategy, on the basis of increasing ownership and use of mobile phone technology (www.budde.com.au/Research/Australia-Mobile-Communications-Statistics-and-Forecasts.html [accessed 21 December 2014]) and decreasing use of postal services.

The published protocol for the DIAMIND RCT (Heatley 2013) is summarised below. The protocol was formulated according to the SPIRIT reporting standards (www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/[last accessed 30 December 2014]).

Aims and objectives: The primary aim of this RCT is to determine whether an SMS reminder system will significantly increase attendance for oral glucose tolerance testing by 6 months postpartum in women who have recently experienced GDM.

Hypotheses: The primary hypothesis is that a SMS reminder system for women who have recently had GDM will increase the number of women who complete oral glucose tolerance testing by 6 months postpartum.

Ethics statement: Ethics approval was obtained from the Women’s and Children’s Health Network Human Research Ethics Committee (REC2200/8/2015).

Methods
- **Study design**: Single centre (Women’s and Children’s Hospital, South Australia), parallel group randomised controlled trial.
- **Inclusion criteria**: Women diagnosed with GDM in their index pregnancy (positive 75 g OGTT with fasting glucose ≥ 5.5 mmol/L and/or two hour glucose ≥ 7.8 mmol/L), with access to a personal mobile phone, whose capillary blood glucose profile measurements prior to hospital
discharge after giving birth are normal (fasting blood glucose < 6.0 mmol/L and 2 hour postprandial blood glucose < 8.0 mmol/L), who provide written, informed consent, are eligible to be included in the trial.

- **Exclusion criteria**: Pregestational diabetes mellitus, triplet/higher order multiple birth or stillbirth in the index pregnancy or requirement for interpreter.
- **Trial entry and randomisation**: Allocation to intervention will be undertaken using a telephone randomisation service (computer-generated random number sequence generation, with balanced variable blocks, and stratification by insulin requirement).
- **Study groups**: Women in the intervention group will receive a text reminder to attend for an oral glucose tolerance test at 6 weeks postpartum, with further reminders at 3 months and 6 months if they do not respond to indicate test completion. Women in the control group will receive a single text message reminder at 6 months postpartum.
- **Blinding**: Baseline data collection will be undertaken blinded. Blinding of participants and blinded collection of primary outcome data will not be possible for this study.
- **Primary study outcome**: Attendance for the oral glucose tolerance test within 6 months postpartum.
- **Secondary study outcomes**: Fasting blood glucose test undertaken by 6 months postpartum; Glycated haemoglobin (HbA1c) test undertaken by 6 months postpartum
- **Sample size**: 276 participants will be required to show an 18% absolute increase in the rate of attendance ($\alpha=0.05$ two tailed, $\beta=80\%$, 5% loss to follow up) from 37% to 55% in the intervention group.
- **Analysis**: Categorical variables will be reported as risk ratios with 95% confidence intervals and continuous outcomes will be reported as means and standard deviations for normally distributed results. Outcome comparisons will be made on an ‘intention-to-treat’ basis. Statistical significance will be defined at the $p = 0.05$ level using a two-sided comparative test.

The trial is registered with the Australian New Zealand Clinical Trials Registry: ACTRN12612000621819.

The DIAMIND randomised controlled trial is currently underway and is now being completed as part of Emer Heatley’s PhD (for which I am a co-supervisor with Professor Caroline Crowther and Professor Bill Hague). Recruitment for this trial has now been completed and the data are being analysed.

### 4.5 Discussion and next steps

Preventing development of type 2 diabetes and other metabolic disease in women who have experienced gestational diabetes mellitus is an important translational and implementation gap, or even a chasm, as expressed by Wilkinson 2014. Women are increasingly becoming aware of the future consequences of gestational diabetes mellitus (Lie 2013), including future health consequences for their children (Damm 2009). However the major health system failure is often inadequate and/or disjointed postpartum care (O’Reilly 2014; Van Ryswyk 2014) with many women not undertaking a glucose test, a vital step in their early postpartum management. A strategy to alert and remind women to take this test and thus determine their subsequent management could therefore ensure that women are offered care which will reduce the risk of future type 2 diabetes as well as gestational diabetes in a subsequent pregnancy.

In the Cochrane systematic review ‘Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance’ described above (Middleton 2014a), I show that the current evidence base for reminder strategies for postpartum glucose testing is very small. I therefore addressed this part of the implementation gap.
by designing a randomised trial of a mobile phone text messaging intervention, which is now being conducted (Heatley 2013).

Thus we are only part of the way along the research/translation cycle for this question (see Figure 4.2).

**Fig 4.2:** Research/translation cycle: Increasing uptake of postpartum testing for type 2 diabetes in women with a history of GDM

Effective reminder strategies and initiatives such as the Australian National Gestational Diabetes Register (http://www.ndss.com.au/en/GD/Diabetes-Register/ [accessed 22/12/14]) will increase awareness of women and health professionals to undertake blood glucose testing to detect impairment. Diabetes prevention will also need effective lifestyle interventions to reduce the risk of type 2 diabetes in women who have experienced gestational diabetes. This is an active field of research with nine ongoing intervention studies (including the DIAMIND RCT) identified by O’Reilly 2014 in a review article covering what is required to prevent type 2 diabetes in women of reproductive age. A further protocol for a trial targeting both mothers and children for preventing future type 2 diabetes has subsequently been published (Hannon 2015).

When available, results of these trials will need to be synthesised and integrated into actionable knowledge such as updated clinical practice guideline recommendations, coordinated care plans between maternity care and primary care providers and local protocols.
One revolution of this research/translation cycle will be completed when this actionable knowledge is implemented and audited. This will determine if the strategies employed have been able to prevent type 2 diabetes in women with a history of gestational diabetes.

Authorship details of key papers:

- Middleton P, Crowther CA. Reminder systems for women with previous gestational diabetes mellitus to increase uptake of testing for type 2 diabetes or impaired glucose tolerance. *Cochrane Database of Systematic Reviews* 2014 (Middleton 2014a). “Philippa Middleton drafted the protocol and developed the search strategy. She acquired copies of potentially eligible papers, selected trials, extracted data, analysed and interpreted data, drafted the review and will update the review. Caroline Crowther commented on the protocol draft, selected trials, extracted, analysed and interpreted data, and commented on drafts of the review.”

- Heatley E, Middleton P, Hague B, Crowther C. The DIAMIND study: postpartum SMS reminders to women who have had gestational diabetes mellitus to test for type 2 diabetes: a randomised controlled trial - study protocol. *BMC Pregnancy Childbirth* 2013;13:92. “EH, PM, WH and CAC are all members of the DIAMIND Study Group. The primary investigator of the DIAMIND Study (EH) prepared the initial draft* of the DIAMIND protocol. All members of the DIAMIND study team participated in the design of the study. The DIAMIND Study Group participated in the protocol development, commented on drafts of the protocol, and have read and approved the final draft of the protocol. All authors read and approved the final manuscript.”

*this built on an earlier draft protocol written by PM.
5.1 Introduction

Globally there are over 2.6 million stillbirths each year, with the vast majority (98%) occurring in low and middle income countries (Lawn 2011). Stillbirth has been a neglected and often hidden issue and is not mentioned in the Millennium Development Goals (Mason 2014) or Global Development Burden of Disease metrics (GBD 2014; Lawn 2011). There is a widespread belief that stillbirth is a natural selection of babies never meant to live (Lawn 2011).

After dramatic declines in stillbirths in high-income countries in the 1940s, this decline has slowed or stalled (Flenady 2011a). For example, the stillbirth rate in Australia has remained static, 1991–2009, the stillbirth rate ranging from 6.4–7.8 per 1,000 births from 1991 to 2009 (AIHW 2014a). There were 2,225 fetal deaths (defined as death of a baby in utero if birthweight is at least 400 grams or gestational age at least 20 weeks) reported in Australia in 2012, representing a fetal death rate of 7.2 per 1,000 births (AIHW 2014b). Stillbirths are three times more frequent than neonatal deaths in Australia (AIHW 2014b).

In Section 5.2, I examine how stillbirth is addressed in Cochrane reviews (and in trials included within the reviews) to see how often stillbirth is reported as an outcome; how often it is reported separately and how often subsumed under a perinatal mortality outcome.

In Section 5.3, I summarise our Lancet paper on the way forward for preventing stillbirths in high-income countries (Flenady 2011a) and in Section 5.4 I outline our systematic review of major risk factors for stillbirth in high-income countries (Flenady 2011b).

Section 5.5 covers our Cochrane overview of antenatal interventions for preventing stillbirth, mapping which interventions have so far been shown to be effective, or to be harmful.

In Section 5.6, I describe my citation analysis of our two high income country stillbirth papers published in the Lancet (Flenady 2011a; Flenady 2011b). This analysis shows the frequency and type of citations made and compares the coverage of Scopus and Google Scholar in capturing citations of these two papers. I also rate each citation as having high, medium or low impact in terms of degree of “calls to action”.

In the conclusions section (5.7), I link the findings of each section, relate these to the likely impact on stillbirth prevention and management and describe the next steps in our stillbirth research initiatives.

5.2 Reporting of stillbirth as an outcome in Cochrane systematic reviews

5.2.1 Aims

My aim was to determine:

- How many and which Cochrane systematic reviews report the outcomes of stillbirth and/or perinatal death;
- Of the Cochrane systematic reviews reporting stillbirth and/or perinatal death, how many and which reviews:
  - report a significant reduction (or increase) in stillbirth;
  - report no significant difference in stillbirth;
  - were judged to have sufficient power to rule out a difference;
How many and which Cochrane systematic reviews do not report the outcomes of stillbirth and/or perinatal death, either because:

- No included trials reported stillbirth and/or perinatal death;
- The Cochrane systematic review did not prespecify stillbirth and/or perinatal death as a review outcome.

### 5.2.2 Methods

By manual inspection of pre-specified and reported outcomes in relevant reviews, I identified 254 Cochrane reviews from The Cochrane Library Issue 4, 2009 where stillbirth and/or perinatal mortality were likely to be relevant outcomes (Middleton 2010a). [A further 150 perinatal Cochrane reviews were considered and found, on the basis of their title and topic, not to be relevant].

### 5.2.3 Results

Nearly 60% of eligible reviews (151/254) reported stillbirth. Only 11 (4.3%) of the 254 Cochrane reviews reported a significant change in stillbirth. A further 139 (54.7%) were unable to confirm or refute stillbirth reductions due to insufficient trials or participants, and only a single review was considered sufficiently powered to rule out a difference in stillbirths between intervention and control.

In the remaining 103 Cochrane reviews, an outcome of stillbirth was not reported. In 72 of these 103 Cochrane reviews (70%, or 28% overall), no included trials reported stillbirth or perinatal mortality even though these outcomes were prespecified by the review. In 31 Cochrane reviews (12% overall), no stillbirth or perinatal mortality outcome was prespecified (see Table 5.1).

### Table 5.1: Reporting of stillbirth in Cochrane reviews (Cochrane Library 4/2009: n = 254)

<table>
<thead>
<tr>
<th>STILLBIRTH AS AN OUTCOME</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome prespecified and reported in Cochrane Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Significant reduction (or increase) in stillbirth</td>
<td>11</td>
<td>4.3%</td>
</tr>
<tr>
<td>2. Not statistically significant (insufficient evidence to confirm or refute)</td>
<td>139</td>
<td>54.7%</td>
</tr>
<tr>
<td>3. Sufficiently powered to rule out significant reduction or increase in stillbirth</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>151</td>
<td>59.5%</td>
</tr>
<tr>
<td>Outcome prespecified but not reported in Cochrane review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. No trials with stillbirth outcome data</td>
<td>72</td>
<td>28.3%</td>
</tr>
<tr>
<td>Outcome not prespecified in Cochrane review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Stillbirth not prespecified and therefore not reported</td>
<td>31</td>
<td>12.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>254</td>
<td></td>
</tr>
</tbody>
</table>

At the time of analysis (in 2010), some examples of the 11 Cochrane reviews showing a significant result for stillbirth prevention included balanced energy and protein supplementation (now Ota 2012b); caesarean section for breech birth (Hofmeyr 2003), and community-based interventions (now Lassi 2014). See 5.5 for an update of Cochrane reviews showing significant results for stillbirth prevention (antenatal interventions).

### 5.2.4 Discussion

As stillbirth is a relatively rare event, it is not surprising that only a small proportion of Cochrane reviews (under 5%) were able to show a significant impact of an intervention or to conclusively rule out any impact. This is also likely to be a reflection of a paucity of randomised trials for some interventions and/or a lack of research – or indeed lack of access to those interventions - in low and middle income countries.

This analysis indicates evidence of selective outcome reporting bias. Of concern is that in four of every 10 Cochrane reviews of interventions where stillbirth was judged to be a relevant outcome,
this outcome was not reported. For one in 10 of these Cochrane reviews, stillbirth was not a prespecified outcome, but for the remaining three out of 10 Cochrane reviews, none of the included trials had reported stillbirths, suggesting under-reporting is more common at the trial level than at the level of the systematic review. In a subsequent examination we made of reviews published by the Cochrane Pregnancy and Childbirth Group in 2012-13, for 24 out 74 eligible reviews (32%), the included trials had not reported stillbirths, indicating no improvement over time (Bain 2014b).

The degree of selective outcome reporting bias is an underestimate as my 2010 analysis was made at the review level and I did not assess whether individual trials had reported stillbirths. For categories 1 to 3 where at least one trial had reported stillbirth, there may have been other trials that did not report stillbirth. For example, in the Cochrane review of magnesium supplementation on pregnancy, only four of the 10 included trials reported stillbirth (Makrides 2014) although in theory all 10 trials could have collected and reported stillbirth as an outcome.

There is a tension between keeping pre-specified outcomes to a minimum and avoiding reporting bias. As outcomes such as stillbirth or perinatal death will be low in many trials, authors (both of trials and reviews) may perceive that including outcomes unlikely to show significant differences between randomised groups may be a ‘waste’ of an outcome and therefore such outcomes may not be pre-specified.

Another difficulty is that fetal and neonatal deaths are competing outcomes – a baby who has died in utero cannot die later and reporting the composite, perinatal mortality, addresses this (Kramer 2014). Denominators for neonatal death outcomes should be therefore adjusted to include only live-born infants, but this is unlikely to change overall findings in systematic reviews in most cases.

It is also important to report which definition of fetal, neonatal and perinatal mortality has been used as they differ substantially. The World Health Organization (WHO) definitions for stillbirth apply to fetuses of at least 1000 g birthweight (or 28 weeks gestation if birthweight unavailable) and early neonatal death (death within seven days) for the definition of perinatal mortality. Other agencies use more inclusive definitions often in addition to the WHO definitions. In South Australia, perinatal death is defined as stillbirths of at least 20 weeks gestation or 400 g birthweight and neonatal deaths occurring within 28 days of birth (Scheil 2013).

### 5.2.5 Conclusions

Our understanding of stillbirths and how to prevent them is limited by incomplete reporting. Full and transparent reporting of fetal deaths and neonatal deaths separately, and how these have been defined, should be adopted as best reporting practice for authors of trials and of systematic reviews. Combined perinatal mortality should also be reported.

### 5.3 Stillbirths: the way forward in high-income countries (summary of Flenady, Middleton et al 2011a)

#### 5.3.1 Aims

Our aim was to give an overall picture of stillbirths in high-income countries by:

- calculating rates over time and between countries;
- documenting causes of stillbirth;
- identifying interventions and priorities for reducing and preventing stillbirths;
- improving standards of care (including audit and autopsy);
- identifying research priorities

#### 5.3.2 Methods

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In this paper, stillbirths were defined as fetal deaths from 22 weeks gestation or at least 500 g birthweight. Data sources for country/region specific stillbirth rates are given in a web appendix to the article. Seven regions contributed consecutive series of stillbirths and cases were classified using the Causes of Death and Associated Conditions system according to usual practices within each region.

Interventions to prevent stillbirths were identified from Bhutta 2011 and from completed Cochrane reviews and Cochrane reviews in progress. Priorities were selected from potentially modifiable risk factors from the high-income stillbirth risk factor synthesis (Flenady 2011b).

Disparities in stillbirth rates within countries and their associations with minority groups and social differences were outlined.

Using the Child Health and Nutrition Research Initiative method (Rudan 2007; Lawn 2011), 153 questions were developed and scored by 21 researchers each for development and delivery; and epidemiology, and six researchers for discovery. Research priority scores were calculated across five criteria for each of the three areas.

### 5.3.3 Results

Across 12 high-income countries in 2008, the UK had the highest rate of 3.8 stillbirths per 1000 births and Norway the lowest rate at 2.2 stillbirths per 1000 births in 2008. In the past twenty years, stillbirth rates have dropped substantially in most high-income countries, but rates have flat-lined in the last decade.

Variation in stillbirth rates between and within high-income countries shows that further reductions are possible. For example there are consistent disparities in rates between the most disadvantaged women and other women. Low educational attainment is associated with increased rates of stillbirth. In many cases, lack of access to care is a major contributing factor, particularly in rural and remote regions.

Increasing prevalence of women with a combination of risk factors such as primiparity, maternal age > 35 years and high BMI may potentially be leading to higher rates of stillbirth.

Having accurate causes of death is very important in understanding how to prevent stillbirths. The wide variation in unexplained cause (10-70%) indicates inadequate post-mortem investigation protocols and differences in approaches to classification of causes of death.

Systematic perinatal audits have shown mortality improvements in several countries and therefore audits able to define and implement improvements in care are likely to reduce rates of stillbirth.

Many important questions remain unanswered. The highest scoring topics identified by respondents to the research priority setting survey were:

- Discovery science: Effects of periconceptual environment, including nutrition and micronutrient status, on embryonic development;
- Epidemiological information: What factors contribute to the excess in stillbirth rates in minority populations?
- Epidemiological measurement: What is the optimum investigation protocol for stillbirth to identify causes and relevant conditions in term of yield, utility and costs?
- Development and delivery: How can smoking cessation programmes be most effectively implemented as part of routine antenatal care?
Key messages

- The variation in stillbirth rates clearly shows that further reduction in stillbirth is possible in high-income countries.
- Women from disadvantaged backgrounds continue to experience stillbirth rates far in excess of non-disadvantaged women in high-income countries and an increased focus on appropriate programmes is needed to address this disparity.
- Maternal overweight and obesity, and smoking are the most important potentially modifiable risk factors for stillbirth in high-income country settings. Implementation of preconception care for all women could reduce these risk factors. Smoking cessation programmes in pregnancy are effective and should be implemented as part of routine care.
- Factors relating to suboptimum professional care contribute to a substantial proportion of stillbirths. Implementation of perinatal mortality audit at the national level is an important step towards addressing quality of care.
- Data for stillbirth are inadequate. A thorough investigation of stillbirth is essential. This includes placental histopathology for all stillbirths and parents being given the option of a high-quality autopsy. Consensus on definition and classification is needed.
- Antepartum stillbirth related to placental dysfunction and very preterm birth are major contributors to stillbirth in high-income countries. Further research is needed on underlying mechanisms to aid early detection and effective management of women at increased risk.

5.3.4 Conclusions

Many stillbirths in high income countries can be prevented, particularly those associated with disadvantage. There are large gaps in awareness and knowledge about stillbirth such as the high proportion of unexplained stillbirths. However strategies such as improved periconceptual care, focusing on nutrition and smoking cessation and a better understanding of the role of placental function in stillbirth are likely to help prevent stillbirths. Better investigation protocols and perinatal mortality audit, as well as access to autopsy as an option for parents are priorities. It is crucial that parents, and communities, are part of the drive to reduce stillbirth.

5.4 Major risk factors for stillbirth in high-income countries (summary of Flenady, Middleton et al: Lancet 2011b)

5.4.1 Aims

To identify priority areas for stillbirth prevention relevant to high-income countries through systematic review and meta-analysis of observational studies.

5.4.2 Methods

We searched Medline, CINAHL and the Cochrane Library from 1998 to 2009 (back to 1990 for studies on education, indigenous status, primiparity and hypertension) and conducted the meta-analyses according to the Meta-Analysis of Observational Studies (MOOSE) standards.

Study inclusion criteria were assessment of at least one risk factor associated with stillbirth (defined as stillbirth of 20 weeks gestation or more, or a birthweight of at least 400 g); conducted in high-income countries and considering risk factors which could potentially be reduced through intervention or management.

Effect estimates were pooled as adjusted odds ratios (aOR) and 95% confidence intervals (using a random effects model). Population attributable risks (PAR) were calculated for each risk factor (p < 0.05), recognising the limitations of confounding and interdependency of risk factors. The Newcastle-Ottawa Scale was used to assess study quality.
5.4.3 Results

Of the 2427 full papers retrieved, 96 studies were ultimately included (76 cohort studies; six prospective and 70 retrospective) and 20 case-control studies) and all studies were judged to be of high quality on the Newcastle-Ottawa Scale. The 96 included studies were conducted in 13 high-income countries.

Although the definition of stillbirth varied, over half the studies included stillbirths from early gestational ages (≥ 20 weeks in 42 studies and ≥ 22 weeks in five studies). Women with multiple pregnancies were excluded from 59 (all) and six studies (higher order only) and 25 studies reported on antenatal stillbirths only.

Meta-analysis revealed that maternal weight, maternal smoking, primiparity, small size for gestational age, placental abruption, and pre-existing maternal diabetes or pre-existing hypertension were the most important and potentially modifiable and demographic risk factors associated with stillbirth (see Table 5.2).

Table 5.2: Most important potentially modifiable and demographic risk factors and attributable stillbirths in HIC

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>aOR (95% CI)</th>
<th>PAR (Australia)</th>
<th>Total preventable - all HIC countries pa</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1.00</td>
<td>12.3% (BMI &gt;25)</td>
<td>8064</td>
</tr>
<tr>
<td>25-30</td>
<td>1.2 (1.09 to 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.6 (1.35 to 1.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>1.00</td>
<td>11.1% (age &gt; 35)</td>
<td>4226</td>
</tr>
<tr>
<td>35-39</td>
<td>1.5 (1.22 to 1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>1.8 (1.4 to 2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;45</td>
<td>2.9 (1.9 to 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any smoking in pregnancy</td>
<td>1.4 (1.27 to 1.46)</td>
<td>6.2%</td>
<td>2852</td>
</tr>
<tr>
<td>Pre-existing hypertension</td>
<td>2.6 (2.1 to 3.1)</td>
<td>6.9%</td>
<td>4242</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td>2.9 (2.1 to 4.1)</td>
<td>4.7%</td>
<td>2194</td>
</tr>
<tr>
<td>Abruption</td>
<td>18.9</td>
<td>15.2%</td>
<td>7716</td>
</tr>
<tr>
<td>SGA</td>
<td>3.9 (3.1 to 5.1)</td>
<td>23.3% (HIC overall)</td>
<td>not calculated</td>
</tr>
<tr>
<td>Primiparity</td>
<td>1.4 (1.33 to 1.51)</td>
<td>14.3%</td>
<td>7434</td>
</tr>
</tbody>
</table>

Abbreviations: aOR: adjusted odds ratio; BMI: body mass index; CI: confidence interval; HIC: high income country; PAR: population attributable risk; SGA: small for gestational age

5.4.4 Discussion

The important role of placental function and pathology is indicated by high population attributable risks for small for gestational age and abruption. Many of the modifiable risk factors for stillbirths in high-income settings identified in this systematic review are linked with socio-demographic factors indicating that improving access to care and taking steps to alleviate poverty and disadvantage can help prevent stillbirths. Intervention and management has the potential to reduce not only stillbirth but other adverse birth and longer term outcomes.

5.5 Overview of interventions during the antenatal period for preventing stillbirth

5.5.1 Aims

To synthesise the evidence from Cochrane reviews on antenatal interventions for preventing stillbirth in high, middle and low-income countries.
(Intrapartum stillbirth, which accounts for 14% of stillbirths in high-income countries and more than 50% of those in low to middle-income countries (Lawn 2011), will be the topic of a subsequent overview.)

5.5.2 Methods

A summary of the methods follows. More detail is available from the published protocol (Ota 2012a). I have conducted a subset of this overview, focusing on stillbirth as the outcome.

Criteria for considering reviews for inclusion

Types of studies
In this overview of reviews, I have included all published Cochrane systematic reviews of randomised controlled trials of antenatal interventions aiming to prevent stillbirth, as long as stillbirth was listed as a primary or secondary outcome.

Types of participants
Pregnant women

Types of interventions
I included all types of antenatal interventions that may be applicable to stillbirth prevention and grouped these into the following seven categories:

- Infection
- Nutrition
- Social/psychosocial; or lifestyle
- Preventing or treating maternal conditions
- Models, work force, systems
- Screening and monitoring of fetal growth and wellbeing
- Other.

Types of outcomes
Stillbirths (as defined by trialist)

Search strategies included:

- previous manual scanning of the Cochrane Database of Systematic Reviews (Middleton 2010a; Bain 2014b);
- manual scanning of new and updated Cochrane reviews (last searched December 2014);
- targeted searches of the Cochrane Database of Systematic Reviews (last searched December 2014), using the following free-text terms: fetal; stillbirth; diet pregnancy; nutrition pregnancy; infection pregnancy; substance pregnancy; alcohol pregnancy; drugs pregnancy; pre-eclampsia eclampsia.

Analysis followed the methods outlined in the Cochrane Handbook of Systematic Reviews of Interventions, including Chapter 22 ‘Overview of reviews’. Where feasible I updated out-of-date reviews. On one occasion I used a recently published systematic review (Imhoff-Kunsch 2012) to help update a review.

I used AMSTAR (Shea 2007) to assess the quality of included systematic reviews. This AMSTAR tool consists of 11 questions addressing design and conduct of systematic reviews (highest score = 11).

5.5.3 Results

I identified 53 Cochrane systematic reviews covering 76 comparisons of antenatal interventions which reported stillbirths. AMSTAR scores were high, with almost all scoring at least 9 out of 11,
indicating that overall quality of the included reviews was high. Details of the reviews are outlined below and in Table 5.3.

Only six comparisons showed clear differences in decreasing rates of stillbirth (shaded green in Table 5.3) and one comparison suggested one intervention may increase stillbirth (abdominal decompression in normal pregnancy).

**Infection**

Seven Cochrane systematic reviews covering 11 interventions addressing infection reported stillbirth. One of these reviews (covering two comparisons) showed significant decreases in fetal loss (and therefore probably in stillbirth) for insecticide-treated nets compared with either untreated nets for preventing malaria (32% relative risk reduction (RRR) or no nets (79% RRR) (Gamble 2006).

**Nutrition**

I found 18 Cochrane systematic reviews addressing nutrition that reported stillbirth and I also included another systematic review (Imhoff-Kunsch 2012) as this facilitated updating of the Cochrane systematic review on marine oil (Makrides 2006). A single comparison (balanced protein/energy versus control) out of 17 comparisons made by these 19 systematic reviews, showed a significant decrease (RRR 38%) in stillbirths (Ota 2012b).

**Social/psychosocial; lifestyle interventions**

Only three Cochrane systematic reviews (with one comparison each) in this category reported stillbirths. There were no significant differences seen for any of the three comparisons (smoking cessation (psychological interventions); smoking cessation (pharmacological interventions); and exercise for diabetic pregnant women).

**Preventing or treating maternal conditions**

In this category, there were 10 Cochrane systematic reviews with 25 comparisons reporting stillbirths, none of which showed clear differences in stillbirths. See Table 5.3 for further details of these comparisons.

**Models, workforce, systems**

In this category, four Cochrane systematic reviews covering five comparisons reported stillbirths. Two of the five comparisons showed significant reductions in stillbirths. These were community interventions in low income countries with a 19% RRR in stillbirths (Lassi 2014) and a 21% RRR for trained versus untrained traditional birth attendants, also in low income countries (Sibley 2012).

**Screening and monitoring of fetal growth and wellbeing**

For this category 14 comparisons in 10 Cochrane systematic review reported stillbirths, with only one comparison showing a difference of borderline significance (immediate versus deferred birth for suspected fetal compromise indicated a 78% RRR in stillbirth (Stock 2012) – see Table 5.3.

**Other**

In one Cochrane systematic review, prophylactic abdominal decompression in normal pregnancy was suggestive of an increased risk of stillbirth, though this did not reach conventional statistical significance (Hofmeyr 2012b).
Table 5.3 Antenatal interventions reporting stillbirths in Cochrane systematic reviews *(clear differences shown in green shading)*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RR/OR and 95% CI</th>
<th>References</th>
<th>AMSTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pregnant women with HIV infection:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Micronutrient supplementation</td>
<td>RR 0.57 (0.32 to 1.01): 1 trial; n = 991</td>
<td>Siegfried 2012</td>
<td>11</td>
</tr>
<tr>
<td>Zinc supplementation</td>
<td>RR 1.31 (0.70 to 2.91): 1 trial; n = 397</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium supplementation</td>
<td>RR 3.05 (0.62 to 15.05): 1 trial; n = 892</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple vs. single daily dose micronutrient supplementation</td>
<td>RR 0.86 (0.51 to 1.44): 1 trial; n = 1105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirals for reducing the risk of mother-to-child transmission of HIV</td>
<td>Results not totalled, but none of the 8 comparisons (5 trials) showed significant differences for stillbirth rates</td>
<td>Siegfried 2011</td>
<td>9</td>
</tr>
<tr>
<td>Antiretroviral therapy (ART) for treating pregnant women with HIV infection</td>
<td>No significant differences for stillbirths in 4 different drug-to-drug comparisons : 4 studies; n = 1946 (2 trials, 2 cohort)</td>
<td>Sturt 2010</td>
<td>9</td>
</tr>
<tr>
<td>Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV</td>
<td>RR 0.99 (0.68 to 1.43): 4 trials; n = 2855</td>
<td>Wiysonge 2011</td>
<td>10</td>
</tr>
<tr>
<td><strong>Preventing malaria in pregnancy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insecticide-treated nets vs. no nets</td>
<td>RR 0.68 (0.48 to 0.98)*: 3 trials; n = 4420</td>
<td>Gamble 2006</td>
<td>9</td>
</tr>
<tr>
<td>Insecticide treated nets vs. untreated nets</td>
<td>RR 0.21 (0.05 to 0.92)*: n’s not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Fetal loss (spontaneous miscarriage or stillbirth)</em></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Drugs vs. none for preventing malaria in pregnant women</td>
<td>RR 1.01 (0.79 to 1.36): 7 trials; n = 9833</td>
<td>Radeva-Petrova 2014</td>
<td>10</td>
</tr>
<tr>
<td>Prophylactic antibiotics for inhibiting preterm labour with intact membranes</td>
<td>RR 0.73 (0.43 to 1.26): 8 trials; n = 7080</td>
<td>Flenady 2013</td>
<td>10</td>
</tr>
<tr>
<td><strong>NUTRITION</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antioxidants (mostly vitamin C and E) vs. no antioxidants</td>
<td>1.20 (0.90 to 1.59): 8 trials; n = 18,921</td>
<td>Rumbold 2005a; b; 2008; 2011</td>
<td>9; 9; 10; 10</td>
</tr>
<tr>
<td>(compiled from four Cochrane reviews)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Balanced protein/energy consumption versus control</td>
<td><strong>RR 0.62 (0.40 to 0.98): 5 trials; n = 3408</strong></td>
<td>Ota 2012b</td>
<td>11</td>
</tr>
<tr>
<td>High protein vs. vitamins and minerals</td>
<td>RR 0.81 (0.31 to 2.59): 1 trial; n = 529</td>
<td>Ota 2012b</td>
<td></td>
</tr>
<tr>
<td>Nutritional advice vs. none</td>
<td>RR 0.37 (0.07 to 1.90): 1 trial; n = 231</td>
<td></td>
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</tr>
<tr>
<td>Calcium supplementation during pregnancy</td>
<td>RR 0.93 (0.73 to 1.18): 6 trials; n = 14,188</td>
<td>Buppasiri 2011; Hofmeyr 2014</td>
<td>10</td>
</tr>
<tr>
<td>(compiled from two reviews)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>RR and CI</td>
<td>Trials, n</td>
<td>Authors Year</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Chapter 5</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Folic acid vs. no folic acid (during pregnancy)</td>
<td>RR 1.73 (0.75 to 3.99): 1 trial; n = 2819</td>
<td>Lassi 2013</td>
<td>9</td>
</tr>
<tr>
<td>Folic acid supplementation vs. no folic acid (periconception)</td>
<td>RR 0.96 (0.51 to 1.83): 4 trials; n = 5994</td>
<td>De-Regil 2010</td>
<td>9</td>
</tr>
<tr>
<td>Folic acid supplementation + other micronutrients vs. other micronutrients (periconception)</td>
<td>RR 1.36 (0.68 to 2.75): 4 trials; n = 5806</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium supplementation</td>
<td>RR 0.73 (0.43 to 1.25): 4 RCTs; n = 5526</td>
<td>Makrides 2014</td>
<td>10</td>
</tr>
<tr>
<td>Marine oil</td>
<td>RR 0.79 (0.50 to 1.27): 8 trials; n = 6871</td>
<td>Makrides 2006</td>
<td>8</td>
</tr>
<tr>
<td>Multiple-micronutrient supplementation vs. none, placebo or up to 2 micronutrients</td>
<td>RR 0.95 (0.85 to 1.06): 13 trials; n=65,206</td>
<td>Haider 2012</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin A supplementation</td>
<td>RR 1.06 (0.98 to 1.14): 1 trial; n = 78,835</td>
<td>van den Broek 2010</td>
<td>10</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td>RR 0.17 (0.01 to 4.06): 1 trial; n = 135</td>
<td>De-Regil 2012</td>
<td>9</td>
</tr>
<tr>
<td>Ginger vs. vitamin B6 for nausea and vomiting in early pregnancy</td>
<td>RR 0.14 (0.01 to 2.72): 1 trial; n = 291</td>
<td>Matthews 2014</td>
<td>9</td>
</tr>
<tr>
<td>2/3 vs. full dose of IV iron for iron-deficiency anaemia in preg.</td>
<td>RR 0.70 95% CI 0.25 to 1.93: 1 trial; n = 507</td>
<td>Reveiz 2011</td>
<td>9</td>
</tr>
<tr>
<td>Energy restricted diet vs. no energy restriction (in women with gestational diabetes)</td>
<td>No stillbirths: 1 trial; n = 124</td>
<td>Han 2013a</td>
<td>9</td>
</tr>
<tr>
<td>Diet and exercise (combined) for preventing gestational diabetes</td>
<td>RR 0.99 (0.29 to 3.42): 1 trial; n = 2202</td>
<td>Bain 2014e submitted</td>
<td>9</td>
</tr>
</tbody>
</table>

**SOCIAL/PSYCHOSOCIAL; LIFESTYLE**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>RR and CI</th>
<th>Trials, n</th>
<th>Authors Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation (psychological interventions)</td>
<td>RR 1.22 (0.76 to 1.95): 7 trials; n = 5411</td>
<td>Chamberlain 2013</td>
<td>9</td>
</tr>
<tr>
<td>Smoking cessation (pharmacological interventions)</td>
<td>RR 1.98 (0.55 to 7.07): 3 trials; n = 1402</td>
<td>Coleman 2013</td>
<td>9</td>
</tr>
<tr>
<td>Exercise for diabetic pregnant women</td>
<td>No stillbirths: 2 trials; n = 48</td>
<td>Cey sens 2006</td>
<td>9</td>
</tr>
</tbody>
</table>

**PREVENTING OR TREATING MATERNAL CONDITIONS**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>RR and CI</th>
<th>Trials, n</th>
<th>Authors Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing asthma in pregnancy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra venous theophylline vs. control</td>
<td>No stillbirths: 1 trial; n = 65</td>
<td>Bain 2014c</td>
<td>9</td>
</tr>
<tr>
<td>Inhaled corticosteroid vs. control</td>
<td>No stillbirths: 1 trial; n = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENO algorithm vs clinical practice guideline algorithm</td>
<td>RR 1.4 (0.07 to 16.38): 1 trial; n = 214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions for treating cholestasis in pregnancy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDCA vs. placebo</td>
<td>RR 0.31 (0.03 to 2.84): 3 trials; n = 233</td>
<td>Gurung 2013</td>
<td>9</td>
</tr>
<tr>
<td>SAMe vs. placebo</td>
<td>No stillbirths: 1 trial; n = 18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- Dexamethasone vs. placebo
- YCHD vs. SAMe
- Danxiaoling vs. yiganling
- Early term delivery vs. expectant management

### Drugs for very high blood pressure during pregnancy:

- Urapidil vs. hydralazine
- Labetalol vs. methyldopa
- Nifedipine vs. prazosin
- Hydralazine vs. diazoxide
- Methyldopa vs. atenolol

<table>
<thead>
<tr>
<th>Interventions</th>
<th>RR (95% CI)</th>
<th>Trials</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urapidil vs. hydralazine</td>
<td>No stillbirths: 1 trial; n = 26</td>
<td>No stillbirths: 1 trial; n = 72</td>
<td>Duley 2013</td>
</tr>
<tr>
<td>Labetalol vs. methyldopa</td>
<td>No stillbirths: 1 trial; n = 149</td>
<td>RR 0.46 (0.18 to 1.13)</td>
<td>1 trial; n = 101</td>
</tr>
<tr>
<td>Nifedipine vs. prazosin</td>
<td>RR 5.30 (0.26 to 107.70)</td>
<td>RR 1.0 (0.07 to 15.26)</td>
<td>1 trial; n = 60</td>
</tr>
<tr>
<td>Hydralazine vs. diazoxide</td>
<td>RR 0.46 (0.18 to 1.13)</td>
<td>1 trial; n = 149</td>
<td></td>
</tr>
<tr>
<td>Methyldopa vs. atenolol</td>
<td>RR 0.46 (0.18 to 1.13)</td>
<td>1 trial; n = 149</td>
<td></td>
</tr>
</tbody>
</table>

### Any hypertensive drug vs. none for mild to moderate hypertension during pregnancy

- RR 1.14 (0.60 to 2.17): 18 trials; n = 2480

### Diuretics for preventing pre-eclampsia

- RR 0.72 (0.40 to 1.27): 5 trials; n = 1836

### Interventionist vs. expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation

- RR 0.20 (0.03 to 1.16): 4 trials; n = 425

### Magnesium sulphate vs. lytic cocktail for eclampsia

- RR 0.33 (0.01 to 7.16): 2 trials; n = 177

### Anticonvulsants for women with pre-eclampsia:

- Magnesium sulphate vs. none/placebo
- Magnesium sulphate vs. phenytoin
- Magnesium sulphate vs. diazepam

<table>
<thead>
<tr>
<th>Interventions</th>
<th>RR (95% CI)</th>
<th>Trials</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium sulphate vs. none/placebo</td>
<td>RR 0.99 (0.87 to 1.12): 3 trials; n = 9961</td>
<td></td>
<td>Duley 2010a</td>
</tr>
<tr>
<td>Magnesium sulphate vs. phenytoin</td>
<td>RR 0.62 (0.27 to 1.41): 1 trial; n = 2165</td>
<td>No stillbirths: 1 trial; n = 18</td>
<td></td>
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</table>

### Magnesium sulphate regimens for women with (pre)-eclampsia

- Loading dose vs. loading dose & maintenance
- Lower vs. standard dose
- Intravenous vs. intramuscular maintenance

<table>
<thead>
<tr>
<th>Interventions</th>
<th>RR (95% CI)</th>
<th>Trials</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose vs. loading dose &amp; maintenance</td>
<td>RR 1.13 (0.66 to 1.92): 1 trial; n = 341</td>
<td></td>
<td>Duley 2010c</td>
</tr>
<tr>
<td>Lower vs. standard dose</td>
<td>RR 0.88 (0.37 to 2.05): 1 trial; n = 50</td>
<td></td>
<td>Duley 2010c</td>
</tr>
<tr>
<td>Intravenous vs. intramuscular maintenance</td>
<td>RR 1.25 (0.09 to 17.02): 1 trial; n = 18</td>
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</tr>
</tbody>
</table>

### Hospitalisation and bed rest for multiple pregnancy

- RR 1.15 95% CI 0.32 to 4.15: 7 trials; n = 1452

### MODELS, WORK FORCE, SYSTEMS

- Reduced antenatal visits vs. standard number of visits
- Community-based intervention packages
- Specialised antenatal clinics for women with multiple preg.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect Size</th>
<th>Study Details</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trained vs. untrained traditional birth attendants</td>
<td>OR 0.69 (0.57 to 0.89): 1 trial; n = 18,699</td>
<td>Sibley 2012</td>
<td>9</td>
</tr>
<tr>
<td>Additionally trained vs. trained traditional birth attendants</td>
<td>RR 0.99 (0.76 to 1.28): 2 trials; n = 27,594</td>
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</tr>
<tr>
<td><strong>SCREENING AND MONITORING OF FETAL GROWTH AND WELLBEING</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Doppler vs. no Doppler ultrasound in normal pregnancy</td>
<td>RR 0.79 (0.32 to 1.97): 4 trials; n = 12160</td>
<td>Alfirevic 2010</td>
<td>9</td>
</tr>
<tr>
<td>Doppler ultrasound vs. none in high-risk pregnancies</td>
<td>RR 0.65 (0.14 to 1.04): 15 trials; n = 9560</td>
<td>Alfirevic 2013</td>
<td>10</td>
</tr>
<tr>
<td>Doppler ultrasound alone vs. CTG alone</td>
<td>RR 0.48 95% CI 0.14 to 1.71: 4 trials; n = 2813</td>
<td></td>
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</tr>
<tr>
<td>Biochemical tests of placental function (oestriol concentrations reported vs. not)</td>
<td>RR 0.56 (0.16 to 1.88): 1 trial; n = 622</td>
<td>Neilson 2012</td>
<td>9</td>
</tr>
<tr>
<td>Utero-placental Doppler ultrasound vs. no Doppler ultrasound</td>
<td>RR 1.44 (0.38 to 5.49): 2 trials; n = 5006</td>
<td>Stampalija 2010</td>
<td>10</td>
</tr>
<tr>
<td>Routine vs. no/concealed/selective ultrasound &gt; 24 weeks</td>
<td>RR 1.11 (0.29 to 4.26): 5 trials; n = 21708</td>
<td>Bricker 2008</td>
<td></td>
</tr>
<tr>
<td>Serial and Doppler ultrasound vs. selective ultrasound</td>
<td>RR 0.84 (0.36 to 1.93): 1 trial; n = 2834</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat digital cervical assessment in pregnancy</td>
<td>OR 1.09 (0.61 to 1.95): 1 trial; n = 5490</td>
<td>Alexander 2010</td>
<td>9</td>
</tr>
<tr>
<td>Weekly endovaginal ultrasound scan vs. no scan</td>
<td>No stillbirths: 1 trial; n = 92</td>
<td>Sharp 2014</td>
<td>9</td>
</tr>
<tr>
<td>Amniocentesis vs. no amniocentesis</td>
<td>No stillbirths: 1 trial; n = 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of decreased fetal movements (vibroacoustic stimulation vs. mock)</td>
<td>No stillbirths: 1 trial; n = 28 (decreased fetal movements subgroup)</td>
<td>Hofmeyr 2012a</td>
<td>9</td>
</tr>
<tr>
<td>Fetal movement counting vs. hormonal analysis</td>
<td>RR 3.19 (0.13 to 78.20): 1 trial; n = 1191</td>
<td>Mangesi 2007</td>
<td>8</td>
</tr>
<tr>
<td>Routine fetal movement counting vs. mixed or undefined counting</td>
<td>Mean stillbirth rate: 0.23 (-0.61 to 1.07) 1 trial; n = 66 clusters (68,654 women)</td>
<td>Mangesi 2007</td>
<td></td>
</tr>
<tr>
<td>Immediate vs. deferred birth for suspected fetal compromise</td>
<td>RR 0.22 (0.05 to 1.00): 1 trial; n = 587</td>
<td>Stock 2012</td>
<td>9</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic abdominal decompression in normal pregnancy</td>
<td>RR 4.68 (0.80 to 27.31): 2 trials; n = 709</td>
<td>Hofmeyr 2012b</td>
<td>9</td>
</tr>
</tbody>
</table>
5.5.4 Discussion

In this overview of antenatal stillbirth prevention, very few interventions showed clear differences. Of these few, most (e.g. insecticide treated nets for malaria prevention and training of traditional birth attendants) are relevant for low-income country settings. It may be that the higher rates of stillbirth in these countries enable more differences to be detected than with the lower rates of stillbirth seen in high-income countries.

However, selective reporting bias (also discussed in 5.2) is also likely to be obscuring true effects of interventions to prevent stillbirth. The outcome of stillbirth may not be reported at all in relevant Cochrane systematic reviews or it may only be reported in the composite form of perinatal mortality. For example, the high profile review on midwife-led continuity models (Sandall 2013) could not be included in my overview. In this review, stillbirth was not reported due to differing gestational definitions, but is included within the outcome ‘Fetal loss/neonatal death equal to/after 24 weeks’.

The authors found that midwife-led continuity models of care are associated with an important 16\% reduction in overall fetal loss and neonatal death but we do not know if this reduction applies to stillbirth or not. Conversely, the potential increase in perinatal mortality (RR 1.67 95\% CI 0.93 to 3.00; 8 trials) reported in the Cochrane systematic review of alternative versus conventional institutional settings (Hodnett 2012) does not allow us to interpret if this indication of harm is applicable to both neonatal mortality and stillbirth.

In the Cochrane systematic review assessing abdominal decompression for suspected fetal compromise (Hofmeyr 2012c), a reduction in perinatal mortality was reported (RR 0.39; 95\% CI 0.22 to 0.71) but could not be included above as stillbirths were not reported separately. Since stillbirth may be increased when abdominal decompression is used in normal pregnancies (Hofmeyr 2012b), separate reporting of stillbirth and neonatal mortality in Hofmeyr 2012c would allow a better understanding of the effects of abdominal decompression under different clinical circumstances.

In summary, this overview was influenced by incomplete evidence from reporting biases, trials with small sample sizes, many of them quite old and not conducted according to today’s standards and perhaps neglect of stillbirth as an issue to be addressed. Better reporting of fetal mortality in existing randomised controlled trials and systematic reviews and further trials will provide better guidance for reducing stillbirth and will be another way to bring stillbirth out of the shadows (Mullan 2011).

5.6 Citation analysis of the two Lancet high income country stillbirth papers (Flenady, Middleton et al 2011a; Flenady, Koopmans, Middleton et al 2011b)

5.6.1 Aim

My aim of this citation analysis was to measure the citation rates of the two Lancet papers; to explore any differences in rates between the two papers; and to relate rates and differences to impact of these citations.

As described above in 5.3 and 5.4, each paper had a different purpose: Flenady 2011a (HIC paper) was a call for action to highlight the neglect of stillbirth in high as well as low-middle income countries and to intensify efforts to reduce the numbers of stillbirths; and Flenady 2011b (SR paper) was a systematic review of risk factors for stillbirth conducted to inform the HIC paper.

5.6.2 Methods

I assessed the citations for both Lancet papers on Google Scholar and Scopus (last assessed on 11 January 2015) and extracted year the citation appeared, the topic of the citing article (stillbirth or other topic), which section(s) in the citing article the citation appeared and if both Lancet papers had been cited in the same article, into an Excel spreadsheet. I then compared the Google Scholar and...
Scopus citation rates of the two Lancet papers and determined the overlap between the two citation systems.

I developed a tool to assess whether citations were passive (not likely to lead to further action) or active (the citation advocates for further work or action). I also made brief summaries of the nature of the citation and then classified citations as having low, medium or high impact (e.g. a call for change or action for the latter) – see Box below.

<table>
<thead>
<tr>
<th>Impact category</th>
<th>Generic explanation</th>
<th>Specific explanation for the two HIC papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>passive; no action proposed</td>
<td>lists rates of stillbirth; or risk factors for stillbirth</td>
</tr>
<tr>
<td>MEDIUM</td>
<td>mixed passive/active</td>
<td>lists or describes barriers to stillbirth</td>
</tr>
<tr>
<td>HIGH</td>
<td>active; further action proposed or advocated</td>
<td>identifies a research gap, calls for action or implementation, discusses disparities or inequities in the area of stillbirth</td>
</tr>
</tbody>
</table>

This was assessed as the impact of the citation only, not of the citing paper overall. For example in Hedegaard 2014 the paper was judged to have a high impact overall (reporting a reduction in stillbirths after introduction of a post-term induction policy) but the citation to the Lancet paper was judged to be low impact (the citation only listed post-term as a risk factor for stillbirth).

Google Scholar includes scholarly articles (journal papers, conference papers, technical reports, or their drafts, dissertations, pre-prints, post-prints, or abstracts) from a wide variety of sources in all fields of research, all languages, all countries, and over all time periods. Content such as news or magazine articles, book reviews, and editorials is not included on Google Scholar (http://scholar.google.com.au/intl/en/scholar/inclusion.html#content – [accessed 30/7/14]).

Scopus is the largest ‘managed’ abstract and citation database of peer-reviewed research literature with more than 20,500 peer-reviewed journals; 360 book series and Articles-in-Press from over 3,850 journals comprising over 50 million records. Approximately two million new records are added each year via daily updates (http://help.elsevier.com/app/answers/detail/a_id/2216/p/8150/c/8428 – [accessed 30/7/14]).

5.6.3 Results

Flenady, Middleton et al 2011: Stillbirths: the way forward in high-income countries (HIC paper):
As at 11/1/15 the HIC paper had received 139 Google Scholar and 91 Scopus citations. In the HIC paper, eight of the 139 Google Scholar citations were invalid (three incorrect links and five duplicates) leaving 131 citations for analysis. The Scopus citations were almost a subset of the Google Scholar citations, with only 8/91 (9%) of Scopus citations not cited by Google Scholar.

For the SR paper, out of a total of 255 Google Scholar citations there were 21 invalid citations (nine incorrect links and 12 duplicates), leaving 234 for analysis. As above, the Scopus citations were almost a subset of the Google Scholar citations, with just 7/152 (5%) of Scopus citations not cited by Google Scholar.

Thus there were 139 (131 + 8) citations overall for analysis for the HIC paper and 241 (234 + 7) for the SR paper. Overall the SR paper was cited nearly twice as much as the HIC paper. Google Scholar yielded almost 50% more valid citations than Scopus.
Most of the articles citing the HIC paper were predominantly about stillbirth (101/139; 73%) with the remainder addressing topics such as obesity, smoking, fetal growth restriction and placental pathology. This was lower for the SR paper (114/241: 47%) with the rest of the citations addressing similar topics such as obesity and smoking, as for the HIC paper.

The pattern of citations over time differed between the HIC and SR papers. Citations to the HIC paper appeared to have peaked in 2013, two years after publication, whereas citations to the SR papers probably have yet to peak (see Figure 5.1).

**Fig 5.1: HIC and SR paper citations by year from 2011 to 2015 (Google Scholar and Scopus combined).**

For the HIC paper, approximately a third each of the 139 citations were classified as having low, medium or high impact:
- low: 49 (35%)
- medium: 42 (30%)
- high: 47 (35%)
- unknown: 1

In contrast, I judged most of the 241 SR paper citations (70%) to be of low impact (reporting only rates or risk factors in the background section). See Figure 5.2.
- low: 168 (70%)
- medium: 43 (18%)
- high: 16 (6%)
- unknown: 14 (6%)
5.6.4 Discussion

With 139 and 241 combined Google Scholar and Scopus citations respectively, both the HIC and SR papers have been well cited since their publication in 2011. In fact the SR paper is the most highly cited publication of the 2011 Lancet Stillbirth series.

Conventional wisdom would therefore dictate that the SR paper has more impact than the HIC paper with almost double the number of citations. However by analysing more deeply and categorising each individual citation into likely high, medium and low impact, the HIC paper with 35% of high impact citations has the potential to make more difference than the SR paper with only 6% of high impact citations. As described above a high impact citation is one that calls for some action rather than citing a ‘convenient’ reference to introduce the topic (as was the case with many of the citations to the HIC paper). A citation impact tool does not appear to have been previously developed although Sibbald 2015 has suggested modified citation analyses reflecting “uptake and interpretation of new knowledge”. This approach clearly needs more development and validation but the above analysis does demonstrate that not all citations are equal and that a simple citation count can be misleading. There are also ramifications for research measurement exercises and related metrics such as profiles of individual researchers, grant peer review and academic promotion parameters, if such approach were to be adopted.

The citation analysis has also shown, consistent with previous work (Middleton 2007a; Middleton 2012a), that Google Scholar outperforms Scopus in capturing citations and thus gives a more complete picture of the extent and range of cites. This also has ramifications for ways in which research performance is currently measured e.g. use of the H-index compiled from Scopus or Web of Science may underestimate a researcher’s performance.

5.7 Overall Conclusions

In this chapter I have shown that stillbirth has been a neglected issue in several ways – it is poorly reported in studies and syntheses and has not been a research priority despite being more common than neonatal mortality.

The two ‘high income’ papers from the 2011 Lancet Stillbirth Series (Flenady 2011a; Flenady 2011b) set out what is needed to reduce stillbirth rates and to better manage how stillbirth is dealt with in our health systems. Although these two papers have been well cited, I have shown that many citations are ‘academic’ and do not serve to advance implementation of stillbirth prevention or better management when stillbirth does occur.
Nonetheless there have been important responses to the call for action. For example a large stepped wedge randomised controlled trial for women to detect and follow fetal movements has recently been funded by the NHMRC (ACTRN12614000291684). The evidence of associations between lifestyle factors such as obesity and smoking has generated attention but translation into effective interventions is difficult and slow.

Stillbirth rates in high income countries show profound disparities. One example is the gap between stillbirth rates for Aboriginal and Torres Strait women which have been double that of other women in Australia. Ibielele 2014 has shown that in Queensland the gap is still there but may be closing. The drop to a 1.5 fold disparity indicates that even more can be done to address disadvantage, which will be a focus of the second Lancet Stillbirth series, due in late 2015.

The risk of dying on the day of birth is not matched until (or if) we reach 92 years of age, highlighting the importance and burden of stillbirth (Walker 2014).

**Fig 5.3: Research/translation cycle for stillbirth prevention and management in high income countries**

*Green text indicates past or current initiatives: Yellow text indicates ongoing or future initiatives; Red text indicates challenges*
Authorship details of key papers:

  
  “Erika Ota (EO), João Paulo Souza (JPS) and Rintaro Mori (RM) participated in the study design. EO drafted the protocol. JPS, Ruoyan Tobe-Gai, RM, Philippa Middleton and Vicki Flenady provided critical comments and valuable suggestions.”

  
  “VF designed the study, oversaw its conduct, and prepared the report with input* from all authors. LK coordinated the review, data extraction, and meta-analysis of included studies. VF, LK, PM, AG, and KG collaborated in data extraction and quality assessment. ME oversaw the comparative risk analysis and calculation of PAR values. All authors reviewed the study findings, and read and approved the final version before submission.”

  *In addition, Philippa Middleton made a major contribution to the discussion section.

  
  “VF compiled the report, with contributions* from all authors. All authors read and approved the final report.”

  *Philippa Middleton made major contributions to several sections including priorities for preventing stillbirth; interventions to reduce stillbirths; and research priorities.
6.1 Introduction

The integration of evidence for antenatal magnesium sulphate for fetal, infant and child neuroprotection provides an example where we can follow the steps of the research/translation cycle right through from problem identification, generation and synthesis of knowledge, making that knowledge actionable and finally through to implementation and audit, as shown in Figure 6.1.

It is also a clear illustration of how long the process of discovery, generation of evidence and uptake into practice can take – even with a drug such as magnesium sulphate which is cheap, readily available and relatively unencumbered by commercial considerations.

The first loop of the research cycle is nearing completion but is still likely to take over 25 years to become firmly established in clinical care. Research into the clinical problem of preventing cerebral palsy to initial implementation of magnesium sulphate into clinical care for this indication has already taken over 20 years, with wider implementation and audit of uptake of magnesium sulphate and health outcomes (survival free of cerebral palsy) anticipated to take several more years. The next iterations of the research cycle are already concentrating on addressing research gaps (such as improving targeting and refinement of how and when magnesium sulphate is used for fetal, infant and child neuroprotection), and auditing progress towards prevention of cerebral palsy.

The **clinical problem** – how to prevent cerebral palsy – has been identified as the top priority for cerebral palsy research in Australia (McIntyre 2010). Overall prevalence of cerebral palsy is 2 to 2.5 per 1000 live births (Vincer 2006) with a much higher risk for very preterm babies - 80-fold increased risk at less than 28 weeks gestational age compared with term births (Moster 2008; Saigal 2008). The most recent Australian Cerebral Palsy Register Report indicated that over 41% of all cerebral palsy births in Australia were preterm; this is compared with 8% of births being preterm in the total population (ACPR Group 2013). One in 500 babies in Australia and New Zealand are diagnosed with cerebral palsy each year – this equates to over 120 babies in New Zealand and over 600 babies in Australia each year.

Cerebral palsy is “an umbrella term covering a group of non-progressive but often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development” (Mutch 1992). It is a complex neurological condition with the characteristic motor and/or postural dysfunction of cerebral palsy often found alongside associated impairments, including intellectual, speech, visual and hearing impairments, and epilepsy (found in over 50%, 60%, 40%, 10% and 30% of Australian children with cerebral palsy at five years of age respectively) (ACPR Group 2013; Novak 2012).

Few interventions have been found to prevent cerebral palsy, which is associated with devastating long-term consequences. Antenatal magnesium sulphate is one of the first perinatal interventions shown to reduce the risk of cerebral palsy and death when given to women prior to very preterm birth.

**Basic research; discovery** – Magnesium sulphate’s essential role in human health has long been known. It is involved in key cellular processes, including limiting damage after brain injury (Mildvan 1987; McIntosh 1989). However the exact mechanism of how magnesium exerts a neuroprotective
effect is not yet clear. Some researchers have also suggested that sulphate, rather than magnesium, is the agent responsible for the fetal neuroprotective effects observed (Dawson 2013).

**Fig 6.1: Research/translation cycle: antenatal magnesium sulphate for fetal neuroprotection**

Observation of an association between antenatal magnesium sulphate and reduced risk of intraventricular haemorrhage in babies with birthweights under 1500 g (Kuban 1992) led the California Cerebral Palsy Group to undertake a case-control study (Nelson 1995). This study showed that in utero exposure to antenatal magnesium sulphate was associated with a significantly marked reduction in the risk of cerebral palsy.

**Applied research** – In turn, Nelson and colleagues’ seminal results paved the way for randomised trials of antenatal magnesium sulphate for fetal, infant and child neuroprotection, firstly in the US (Mittendorf 2002) and Australia and New Zealand (Crowther 2003); then France (Marret 2007) and another US trial (Rouse 2008). These four trials were pooled in a Cochrane review showing for the first time that magnesium sulphate given to women prior to preterm birth can reduce the risk of combined death or cerebral palsy, and cerebral palsy alone (Doyle 2009) – see 5.2. (A fifth randomised trial of magnesium sulphate used for maternal neuroprotection in women with pre-eclampsia (Magpie 2006) was also included in this Cochrane systematic review.)
In order to translate these research findings into recommendations for clinical practice, we developed clinical practice guidelines for Australia and New Zealand (Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010) – see 5.3. The WISH project (Working to Improve Survival and Health for babies born very preterm) was established to address implementation barriers identified in the guidelines and to provide implementation support to Australian and New Zealand tertiary maternity centres (5.4).

<table>
<thead>
<tr>
<th>Summary points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-quality research evidence has clearly shown that antenatal magnesium sulphate prior to imminent, early preterm birth significantly increases the chances of children surviving free of cerebral palsy;</td>
</tr>
<tr>
<td>• Antenatal magnesium sulphate prior to early preterm birth had not previously been used routinely for the indication of fetal, infant and child neuroprotection;</td>
</tr>
<tr>
<td>• Evidence-based recommendations in the form of clinical practice guidelines have been formulated to support clinicians deal with this ‘translational flashpoint’.</td>
</tr>
<tr>
<td>• This translation process is likely to be accelerated with active implementation strategies compared with passive dissemination, and by identifying and addressing barriers to implementation.</td>
</tr>
<tr>
<td>• Implementation interventions and strategies such as the WISH project are needed to promptly increase uptake into routine care, thereby preventing unnecessary deaths or children surviving, but with cerebral palsy;</td>
</tr>
<tr>
<td>• As new evidence is generated (from the AMICABLE individual participant meta-analysis for example), this will be fed back into the research cycle with any ensuing practice changes formulated and their implementation supported.</td>
</tr>
</tbody>
</table>

6.2 Overall aims
To assess how knowledge about antenatal magnesium sulphate for fetal, infant and child neuroprotection has been generated, synthesised and implemented;

To describe and discuss interactions between these processes;

To describe and quantify the impact of knowledge generation, synthesis and implementation in this area on clinical practice and on health outcomes.

6.3 Knowledge synthesis: ‘Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus’ (Cochrane systematic review)
I led the synthesis and took other key roles in preparing this Cochrane systematic review on ‘Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus’ - I searched the literature, extracted details of the study methods and results, entered the data into Review Manager, wrote the initial updated synthesis of results and contributed to all versions of the review (Doyle 2009). This landmark review, showing that magnesium sulphate can prevent cerebral palsy, has been recommended by F1000Prime (http://f1000.com/prime/1149866#1). A summary of this review follows.

We prespecified the study criteria to be all published, unpublished and ongoing randomised trials with reported data comparing outcomes for women at risk of preterm birth given prenatal magnesium sulphate with outcomes in controls, whether treated or not with placebo. Trials were included if the primary aim of the study was to prevent neurological abnormalities in the unborn baby, or if the primary aim was otherwise but long-term neurological outcomes were reported for the infants. The trials had to use some form of random allocation and report data on one or more of the prestated outcomes. Quasi-randomised trials were excluded.
Magnesium sulphate given to the women at risk of preterm birth, administered intravenously, intramuscularly or orally, had to be compared with either placebo or no placebo. Trials where magnesium sulphate was used with the prime aim of tocolysis, prevention and treatment of eclampsia, maintenance therapy after preterm labour or as a dietary supplement in pregnancy were not included (unless they reported long-term neurological outcomes in the children), as those trials are covered in separate Cochrane systematic reviews.

Primary outcomes were chosen to be most representative of the clinically important measures of effectiveness and safety, including serious outcomes, for the women and their infants. Combined outcomes were used for the main analyses, rather than all their components:

For the infants/children
- Fetal, neonatal or later death.
- Neurological impairments (developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than one standard deviation (SD) below the mean), cerebral palsy (abnormality of tone with motor dysfunction), blindness (corrected visual acuity worse than 6/60 in the better eye), or deafness (hearing loss requiring amplification or worse)), or neurological disabilities (abnormal neurological function caused by any of the preceding impairments) at follow up later in childhood. Substantial gross motor dysfunction (defined as motor dysfunction such that the child was not walking at age two years or later, or the inability to grasp and release a small block with both hands).
- Major neurological disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than two SD below the mean)).
- Paediatric mortality combined with cerebral palsy, substantial gross motor dysfunction, neurological impairment, or major neurological disability (these combined outcomes recognise the competing risks of death or survival with neurological problems).

The major paediatric outcomes were death or neurological (cerebral palsy, impairment or disability), or combinations of death with the neurological outcomes.

For the women
- Serious adverse cardiovascular/respiratory outcome (maternal death, respiratory arrest, cardiac arrest).
- Adverse effects severe enough to stop treatment.

We included five trials (6145 babies) in the review (Crowther 2003; Magpie 2006; Marret 2006; Mittendorf 2002; Rouse 2008). In Magpie 2006, only the subset of infants born preterm were included in this review. Mittendorf 2002 included a tocolytic arm as well as a fetal neuroprotective arm. Since both Magpie 2006 and Mittendorf 2002 reported long-term child outcomes, they were included in the overall analyses of the review even though antenatal magnesium sulphate was not used for fetal neuroprotective intent in Magpie 2006 and for only part of Mittendorf 2002.

Two of the five trials (Crowther 2003; Rouse 2008) were at low risk of bias for all components (see Figure 6.2). Magpie 2006 was at unclear risk of bias for incomplete outcome data as only some children (~2/3rds) were selected for follow-up. In Marret 2006, blinding and incomplete outcome data were judged to be at unclear risk of bias (not all clinicians were blinded and a substantial proportion of children were not assessed with a clinical examination). All five risk of bias components in Mittendorf 2002 were judged to be at unclear risk of bias due to lack of reporting or insufficient descriptions and the tocolytic arm was not blinded.
Antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (risk ratio (RR) 0.68; 95% confidence interval (CI) 0.54 to 0.87; five trials; 6145 infants) – see Figure 6.3.

There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants). Overall there were no significant effects of antenatal magnesium therapy on combined rates of mortality with cerebral palsy, although there were significant reductions for the neuroprotective groups RR 0.85; 95% CI 0.74 to 0.98 (random effects model); four trials; 4446 infants (Crowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008) – see Figure 6.4.

No statistically significant effect of antenatal magnesium sulphate therapy was detected on paediatric mortality (RR 1.04; 95% CI 0.92 to 1.17; five trials; 6145 infants), or on other neurological impairments or disabilities in the first few years of life. There were higher rates of minor maternal side effects in the magnesium sulphate group, but no significant effects on major maternal complications.
In the Cochrane systematic review, the main implication for clinical practice was that a fetal neuroprotective role of antenatal magnesium sulphate therapy given to women at risk of preterm birth is now established. The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155). Given the beneficial effects of magnesium sulphate on substantial gross motor function in early childhood, the implications of research were that outcomes later in childhood need to be evaluated to determine the presence or absence of later potentially important neurological effects, particularly on motor or cognitive function.
6.4 Making knowledge actionable: Antenatal Magnesium Sulphate for Neuroprotection Guidelines

Development process and methods

In 2009/10 Professor Caroline Crowther and myself led the development of bi-national evidence-based guidelines (Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). A summary of the Guideline follows.

In late 2009, we established a multidisciplinary expert advisory panel to oversee development of these guidelines, which were developed according to the requirements of the Australian National Health and Medical Research Council and the (then) New Zealand Guidelines Group. We intended the guidelines to be relevant for health professionals who care for women at risk of preterm birth and their babies; for pregnant women and their partners and families; and for policy makers in maternity care.

The Panel formulated key clinical questions with several components:

| Whether administration of magnesium sulphate to women prior to preterm birth: |
| Improves health outcomes for the fetus, infant and child |
| Causes adverse outcomes for the women; or the fetus, infant and child |
| Varies by: |
| • Gestational age magnesium sulphate is given; |
| • Time magnesium sulphate is planned to be given prior to preterm birth; |
| • Regimen (dosing and routes of administration); |
| • Number of babies in utero; |
| • Reason women are considered to be at risk of preterm birth; |
| • Parity of the women; |
| • Mode of birth and interaction with magnesium sulphate; |
| • Combined effect of antenatal corticosteroids and magnesium sulphate. |

Each question was addressed in the following format:

- A description of the studies comprising the relevant evidence;
- The main results from these studies;
- The formulation of guidance process, consisting of:
  - A summary of the judgements from the evidence statements;
  - Use of judgements to formulate recommendations (and good practice points);
  - Implications for implementing the recommendations;
  - Further research required.

Evidence base

Four of the five trials in the Doyle 2009 Cochrane systematic review (see 5.2) formed the evidence base for the effectiveness of antenatal use of magnesium sulphate for fetal, infant or child neuroprotective intent. The four trials were Crowther 2003; Marret 2006; Mittendorf 2002 (neuroprotective arm only); and Rouse 2008.

The evidence for potential harms used in the clinical practice guideline was taken from a wider evidence base which comprised three additional Cochrane systematic reviews besides Doyle 2009. These reviews were Crowther 1998*; Crowther 2002**; and Duley 2003***.

*now Han 2013b; **now Crowther 2014 [Subsequently myself and Caroline Crowther have led the update of the Crowther 2002 Cochrane systematic review (Crowther 2014)].
***now Duley 2010a

Formulating and grading recommendations and other guidance
Evidence-based recommendations were formulated and graded using the NHMRC FORM system (Middleton 2005). I co-led the development of the FORM system, which is described in Hillier 2011. NHMRC grades of recommendation are intended to indicate the strength of the body of evidence underpinning the recommendation, to assist users of the clinical practice guidelines to make appropriate and informed clinical judgments. Grade A or B recommendations are generally based on a body of evidence that can be trusted to guide clinical practice, whereas Grade C or D recommendations must be applied carefully to individual clinical and organisational circumstances and should be interpreted with care (Hillier 2011).

When there is insufficient evidence to make an evidence-based recommendation, good practice points can be formulated through consensus to help implementation. Implementation implications indicate potential barriers to implementation, resource requirements and factors which may lead to variation in uptake, such as differential access and equity issues. Research recommendations outline priorities for further studies or other actions (Hillier 2011).

**Clinical recommendations of the Clinical Practice Guideline**

This set of recommendations was formulated to be used as one overall recommendation:

<table>
<thead>
<tr>
<th>CLINICAL RECOMMENDATIONS (Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010)</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In women at risk of early preterm* imminent birth#, use magnesium sulphate for neuroprotection of the fetus, infant and child: *when gestational age is less than 30 weeks #when early preterm birth is planned or definitely expected within 24 hours. (When birth is planned, commence magnesium sulphate as close to four hours before birth as possible.)</td>
<td>A</td>
</tr>
<tr>
<td>intravenously with a 4 gram loading dose (slowly over 20-30 minutes) and 1 gram per hour maintenance dose via intravenous route, with no immediate repeat doses. Continue regimen until birth or for 24 hours, whichever comes first.</td>
<td>C</td>
</tr>
<tr>
<td>regardless of plurality (number of babies in utero).</td>
<td>B</td>
</tr>
<tr>
<td>regardless of the reason women (at less than 30 weeks gestation) are considered to be at risk preterm birth.</td>
<td>B</td>
</tr>
<tr>
<td>regardless of parity (number of previous births for the woman)</td>
<td>B</td>
</tr>
<tr>
<td>regardless of anticipated mode of birth</td>
<td>B</td>
</tr>
<tr>
<td>whether or not antenatal corticosteroids have been given</td>
<td>B</td>
</tr>
</tbody>
</table>

**Good practice points from the Clinical Practice Guideline**

**Timing:** If birth before 30 weeks is planned or expected to occur sooner than four hours (e.g. scheduled caesarean or late presentation to hospital), administer magnesium sulphate to women at risk of preterm birth, as there is still advantage likely from administration within this time.

**Urgent delivery:** In situations where urgent delivery is necessary because of actual imminent maternal or fetal compromise (e.g. severe fetal distress or antepartum haemorrhage), then birth should not be delayed to administer magnesium sulphate.

**Repeat doses:** In the event that birth does not occur after giving magnesium sulphate for neuroprotection of the infant, and preterm birth (less than 30 weeks gestation) again appears imminent (planned or definitely expected within 24 hours), a repeat dose of magnesium sulphate may be considered at the discretion of the attending health professional.

**Locations of administration of antenatal magnesium sulphate:** The locations of administration of antenatal magnesium sulphate intravenously to women should be determined by each individual maternal facility.

**Monitoring:** During administration of magnesium sulphate intravenously, women should be regularly assessed as detailed in individual obstetric unit protocols. Resuscitation and ventilatory support should be immediately available, if needed, during administration of magnesium sulphate.
Should hypotension or respiratory depression occur prompt medical review is recommended. This may include cessation of magnesium sulphate.

**Loading:** A minimum assessment should include checking pulse, blood pressure, respiratory rate and patellar reflexes before loading dose, 10 minutes after loading dose infusion has started and at the end of the loading dose infusion (20-30 minutes). The infusion should be stopped if respiratory rate decreases more than 4 breaths a minute below baseline, or is less than 12 breaths per minute; or diastolic blood pressure decreases more than 15 mmHg below baseline level.

**Maintenance:** While the maintenance infusion is running, observe for any adverse effects. The minimum assessments should include checking pulse, blood pressure, respiratory rate, patellar reflexes and urine output 4-hourly. Stop infusion if respiratory rate is less than 12 breaths a minute; if patellar reflexes are absent, if hypotension occurs or if urine output is less than 100 mL over 4 hours.

**Toxicity:** Magnesium toxicity is unlikely with the regimens recommended in these guidelines and serum magnesium concentrations do not need to be routinely measured (RCOG 2006). In women with renal compromise, serum magnesium monitoring is recommended. Calcium gluconate (1 g (10 mL of 10% solution) slowly via intravenous route over 10 minutes) can be given if there is clinical concern over respiratory depression.

**Potential interactions:** There is a potential theoretical interaction between magnesium sulphate and nifedipine of hypotension and neuromuscular blockade effects, although this is seldom reported in clinical practice (Ben-Ami 1994; Snyder 1989). Regular monitoring of the mother is recommended as detailed in individual obstetric unit protocols. If hypotension occurs, nifedipine and magnesium sulphate administration should cease and the woman reviewed by a medical practitioner.

**Implementation implications of the Clinical Practice Guideline**

**Changes in usual care:** While intravenous magnesium sulphate administration is standard care to prevent and treat eclampsia, in 2009 only a few obstetric units in Australia and New Zealand were using antenatal magnesium sulphate for fetal, infant, and child neuroprotection.

**Resource implications:** Although magnesium sulphate is an inexpensive drug, setting up, maintenance and monitoring magnesium sulphate infusions will incur additional staff time. There will also be training needs, but these should be minimal as all units will have experience with magnesium sulphate infusion to treat or prevent eclampsia. Less than 1.2% of all births before 30 weeks gestation; around 3500 such births occur in Australian (AIHW 2009) and 640 in New Zealand each year. Up to 10% of these babies will have been exposed in utero to magnesium sulphate as treatment for prevention and treatment of eclampsia. If all other women who gave birth before 30 weeks gestation were given magnesium sulphate for neuroprotection of the fetus, infant and child, up to 4104 more women in Australia and New Zealand each year would require additional care and monitoring. (This figure does not include a small number of women at less than 30 weeks gestation where birth is planned or definitely expected within 24 hours and who do not actually give birth before 30 weeks gestation.) On the other hand, fewer cases of cerebral palsy will mean substantial savings at the overall health systems and societal level.

**Changes in the way care is currently organised:** It is acknowledged that while all tertiary obstetric units dealing with babies likely to be born at or before 30 weeks will already have established protocols and systems that will enable them to administer magnesium sulphate intravenously to women at risk of preterm birth less than 30 weeks gestation, appropriate staffing structures may not be in place to enable the safe administration of magnesium sulphate. The ideal setting for babies to be born before 30 weeks is a tertiary specialist unit. Given that the clinical indication for magnesium sulphate is planned or definitely expected preterm birth before 30 weeks then its use will generally be within tertiary obstetric units. Women threatening to give birth before 30 weeks in other settings, and fulfilling all other guideline criteria, may be eligible to receive magnesium sulphate after consultation with their tertiary obstetric network, depending on the non-tertiary unit’s service capability and staffing.
Magnesium sulphate infusions should not be used during antenatal transfer unless resuscitation and ventilator support are immediately available. If a clinical decision is made to transfer a woman who has received magnesium sulphate in another setting to a tertiary obstetric unit, the magnesium sulphate infusion can be stopped during the transfer.

**Barriers to implementation:** Barriers to implementation will include finding the extra time and staff required to administer magnesium sulphate to more women. However, as magnesium sulphate infusions, in the regimens recommended, are already widely practised for treatment of severe pre-eclampsia and eclampsia at these gestational ages, training needs should be minimal as all units will have experience.

Monitoring women after that have received antenatal infusions of magnesium sulphate is usually recommended. Monitoring formed part of the published study methods for two of the included randomised controlled trials (Crowther 2003; Marret 2006). There is, however, no consensus on what form this monitoring should take. For example the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) state that obstetric units should determine their own protocols for monitoring outcomes (SOMANZ 2008). Examples of protocols are provided in Appendix H of the guidelines. As toxicity is unlikely with the regimens recommended in these guidelines, routine monitoring of serum magnesium sulphate concentrations should not be required.

**Research recommendations from the Clinical Practice Guideline**

These research recommendations were derived from Clinical Practice Guideline Panel discussions during the development of the guidelines.

**Prevention of cerebral palsy:** How to prevent cerebral palsy and identifying causes and causal pathways are priority research questions.

**Follow up of children in existing trials:** Continuing the follow up of children in the existing trials is necessary to elucidate if the benefits from antenatal magnesium sulphate seen in early childhood translate into later benefits.

**Audit of antenatal magnesium use and rates of cerebral palsy:** It will be important to monitor the antenatal use of magnesium sulphate for neonatal neuroprotection; and to link data to national childhood cerebral palsy registers and databases.

**Existing trials:** Individual triallists should be approached to provide unpublished data, for subsequent revisions of the Cochrane systematic review ‘Magnesium sulphate for women at risk of preterm birth for the neuroprotection of the fetus’ (Doyle 2009) where possible, on: optimal timing of magnesium sulphate administration; optimal treatment regimens; gestational age breakdown or available gestational age groups (at trial entry); reasons women were considered to be at risk of preterm birth and health outcomes; plurality and health outcomes; parity and health outcomes; mode of birth and health outcomes; use of antenatal corticosteroids and health outcomes.

**Individual participant meta-analyses:** Individual participant meta-analyses through an international collaboration of triallists will permit further exploration of: gestational age when magnesium sulphate was administered and health outcomes; whether differences in timing of magnesium sulphate administration result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy; whether different magnesium sulphate regimens result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy; whether different magnesium sulphate regimens result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy; whether different magnesium sulphate regimens result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy; influence of parity; whether mode of birth modifies neurodevelopmental outcomes; whether differences in use of antenatal corticosteroids result in differences in outcomes such as cerebral palsy and combined death and cerebral palsy.

**Biomarkers for cerebral palsy:** Investigations to identify biomarkers for cerebral palsy to allow a more targeted use of antenatal administration of magnesium sulphate.

**Further randomised controlled trials:** Further randomised trials are needed, comparing:

- antenatal magnesium sulphate with placebo when given to women at risk of preterm birth at 30 weeks gestation or more, that assess mortality, cerebral palsy, and combined death and cerebral palsy;
demonstrated different speeds of administering the loading dose of magnesium sulphate to establish if slower loading reduces maternal adverse effects;
- optimal timing of the antenatal administration of magnesium sulphate prior to preterm birth;
- loading dose versus loading dose versus maintenance; different loading doses (4 g versus 6 g);
- use of repeat doses of magnesium sulphate; treatment of the very preterm infant with magnesium sulphate after birth.

Approval by NHMRC

Following a process of consultation, the National Health and Medical Research Council approved these guidelines in November 2010.

6.5 Implementation; Audit and feedback: The WISH Project (Working to Improve Survival and Health for babies born very preterm)

The WISH Project

I co-lead the WISH (Working to Improve Survival and Health for babies born very preterm) Project with Professor Caroline Crowther. The study commenced in 2011 and has been funded by a Cerebral Palsy Alliance Innovative Research Grant.

6.5.1 Aims of the WISH Project

The aims of the WISH Project (Bain 2013a; Bain 2013b; Crowther 2013b) are to monitor and improve uptake of the use of antenatal magnesium sulphate as a neuroprotective therapy immediately prior to imminent (birth planned or definitely expected within 24 hours), early preterm birth (less than 30 weeks gestation) to reduce the risk of babies dying or having cerebral palsy.

6.5.2 Methods

The WISH Project is a prospective cohort study, with a qualitative component assessing barriers and enablers to practice change. The methods are outlined in the published protocol (Crowther 2013b). The 25 Australian and New Zealand tertiary level maternity hospitals were provided with a package of implementation strategies chosen on the basis of likely benefit. Strategies to guide the introduction and local adaptation of guideline recommendations, in-service education (Grimshaw 2006; Forsetlund 2009), academic detailing (O’Brien 2007), reminders (Grimshaw 2006), and audit and feedback (Chaillet 2006; Grimshaw 2006; Ivers 2012). Each hospital was provided with a Guideline Action Pack (GAP) which included the NHRMC approved guidelines, educational materials, health professional and consumer information, posters and reminders (Giguère 2012). Each hospital has been strongly encouraged to form a local implementation group to use the GAP materials to suit local needs.

The WISH Project has been approved by the Human Research Ethics Committee of the Women’s and Children’s Health Network, Adelaide, Australia.
Data collection, management, and analyses

For all eligible hospital sites: The 25 eligible hospital sites across Australia and New Zealand were surveyed using a web-based system in Year 1 and this has been repeated later in the intervention phases. The surveys collected information on demographic information (including participating hospital, position in hospital of respondent); local guideline information (including whether a local guideline for antenatal magnesium sulphate for fetal neuroprotection is being followed; the nature of the guideline; the availability of the guideline; methods used to release the guideline to health professionals; perceived barriers and enablers to guideline implementation); WISH Project strategies and materials (including whether a local implementation group/leader is in place; whether educational sessions have been held; and the use and usefulness of the GAP materials: PowerPoint presentation, health professional and consumer information brochures, posters and reminder hospital record inserts); and evaluation of uptake (whether a process is in place to evaluate uptake; methods used; and approximations). Questions largely provided Yes, No and Unsure options, with the opportunity to add comments. Views on WISH Project strategies and GAP materials were elicited by seeking the level of usefulness using a five-point Likert scale (very useful; somewhat useful; undecided; not really useful; not at all useful).

WISH Project outcomes for the early intervention phase (Year 1) relating to local implementation of a guideline for antenatal magnesium sulphate and WISH project strategies and materials were compared with the later intervention stages (Years 2 and 3).

For hospital sites undertaking an in-depth assessment of barriers and enablers: Face-to-face interviews were conducted with randomly selected, consenting health professionals (obstetric and neonatal) during the early phase of the intervention, and again in the later intervention phase. Interviewees were asked a range of semi-structured questions regarding their awareness and use of the magnesium sulphate clinical practice guidelines, and perceived factors influencing the uptake of this therapy (including barriers and enablers to use, and suggestions to improve uptake locally).

Qualitative data from semi-structured interviews with health professionals involved in the care of women at risk of an early birth were transcribed and grouped into themes, using one or more of the theoretical frameworks of behaviour change and motivation that have been used for analysis of barriers and enablers in the translation from ‘knowing to doing’ (Cane 2012; Michie 2011).

For hospital sites participating in the ‘WISH audit of uptake and health outcomes data collection’: All eligible women giving birth after 22 completed weeks gestation and before 30 weeks gestation (excluding known lethal congenital anomalies) at the participating hospitals were given the project information sheet and counselled by a member of the research team about participating in the project. Women were then given the opportunity to discuss their participation with their families. Informed, written consent was obtained by the research team if the woman agreed to participate in the project.

For the woman and her baby, consent to enrol in the project provided consent to access information from the maternal and neonatal clinical records. Mothers of children who survive to primary hospital discharge will be invited to complete the Ages and Stages Questionnaire at 12 and 24 months corrected age, providing information about their child’s health and development (Bricker 1995).

Information was collected from the maternal case record on maternal demographic characteristics, mode of birth, reason for preterm birth, use of antenatal corticosteroids, tocolysis, eligibility for magnesium sulphate, and whether magnesium sulphate was given. If magnesium sulphate was given, the reason for magnesium sulphate, total dose administered, gestational age given, whether loading, maintenance or repeat doses were used, and timing prior to birth was recorded together with any adverse effects. For the infant, stillbirth and death of live-born infants prior to primary hospital discharge was collected.
Information on early child health has been sought from the child health record up to two years corrected age, in liaison with the family, from any formal paediatric assessment of motor function and psychological assessment.

Project outcomes for the early phase of the project (Year 1) were compared with the later intervention phase (Years 2 and 3). The proportion of eligible women prescribed magnesium sulphate were analysed with Chi² tests (p values of 0.05 regarded as statistically significant) for the earlier period, compared with the later period. Similarly, the rates of death prior to primary hospital discharge for the earlier project period were compared with the later period. Individual adverse events were presented as average rates per woman receiving magnesium sulphate. Uptake of magnesium sulphate and rates of death prior to primary hospital discharge after birth were graphed over time to assess trends; the proportion of infants born during Year 1 with cerebral palsy (identified by age two) will be compared with proportions identified in the literature and with proportions born during Years 2 and 3.

Outcomes

**All eligible hospital sites:** Local guideline information including the proportion of eligible sites following a guideline for antenatal magnesium sulphate; evaluation of uptake, including the proportion of eligible sites evaluating uptake of antenatal magnesium sulphate; perceived usefulness of WISH Project active implementation strategies and materials, including the proportion of eligible hospital sites using the WISH GAP materials, and the proportion of hospitals that perceive the WISH GAP materials to be useful.

**In-depth assessment of barriers and enablers:** barriers and enablers to the use of antenatal magnesium sulphate as perceived by health care professionals.

**WISH audit of uptake and health outcomes:** For the three hospitals participating in the formal WISH audit, the health outcomes are:

**Primary:**
- proportion of women giving birth after 22 completed weeks gestation and before 30 weeks gestation (excluding known lethal congenital anomalies) receiving antenatal magnesium sulphate (judged to be eligible for such treatment according to the bi-national clinical practice guidelines);
- deaths prior to primary hospital discharge of babies born after 22 completed weeks gestation and before 30 weeks gestation;
- cerebral palsy at early childhood follow-up (two years corrected age) in babies born alive after 22 weeks completed gestation and before 30 weeks gestation.

**Secondary:**
- serious adverse events related to administration of magnesium sulphate therapy;
- total dose of magnesium sulphate administered per woman.

**6.5.3 WISH Project results**

The WISH Project has fostered rapid implementation of antenatal magnesium sulphate (with nearly all 25 tertiary maternity centres now reporting that they use this beneficial treatment and that they follow guidelines for its use). However substantial variation in uptake rates across sites is still evident. For example estimates from the nine sites with rates available in 2013 ranged from 56% to 100% uptake; median: 88% mean: 86% - see Figure 6.5. The uptake rates from the Women’s and Children’s Hospital (WCH) in Adelaide from 2009 to 2012 showed a steady rise from 2010 when the bi-national guidelines were released (Figure 6.6); (Middleton 2013).
We undertook further qualitative work to explore knowledge and behaviours, attitudes, experiences of health professionals and possible reasons for any evidence-practice gaps (Bain 2014d submitted). In this study, semi-structured one-to-one interviews were conducted across two time periods with health professionals from the Women’s and Children’s Hospital, Adelaide, South Australia. These comprised ‘obstetric’ (including consultant obstetricians, trainee medical officers and midwives) and ‘neonatal’ (including consultant neonatologists and trainee medical officers). The study gained ethical approval from the Women’s and Children’s Health Network Human Research Ethics Committee (REC2304/8/13).

The first phase of interviews took place from May to August 2011 (following publication of the NHMRC approved clinical practice guidelines in March 2010 and prior to dissemination of the WISH Project GAP materials), and the second phase of interviews was undertaken between August 2012 and February 2013. Randomly selected participants were asked about their practices regarding administering (obstetric staff) or advising administration of (neonatal staff), antenatal magnesium sulphate for fetal neuroprotection. The interviewers also asked participants a set of open-ended questions to explore uptake of the recommendations from the clinical practice guidelines; barriers and enablers were discussed, and views regarding possible solutions were elicited.
Interviews were transcribed verbatim with responses related to knowledge and use of antenatal magnesium sulphate tabulated and summarised narratively and using percentages. Responses relating to barriers and enablers were coded using the relevant conceptual domains of the 14-domain Theoretical Domains Framework (TDF) (Cane 2012).

In 2011, 24 health professionals were interviewed (10 obstetricians, eight midwives and six neonatologists) and in 2012-3 there were 21 participants (eight obstetricians, eight midwives and five neonatologists). Fourteen of the 45 participants were trainee medical officers. Participants from the later time period were more likely to report that they administer or advise their colleagues to administer magnesium sulphate to women at risk of preterm birth (86% (18/21) in 2012-13 versus 46% (11/24) in 2011). In 2012-13, 71% (15/21) health professionals mentioned a reduction in cerebral palsy as a benefit of treatment, compared with 54% (13/24) in 2011.

Responses regarding barriers and enablers fell into eight of the 14 TDF domains:

- The two closely aligned domains of skills and knowledge were seen as enabling (e.g. through in-service training and information for both health professionals and women).
- The domain of memory, attention and decision processes relates to factors that influence whether an individual remembers or chooses to take a particular action. This domain was often perceived as a barrier – “not thinking of it” as a consequence of being in a hurry or as a result of infrequent use, but one which participants thought could be addressed by reminders or electronic alerts.
- The main barriers related to the domain of environmental context and resources were the unpredictability of preterm birth and the time taken to prepare the magnesium sulphate solution.
- A common enabling response to the domain of beliefs about consequences was the shared belief of staff and families that magnesium sulphate could improve health outcomes, while others felt less convinced by the evidence.
- The domain of social influences usually worked as an enabler, with midwives and obstetricians advocating for and prompting the use of magnesium sulphate as “accepted best practice”.
- For the domain of professional role and identity, several neonatologists noted that administering antenatal magnesium sulphate was outside their professional role and they may not be as proactive about advocating that it be given to women at risk of preterm birth.
- The reinforcement domain relates to anticipated rewards, incentives or punishments. Two enablers were suggested by participants for this domain – audit and feedback; and establishment of a key performance indicator for hospital involvement in clinical research and uptake of new and effective research findings.

In a separate analysis, I linked the Michie Behaviour Change Wheel components of capability, opportunity and motivation (Michie 2011; Michie 2014) with health professionals’ behaviour. Obstetricians and midwives administering antenatal magnesium sulphate for fetal neuroprotection displayed high levels of opportunity and physical capability (knowledge and skills); and high motivation (i.e. preventing cerebral palsy). Social opportunity is being consolidated through strong clinical leadership and additional reinforcement through training and feedback was welcomed (Middleton 2012b; Middleton 2012c; Middleton 2014b).

Both sets of qualitative findings complement each other - and our quantitative findings of a rapid uptake of magnesium sulphate given to women at risk of preterm birth after release of the bi-national clinical practice guidelines as discussed above are also in line with the qualitative findings.

In a sub-audit of women who were eligible for antenatal magnesium sulphate for fetal neuroprotection, a significant reduction over time was seen in the proportion of eligible mothers not
receiving treatment (23/102 (23%) in 2012-13 compared with the earlier period. In 2010, lack of awareness of the clinical practice guidelines was a principal factor contributing to non-receipt. In contrast, for the majority of women not receiving magnesium sulphate in 2012-13 (19/23, 82%), birth was immediately imminent (advanced labour/rapid progression of labour) or indicated (actual/suspected maternal/fetal compromise). For three women (13%), a poor neonatal prognosis was expected (treatment declined/not indicated), and for one woman (4%), there was lack of guideline awareness by staff. For 17% (4/23) of women there was documentation that antenatal magnesium sulphate treatment was considered (Siwicki 2014; Siwicki 2014 submitted).

It was also encouraging to see that many of our implementation strategies included in the design of the WISH Project, such as reminders, key leaders and audit and feedback were suggested by staff as enablers which were already counteracting some of the barriers. Even so, barriers remain around the complexity of administering antenatal magnesium sulphate and the unpredictability of preterm birth.

6.5.4 Discussion and next steps

For this clinical application of magnesium sulphate, the first loop of the research/translation cycle has followed a fairly ‘classical’ path from problem identification/discovery through knowledge creation and synthesis, guideline development and implementation. Generating the knowledge that antenatal magnesium sulphate has a fetal neuroprotective effect took two decades (the 1990s for the animal studies and the case-control studies, and the 1990s/2000s for the human RCTs). The subsequent parts of the research/translation cycle have been comparatively quicker (taking about five years), which can be attributed to the power of synthesis, followed by a rapid guideline development process (Middleton 2010b) and an intensive implementation and audit phase (funded by the Cerebral Palsy Alliance).

In 2014, the Cerebral Palsy Alliance granted our research group further funds to follow up children from the WISH study. We plan to link data with state and national cerebral palsy registries when the first ‘WISH’ children turn five in 2016 (in addition to follow-up assessments of children at two years’ corrected age). We will test the hypothesis that optimised implementation of antenatal magnesium sulphate will increase and sustain the appropriate use of antenatal magnesium sulphate, leading to an increased chance that babies born very early will survive free of cerebral palsy. The children for follow-up in the cohort were born over a three-year period from August 2011 to July 2014. Follow-up strategies will be by parental questionnaires (Ages and Stages – Bricker 1995), medical record review and data linkage (anticipated to be the Australian and New Zealand cerebral palsy registries).

The next orbit of the cycle has already commenced - for example by addressing some of the research gaps identified during development of the clinical practice guidelines (Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). In the Guidelines we formulated seven categories of research recommendations, with considerable progress already made in three of the larger categories: individual participant data meta-analysis (IPD), further randomised controlled trials (RCTs) and audit activity other than in the WISH Project.

**IPD:** Our research group has been funded by the NHMRC to conduct an IPD in this area and we are working in collaboration with international colleagues to finalise an IPD of the five fetal neuroprotection RCTs and the single maternal neuroprotection RCT included in the antenatal magnesium sulphate fetal neuroprotection Cochrane review (Doyle 2009). IPD analysis generates knowledge which can guide more sophisticated and targeted use of antenatal magnesium e.g. optimal timing for highest neuroprotective impact and optimal regimens for minimising maternal adverse effects. The Antenatal Magnesium Individual participant data international Collaboration: Assessing the Benefits for babies using the best Level of Evidence (AMICABLE) protocol is described in AMICABLE 2012, with final results expected to be available in 2015.
**RCTs**: A RCT from our research group comparing different speeds of administering the loading dose of antenatal magnesium sulphate has already been completed (Bain 2014a), finding that a slower rate of administering the loading dose of magnesium sulphate did not reduce the occurrence of maternal adverse effects overall. However flushing and warmth 20 minutes into administration was reduced with a slower infusion rate over 60 minutes.

Another RCT from our research group (with myself as CiB) is assessing the effects of antenatal magnesium sulphate at later gestational ages than currently recommended in the bi-national guidelines. The MAGENTA trial (ACTRN12611000491965), recently funded by the NHMRC, aims to assess whether giving magnesium sulphate (compared with placebo) to women immediately prior to preterm birth between 30 and 34 weeks gestation reduces the risk of death or cerebral palsy in their children at two years’ corrected age (Crowther 2013a). Recruitment of the required 1676 babies commenced in 2012.

**Other audit activity**: The Australian and New Zealand Neonatal Network (ANZNN) now collects data on magnesium sulphate given to the mother during the six hours immediately before birth, either because of maternal pre eclampsia or specifically for fetal neuroprotection (ANZNN 2014). This will provide audit data for high-risk neonates admitted to a newborn nursery (baby was less than 32 weeks completed gestation, or < 1500 g birth weight, or received assisted ventilation or received major surgery) [www.npesu.unsw.edu.au/sites/default/files/npesu/page/ANZNN%20Registration%20criteria%2020109.pdf].

**Adverse effects (maternal and neonatal)**: A systematic review from our research group has shown that while antenatal magnesium sulphate is not associated with serious maternal adverse events, vigilance in its use is essential (Bain 2013a). We are also collaborating with Canadian colleagues on a systematic review of adverse effects of antenatal magnesium sulphate on neonates.

**Other progress in addressing research gaps by our group and other groups**:

- Melatonin and creatine are being investigated as other antenatal interventions to prevent cerebral palsy, with pre-clinical and early human studies underway (Alers 2013; Dickinson 2014; Miller 2014; Wilkinson 2013) and use of erythropoietin in newborns is the subject of a randomised controlled trial recently funded by the NHMRC (ACTRN12614000669695).
- School-age follow up of children from the Crowther 2003 RCT of antenatal magnesium sulphate for fetal, infant and child neuroprotection has been published (Doyle 2014).
- A study of the fetal neuroprotective mechanisms of magnesium sulphate, led by Professor Crowther in New Zealand has been funded by the New Zealand Health Research Council.
- The Adelaide Cerebral Palsy Group is undertaking a number of genetic studies of cerebral palsy (McMichael 2014).

**Comparisons with other clinical practice guidelines (CPGs)**

Guidelines containing recommendations for antenatal use of magnesium sulphate for fetal neuroprotection have subsequently been published in North America and the UK. While Canada and US CPGs (ACOG 2012; SOGC 2011) support the use of magnesium sulphate for this indication, a scientific impact paper from the Royal College of Obstetricians and Gynaecologists (RCOG 2011) is less supportive. Reasons stated for UK clinicians not changing their practice are that large numbers are needed to treat for benefit and the possibility of adverse neonatal outcomes following antenatal magnesium sulphate administration. However the RCOG paper does acknowledge that the synthesis of studies shows a clear reduction in cerebral palsy with magnesium sulphate and notes that the “Australian guideline from the Adelaide group provides a well-reasoned, practical guide on which to base local clinical guidelines”.

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The Canadian evidence-based guidelines recommend administration of antenatal magnesium sulphate for fetal neuroprotection up to 32 weeks gestation (SOGC 2011) in contrast to the Australian and New Zealand recommendation of up to 30 weeks gestation. The relevant US guidelines also specify a 32 week threshold but instead of a formal recommendation state that “Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials” [i.e. Crowther 2003 or Rouse 2008] (ACOG 2012). The Canadian group have also shown antenatal magnesium sulphate for fetal neuroprotection to be a cost-effective strategy with a saving of $1.5 million for each case of cerebral palsy averted (Bickford 2013).

Several groups in the US and Australia have recently published rates of uptake of antenatal magnesium sulphate for fetal neuroprotection, all noting the feasibility of implementation. In the first year after the Australian and New Zealand CPG was released, a Melbourne tertiary maternity hospital reported a 45% uptake rate (Ow 2012) and Tan 2014 recently reported an 82% uptake rate for a New Zealand tertiary maternity hospital. In the three years after implementation, one US centre reported a 95% uptake of magnesium sulphate for eligible women with pre eclampsia, preterm labour, or preterm prelabour rupture of membranes whereas women giving birth preterm due to fetal growth restriction received magnesium sulphate less than half the time (44%) (Gibbins 2013). Another US centre found 75% uptake for eligible women and reported current barriers to be short time frame from presentation to birth, unanticipated birth and treatment not considered by healthcare provider (Meyer 2014). Making editorial comment on the Gibbins 2013 audit report, Repke 2013 highlighted the importance of, and need for, professional solidarity as perinatal health professionals move towards greater adoption of national protocols.

6.6 Overall conclusions

This case study of implementation of antenatal magnesium sulphate for fetal, infant and child neuroprotection shows that translation of knowledge into policy and practice action and behaviour change is often complex and lengthy, even with compelling evidence of effectiveness.

However our planned implementation process, starting with the translational flashpoint achieved by the Doyle 2009 Cochrane systematic review, demonstrates that translation from the synthesis stage can be managed and fast-tracked. Our rapid yet rigorous development of Australian and New Zealand guidelines shortly after conclusive evidence of the effects of antenatal magnesium sulphate on fetal neuroprotection became apparent in 2009, has been crucial to implementation into practice in these two countries by producing actionable policy and practice recommendations. These guidelines have recently been highlighted by the NHMRC as robust and trustworthy guidelines that are making a difference (Ghersi 2015). The WISH Implementation Project has provided tools and strategies to turn these recommendations into behaviour change at the health system and individual health professional level. It is also using behaviour change theory to understand the implementation barriers and enablers and to change systems and processes accordingly.

In less than five years, with the support of the bi-national WISH implementation program, use of antenatal magnesium sulphate for this indication has risen from practically nil to an estimated uptake of at least 70% across Australia and New Zealand. Work is continuing on addressing research gaps identified in the Australian and New Zealand guidelines, such as follow-up of cerebral palsy rates and an RCT to assess whether the neuroprotective effects of magnesium sulphate also extend to antenatal administration at later gestational ages.

Results of the WISH Follow-up Study will indicate whether the high uptake of appropriate use of magnesium sulphate for fetal, infant and child neuroprotection is sustained in future years across Australia and New Zealand – and mostly importantly whether uptake translates into reduced rates of cerebral palsy and improved survival free of disability.
Chapter 7
Concluding remarks

My overall aim was to investigate the contribution made by Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health to improvements in the health and wellbeing of women, babies and their families in Australia and internationally; and to inform future strategies for improving translation and implementation of research into health impacts.

I met my specific aims by:

- using bibliometric and social network analysis to assess the impact of the findings from Australian randomised controlled trials and Cochrane systematic reviews in maternal and perinatal health (Chapter 2).
- determining triallists’ views about what impact their research has made or is making, and exploring factors influencing behaviour change and impact (Chapter 3).
- assessing how knowledge has been generated, synthesised and implemented and commenting on the interaction between these processes and their impact on clinical practice and on health outcomes in three key areas: gestational diabetes mellitus, stillbirth and cerebral palsy (Chapters 4-6).
- summarising my findings then using this new knowledge to propose extensions to the research/translation cycle outlined in Chapter 1 to become a research, translation and impact cycle; and proposing strategies for improving the translation and implementation of new and synthesised knowledge to maximise health impact.

A summary of my findings and their implications follows. I then detail the steps of the expanded research, translation and impact cycle and the strategies for enhancing the processes involved. Finally I outline priorities for further research.

7.1 Summary and significance of findings

In the bibliometric analyses of Chapter 2, higher citation rates of my 1986-2010 cohort of 306 randomised controlled trials were associated with multicentre design, larger sample sizes, trials which reported positive findings, NHMRC or similar funding, publication in high impact journals, and inclusion in Cochrane systematic reviews and clinical practice guidelines. Larger sample sizes showed similar associations, except for a link with maternal focus but no association with positive findings.

In the 2011-2014 cohort, trials had substantially larger sample sizes, numbers of multicentre trials and funding success compared with 1986-2010. This may be an indication of greater collaboration and stronger trials network development. Many Cochrane systematic reviews with one or more Australian authors and/or including Australian maternal and perinatal randomised controlled trials are scoring well in emerging citation and social media systems such as Altmetric. These systems tap into diverse dissemination and translation sources and are revealing the diversity of audiences interested in evidence-based material.

In Chapter 3, blockages were apparent early in the research/translation cycle with triallists reporting that they thought their fellow health professionals knew about their trial findings only 50% of the time, and when trial results were known, there was often relatively low confidence in the findings. Lack of skills was not seen to be a significant issue, and fewer trials than expected were perceived to have implementation barriers. The survey data indicated that it was common for the process of translation to be disrupted quite early, even commencing at the knowledge creation stage. There is lack of clarity about who is responsible for translation and implementation, with some triallists evincing little interest in being involved in these processes.
There were links between trialists’ ratings of uptake and impact and trial characteristics and impact. The strongest correlations with impact were for multicentre trials, and the trial being cited in a clinical practice guideline. Uptake was associated with trials having NHMRC funding, sample sizes greater than 100, positive findings and being included in a Cochrane review, but these did not extend or flow on to associations with perceived impact on health outcome.

Chapter 4 illustrates how an important research gap could be closed which then paves the way to progress further through the research/translation cycle to the next step (in this case, postnatal lifestyle management). Women who have experienced gestational diabetes are increasingly more aware of its long term consequences, including the future health of their children. Postpartum care of these women is often inadequate and/or disjointed, with many women not undertaking a glucose tolerance test for diabetes, a vital step in their postpartum management. A strategy to alert and remind women to undertake this test is therefore an important part of care for these women and part of the process to reduce the risk of future type 2 diabetes as well as gestational diabetes in any subsequent pregnancies.

Chapter 5 shows that stillbirth is poorly reported in randomised controlled trials and research syntheses, leading to knowledge about effective preventative interventions being obscured. Stillbirth has not been a research or policy priority despite being more common than neonatal mortality. The two ‘high income’ papers from the 2011 Lancet Stillbirth Series (Flenady 2011a; Flenady 2011b) have been well cited and many of these citations indicate or advocate implementation of improved care and management practices. However the majority of the citations serve ‘academic’ purposes only. If citations with potential for high impact were rated more highly than other citations, this would have considerable ramifications for research measurement exercises and related metrics such as profiles of individual researchers, grant peer review and academic promotion parameters. The next steps in the research/translation cycle are to keep “bringing stillbirth out of the shadows”; to reduce stillbirths; to improve investigation and management practices; and to work to close disparity gaps.

The antenatal magnesium sulphate for fetal, infant and child neuroprotection story in Chapter 6 shows that translation of knowledge into policy and practice action is often complex and lengthy, even with compelling evidence of effectiveness and rapid development of actionable knowledge (in this case clinical practice guidelines). However it is also a demonstration that translation and implementation can be fast-tracked by ensuring that the steps in the research/translation cycle are planned and executed as soon they can be; and that implementation barriers are pre-empted and addressed. The WISH Project has been highly successful in increasing uptake using a variety of implementation strategies and using behaviour change theory to address implementation barriers.

Over a decade ago, the then National Institute of Clinical Studies (NICS) concluded that translation and implementation of research into practice is a difficult process (Easton 2003). Nonetheless, in this survey, recipients of NHMRC grants (in cancer, heart failure, venous thromboembolism prophylaxis, pressure area care, pain management and emergency department care) reported that 15 out of 63 (24%) grants had resulted in some form of translation into practice – practice changes, clinical practice guidelines or action by decision makers. Consistent with my findings, future confidence was highest when many researchers were involved in a study and reduced when resistance to change was encountered, or when findings were interim or needed replication. NICS survey respondents believed that translation and implementation were ultimately their responsibility but identified similar barriers to my respondents. These barriers included need for funding, support from implementing organisations and not knowing where to go to gain these supports.

Cohen and colleagues have recently designed and applied an impact assessment tool covering corroboration, attribution, reach, and importance, with broadly similar findings to those of Easton 2003 (Cohen 2015). Nineteen (38%) of their 50 cases (NHMRC-funded research) were judged to have ‘real world’ impact, which was assessed through survey methods and triangulated with documentary
analysis. Of these 19, six cases (12% overall) were judged to have high impact. In my study, triallists’ self-rating of high impact was nearly double at 21%. Further work and direct comparison of methods would be required to establish whether Australian maternal and perinatal randomised controlled trials have higher than average impact or whether triallists’ ratings may be influenced by a degree of ‘optimism’ bias.

In late 2014, Dembe and colleagues published their Translational Research Impact Scale (TRIS) to measure “the true value of research” in a consistent way (Dembe 2014). Still in development and yet to be tested in the field, the TRIS comprises 72 impact indicators across three broad research impact domains. Many of the impact indicators particularly in Domain 2 (translational impacts) and Domain 3 (societal impacts) address both the assessment of ‘real world’ impact and health professional, health user and health system behaviours. Hanney and colleagues have also proposed a ‘process marker’ model to measure and understand time lags in translation in policy and practice and move away from a focus on “an increasingly complex series of translation ‘gaps’” (Hanney 2015) which shares some of the features of a research translation and implementation cycle.

Finding a robust way to measure research impact and better still, to be able to shape research and implementation throughout the cycle has remained elusive. As one of the architects of the Payback model has stated “The ‘holy grail’ is to find short term indicators that can be measured before, during or immediately after the research is completed and that are robust predictors of the longer term impact or payback from the research” (Buxton 2011). Perhaps four years later, we are a little closer to finding ways to measure and increase impact of health research on health outcomes.

7.2 Incorporating impact: the research, translation and impact cycle

Without a focus on impact, translation of research may stop too short. Using a research, translation and impact cycle (Figure 7.1) can explain, predict and even shape the processes of practice and policy change and impact on health. The cycle can be used at different scales – ranging from small components of larger questions (such as increasing uptake of postpartum glucose tests to detect type 2 diabetes) to mapping what needs to be done to prevent stillbirth.

As suggested by El-Jardali 2015, the whole process of research and translation ideally needs to be driven from the start by intended or desired impacts. Implementation in particular needs to be underpinned by behaviour change theory, so that effective interventions are not blocked by poor uptake. The same teams do not have to carry out all stages, but coordination, collaboration and embedding of translation processes in health services will help accelerate the transfer of research into practice.

I found the Behaviour Change Wheel (Michie 2014) and the Theoretical Domains Framework (Cane 2012) helpful in increasing understanding of the behavioural patterns of health professionals described in the survey in Chapter 2 and in the WISH Project outlined in Chapter 6. Use of a theoretical framework pinpointed that skills (an aspect of capability) and desire to improve health outcomes (a component of motivation) were enabling implementation. Knowledge (another aspect of capability) was not optimal overall, but was high for the specific area of antenatal magnesium sulphate for fetal neuroprotection. The theoretical framework also identified barriers in reflective motivation (e.g. remembering to administer magnesium sulphate in a busy antenatal environment) and in opportunity (e.g. unpredictability of when preterm birth will happen; and time taken to prepare the magnesium sulphate solution). Thus specific barriers are linked with specific behaviours and system characteristics, which can then be analysed to see what is feasible to change and thus increase uptake and impact.

Steps of the research, translation and impact cycle (see Figure 7.1)

As shown by the examples discussed in this thesis, not all steps of the cycle will apply to every example of implementation (e.g. trial results sometimes are prematurely implemented before being
included in a systematic review or clinical practice guideline), steps may not happen in the order outlined below and iterations through the cycle may follow different patterns. Nonetheless this type of simple schema can help to guide researchers and implementers through the translational processes.

**Step 1: Question identification**

In this step, the aim is to ask the right set of questions, where answers can ultimately have important impacts on health outcomes. In Chapter 3 I have shown that we are not always asking the right questions and perhaps have wasted resources on trying to address some of the less important questions. Although priority setting is much discussed at present, it remains contentious, with some researchers concerned about lack of funding for topics not designated as priorities by national or other bodies. It is essential for the maternal and perinatal community to work with parents and other community members throughout the cycle but particularly in identifying the most important questions to answer. The recent formation of a Consumer Advisory Panel within the Perinatal Society of Australia and New Zealand is a very positive development.
Step 2: Knowledge creation
Encouraging better quality in design of trials, optimising recruitment and providing infrastructure support for multicentre trials are some ways to reduce waste and uncertainty (Ioannidis 2014b) and help implementers to distinguish between true null trials and underpowered trials. Lifestyle interventions often present challenges in design and interpretation. Advances in using behavioural change theory in design and conduct of lifestyle studies need to be taken up by triallists and further developed. In Chapter 2 we saw some concerning evidence of ‘chasms’ between maternal and perinatal research groups (e.g. between public health researchers and clinical researchers). If these chasms remain, there will continue to be adverse effects on trial design and how new knowledge is created. Behavioural aspects such as lower rates of belief and trust in results generated outside particular disciplines or even geographic areas also need to be addressed.

Step 3: Knowledge synthesis
As for step 2, Knowledge creation, it is important that the right questions are addressed by systematic reviews and that these reviews are kept up to date. It is crucial that syntheses also use the best available methods and comply with standards such as core outcomes, because syntheses ought to be the main currency of translation. Complex interventions, including many lifestyle interventions, often prove hard to synthesise and interpret. Developments in reporting and integrating complex behavioural interventions need to further developed and used in the knowledge synthesis stage.

Step 4: Making knowledge actionable
In this step, knowledge, ideally already synthesised, needs to be made implementation ready. In clinical practice guidelines, this is often done by developing recommendations that take into account not only the evidence, but also values and context, and anticipated impact on health outcomes. There are equivalent processes than can be adopted for other types of policy documents and policy dialogues. Accumulated uncertainties can make this step very difficult, so time and resources are required for the extensive consultations and discussions that are required. While implementation is a separate stage in the research, translation and impact cycle, policy development needs to consider implementation implications across systems and anticipate potential barriers to uptake.

Step 5: Implementation
This step can involve preparation of an implementation plan and perhaps formal studies to assess implementation strategies. Implementation science is a young but growing field, with knowledge about behaviours (of health professionals and health users), and how to change these, at its core. As the interface between research and practice/policy, implementation has to navigate the sometime difficult areas of entrenched systems and vested interests (financial or otherwise). Despite the many challenges, implementation must be carefully designed and conducted and regarded (and funded) as an important endeavour in its own right and not an optional ‘tack-on’.

Step 6: Audit and feedback
The audit step is crucial in closing the first loop of the research, translation and impact cycle. For both uptake and outcomes, the optimal situation would be provision of relevant data as soon as it is generated, so that progress towards desired change can be monitored and that changes made iteratively to improve impact. Further development of tools for measuring impact will assist the audit and feedback step and have the potential to drive further rotations of the research, translation and impact cycle.

7.3 What’s still to be done?
Further work is required on how to improve conduct and efficiency of trials (e.g. improved recruitment and collaboration) and in monitoring trial characteristics and performance. We need to understand the potential (and limitations) of hybrid bibliographic/social network systems for
knowing who is using research findings and how this might influence future impact. There is a need for more qualitative research on the motivations of researchers and users of research. More economic analyses, assessing returns on investment, are also required.

Null study results can present large challenges for implementation and the development of more standardised approaches is likely to aid the processes of translation. Lifestyle interventions were raised as an area (generally in the triallists’ area and specifically in diabetes prevention and reducing stillbirth) where translation can be problematic and where achieving behaviour change is often difficult. Thus there is a need for greater knowledge about designing interventions and implementing them, using behaviour change theory and designing interventions that are feasible and acceptable to women and families.

Stillbirth is an under-researched area, requiring higher priority from researchers, funders and policymakers. This will not be successful without attitudinal changes from carers, parents and the wider community. Understanding and reducing disparity in stillbirth (and other perinatal outcomes) must also be a high priority.

In the case of antenatal use of magnesium sulphate for fetal neuroprotection, the Australian and New Zealand clinical practice guidelines have provided a roadmap of research priorities, with many of the suggested studies underway. Further work on behaviour change will aid implementation, as will ways to efficiently feedback uptake and outcomes to health care professionals.

Assessment of research and its impact is of great interest to many parts of the research community. It is becoming clearer that the traditional tools are not adequate to do this and newer systems and tools such as the Translational Research Impact Scale need to be field tested and refined. This may have substantial ramifications for assessing the research performance of individuals and grant success, but more importantly, may allow us to improve design of research and its impact on societies and systems.

In my thesis, I have shown that while much maternal and perinatal research in Australia has contributed greatly to better health and better health systems, the processes in the research, translation and impact cycle can be vastly improved. I have outlined ways to make research more implementation ready and demonstrated how coordinated approaches can rapidly and effectively influence uptake and impact. I trust that my work will contribute to further debate, discussion and development of more rapid and robust ways to assess ‘real world’ impact on health and wellbeing.
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