


## ORIGINAL RESEARCH

# Supplemental prophylactic intervention for chemotherapy-induced nausea and emesis (SPICE) trial: Protocol for a multicentre double-blind placebo-controlled randomised trial

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### Abstract

**Aim:** There is significant recent interest in the role of ginger root (*Zingiber officinale*) as an adjuvant therapy for chemotherapy-induced nausea. The supplemental prophylactic intervention for chemotherapy-induced nausea and emesis (SPICE) trial aims to assess the efficacy by reduced incidence and severity of chemotherapy-induced nausea and vomiting, and enhanced quality of life, safety and cost effectiveness of a standardised adjuvant ginger root supplement in adults undergoing single-day moderate-to-highly emetogenic chemotherapy.

**Methods:** Multisite, double-blind, placebo-controlled randomised trial with two parallel arms and 1:1 allocation. The target sample size is  $n = 300$ . The intervention comprises four capsules of ginger root (totalling 60 mg of active gingerols/day), commencing the day of chemotherapy and continuing for five days during chemotherapy cycles 1 to 3. The primary outcome is chemotherapy-induced nausea-related quality of life. Secondary outcomes include nutrition status; anticipatory, acute and delayed nausea and vomiting; fatigue; depression and anxiety; global quality of life; health service use and costs; adverse events; and adherence.

**Results:** During the five-month recruitment period from October 2017 to April 2018 at site A only, a total of  $n = 33$  participants ( $n = 18$  female) have been enrolled in the SPICE trial. Recruitment is expected to commence at Site B in May 2018.

**Conclusions:** The trial is designed to meet research gaps and could provide evidence to recommend specific dosing regimens as an adjuvant for chemotherapy-induced nausea and vomiting prevention and management.

**Key words:** cancer, chemotherapy, ginger, nausea, randomised controlled trial, vomiting.

### Introduction

Despite significant advances in anti-emetic therapy, chemotherapy-induced nausea (CIN) is a persistent problem

for many chemotherapy patients. Combination anti-emetics now manage vomiting well but control of nausea, which affects over 66% of chemotherapy patients, is elusive.<sup>1</sup> Defined as an unpleasant, subjective feeling of discomfort associated with the need to vomit, symptoms of nausea include queasiness, headaches, dizziness and discomfort or pain in the stomach, back or throat.<sup>2</sup> Recent research has suggested the burden of CIN could be cumulative with each chemotherapy cycle.<sup>3</sup> As well as contributing to poorer quality of life (QoL), social wellbeing and health care costs,<sup>1,4,5</sup> CIN often inhibits food intake, influencing malnutrition rates of up to 50–60% in chemotherapy patients.<sup>6,7</sup> In turn, malnutrition adversely affects important clinical outcomes such as the ability to complete the chemotherapy regimen and ultimately, survival.<sup>8</sup>

There is significant recent interest in the role of ginger root (*Zingiber officinale*) as an adjuvant therapy to decrease

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the incidence and severity of CIN and vomiting (CINV).<sup>9,10</sup> While the exact mechanism of action is unknown, available evidence suggests multiple active constituents within ginger (particularly gingerols and shogaols) beneficially affect CIN pathways.<sup>11–13</sup> Ginger is believed to impose antagonistic effects on 5-HT<sub>3</sub>, muscarinic and histaminergic receptors; regulate gastric emptying and gastrointestinal motility; and play a role in reducing oxidative stress and inflammation.<sup>11</sup>

Recent systematic reviews<sup>9,10</sup> identified seven clinical studies that investigated supplemental ginger to treat CIN. These identified promising evidence to support the use of adjuvant ginger in the chemotherapy setting. However, the reviews identified major limitations in existing research approaches. These limitations included failure to record the emetogenicity of the chemotherapy regimen, the use of non-standardised supplements, small sample sizes, failure to consider potential confounding variables, scant information about how well patients tolerate ginger in this context and dosing regimens not cognizant of the pharmacokinetics of ginger. These limitations preclude the routine use of ginger in the clinical chemotherapy setting.

Informed by a pilot RCT,<sup>14,15</sup> the RCT outlined in this protocol aims to assess the efficacy (reduced incidence and severity of CINV, enhanced QoL), safety and cost effectiveness of a standardised adjuvant ginger root supplement in adults undergoing single-day moderate to highly emetogenic chemotherapy.

## Methods

This protocol for the supplemental prophylactic intervention for chemotherapy-induced nausea and emesis (SPICE) trial, which is a multisite, double-blind placebo-controlled randomised study with two parallel arms and 1:1 allocation, is reported according to the SPIRIT 2013 Statement<sup>16</sup> and CONSORT 2010 Statement.<sup>17</sup>

The SPICE trial is undertaken according to the National Health and Medical Research Council's (NHMRC) National Statement of Ethical Conduct in Human Research (2007),<sup>18</sup> the NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)<sup>19</sup> and the CPMP/ICH Note for Guidance on Good Clinical Practice.<sup>20</sup> All patients who meet the selection criteria will be invited to participate via written informed consent. In those cases where informed consent cannot be obtained, the patient is not eligible for inclusion. To maintain good clinical practice, any patient identified as malnourished (Patient-Generated Subjective Global Assessment (PG-SGA) rating B or C) at baseline will be referred to the usual care dietitian at the site for medical nutrition therapy. Ethics approval for the SPICE trial has been obtained from the Metro South Human Research Ethics Committee (reference: HREC/17/QPAH/333) and the Bond University Human Research Ethics Committee (reference: 0000016144). The SPICE Trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12616000416493p) and Therapeutic Goods Administration (Clinical Trial CT-2017-CTN-02280-1 v2) in Australia.

Participants are prospectively and consecutively recruited from the cancer care units at two hospitals in Brisbane, Queensland, Australia, from October 2017 to April 2019. Participant eligibility criteria are outlined in Table 1.

The primary outcome variable is CIN-related QoL measured by the Functional Living Index – Emesis (FLIE). Informed by pilot data ( $n = 51$ ), the FLIE score (mean (SD) score:  $54 \pm 13$ , with an expected effect size of seven<sup>14</sup> between control and intervention groups, suggests a minimum of 246 participants ( $n = 123$  per group) are required (90% power; type I error of  $\leq 5\%$ ; two-tailed), allowing for 30% attrition and 15% for multivariable modelling. To ensure the power of the study for both the primary and secondary variables, a sample size of 246 will be considered acceptable, with a target sample size of 300 allowing for attrition considered desirable.

Participants will be randomised into intervention and placebo groups (1:1) using the method of minimisation, stratified by chemotherapy category (moderate vs high emetogenicity), gender, age ( $<55$ ,  $\geq 55$  years) and by facility site. The randomisation process is to be managed by an independent third party (biostatistician at the NHMRC Clinical Trials Centre, University of Sydney). The biostatistician will notify the research assistant by telephone or email of the blinded number on the supplement label of each patient only after participants are deemed eligible.

To ensure blinding of participants, supplement and placebo capsules are overencapsulated with a non-gelatin capsule and labelled by an independent third party, using a blinded sequence supplied by the biostatistician, prior to delivery to the study sites. All researchers involved in recruitment, implementation, data collection and analysis will be blinded to the allocation until all study data collection has been completed. The overencapsulated supplement and placebo capsules are identical in appearance. All participants will be provided the supplement or placebo in identical glass bottles of 60 capsules with a single desiccant for use throughout the entire treatment period. At the end of the treatment period for each cycle, the research assistant will contact each participant to obtain their perceptions of which group they were allocated to. This will determine the adequacy of the study's blinding procedures.

The experimental treatment is a non-synthetic standardised ginger root extract manufactured by Bluebonnet Nutrition Corporation (Sugar Land, TX, USA). This preparation is in capsule form, standardised to contain 5% gingerols (15 mg active ingredient per capsule). High-performance liquid chromatography analysis will be completed within the last three months of the study on the supplement product and compared to the manufacturers Certificate of Analysis (dated 16 January 2017) to ensure the active ingredient was stable throughout the study period. Participants in the intervention group will be prescribed a regimen of four capsules per day (60 mg gingerols in total), which is expected to maintain a peak serum concentration of primary ginger compounds as demonstrated in pilot data.<sup>15</sup> The four capsules will be consumed at regular intervals throughout the day with food (e.g. breakfast, lunch, afternoon tea, dinner)

**Table 1** SPICE trial participant eligibility criteria

<i>Inclusion criteria</i>	<i>Exclusion criteria</i>
Chemotherapy-naïve patients (no prior history of chemotherapy).	Concurrent radiotherapy.
Scheduled for chemotherapy classed as moderately or severely emetogenic.	Non-English speaking persons.
Scheduled for single or combined agent single-day chemotherapy regimen repeated in two, three or four-week cycles. <sup>2</sup>	People with severe cognitive impairment preventing their ability to fully understand the purpose of the study, adhere to the intervention and complete data collection forms.
Aged >18 years.	Pregnant or lactating women.
Adequate physical function: baseline Karnofsky score > 60.	Concurrent use of other ginger-containing supplements and ingestion of any amount of fresh or dried ginger from 24 hours prior to chemotherapy to 7-days post-chemotherapy (cycles 1–3). <sup>3</sup>
	History of adverse reactions to ginger.
	Experiencing significant nausea and vomiting for reasons other than chemotherapy including:
	Prescribed medications with nausea-related side-effects, e.g. newly-prescribed opioids.
	Diagnosed with malignancies that might cause nausea and vomiting due to the position of the cancer e.g. gastrointestinal cancer.
	Metabolic risk factors for nausea e.g. electrolyte imbalances.
	Mechanical risk factors for nausea e.g. intestinal obstruction.
	Chronic alcohol use as indicated by >14 standard drinks per week (exceeding Australian Guidelines to Reduce Health Risks from Drinking Alcohol; predictive factor for decreased CIN risk). <sup>21,22</sup>
	Severe thrombocytopenia or likely to experience severe thrombocytopenia (platelets <50 × 10 <sup>9</sup> /L) (medical note observation).
	Gallstones or liver disease (including liver cancer).
	Prescribed warfarin, anti-coagulant therapy, hypoglycaemics, insulin, cyclosporine, tacrolimus, and nonsteroidal anti-inflammatory drugs.
	Swallowing difficulties preventing supplement ingestion.
	Self-prescribed nausea therapies or complementary products.

<sup>1</sup> Moderate to highly emetogenic chemotherapy regimens informed by the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) guideline from the Perugia consensus conference.<sup>23</sup>

<sup>2</sup> Includes regimens with more than one type of chemotherapy agent delivered in single day doses ≥7 days apart (e.g. as with AC-T regimens used in the treatment of breast cancer whereby cyclophosphamide and doxorubicin are administered on day one of the treatment cycle and paclitaxel is administered on Days 1, 8 and 15 of a 21-day cycle).

<sup>3</sup> Patients who plan to consume ginger during this period will be excluded from eligibility. However, once consented and commenced the intervention, participants who consume any ginger other than the study product will be included and concurrent consumption of oral ginger will be accounted for statistically. Participants will be regularly reminded to avoid consuming ginger and asked about any purposeful or incidental consumption.

wherever possible; however, if adherence is difficult, patients may take two capsules in the morning and two in the afternoon. Capsules will be consumed daily in addition to usual diet. The usual diet is unmodified, although participants will be advised to consume no fresh ginger or ginger-containing products. The placebo capsules given to the control group contain 150–200 mg of the inner filler microcrystalline cellulose and will be prescribed the same dosing regimen as the intervention group. Supplementation will begin on the day of chemotherapy (Day 1 of each cycle) and continue for four days post-chemotherapy, that is, a supplementation period of five days (Days 1–5). This will be repeated for the first three chemotherapy cycles; so

that participants will consume a total of 60 capsules during the treatment period.

Anti-emetic medications prescribed by medical teams are permitted during the trial. These include, but are not limited to, 5-HT<sub>3</sub> antagonists (e.g. ondansetron), corticosteroids (e.g. dexamethasone) and NK-1 receptor antagonists (e.g. aprepitant).

Outcomes will be assessed at baseline (T0; >5 days prior to chemotherapy), 1 day prior to chemotherapy (T1), on the day of chemotherapy (T2), 4 days post-chemotherapy (T3) and 5–8 days post-chemotherapy (T5) for three chemotherapy cycles, as detailed in Table 2. Time points T1–T4 will be repeated for each chemotherapy cycle. Data

**Table 2** Study procedure and time points in the SPICE trial

<i>Study procedure</i>	<i>T0 (baseline)</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	<i>T4</i>
Time in CTX cycle	>5-days pre- CTX	Day before CTX	Day of CTX	4-days post-CTX	5–8 days post-CTX
CTX cycle	1 only	1,2 and 3	1,2 and 3	1,2 and 3	1,2 and 3
Method of data collection	Patient interview	Telephone interview	Patient interview	Telephone interview	Telephone interview
Screened and consented	✓ <sup>1</sup>				
Participant characteristics	✓ <sup>1</sup>				
Delivery of supplements	✓				
Delivery of Participant Booklet	✓				
Nutrition status (Scored PG-SGA)	✓ <sup>1</sup>		✓ (Cycles 2 and 3 only)		
Supplements consumed					
CIN-related QoL (FLIE-5DR)		✓		✓	
Global QoL (EQ-5D-5 L)		✓		✓	
Anticipatory nausea and vomiting		✓			
Nausea and vomiting (MAT)			✓ <sup>2</sup>	✓	
Depression and anxiety (HADS)			✓		
Fatigue (FACIT-F)			✓		✓
Health service use				✓ <sup>1,3</sup> (Cycle 3 only)	
Assessment of blinding and adherence					✓ <sup>4</sup>
Assessment of concurrent ginger intake	✓	✓	✓	✓	✓
Adverse events					✓ <sup>1</sup>

<sup>1</sup> Data used to inform this outcome also obtained from observation of medical record and/or discussions with treating multidisciplinary team.

<sup>2</sup> Should be completed at the end of the day of, or on the day after chemotherapy.

<sup>3</sup> Data used to inform this outcome also obtained from data registries.

<sup>4</sup> Data also obtained by return of supplement bottles containing unused supplements.

CTX, chemotherapy; EQ-5D-5L, EuroQol's five dimension, 5-level scale; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FLIE-5DR, Functional Living Index Emesis 5 Day Recall; HADS, Hospital Anxiety and Depression Scale; MAT, Multinational Association for Supportive Care in Cancer (MASCC) Anti-emesis Tool; PG-SGA, Patient Generated Subjective Global Assessment.

collection will be in person via interview at the hospital for baseline data; however, subsequent data will be collected via a participant booklet containing all questionnaires, which the participant takes home. The participants will be given the instructions to complete the assessment tools either alone or via telephone interview with the research assistant according to the participants' preference and needs.

Participant characteristics will be collected by patient medical notes, the participant booklet and patient interview. The participant characteristics and potentially confounding variables to be recorded include age, gender, English as a first language, highest level of education attained, ethnicity, country of birth, type of primary cancer diagnosis, type of secondary cancer diagnosis, other medical diagnoses, previous cancer diagnosis followed by remission, medications including anti-emetic dosing schedules, supplements, surgical history, alcohol use and previous experience with nausea and vomiting. Concurrent ingestion of ginger-containing products will be recorded using participant interviews at each time point. Adherence to the supplementation protocol will be assessed by collection of supplement containers. All unused supplements will be collected after T3 of the third and final chemotherapy cycle.

All tools in the SPICE trial are recognised as valid, reliable and feasible in the cancer setting and this protocol has been successfully piloted by the research team.<sup>15</sup> The primary outcome is CIN-related QoL measured by the Functional Living Index – Emesis – 5 Day Recall (FLIE-5DR). The FLIE-5DR is a validated nausea and vomiting-specific self-reported outcome measure that investigates the specific impact of chemotherapy-related nausea and vomiting on patients' activities of daily living.<sup>1</sup> It has a total of 18 items; nine items in each of the nausea and vomiting scales, the first item of which rates the extent of nausea or vomiting experienced in the previous five days. The remaining items examine patients' social, recreational and leisure activities, their ability to undertake normal tasks, their enjoyment of eating and drinking and the hardship caused by their nausea and vomiting on themselves and their carers. Each response is ranked on a 7-point scale. The FLIE score is determined by summing the responses to the nine questions in each scale. Therefore the range of total scores possible per scale is 9 to 63, with a higher score corresponding to less hardship and less impact of nausea or vomiting on daily life.<sup>1</sup> No or minimal impact on daily life is defined as an average FLIE item score of more than 6 on the 7-point scale or a total FLIE score of more than 54.<sup>1</sup> The FLIE has

excellent internal reliability, with a Cronbach's  $\alpha > 0.90$  for both subscales on all assessment points.<sup>24,25</sup>

Secondary outcomes are nutrition status, incidence of nausea and vomiting, anxiety and depression, fatigue, QoL, health service use and costs and changes to the gastrointestinal microbiota. The impact of participants' nutrition status will be measured via patient interview and physical assessment using the valid and reliable scored Patient-Generated Subjective Global Assessment (PG-SGA)<sup>26</sup> by the research assistant (an Accredited Practising Dietitian) who is blinded to participant allocation. The scored PG-SGA provides a global rating of either A (well nourished), B (suspected or moderately malnourished) or C (severely malnourished) as well as a continuous score, with typical scores ranging from 0 to 30. A higher score reflects a higher risk of malnutrition, more nutritional symptoms and an increased need for nutrition intervention and symptom management.

The EQ-5D-5 L will measure health-related QoL. The EQ-5D-5 L considers five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses are coded and converted to a single index value, which is country-specific. The 5-level version of the EQ-5D (termed EQ-5D-5L) has better sensitivity and reliability in cancer patients than the original tool, while ensuring less participant burden.<sup>27</sup>

Acute and delayed nausea and vomiting will be assessed by the Multinational Association of Supportive in Cancer Anti-emesis (MAT) tool, which considers the day of chemotherapy and four days after chemotherapy. Questions refer to the occurrence, duration and frequency of delayed nausea and vomiting. The total sum of all items allows for possible scores of 4 to 48, where higher scores indicate more severe nausea and vomiting. The MAT has good validity and reliability and entails low participant burden.<sup>28</sup> To capture anticipatory nausea and vomiting, the questions of the MAT will be adapted into a new questionnaire specific to the SPICE trial. The questionnaire will have four questions, with two binomial 'yes/no' questions and two Likert scale questions (rated 0–10). Each question will reflect the nausea and vomiting experienced in the 24 hours before the commencement of chemotherapy, and scoring will match that of the MAT.

As anxiety and depression are predictive factors for CINV,<sup>22,29</sup> the Hospital Depression and Anxiety Scale (HADS) will be implemented; a 14-item questionnaire capturing participants' perceptions of the frequency and severity of aspects of anxiety and depression. Summed scores for anxiety and depression are scored 0–21, where 0–7 indicates normal anxiety or depression, 8–10 indicates borderline abnormal anxiety or depression and 11–21 indicates abnormal anxiety or depression. The HADS has demonstrated good validity and reliability in both the general population and patients undergoing cancer treatment.<sup>30</sup>

Fatigue will be assessed by the Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale, which considers the fatigue levels of participants and its impact upon activities of daily living over a seven-day recall period. The 13-item scale, which utilises a 5-point Likert scale, has

demonstrated internal and external reliability, content validity and responsiveness.<sup>31</sup>

Health service use and costs will be assessed in three ways:

- 1 Participant calendar of health service use and costs: In the calendar, participants will record the occasion and cost of purchase of antiemetic medication, cost of consultations to a health care professional, cost of consultations to complementary health providers, cost of home care packages, aged care packages and private domiciliary or personal care (including the level of care, service provided, cost of service).
- 2 Dietitian health service use and costs: Medical records will be observed after the participants' intervention phase for the number of consultations provided by a usual care dietitian at each hospital site. Cost of consultations will be estimated to reflect the average oncology dietitian salary, including the average on-costs, payable by Queensland Health. Queensland Health salary costs will apply to both hospital sites.
- 3 Hospitalisations during treatment period: the medical records will be observed for inpatient admission of patients, and a standardised unit cost per hospital day will be assigned.

The intention-to-treat (ITT) and per protocol (PP) populations will be analysed under the following conditions: if less than 20% of the data are missing, ITT will be used and missing data accounted for statistically; if over 20% of the data are missing, PP will be used and missing cases will be excluded from analysis. Baseline characteristics will be described and compared between groups using independent *t*-test analysis or Mann–Whitney *U* tests for continuous variables as appropriate, and chi-square for categorical variables. The primary outcome is the difference in the impact of nausea on QoL (CIN-related QoL as assessed by FLIE, continuous scale) at Day 5 (4-days post-chemotherapy) between the intervention and placebo groups. It will be calculated by an independent *t*-test as well as repeated measures (over the three chemotherapy cycles), based on mean differences between groups, adjusting for baseline. Multiple imputation will be used to input missing data for covariates and FLIE scores if ITT is applied. Adjusted results will be calculated using a multiple linear regression model including the stratification factors (recruitment site, emetogenicity, gender and age) and other known risk factors for nausea such as gender, age, anxiety, previous history of gestational nausea and patient expectations of treatment. Secondary outcomes will also be analysed at Day 5 (4-days post-chemotherapy) between the intervention and placebo groups and will be calculated based on mean differences, adjusting for baseline, using an independent *t*-test for continuous variables (global QoL, fatigue, PG-SGA score) and chi-square for categorical variables (PG-SGA global rating).

The mean costs of each arm of the trial will be calculated and compared by combining the health service unit cost data. Cost data in each of the arms will be analysed in combination with quality-adjusted life years measured by the

EQ-5D-5 L. Full methodology for the economic analysis will be published separately.

Adverse events will be monitored by observation of the medical record as well as a brief discussion with patients 5 days after each chemotherapy cycle. All adverse events reported by the participant in response to questioning or observation by the research assistant will be recorded. All adverse events will be reported to the Principal Investigator and assessed for seriousness and relationship to the study product. The Human Research Ethics Committee and treating team will also be notified. Emergency unblinding will occur for serious adverse events deemed related to the study product.

## Results

Recruitment commenced at Site A in October 2017 and is expected to commence at Site B in May 2018. During the initial five-month recruitment period up until April 2018 at site A, a total of  $n = 33$  participants have been enrolled in the SPICE trial, leading to an average recruitment rate of seven per month. The response rate is 85%. Eighteen (55%) participants are female with a mean age of  $59 \pm 12$  years. Lung cancer accounts for the primary diagnosis of  $n = 12$  (36%) participants; breast  $n = 7$  (21%); lymphoma  $n = 4$  (12%); and other cancers  $n = 8$  (24%). Of the  $n = 33$  enrolments,  $n = 15$  have completed the intervention with 100% of outcome data collected. Incomplete data have been collected on  $n = 7$  participants due to withdrawal from the study for reasons such as treatment changes leading to study ineligibility, or inability to continue to manage taking the interventional. Among the  $n = 15$  that have completed the intervention, all consumed at least 87% of capsules, indicating good adherence to the intervention. There have been no reported serious adverse events relatable to the study intervention.

## Discussion

Despite significant advances in anti-cancer treatments and anti-emetic medication, low risk and cost-effective therapies to improve nausea-related QoL, symptom management and ultimately the survival of patients undergoing chemotherapy are needed. Although several clinical trials now indicate that ginger has potential as an adjuvant CINV therapy, further investigation by way of this larger, well-controlled study is necessary. This study, aiming to be completed in April 2019 with a target sample size of  $n = 300$ , will determine the safety of ginger supplementation; examine the precise ginger formulation and dosing regimen needed; control potential confounders; and indicate the capacity of ginger to ameliorate CINV-related effects such as fatigue and compromised nutrition.

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## Conflict of interest

All third parties, including Bluebonnet Nutrition Corporation, The University of Sydney and The University of Queensland, are not affiliated with the study beyond commercial services. All authors declare no potential or existing financial or other conflicts of interest.

## Authorship

SM and MC lead drafting of the manuscript. All authors contributed to study concept and revision of the manuscript. The authors acknowledge the contributions provided by Dr Catherine Shannon (Mater Health Services), Dr Barbara van der Meij (Mater Health Services and Bond University), Mr Ian McPherson (Princess Alexandra Hospital) and Ms Lynette de Groot (Mater Health Services), which have enabled the successful commencement of the study in the trial sites. The authors also acknowledge Chris Brown, Biostatistician at the NHMRC Clinical Trials Centre, University of Sydney, for assisting in the correct reporting of the randomisation, allocation and blinding methods.

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