Design and statistical analysis plan for a trial comparing a conservative fluid management strategy with usual care in patients after cardiac surgery: the FAB study

Rachael Parke, Eileen Gilder, Michael Gillham, Laurence Walker, Michael Bailey and Shay McGuinness, on behalf of the Fluids After Bypass Study Investigators

Demand for cardiac surgery and casemix complexity have increased in recent years, as results have improved and mortality has decreased, and demand frequently exceeds capacity.[1,2] Post-operative morbidity and frequency of complications are significant, with patients sometimes requiring a prolonged post-operative stay in the intensive care unit (ICU) or post-operative ward.[3,4] Provision of cardiac surgery services and waiting times may be affected by limited availability of critical resources such as operating theatre time, and surgeon and bed availability. New and innovative ways of caring for cardiac surgery patients are required to meet the challenges of providing care.

Fluid administration is a ubiquitous component of ICU care, with about a third of all adult ICU patients receiving fluid resuscitation on any given day[5] and more than 93% of cardiac surgery patients receiving at least one fluid bolus after surgery.[6] Major cardiac surgery typically results in some degree of post-operative haemodynamic instability that is managed in the ICU with intravenous (IV) fluid, inotropes and vasopressors. The intent of fluid administration is to prevent the development of organ dysfunction, but it may also have deleterious effects. In other surgical groups, liberal IV fluid administration and a positive fluid balance has been associated with adverse outcomes such as delayed wound healing; poor pulmonary, renal and gastrointestinal function; and increased risk of morbidity and mortality.[7-13] A reliable protocol for determining the optimal amount of IV fluid to administer after major surgery has not been established.

Numerous studies in other patient groups have shown positive outcomes, such as reduction in tissue oedema and better wound healing, when a more restrictive fluid administration regimen is used.[7,8,14] The optimal use of post-operative IV fluid after major surgery is the subject of ongoing investigation in several patient groups, including those undergoing upper and lower gastrointestinal surgery and hepatic surgery. There is no evidence that a restrictive fluid approach has adverse effects on either haemodynamic or renal status.[15]

To our knowledge, only one previous study of peri-operative fluid restriction in patients undergoing cardiac

ABSTRACT

Background: Cardiac surgery is one of the most frequently performed major surgical procedures. Following surgery, haemodynamic instability and prevention of organ dysfunction may be treated in the intensive care unit (ICU) with intravenous fluid, inotropes and vasopressors. In other surgical groups, liberal intravenous fluid administration and a positive fluid balance have been associated with adverse outcomes and increased risk of morbidity and mortality. There is a paucity of evidence to guide intravenous fluid administration in cardiac surgery patients. We have previously shown that a protocol-guided strategy avoiding unnecessary fluid administration significantly reduces fluid loading.

Objective: To present the design and statistical analysis plan for a randomised controlled trial comparing a conservative fluid management strategy to usual care in patients after cardiac surgery.

Methods: We designed a prospective, multicentre, parallel-group, randomised controlled trial —the FAB (Fluids After Bypass) study. A total of 700 patients undergoing cardiac surgery using cardiopulmonary bypass who have a European System for Cardiac Operative Risk Evaluation (EuroSCORE) II ≥ 0.9 will be enrolled in this study and randomly allocated to a protocol-guided strategy using stroke volume variation to guide administration of bolus fluid or to usual care fluid administration in a 1:1 ratio, stratified by centre. Study treatment will be administered from post-operative admission to the ICU until de-sedation or for a 24-hour period (whichever is shorter). The primary outcome is ICU length of stay. Secondary endpoints include quality of life and disability-free survival at 3 and 6 months after surgery, and process-of-care, physiological and safety measures.

Conclusion: This trial aims to determine whether a protocol-guided strategy that avoids unnecessary fluid administration reduces ICU length of stay and improves outcomes in higher-risk adults undergoing cardiac surgery.

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Table 1. Results of feasibility study[16]

Variable	Intervention (*n* = 70)	Usual care (*n* = 74)	*P*
Patient age in years, mean (range)	65.4 (38–86)	61.2 (18–86)	
Men	61 (52%)	56 (48%)	
IV fluid administration in mL, median (IQR)			
Bolus fluid to extubation	1620 (500–3410)	2520 (1440–5250)	< 0.001
All fluids to extubation	2050 (910–4280)	2980 (2070–6580)	0.001
Ventilation-free period in hours, median (IQR)	13.1 (8.0–15.6)	11.6 (1.0–15.0)	0.04
ICU length of stay in hours, median (IQR)	22.7 (20–46)	26.0 (21–48)	0.23

ICU = intensive care unit. IQR = interquartile range. IV = intravenous

surgery has been conducted.[16] Although it could be argued that many cardiac surgery ICUs have adopted a restrictive approach to peri-operative fluid management, we are not aware of any evidence showing that cardiac surgery patients receive less fluid, and little evidence on the effectiveness of this strategy has been published. There is also little high level evidence regarding the most appropriate timing for fluid administration, triggers, type of fluid, or indicators of success of therapy. Bolus fluid therapy is frequently used as first-line therapy to treat hypotension and may contribute to the development of a positive fluid balance.[17]

Several large clinical trials and meta-analyses have shown how fluid administration affects outcomes such as mortality and the requirement for renal replacement therapy. However, none of these have reported outcomes in a population of predominantly cardiac surgery patients, and some have deliberately excluded those undergoing cardiac surgery.[18] So, in this patient population, there is little evidence to inform clinical decision making.

Feasibility work by this group

After completing a single-centre observational study,[19] we undertook a multicentre, prospective, observational study of fluid administration.[6] We enrolled 235 patients, of whom 93.6% (*n* = 220) received at least one bolus of fluid (range, 0–24). The median amount of fluid given per patient for volume expansion up to the time of extubation (censured at 24 hours after ICU admission for those still intubated at that point) was 2047 mL, representing 77% of the total bolus fluid administered in the 24-hour period. This showed that fluid boluses are responsible for a large proportion of the positive fluid balance seen after cardiac surgery. Therefore any intervention must aim to restrict fluid administration in patients who have adequate cardiac output and are unlikely to be fluid responsive, and also provide alternative management options for hypotension.

We then designed a strategy to reduce bolus fluid administration using stroke volume variation (SVV) to identify patients who were unlikely to benefit from IV fluid administration, and thus restrict further fluid in these patients, and undertook a single-centre feasibility study of the proposed strategy.[16] This demonstrated that the proposed protocol-guided strategy was easy to implement and efficacious —we could successfully deliver the strategy and achieve a reduction in amount of fluid given. It also resulted in reductions in ventilation time and ICU length of stay (Table 1).[16]

The results of the feasibility study, while encouraging, do not justify proceeding directly to a definitive phase 3 trial. Therefore, we intend to conduct a multicentre, phase 2 equivalent, prospective, randomised controlled, interventional, superiority trial of a protocol-guided fluid administration strategy after cardiac surgery in patients with a EuroSCORE II ≥ 0.9.

Study hypothesis

We hypothesise that in patients with a EuroSCORE II ≥ 0.9 who undergo cardiac surgery, the use of a protocol-guided strategy to guide fluid administration will reduce ICU length of stay and, furthermore, improve patient outcomes.

Methods and analysis

Trial design

The FAB (Fluids After Bypass) study is a 700-patient, multicentre, parallel-group, open-label, prospective, randomised controlled, superiority trial.

Setting, patients and recruitment

All five public hospitals in New Zealand that undertake cardiac surgery will recruit patients. Ethics approval and local

site governance approval was obtained at all participating sites before study commencement. All patients must provide written informed consent to participate in the study after a research nurse or study site investigator has discussed the study with them and provided them with written information about the study.

Inclusion criteria

To be included in the study, patients must meet all of the following criteria:

- aged 16 years or older;
- having elective cardiac surgery using cardiopulmonary bypass; and
- pre-operative EuroSCORE II $\geq$ 0.9.

Exclusion criteria

Patients who meet one or more of the following criteria will be excluded from the study:

- emergency procedure;
- contraindication to SVV monitoring,
  - atrial fibrillation,
  - intra-aortic balloon pump in situ or anticipated,
  - open chest,
  - critical post-operative condition (patient not expected to survive > 24 hours after post-operative admission to ICU);
- extracorporeal membrane oxygenation or ventricular assist device in situ or anticipated;
- indication for specific fluid management strategy after surgery,
  - adult congenital heart surgery,
  - end-stage renal failure requiring dialysis;
- enrolment not considered to be in the patient's best interest.

Patients who meet one or more of the exclusion criteria on post-surgical admission to the ICU will receive standard care and have all data collected and analysed as per the study protocol.

Randomisation, allocation concealment and blinding

Randomisation will be performed pre-operatively by the ICU research staff with the use of sequentially numbered, opaque, sealed envelopes prepared by a person not involved in the study. A permuted block randomisation method with variable block size, stratified by hospital and generated by the study statistician, will be used to allocate patients in a 1:1 ratio. This is a pragmatic effectiveness trial of a treatment algorithm. Although blinding of treating clinicians to allocation is highly desirable, it is not feasible in this study. Patients selected for inclusion in the study will be blinded to treatment allocation. We will minimise bias by: ensuring concealment of allocation before randomisation; using a protocol-guided treatment in the intervention arm; using a robust outcome measure (ICU length of stay) as recorded in the clinical information systems at each site; and having blinded research staff collect data and conduct patient follow-up calls regarding quality of life and recovery. The issue of contamination of groups owing to the unblinded nature of the study was prospectively assessed in the feasibility study and not found to be significant.[16]

Study interventions

Study treatment will be administered from admission to the ICU until the time that routine post-operative sedation is stopped or for a 24-hour period (whichever is shorter). The study will assess the intervention (a protocol-guided strategy) and usual care.

Intervention arm

Patients in the intervention arm will be treated with IV fluid according to a protocol-guided strategy for post-operative administration of bolus fluid (Figure 1). This protocol first asks bedside clinicians to decide whether the patient has an inadequate cardiac output (by direct measurement or pragmatic clinical indicators such as low urine output). If it is decided that cardiac output is inadequate, the clinician is next asked to measure SVV, to assess the likelihood of the patient being volume responsive.[20] Then, for patients with SVV > 13%, the clinician is advised to give bolus fluid. This ensures that fluid is only administered to patients who are objectively determined as having cardiac output that is inadequate but likely to increase in response to IV fluid.

Usual care arm

Patients in the usual care arm will receive IV fluid as determined by local protocols and the bedside clinician.

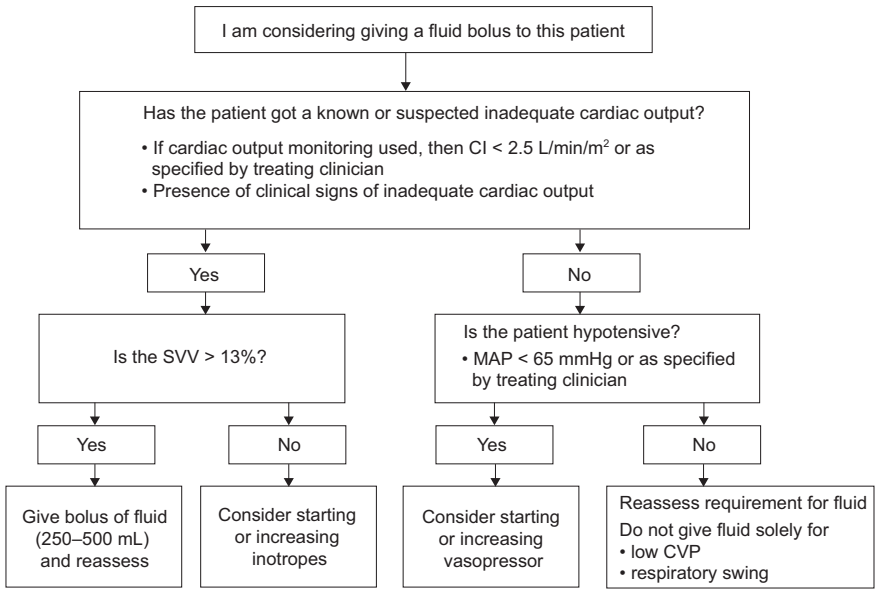
Both arms

All other ICU care will remain unchanged for patients in both groups. Ultimately, decisions about fluid administration, type of fluid administered and compliance with the fluid-administration protocol will rest with the treating clinicians. Reasons for non-compliance will be collected and analysed.

Outcome measures

The primary outcome measure is ICU length of stay up to Day 28 post-enrolment. Secondary outcome measures are shown in Table 2.

Figure 1. Fluid administration protocol from admission to the ICU until the time that routine post-operative sedation is stopped or for a 24-hour period (whichever is shorter)



CI = cardiac index. CVP = central venous pressure. MAP = mean arterial pressure. SVV = stroke volume variation.

Study management and data collection

All study data will be collected by trained staff at each study site using a paper case report form (CRF) or electronic CRF. Completed paper CRFs will be uploaded into a password-protected database. Data will be collected from each patient's medical and hospital notes as soon as possible after it is made available.

Patients will be followed up until death or 6 months after study enrolment (whichever occurs first). Data collection will be restricted primarily to those variables necessary to define clinical characteristics, including: baseline demographics, primary outcome measure, physiological parameters, diagnostic interventions, therapeutic interventions, deaths and other serious adverse events, and patient-reported outcomes (Table 3). Patients who are alive at 3 and 6 months after enrolment will be contacted by telephone or email to answer questions regarding quality of life and recovery.

Data will be entered by study site research staff into a web-based database managed by the Medical Research Institute of New Zealand. The events schedule for outcome assessment and data collection is shown in Table 4.

Data quality

Several procedures to ensure data quality and protocol standardisation will help to minimise bias. These include: a start-up meeting for all research coordinators and investigators to ensure consistency in procedures (held before study commencement); use of a detailed data dictionary that defines the data to be collected on the CRF; timely validation of data, resolution of queries, and correction of data if errors are found during quality-control checks (performed by the coordinating centre); at least one site visit for data monitoring purposes at each site (after the tenth patient has been enrolled at the site).

Data monitoring

A data safety monitoring board (DSMB) was appointed before study commencement. This independent committee comprises a statistician and two senior academic clinicians with experience in undertaking randomised controlled clinical trials. The DSMB has formulated terms of reference for the conduct and remit, including assessment for early termination, and will use data from an interim analysis to carry out a safety assessment.

Sample size and power

Sample size calculations were based on findings from our feasibility study, in which there was a median difference of > 20 hours in ICU length of stay between the intervention and usual care arms.[16] Based on an observed standard deviation of 56 hours,[16] including 590 patients in this study will have 90% power (2-sided $P = 0.05$) to detect a 15-hour difference, and 80% power (2-sided $P = 0.05$) to detect a 13-hour difference in ICU length of stay — differences that are conservative compared with what we have previously observed. Such differences are clinically relevant as they enable discharge of patients from the ICU 2 days after surgery or sooner, which enables a new patient to be admitted on that day and resolves a principal barrier to increasing the hospital's capacity for cardiac surgery. By recruiting 700 eligible patients (ie, about 15% extra patients), we further allow for inflation due to one interim analysis, a 3% drop-out rate, and potential non-normality in ICU length of stay.[23]

Statistical analysis plan

The primary analysis will be based on the intention-to-treat principle and will include all patients who are assigned to a study arm. Data will initially be assessed for normality

Table 2. Outcomes of study

Primary outcome measure	▪ ICU length of stay to Day 28 post-enrolment (hours)
Secondary outcome measures	▪ Incidence of wound infections
	▪ Development of organ dysfunction using the SOFA score
	▪ All-cause mortality to Day 180
	▪ Quality of life at Days 90 and 180 using the EQ-5D-5L instrument
	▪ Disability-free survival at Days 90 and 180 using WHODAS 2.0[21]
	▪ Development of AKI according to KDIGO criteria
Process-of-care measures	▪ Amount of fluid administered (mL) up to Day 3 if still in ICU
	▪ Overall fluid balance (mL) for Days 1–3 (if in ICU)
	▪ Requirement for red blood cell, platelet, fresh frozen plasma or cryoprecipitate transfusion
	▪ Duration of mechanical ventilation (hours)
	▪ Requirement for vasopressor therapy in ICU
	▪ Requirement for diuretic therapy in hospital
	▪ Hospital length of stay (days)
Tertiary outcome measures	▪ Lowest haemoglobin level measured in hospital
	▪ Creatinine measures
	▸ Greatest change in creatinine level from baseline to hospital discharge
	▸ Daily creatinine levels (if measured) for first 72 hours after surgery
	▸ Fluid balance-adjusted serum creatinine level[22]
	▪ Highest and lowest base excess (if measured) for first 72 hours after surgery
	▪ Daily mean arterial pressure, heart rate and respiratory rate recorded to Day 3
	▪ Incidence of arrhythmias (eg, atrial fibrillation) to hospital discharge
	▪ Requirement for renal replacement therapy up to 6 months
	▪ Return to theatre due to bleeding

AKI = acute kidney injury. ICU = intensive care unit. KDIGO = Kidney Disease: Improving Global Outcomes. SOFA = Sequential Organ Failure Assessment. WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0.

and log-transformed where appropriate. Between-group comparisons will be performed using χ^2 tests for equal proportion, Student *t* tests for normally distributed data and Wilcoxon rank sum tests otherwise, with results reported as *n* (%), mean (standard deviation) or median (interquartile range) respectively. To account for between-study heterogeneity and ensure that observed effects are not due to baseline imbalances, hierarchical multivariable sensitivity analysis adjusting for site and imbalanced variables will also be performed using mixed linear modelling for continuously normally distributed variables and logistic regression for binomial outcomes.

Two sensitivity analyses will be conducted:

- modified intention-to-treat analysis, excluding all patients who met secondary screening criteria (which identify patients in whom the use of SVV is not reliable) on post-operative admission to the ICU; and
- per-protocol analysis, including all patients for whom a non-compliant treatment was used, which is defined as administration of a fluid bolus when the SVV is not > 13% (ie, patients assigned to the intervention arm but swapped to the usual care arm).

All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), and a 2-sided $P = 0.05$ will used to indicate statistical significance. Pre-defined subgroup analyses, for each type of surgery and each study site, will be performed. One blinded interim analysis will be conducted when 50% of patients have been enrolled and subsequently discharged from the ICU, and data from this analysis will be used by the DSMB for their safety assessment.

To investigate whether there is an association between familiarity with use of the intervention and outcome, we will assess whether enrolment number is related to outcome at each study site. If it is, this will be controlled for as a covariate.

Ethics approval

The study has been approved by the Northern B Health and Disability Ethics Committee (16/NTB/153).

Dissemination

The rationale for and design of the FAB study has been presented to staff at each participating site, and delegates at national meetings of cardiac surgeons, anaesthetists and intensive care specialists, resulting in positive feedback on the study and support regarding its importance. The final results will be presented in 2019 at one or more major scientific meetings. The main results will be published in a major peer-reviewed scientific journal and communicated at international and national scientific meetings that discuss care of cardiac surgery patients. We will also ensure that results are provided to study patients, their family and whanau (immediate and extended family), and

Table 3. Data to be collected

Baseline	▪ Age, sex, ethnicity
	▪ Pre-operative EuroSCORE II
	▪ Weight and height
	▪ Pre-operative serum creatinine and haemoglobin levels
	▪ Pre-operative quality-of-life (EQ-5D-5L) score and WHODAS 2.0 score
Intra-operative period	▪ Type of surgery completed
	▪ Duration of bypass and cross-clamp time
	▪ Use of haemofiltration, diuretics or mannitol on bypass
First 24 hours after surgery if in ICU	▪ Volume and type of fluid administered (crystalloid, colloid or blood products)
	▪ Reason for fluid administration
Post-operative Days 1, 2 and 3	▪ Fluid data (total fluids in, total fluids out, total bolus fluid given, total blood loss, total urine output if still in ICU)
	▪ Volume and type of fluid administered (crystalloid, colloid or blood products)
	▪ SOFA score (if in ICU)
	▪ Serum creatinine, lactate and haemoglobin levels (if measured)
	▪ Requirement for inotropic agents while in ICU
	▪ Mean arterial pressure, heart rate and respiratory rate recorded closest to 08:00 hours if in ICU
	▪ Daily bodyweight
Hospital discharge	▪ Highest creatinine level measured during hospital stay
	▪ Creatinine level measured closest to hospital discharge
	▪ Lowest haemoglobin level measured during hospital stay
	▪ ICU length of stay after surgery —both time of being ready for ICU discharge and time of actual ICU discharge will be collected and reported to account for the potential effect of "bed block"
	▪ Hospital length of stay after surgery
	▪ Requirement for diuretic therapy in hospital and at hospital discharge
	▪ Post-operative complications including use of IABP; return to theatre due to bleeding; reintubation; ICU readmission; surgical wound infection; atrial fibrillation; need for RRT
	▪ Patient-reported quality-of-life score (EQ-5D-5L) and WHODAS 2.0 score
3-month follow-up	▪ Mortality (if deceased, cause of death will be collected)
	▪ Surgical wound infection
	▪ Ongoing RRT in those who were still receiving RRT at hospital discharge
	▪ Patient-reported quality-of-life score (EQ-5D-5L) and WHODAS 2.0 score
6-month follow-up	▪ Mortality (if deceased, cause of death will be collected)
	▪ Ongoing RRT in those who were still receiving RRT at 3 months
	▪ Patient-reported quality-of-life score (EQ-5D-5L) and WHODAS 2.0 score

EuroSCORE = European System for Cardiac Operative Risk Evaluation. IABP = intra-aortic balloon pump. RRT = renal replacement therapy. SOFA = Sequential organ failure assessment. WHO-DAS 2.0 = World Health Organization Disability Assessment Schedule 2.0.

Table 4. Schedule of events

Assessment	Pre-operative period (Days –30 to 0)	Day of surgery (Day 0)	Post-operative ICU (Days 0–28)	Hospital discharge	Day 90 ± 7 days	Day 180 ± 14 days
Screening for eligibility	X					
Consent	X					
Randomisation	X	X				
Baseline demographics	X					
Surgical details		X				
Intervention applied			X			
Pre-operative laboratory values	X					
Post-operative laboratory values			X	X		
Assessment of complications				X		
Adverse event evaluation		X	X	X	X	X
Mortality, EQ-5D-5L and WHODAS 2.0	X			X	X	X

EQ-5D-5L = Five-level EuroQol five dimensions questionnaire. ICU = intensive care unit. WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0.

key stakeholders such as district health boards and Māori research review committees.

The study will be published in the names of the individual investigators, the trial management committee and in the group name "Fluids After Bypass study investigators". Full credit will be assigned to all collaborating investigators, research nurses and institutions. All authors will comply with internationally agreed requirements for authorship and will approve the manuscript before submission. We will also ensure translation of knowledge to all ICUs in New Zealand with concurrent recommendations for change in practice based on the study findings.

Conclusions

Our preliminary evidence suggests that a strategy guiding fluid administration to patients after cardiac surgery can reduce ICU length of stay, but a large multicentre, randomised controlled trial is required to determine this definitively. The FAB study is designed to answer this question and provide high level evidence to inform fluid administration in this patient group.

Competing interests

None declared.

Author details

Rachael Parke[1-4]
Eileen Gilder[1,2]
Michael Gillham[1]
Laurence Walker[1]
Michael Bailey[4]
Shay McGuinness[1,3,4]
on behalf of the Fluids After Bypass Study Investigators*

1 Auckland City Hospital, Auckland, New Zealand.
2 University of Auckland, Auckland, New Zealand.
3 Medical Research Institute of New Zealand, Wellington, New Zealand.
4 Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia.

Correspondence: rparke@adhb.govt.nz

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*** Fluids After Bypass Study Investigators:**

- Auckland City Hospital: Rachael Parke, Eileen Gilder, Magdalena Butler, Keri-Anne Cowdrey, Jane Dalton, Stephnie Long, Samantha Ryan, Philippa Neal, Shay McGuinness,

Michael Gillham, Laurence Walker, Sara Allen, Alastair McGeorge, Andrew McKee, Henry Connell, Bevan Vickery, David Sidebotham
- Christchurch Hospital: Jan Mehrtens, David Knight
- Dunedin Hospital: Dawn France, Robyn Hutchison, Chris Walker
- Waikato Hospital: Kara Trask, Sarah Rogers, Caitriona Fiske, Annette Forrest
- Wellington Hospital: Georgia Hill, Anna Hunt, Charlotte Latimer-Bell, Paul Young

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Author contributions

All authors have been involved in conceiving and designing the study, and drafting this manuscript, and have provided final approval for this manuscript. Rachael Parke and Shay McGuinness were responsible for study design, study funding, and drafting of the manuscript. Eileen Gilder, Michael Gillham, Laurence Walker and Michael Bailey were responsible for study design.

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