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Reducing Implant Infection in Orthopaedics (RIIiO): Results of a pilot study comparing the influence of forced air and resistive fabric warming technologies on postoperative infections following orthopaedic implant surgery

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SUMMARY

Background: Active warming during surgery prevents perioperative hypothermia but the effectiveness and postoperative infection rates may differ between warming technologies.
Aim: To establish the recruitment and data management strategies needed for a full trial comparing postoperative infection rates associated with forced air warming (FAW) versus resistive fabric warming (RFW) in patients aged >65 years undergoing hemiarthroplasty following fractured neck of femur.
Methods: Participants were randomized 1:1 in permuted blocks to FAW or RFW. Hypothermia was defined as a temperature of <36°C at the end of surgery. Primary outcomes were the number of participants recruited and the number with definitive deep surgical site infections.

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Forced air warming
Resistive fabric warming
Hemiarthroplasty

Findings: A total of 515 participants were randomized at six sites over a period of 18 months. Follow-up was completed for 70.1%. Thirty-seven participants were hypothermic (7.5% in the FAW group; 9.7% in the RFW group). The mean temperatures before anaesthesia and at the end of surgery were similar. For the primary clinical outcome, there were four deep surgical site infections in the FAW group and three in the RFW group. All participants who developed a postoperative infection had antibiotic prophylaxis, a cemented prosthesis, and were operated under laminar airflow; none was hypothermic. There were no serious adverse events related to warming.

Conclusion: Surgical site infections were identified in both groups. Progression from the pilot to the full trial is possible but will need to take account of the high attrition rate.

Introduction

All surgical patients are at risk of a wound infection and there are many factors influencing that risk following hip fracture surgery, including age, lifestyle, poor pre-fracture health status, frailty, and previous infection [1]. Patients who develop a surgical site infection (SSI) have one-year mortality at least three times that of patients who do not suffer postoperative infections [2]. Treatment for deep SSI doubles operative costs, triples investigation costs, and quadruples ward costs [3].

Following a landmark study by Lidwell *et al.* in 1982, demonstrating a relative reduction of 61% in postoperative infection rate among patients undergoing total hip or knee replacement surgery, ultra-clean laminar airflow (LAF) became common practice and was routinely installed into new-build orthopaedic operating theatres as a strategy to prevent infection [4]. LAF is currently used in more than 60% of hospitals in the UK but it is costly, there are reservations about its effectiveness in preventing infection, and there is some suggestion that it may even cause harm [5—11]. Despite limited evidence, an International Consensus meeting on prosthetic joint infections concluded that LAF is no longer considered necessary [12]. It is not currently recommended by the World Health Organization for reducing the risk of infection during arthroplasty surgery and it is no longer advised by some in new-build operating theatres [7,13]. It is possible, however, that the type of warming used may be influencing the protective effects of LAF and, therefore, that such advice is premature [8,14].

A core temperature of 2°C below normal increases the incidence of wound infection three-fold [15]. Preventing inadvertent perioperative hypothermia (IPH) by patient warming not only reduces the rates of wound infection but also decreases morbidity and mortality, and is recommended by the National Institute for Health and Care Excellence (NICE) for all operations on all high-risk patients and those with operations lasting longer than 30 min. Several intraoperative warming methods exist but a systematic review of 67 randomized controlled trials involving patient warming systems from 1964 to 2015 failed to identify which method is associated with the fewest postoperative complications [15—25]. Forced air warming (FAW), which warms the patient by convection, has historically been considered the most effective non-invasive method of transferring heat to the patient and is commonplace in orthopaedic surgery. This is despite growing concern that FAW may interfere with LAF [26].

Mobilization of non-sterile air from floor level, increased concentration of particles over the surgical site, elevated microbial counts in the operating theatre, and micro-organisms found in both the hoses and blower systems, for example, may compromise the sterility of the surgical site [27—33]. In addition, disruption of LAF by FAW has been shown in studies with neutral-buoyancy detergent bubbles, high-fidelity predictive fluid flow simulations, and modelling of temperature gradients [27—36]. An International Consensus meeting discussed these issues but agreed that there was no direct evidence to definitively link FAW with an increased risk of SSIs, similar to several reviews on this topic [12,37—40]. In the absence of a large-scale trial, therefore, this controversy is likely to remain unanswered.

A single-centre observational study over a 2.5-year period found that the risk of developing deep SSI up to 60 days after surgery fell by more than two-thirds when FAW was replaced with an alternative method, resistive fabric warming (RFW), which warms patients by air-free conduction [27]. This was a retrospective study prone to confounding due to a lack of control for antimicrobial prophylaxis before surgery and other risk factors for SSI. A well-conducted randomized controlled trial comparing postoperative infection rates associated with FAW and RFW would be large, challenging, and expensive. The current pilot study was carried out to evaluate a protocol for such a trial.

Methods

The methodological details summarized here have already been published in full [41]. The Consolidated Standards of Reporting Trials (CONSORT) checklist and flow chart are shown in Appendices A and B respectively.

Trial registration

ISRCTN 74612906 (http://www.isrctn.com/ISRCTN74612906).

Objective and outcomes

The primary objective of the RIIiO pilot study was to establish the recruitment and data management strategies needed for a full trial to compare postoperative infection rates associated with FAW and RFW. As such, the primary outcomes of the pilot study were the number of participants recruited and the number of definitive deep SSIs.

Occurrence of superficial SSI, IPH, length of hospital stay, patient-reported outcome measures (EQ-5D-5L), and serious adverse events (SAEs), including death, were secondary outcomes.

Participants, randomization, and intervention

Adults undergoing hemiarthroplasty following hip fracture were recruited between April 3rd, 2017 and September 18th, 2018 from six National Health Service hospitals in England comprising a mixture of district general and large teaching hospitals. Prior to surgery, participants were randomized 1:1 in permuted blocks to FAW or RFW during surgery. Temperature was recorded at induction of anaesthesia, at 30 min intervals during surgery, at the end of surgery, and upon arrival in the recovery room. IPH was defined as a core temperature of $<36^{\circ}C$ at the end of surgery, or, if this measurement was not available, either upon arrival in the recovery room or the last core temperature measured during surgery [41]. Data were housed in an established software package (MACRO; Elsevier, Amsterdam, The Netherlands), which was also used to execute the randomization. Each site was expected to recruit a minimum of two participants a week; there was no maximum recruitment target.

Assessments and blinding

Baseline assessments included (i) age, gender, and body mass index (BMI; kg/m^2), (ii) the American Society of Anaesthesiologists (ASA) physical status classification, (iii) the use of antimicrobial prophylaxis, immunosuppressants, and use of a cemented or uncemented prosthesis, and (iv) comorbidities including a history of ischaemic heart disease, peripheral vascular disease, stroke, dementia, kidney disease/renal failure, diabetes mellitus, rheumatoid arthritis, systemic autoimmune disease, human immunodeficiency virus, and active malignancy. A comorbidity index, with a maximum score of 11, was calculated from the sum of the number of comorbidities of each participant. The participants were followed up for signs of deep SSI (the primary endpoint) at 30 ($\pm$7) days and 90 ($\pm$14) days after surgery and superficial SSI (a secondary endpoint) at 30 ($\pm$7) days. Definitions of deep and superficial SSI were adapted from the Centers for Disease Control and Prevention SSI criteria published in January 2016 [42]. Clinic attendance, readmission to hospital, or return to theatre post randomization with signs and symptoms at the site of surgery were considered potential primary endpoints. To limit bias, the potential primary endpoints were assessed by an independent endpoint review committee who were blinded to the randomized allocation.

Statistical analysis

Normally distributed continuous variables were summarized by means and standard deviations, skewed continuous variables by medians and interquartile ranges, and categorical variables by frequencies and percentages. The EQ-5D-5L index value was calculated using the Stata command eq5dmap, the approach recommended by NICE [43,44]. All analyses were performed in Stata 15.1 (Release 15; StataCorp, College Station, TX, USA) and followed intention-to-treat principles.

Results

Recruitment and retention

In all, 634 patients were assessed for eligibility, of whom 515 were randomized to FAW ($N = 255$) or RFW ($N = 260$). Figure 1 shows the progress of the randomized patients through the trial in a CONSORT diagram, reflecting the numbers theoretically available for analysis based on consent [45]. Table I shows the distribution of recruitment by site. Overall, the average recruitment rate was 1.9 participants per week per site and follow-up was completed for 70.1% of the randomized participants. Twenty-eight randomized participants (5.4%) did not receive their allocated warming technology. Six participants who were randomized to FAW (2.4%) received RFW and 22 participants randomized to RFW (8.5%) received FAW. Ninety-three participants (18.1%) were withdrawn from the study; reasons for withdrawal are stated in Supplementary Table S1. Twenty-eight of the withdrawn participants (30.1%) either had a surgical procedure other than hemiarthroplasty or no surgery at all. Most patients (443/515; 86.0%) were recruited under consultee consent; 117/515 participants (22.7%) did not consent to follow-up and 54/515 participants (10.5%) died before follow-up could be completed.

Baseline and surgical characteristics

The baseline and surgical characteristics of the participants by randomization group are shown in Tables II and III. The average age was 85.2 years (SD: 7.5). The majority of participants were ASA grade III. There were almost twice as many females ($N = 293$) as males ($N = 150$). The mean BMI was similar for the two groups. Use of immunosuppressants was recorded for a minority of participants ($N = 18$). For participants for whom relevant data were available, 252/349 (72.2%) had one or more comorbidity. One-third of randomized participants had dementia; diabetes mellitus, ischaemic heart disease and stroke were the next most frequent comorbidities (Supplementary Table S2). Laminar flow ventilation was recorded as used for 435 of 465 participants who underwent surgery (93.6%). Use of antimicrobial prophylaxis before surgery was recorded for 432 participants (92.9%) and insertion of an antibiotic-loaded cemented prosthesis for 350 participants (75.3%).

Primary endpoint deep SSIs and secondary endpoint superficial SSIs

The primary endpoint was identification of a deep SSI within 90 days of surgery. Superficial SSI identified within 30 days of surgery was a secondary endpoint. Endpoint data were missing in 26 and 28 patients in the FAW and RFW arms, respectively, at 90 days and in 21 and 14 patients, respectively, at 30 days.

Deep SSI occurred in 4/223 (1.8%) participants randomized to FAW and in 3/221 (1.4%) randomized to RFW (Table IV). All deep SSIs were confirmed as 'definite' by an independent blinded endpoint review committee. Overall, the deep SSI rate

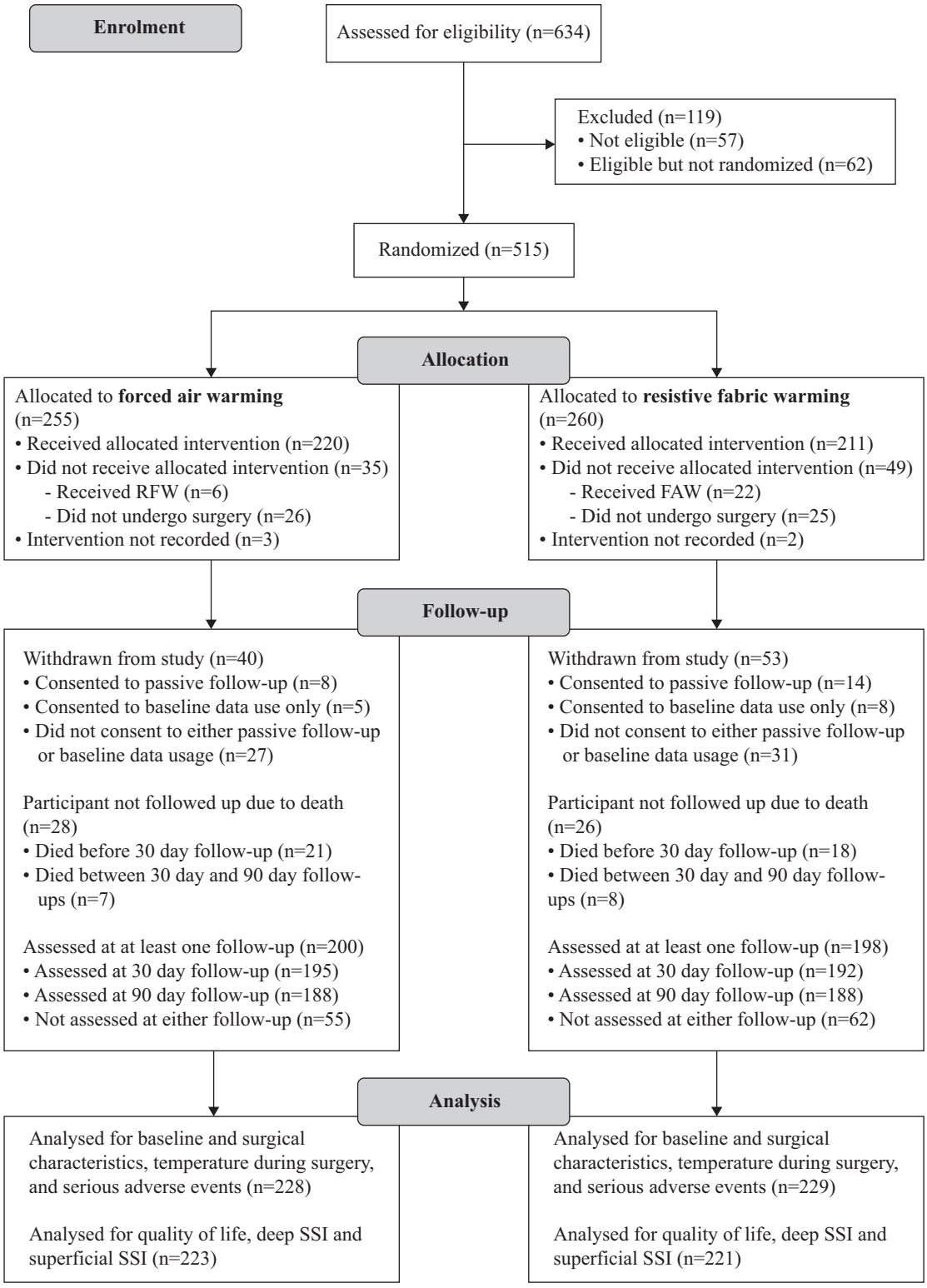

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram, extension to randomized pilot and feasibility studies, showing the number of patients and their flow through the trial from screening for eligibility to analysis. RFW, resistive fabric warming; FAW, forced air warming; SSI, surgical site infection.

was 1.6% of those with data available. Superficial SSI occurred in 7/201 (3.5%) in the FAW group and in 1/207 (0.5%) in the RFW group within 30 days of surgery, as determined by the local principal investigators.

Of the 15 infected participants in total, eight were female (two deep; six superficial) and six were male (five deep; two superficial). All of the participants who developed an infection were operated on under LAF, received antibiotic prophylaxis,

Table I
Numbers recruited by site with data obtained at baseline and follow-up at 30 days and 90 days

Recruitment site	No. recruited	No. of weeks open to recruitment	Average no. of recruits per week	No. baselined	No. followed up at 30 days	No. followed up at 90 days
Queen Elizabeth The Queen Mother Hospital, East Kent	109 (21.2%)	33	3.3	91 (83.5%)	76 (69.7%)	71 (65.1%)
Heartlands Hospital, Birmingham	104 (20.2%)	44	2.4	102 (98.1%)	71 (68.3%)	64 (61.5%)
Princess Royal Hospital, Brighton	99 (19.2%)	53	1.9	83 (83.8%)	69 (69.7%)	73 (73.7%)
Milton Keynes University Hospital, Milton Keynes	75 (14.6%)	50	1.5	67 (89.3%)	60 (80.0%)	58 (77.3%)
Northumbria Specialist Emergency Care Hospital, Cramlington	70 (13.6%)	52	1.4	68 (97.1%)	54 (77.1%)	54 (77.1%)
Horton General Hospital, Banbury	58 (11.3%)	67	0.9	58 (100%)	57 (98.3%)	56 (96.6%)
Total	515		1.9	469 (91.1%)	387 (75.1%)	376 (73.0%)

and had a cemented prosthesis. Two of the participants who developed infections were receiving immunosuppressants (one deep SSI and one superficial SSI).

Secondary endpoint inadvertent perioperative hypothermia

All recruitment sites used BairHugger (Arizant Healthcare, Inc., Eden Prairie, MN, USA) for their method of FAW. For RFW, either UniqueTemp® (Geratherm, Geschwenda, Germany) or the Alpha Patient Warming System (Inditherm Medical, Wath-upon-Dearne, UK or Inspiration Healthcare, Leicester, UK) was used. Thirty-seven participants in total were classed as hypothermic (temperature <36°C) at the last available temperature measurement; 16/213 (7.5%) participants in the FAW group and 21/217 (9.7%) in the RFW group. None of the hypothermic participants developed a postoperative infection. The mean temperatures before anaesthesia (36.7°C for the FAW group ($N = 199$) and 36.8°C for the RFW group ($N = 202$)) and at the end of surgery (36.7°C for the FAW group ($N = 153$) and 36.5°C for the RFW group ($N = 168$)) were similar between the two groups (Supplementary Table S3).

Other secondary endpoints

The mean duration of surgery and the median length of hospital stay were similar between the two groups (Supplementary Table S4), as were the patient-reported outcome measures for quality of life (Supplementary Table S5). There were 121 SAEs reported in the FAW group and 102 SAEs reported in the RFW group. Most SAEs required new or prolongation of existing hospitalization or resulted in death (Supplementary Table S6). None of the SAEs recorded were related to the trial interventions. A total of 73 participants died; of those included in the final analysis, 39/457 (8.5%) died within 30 days of surgery.

Discussion

Whether or not FAW and RFW are equally effective at preventing IPH is debatable. As recently reviewed by Ackermann *et al.*, there are many studies claiming that RFW is as effective as FAW whereas others have shown that the incidence of IPH is higher with RFW and rates of re-warming are slower than with FAW [40,46]. In our study, the number of hypothermic patients for the two groups and the mean temperatures at the end of surgery were similar, suggesting that FAW and RFW are both effective.

Baseline data collected in our study included the most widely recognized risk factors for SSI in this population, including age, ASA score, BMI, and comorbidities. Patients showed similar demographics to previous studies although a higher proportion were comorbid as compared to a study by Roche *et al.* [47–49]. As a result of the randomization process, reported risk factors were evenly distributed between the groups in our study (Table III).

Definitive infections were confirmed in both groups and for both sexes. Deep SSI rates in the literature range from as low as 0.7% to as high as 5.1% [50,51]. Such variation may be due to differences in recording, classification, and definition and because few studies report deep SSI as a primary outcome [52]. No statistical comparison of the number of infections with FAW versus RFW can be made from these pilot data but a potential disparity between deep and superficial SSIs reinforces the need for clearly defined criteria. The study was designed on the basis of an anticipated 2.5% event rate. The observed event rate for deep SSI (1.6%) was lower than expected, but, as there was only a small number of deep SSIs, there is not enough evidence

Table II
Recorded baseline by allocated intervention

Risk factor	Forced air warming			Resistive fabric warming			Overall		
	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*N*
Age (years)	85.3	7.5	221	85.0	7.4	222	85.2	7.5	443
Height (m)	1.6	0.1	174	1.6	0.1	181	1.6	0.1	355
Weight (kg)	63.9	15.8	172	63.8	15.3	182	63.8	15.5	354
Body mass index (kg/m^2)	23.7	4.8	167	23.6	4.8	176	23.6	4.8	343

Table III
Surgical participant demographics by allocated intervention[a]

Variable	Forced air warming		Resistive fabric warming		Overall	
	No.	%	No.	%	No.	%
Gender						
Female	137	62.0	156	70.3	293	66.1
Male	84	38.0	66	29.7	150	33.9
ASA physical status						
II	31	14.2	36	16.4	67	15.3
III	142	64.8	147	67.1	289	66.0
IV	45	20.5	36	16.4	81	18.5
V	1	0.5	0	0.0	1	0.2
Immunosuppressants						
No	211	95.9	213	95.9	424	95.9
Yes[b]	9	4.1	9	4.1	18	4.1
Comorbidity score[c]						
0	47	28.0	50	27.6	97	27.8
1	58	34.5	76	42.0	134	38.4
2	42	25.0	35	19.3	77	22.1
3	17	10.1	15	8.3	32	9.2
4	4	2.4	3	1.7	7	2.0
5	0	0.0	2	1.1	2	0.6
Laminar flow						
No	3	1.4	4	1.8	7	1.6
Yes	218	98.6	217	98.2	435	98.4
Surgical procedure						
Cemented prosthesis[d]	170	76.9	180	81.1	350	79.0
Uncemented prosthesis	51	23.1	42	18.9	93	21.0
Antimicrobial prophylaxis						
No	8	3.6	1	0.5	9	2.0
Yes[e]	212	96.4	220	99.5	432	98.0

ASA, American Society of Anesthesiologists.
[a] Analysis followed intention-to-treat principles in this pilot study; participants were analysed in the group to which they were randomized, regardless of the procedure they received.
[b] Recorded immunosuppressants included prednisolone/systemic steroid therapy and methotrexate.
[c] Comorbidity score is the sum of the number of comorbidities of each participant. Maximum score was 11.
[d] Including Palacos, Simplex, Copal, Optipac.
[e] Flucloxacillin, teicoplanin, coamoxiclav (or augmentin), cefuroxime (or ceftriaxone), gentamicin, tazocin or metronidazole.

Table IV
Number of definitive surgical site infections (SSIs) (primary endpoints) and recorded superficial SSIs (secondary endpoints) by allocated intervention for participants with complete data

	Forced air warming	Resistive fabric warming	Overall
Deep SSI by 30 days[a]	2	2	4
Deep SSI by 90 days[a]	2	1	3
Superficial SSI by 30 days[b]	7	1	8
Total	11	4	15

[a] Confirmed as 'definite' by an independent blinded endpoint review committee on the basis of symptoms of infection, repeat surgery, radiological evidence, deep tissue histology, and culture results.
[b] Determined by the local principal investigator on the basis of symptoms of infection, if the wound was opened and if a secondary specimen was taken for culture results.

to indicate that the expected event rate was substantially greater than the observed rate.

Recruitment to the trial was more difficult than anticipated with only half of the sites reaching the expected target. The progression rule from the pilot study to the full trial included a projected recruitment of 100 participants per year or two participants per week at each pilot site [41]. The overall average recruitment rate was close at 1.9 participants per site per week. There were fewer hemiarthroplasties than anticipated at the start of the study and fewer resources than expected at some of the sites. Recruitment was greatest in the large teaching hospitals but retention was greatest in a small general hospital. Eligible patients who were not randomized were most frequently missed due to the nature of the emergency setting (e.g. weekend operations, altered surgery schedules etc.). Poor communication was the main reason why 28 randomized participants did not receive their allocated warming technology. In addition to the emergency setting mandating a need for a two-step consent process, the high average age of the participants and the frequency of dementia may have contributed to the higher than expected withdrawal rate. There was also a substantial number of deaths before follow-up could be completed. Such high attrition needs to be accounted for in the sample size calculation for a full trial of the same design.

This pilot study has demonstrated that, keeping the same trial design (i.e. detecting an absolute difference in infection rate of 1%, with 90% power and 5% significance level) and allowing for 25–30% attrition, a full trial will require 10,788–11,219 participants. This would involve either a large number of recruitment sites, a prolonged recruitment period, or adoption by an established cohort study.

To date, more than 200 million patients have been warmed by the 3M Bair Hugger system despite theoretical concerns that it may be associated with a risk of postoperative SSI. Although alternative systems are available, FAW is likely to continue as the market leader. This study found no safety concerns with either FAW or RFW and they were both similarly effective at maintaining normothermia. Definitive SSIs were identified with both FAW and RFW. A very large, multi-centre superiority trial is required to determine which patient warming method is associated with the fewest infections.

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Conflict of interest statement
Professor M. Reed has received research funding from 3M on an unrelated topic. Dr C.M. Harper has been paid honoraria by 3M.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.08.019.

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