ARTICLE TITLE

Reducing Implant Infection in Orthopaedics (RIIiO): Results of a Pilot Study Comparing the Influence of Forced Air and Resistive Fabric Warming Technologies on Post-Operative Infections following Orthopaedic Implant Surgery

Running Title:

Outcome of the RIIiO Pilot Study

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Abbreviations:

Surgical Site Infection (SSI); Inadvertent Perioperative Hypothermia (IPH); Forced Air Warming (FAW); Resistive Fabric Warming (RFW); Laminar Airflow (LAF); Serious Adverse Event (SAE); American Society of Anaesthesiologists (ASA)

ABSTRACT

Background: Active warming during surgery prevents perioperative hypothermia but the effectiveness and post-operative infection rates may differ between warming technologies. We report results of a pilot study in patients over the age of 65 undergoing hemiarthroplasty following fractured neck of femur.

Aim: To establish the recruitment and data management strategies needed for a full trial comparing post-operative infection rates associated with forced air versus resistive fabric warming.

Methods: Participants were randomised 1:1 in permuted blocks to forced air or resistive fabric warming. Hypothermia was defined as a temperature of <36ºC at the end of surgery. Primary outcomes were the number of participants recruited and the number with definitive deep surgical site infections.

Findings: 515 participants were randomised at 6 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 4 deep surgical site infections in the forced air warming group and 3 in the resistive fabric warming group. All participants who developed a post-operative infection had antibiotic prophylaxis, a cemented prosthesis and were operated under laminar airflow; none were 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.

Keywords:

Surgical Site Infection; Inadvertent Perioperative Hypothermia; Forced Air Warming; Resistive Fabric Warming; Hemiarthroplasty

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

INTRODUCTION

All surgical patients are at risk of a wound infection and there are many factors that influence 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 post-operative 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, which demonstrated a relative reduction of 61% in post-operative infection rate amongst patients undergoing total hip or knee replacement surgery [4], ultra clean laminar airflow (LAF) became common practice and was routinely installed into new-build orthopaedic operating theatres as a strategy to prevent infection. LAF is currently used in more than 60% of hospitals in the UK [5] but it is costly, there are reservations about its effectiveness in preventing infection [6-10], and there is some suggestion that it may even cause harm [10 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 (WHO) [13] for reducing the risk of infection during arthroplasty surgery and it is no longer advised by some in new build operating theatres [7]. It is possible, however, that the type of warming

used may be influencing the protective effects of LAF [8] 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 [15-21] and is recommended by the National Institute for Health and Care Excellence (NICE) [22 23] for all operations on all high risk patients and those with operations lasting longer than 30 minutes. Several intraoperative warming methods exist [24] but a systematic review of 67 randomised controlled trials involving patient warming systems from 1964 to 2015, failed to identify which method is associated with the fewest post-operative complications [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].

Mobilisation of non-sterile air from floor level [27], increased concentration of particles over the surgical site [28], elevated microbial counts in the operating theatre [29], and micro-organisms found in both the hoses and blower systems [30-33], for example, could potentially be compromising the sterility of the surgical site. In addition, disruption of LAF by FAW has been shown in studies with neutral-buoyancy detergent bubbles [27 34], high-fidelity predictive fluid flow simulations [35] and modelling of temperature gradients [36]. An International Consensus meeting discussed these issues but agreed there was no direct evidence to definitively link FAW with an increased risk of SSIs [12], similar to several reviews on this topic [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 [27] found that the risk of developing deep SSI up to 60 days after surgery fell by over two thirds when FAW was replaced with an alternative method, resistive fabric warming (RFW), which warms patients by air-free conduction. 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 randomised controlled trial comparing post-operative infection rates associated with FAW and

RFW would be large, challenging and expensive. The pilot study reported here was carried out to evaluate a protocol for such a trial.

METHODS

The methodological details summarised here have already been published in full [41]. The CONSORT checklist and flowchart are shown in Appendices A and B respectively.

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 post-operative 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, Randomisation and Intervention

Adults undergoing hemiarthroplasty following hip fracture were recruited between 3rd April 2017 and 18th September 2018 from 6 NHS hospitals in England comprising a mixture of district general and large teaching hospitals. Prior to surgery, participants were randomised 1:1 in permuted blocks to either FAW or RFW during surgery. Temperature was recorded at induction of anaesthesia, at 30 minute intervals during surgery, at the end of surgery and upon arrival in the recovery room. IPH was defined as a core temperature of <36ºC 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), which was also used to execute the randomisation. Each site was expected to recruit a minimum of 2 participants a week; there was no maximum recruitment target.

Assessments and Blinding

Baseline assessments included (i) age, gender and BMI, (ii) the American Society of Anaesthesiologists (ASA) physical status classification, (iii) the use of antimicrobial

prophylaxis, immuno-suppressants and use of a cemented or un-cemented 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, HIV, 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 (± 7) days and 90 (± 14) days after surgery and superficial SSI (a secondary endpoint) at 30 (± 7) days. Definitions of deep and superficial SSI were adapted from the Centers for Disease Control surgical site infection criteria published in January 2016 [42]. Clinic attendance, re-admission to hospital, or return to theatre post-randomisation 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 randomised allocation.

Statistical Analysis

Normally distributed continuous variables were summarised 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 [43], the approach recommended by NICE [44]. All analyses were performed in Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and followed intention-to-treat principles.

RESULTS

Recruitment and Retention

Six hundred and thirty-four patients were assessed for eligibility, of which 515 were randomised to either FAW (n=255) or RFW (n=260). Figure 1 shows the progress of the randomised 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 randomised participants. Twenty-eight

randomised participants (5.4%) did not receive their allocated warming technology. Six participants who were randomised to FAW (2.4%) received RFW and 22 participants randomised to RFW (8.5%) received FAW. Ninety-three participants (18.1%) were withdrawn from the study; reasons for withdrawal are given in Table SI. 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 randomisation group are shown in Table II. 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 immuno-suppressants 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 randomised participants had dementia; diabetes mellitus, ischaemic heart disease and stroke were the next most frequent comorbidities, as shown in Table SII. 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 at 30 days.

Deep SSI occurred in 4/223 (1.8%) participants randomised to FAW and in 3/221 (1.4%) randomised to RFW (Table III). All deep SSIs were confirmed as ‘definite’ by an independent blinded endpoint review committee. Overall, the deep SSI rate 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, 8 were female (2 deep; 6 superficial) and 6 were male (5 deep; 2 superficial). All of the participants that developed an infection were operated on under LAF, received antibiotic prophylaxis and had a cemented prosthesis. Two of the participants who developed infections were receiving immuno-suppressants (1 deep SSI and 1 superficial SSI).

Secondary Endpoint IPH

All recruitment sites used BairHugger (from Arizant Healthcare Inc, a 3M™ company) for their method of FAW. Either ®UniqueTemp° (from Geratherm®) or the Alpha Patient Warming System (from Inditherm Medical or Inspiration Healthcare) was used as the type of RFW. 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 post-operative 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, as shown in Table SIII.

Other Secondary Endpoints

The mean duration of surgery and the median length of hospital stay were similar between the two groups (Table SIV), as were the patient reported outcome measures for quality of life (Table SV). 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 hospitalisation or resulted in death, as shown in Table SVI. 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. [40], there are many studies that claim RFW is as effective as

FAW whilst others have shown that the incidence of IPH is higher with RFW and rates of re-warming are slower than FAW [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 recognised risk factors for SSI in this population, including age, ASA score, BMI and comorbidities. Patients showed similar demographics to previous studies [47 48] although a higher proportion were comorbid as compared to a study by Roche et al. [49]. As a result of the randomisation process, reported risk factors were evenly distributed between the groups in our study (Table II).

Definitive infections were confirmed in both groups and for both sexes. Deep SSI rates in the literature range from as low as 0.7% [50] to as high as 5.1% [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 were only a small number of deep SSIs, there is not enough evidence 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 randomised 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 randomised 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 were 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 a 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.

CONCLUSION

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 post-operative surgical site infection. 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 Mike Reed has received research funding from 3M™ on an unrelated topic. Dr C Mark Harper has been paid honoraria by 3M™.

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TABLES

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

Recruitment Site	Number Recruited	Number of Weeks Open to Recruitment	Average Number Recruits per Week	Number Baselined	Number followed up at 30 days	Number followed up at 90 days
Queen Elizabeth The Queen Mother Hospital [a]	109 (21.2%)	33	3.3	91 (83.5%)	76 (69.7%)	71 (65.1%)
Heartlands Hospital [b]	104 (20.2%)	44	2.4	102 (98.1%)	71 (68.3%)	64 (61.5%)
Princess Royal Hospital [c]	99 (19.2%)	53	1.9	83 (83.8%)	69 (69.7%)	73 (73.7%)
Milton Keynes University Hospital	75 (14.6%)	50	1.5	67 (89.3%)	60 (80.0%)	58 (77.3%)
Northumbria Specialist Emergency Care Hospital [d]	70 (13.6%)	52	1.4	68 (97.1%)	54 (77.1%)	54 (77.1%)
Horton General Hospital [e]	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%)**

[a] East Kent; [b] Birmingham; [c] Brighton; [d] Cramlington; [e] Banbury

Table II: Recorded baseline and surgical participant demographics by allocated intervention[a]

	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
BMI (kg/m2)	23.7	4.8	167	23.6	4.8	176	23.6	4.8	343
	n	**%**		**n**	**%**		**n**	**%**	
Gender									
Female	137	62.0		156	70.3		293	66.1	
Male	84	38.0		66	29.7		150	33.9	
ASA Physical Status									
ASA II	31	14.2		36	16.4		67	15.3	
ASA III	142	64.8		147	67.1		289	66.0	
ASA IV	45	20.5		36	16.4		81	18.5	
ASA V	1	0.5		0	0.0		1	0.2	
Immuno-suppressants									
No	211	95.9		213	95.9		424	95.9	
Yes[b]	9	4.1		9	4.1		18	4.1	
Comorbidity score [b]									
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	
Un-cemented 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	

[a] Analysis followed intention to treat principles in this pilot study; participants were analysed in the group they were randomised to, regardless of the procedure they actually received.

[b] Recorded immuno-suppressants included Prednisolone/systemic steroid therapy and Methotrexate

[c] Comorbidity score is a 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 III: Number of definitive 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

FIGURE 1

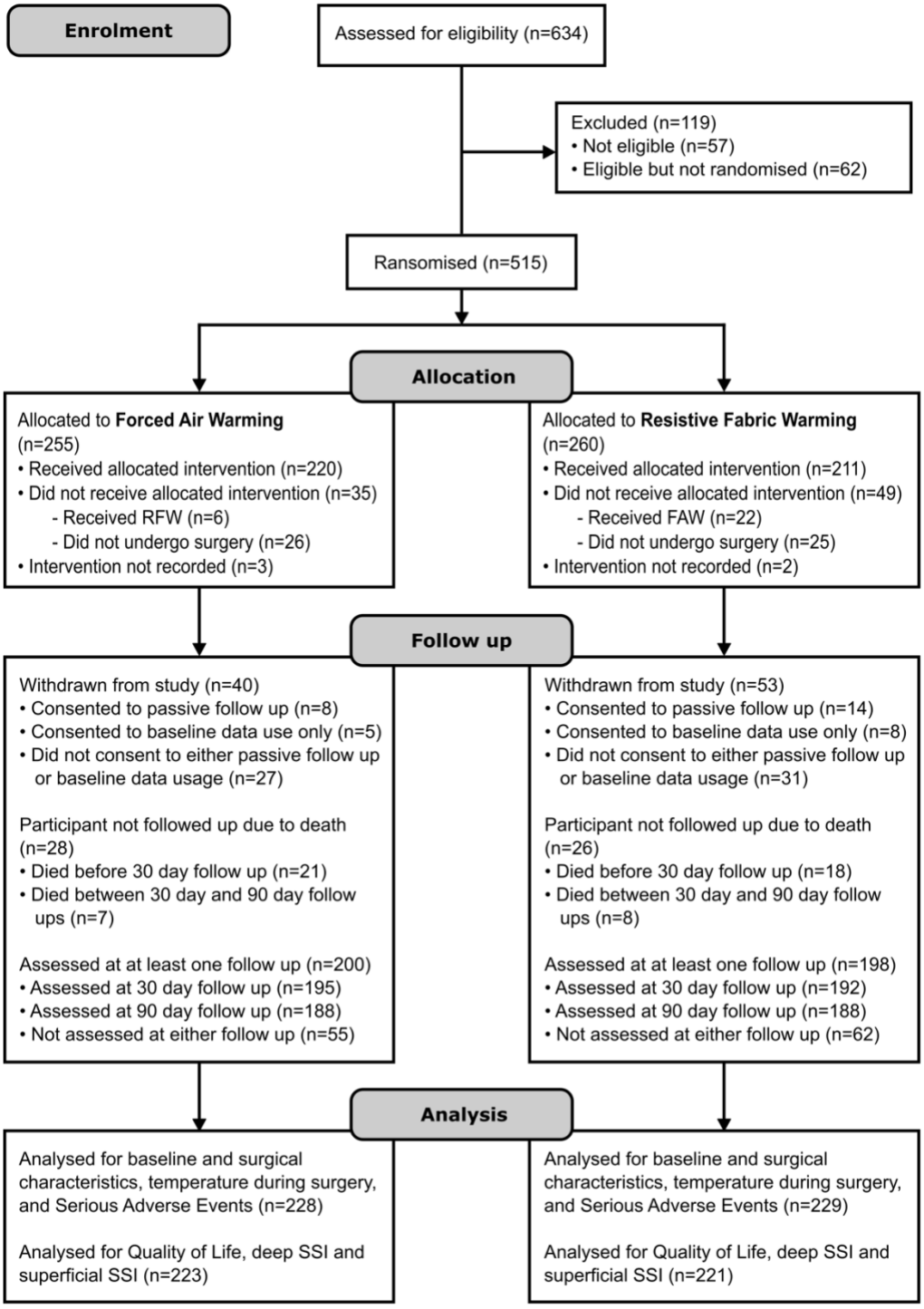

Enrolment
Assessed for eligibility (n=634)
Excluded (n=119)
• Not eligible (n=57)
• Eligible but not randomised (n=62)
Ransomised (n=515)
Allocation
Allocated to Forced Air Warming (n=255)
• Received allocated intervention (n=220)
• Did not receive allocated intervention (n=35)
- Received RFW (n=6)
- Did not undergo surgery (n=26)
• Intervention not recorded (n=3)
Allocated to Resistive Fabric Warming (n=260)
• Received allocated intervention (n=211)
• Did not receive allocated intervention (n=49)
- Received FAW (n=22)
- Did not undergo surgery (n=25)
• Intervention not recorded (n=2)
Follow up
Withdrawn from study (n=40)
• Consented to passive follow up (n=8)
• Consented to baseline data use only (n=5)
• Did not consent to either passive follow up or baseline data usage (n=27)
Participant not followed up due to death (n=28)
• Died before 30 day follow up (n=21)
• Died between 30 day and 90 day follow ups (n=7)
Assessed at at least one follow up (n=200)
• Assessed at 30 day follow up (n=195)
• Assessed at 90 day follow up (n=188)
• Not assessed at either follow up (n=55)
Withdrawn from study (n=53)
• Consented to passive follow up (n=14)
• Consented to baseline data use only (n=8)
• Did not consent to either passive follow up or baseline data usage (n=31)
Participant not followed up due to death (n=26)
• Died before 30 day follow up (n=18)
• Died between 30 day and 90 day follow ups (n=8)
Assessed at at least one follow up (n=198)
• Assessed at 30 day follow up (n=192)
• Assessed at 90 day follow up (n=188)
• Not assessed at either follow up (n=62)
Analysis
Analysed for baseline and surgical characteristics, temperature during surgery, and Serious Adverse Events (n=228)
Analysed for Quality of Life, deep SSI and superficial SSI (n=223)
Analysed for baseline and surgical characteristics, temperature during surgery, and Serious Adverse Events (n=229)
Analysed for Quality of Life, deep SSI and superficial SSI (n=221)

FIGURE LEGEND

Figure 1. CONSORT flow diagram, extension to randomised pilot and feasibility studies, showing the number of patients and their flow through the trial from screening for eligibility to analysis.