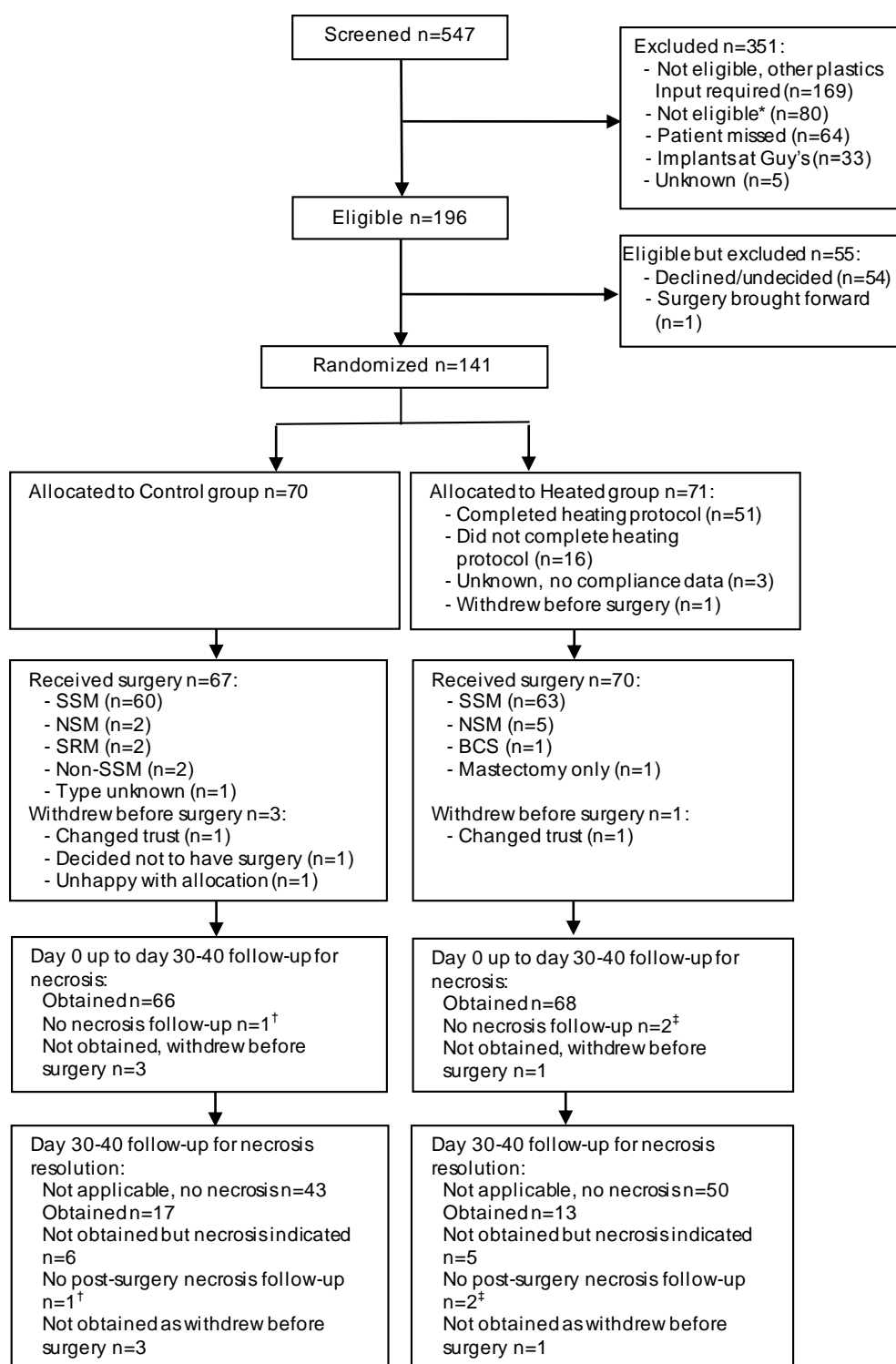


## Participant flow



\*Other reasons not eligible (n=80): Delayed reconstruction (n=33), Mastectomy only (19), WLE/BCS (17), Non-SSM (7), Latex allergy (3) and NSM (1). <sup>†</sup>Patient had SRM. <sup>‡</sup> Patients had NSM and mastectomy only. <sup>§</sup>If did not withdraw prior to surgery and provided data on compliance. <sup>§</sup>Follow-up for necrosis: day 0 up to 30-40 days if did not withdraw prior to surgery.

## Baseline characteristics

Baseline characteristic	N Control/ N Heated	Control	Heated	Total
Age (years)	70/71			
Mean (SD)		50.5 (9.3)	50.6 (9.5)	50.6 (9.4)
Median (IQR)		49.7 (45.1, 54.9)	49.6 (44.1, 58.3)	49.6 (44.7, 57.5)
Height (metres)	70/71			
Mean, SD		1.6 (0.1)	1.6 (0.1)	1.6 (0.1)
Median, IQR		1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)
Weight (kilograms)	70/71			
Mean, SD		76.8 (14.0)	72.6 (14.0)	74.7 (14.1)
Median, IQR		74.0 (66.8, 84.5)	71.0 (61.9, 83.8)	72.2 (64.0, 83.8)
BMI	70/71			
Mean, SD		28.6 (5.2)	27.7 (5.1)	28.1 (5.2)
Median, IQR		28.1 (24.7, 31.8)	27.0 (23.9, 30.5)	27.4 (24.4, 31.0)
Ethnicity (n, %)	70/71			
White		47 (67%)	52 (73%)	99 (70%)
Black		19 (27%)	13 (18%)	32 (23%)
Asian		1 (1%)	1 (1%)	2 (1%)
Mixed race		2 (3%)	3 (4%)	5 (4%)
Other		1 (1%)	2 (3%)	3 (2%)
Diabetic* (n, %)	70/71			
Diabetic		1 (1%)	4 (6%)	5 (4%)
Not Diabetic		69 (99%)	67 (94%)	136 (96%)
Insulin dependent (n, %)	1/4			
Insulin dependent		0 (0%)	1 (25%)	1 (20%)
Non-insulin dependent		1 (100%)	3 (75%)	4 (80%)
Hypertensive (n, %)	70/71			
No		63 (90%)	63 (89%)	126 (89%)
Yes		7 (10%)	8 (11%)	15 (11%)
Smoker* (n, %)	70/71			
Smoking		8 (11%)	10 (14%)	18 (13%)
Not smoking		62 (89%)	61 (86%)	123 (87%)
Smoking history (cigarettes/day)	6/9			
Mean, SD		6.0 (3.9)	8.0 (5.4)	7.2 (4.8)
Median, IQR		6.5 (2.0, 10.0)	10.0 (3.0, 10.0)	8.0 (2.0, 10.0)
Smoking history (packs/year)	7/9			
Mean, SD		8.6 (5.1)	13.8 (11.0)	11.5 (9.0)
Median, IQR		8.0 (5.0, 15.0)	11.0 (2.0, 23.0)	10.5 (3.5, 16.5)
BRCA carrier* (n, %)	70/71			
Carrier		13 (19%)	13 (18%)	26 (18%)
Not a Carrier		57 (81%)	58 (82%)	115 (82%)
Neoadjuvant therapy (n, %)	70/70			
None		48 (69%)	53 (76%)	101 (72%)
Chemotherapy		16 (23%)	11 (16%)	27 (19%)
Radiotherapy		2 (3%)	2 (3%)	4 (3%)
Chemotherapy + radiotherapy		4 (6%)	4 (6%)	8 (6%)
Previous breast surgery on study breast (n, %)	70/71			
No		55 (79%)	53 (75%)	108 (77%)
Yes		15 (21%)	18 (25%)	33 (23%)

<b>Baseline characteristic</b>	<b>N Control/ N Heated</b>	<b>Control</b>	<b>Heated</b>	<b>Total</b>
Type of previous breast surgery (n, %)	15/18			
Augmentation		0 (0%)	1 (6%)	1 (3%)
Reduction		0 (0%)	2 (11%)	2 (6%)
Wide local excision		5 (33%)	6 (33%)	11 (33%)
Wide local excision + radiotherapy		10 (67%)	9 (50%)	19 (58%)
Oncological reason for mastectomy	70/71			
No		12 (17%)	12 (17%)	24 (17%)
Yes		58 (83%)	59 (83%)	117 (83%)
Prophylactic reason for mastectomy	70/71			
No		58 (83%)	59 (83%)	117 (83%)
Yes		12 (17%)	12 (17%)	24 (17%)

\*minimisation variables. Note: percentages are rounded so might not always sum to 100%.

## Outcome measures

Skin necrosis within 30-40 days post-surgery by treatment group

Necrosis outcome	N Control/ N heated	Control	Heated
<b>Post-operative skin necrosis (n, %)</b>	66*/68**		
No		43 (65%)	50 (74%)
Yes		23 (35%)	18 (26%)
<b>Depth of necrosis at first occurrence (n, %)</b>	62/64		
A – none		44 (71%)	50 (78%)
B – colour change		11 (18%)	9 (14%)
C – partial thickness		7 (11%)	4 (6%)
D – full thickness		0 (0%)	1 (2%)
<b>Area of necrosis at first occurrence</b>			
Total area if necrosis present (mm <sup>2</sup> )	18/14		
Mean (SD)		1260.7 (1423.0)	1397.1 (1829.4)
Median (IQR)		850.0 (100.0, 2700.0)	700.0 (400.0, 1300.0)
Mix, Max		2.0, 4500.0	200.0, 6900.0
By SKIN score			
Area of colour change (mm <sup>2</sup> )	11/9		
Mean (SD)		962.9 (1413.0)	1616.7 (2132.8)
Median (IQR)		300.0 (50.0, 1020.0)	700.0 (600.0, 1300.0)
Mix, Max		2.0, 4500.0	250.0, 6900.0
Area of partial thickness (mm <sup>2</sup> )	7/4		
Mean (SD)		1728.6 (1411.2)	1202.5 (1303.9)
Median (IQR)		1500.0 (250.0, 3300.0)	730.0 (355.0, 2050.0)
Mix, Max		50.0, 3400.0	250.0, 3100.0
Area of full thickness (mm <sup>2</sup> )	0/1		
Mean (SD)		-	200.0 (-)
Median (IQR)		-	-
Mix, Max		-	-
Total area for all patients (including area=0mm <sup>2</sup> for none)	61/64		
Mean (SD)		372.0 (953.8)	305.6 (1014.6)
Median (IQR)		0.0 (0.0, 50.0)	0.0 (0.0, 0.0)
Mix, Max		0.0, 4500.0	0.0, 6900.0
<b>Maximum depth of necrosis over 30-40 day follow-up (n, %)</b>	62/64		
A – none		44 (71%)	50 (78%)
B – colour change		10 (16%)	9 (14%)
C – partial thickness		6 (10%)	3 (5%)
D – full thickness		2 (3%)	2 (3%)
<b>Maximum area of necrosis over 30-40 day follow-up</b>			
Total area if necrosis present (mm <sup>2</sup> )	18/14		
Mean (SD)		1288.4 (1432.8)	1397.1 (1829.4)
Median (IQR)		850.0 (100.0, 2700.0)	700.0 (400.0, 1300.0)
Mix, Max		2.0, 4500.0	200.0, 6900.0

<b>Necrosis outcome</b>	<b>N Control/ N heated</b>	<b>Control</b>	<b>Heated</b>
By SKIN score			
Area of colour change (mm <sup>2</sup> )	11/9		
Mean (SD)		1029.2 (1471.3)	1616.7 (2132.8)
Median (IQR)		485.0 (50.0, 1020.0)	700.0 (600.0, 1300.0)
Mix, Max		2.0, 4500.0	250.0, 6900.0
Area of partial thickness (mm <sup>2</sup> )	7/4		
Mean (SD)		1766.7 (1542.0)	1450.0 (1477.3)
Median (IQR)		1800.0 (250.0, 3300.0)	1000.0 (250.0, 3100.0)
Mix, Max		50.0, 3400.0	250.0, 3100.0
Area of full thickness (mm <sup>2</sup> )	0/1		
Mean (SD)		- (-)	200.0 (-)
Median (IQR)		- (-)	- (-)
Mix, Max		-	-
Total area for all patients (including area=0mm <sup>2</sup> for none)	61/64		
Mean (SD)		380.2 (965.8)	305.6 (1014.6)
Median (IQR)		0.0 (0.0, 50.0)	0.0 (0.0, 0.0)
Mix, Max		0.0, 4500.0	0.0, 6900.0
<b>Necrosis resolved/fully healed within 30-40 day follow-up (n, %)</b>	<b>17/13</b>		
No		8 (47%)	7 (54%)
Yes		9 (53%)	6 (46%)

\*Necrosis outcome missing for n=1 patient in control group who had SRM. The remaining n=3 control patients without the necrosis outcome withdrew prior to surgery \*\* Necrosis outcome missing for n=2 patients in heated group who had NSM or mastectomy only. The remaining n=1 heated patient without the necrosis outcome withdrew prior to surgery. All measurements reported here by primary clinical assessor.

#### Necrosis presence by minimisation variables

<b>Minimisation variable</b>	<b>Control</b>		<b>Heated</b>	
	<b>Necrosis (N=23) N (%)</b>	<b>None (N=43) N (%)</b>	<b>Necrosis (N=18) N (%)</b>	<b>None (N=50) N (%)</b>
Smoking				
Yes	3 (13%)	4 (9%)	2 (3%)	7 (14%)
No	20 (87%)	39 (91%)	16 (20%)	43 (86%)
Diabetic				
Yes	1 (4%)	0 (0%)	0 (1%)	4 (8%)
No	22 (96%)	43 (100%)	18 (22%)	46 (92%)
Type of reconstruction				
Implant	4 (17%)	9 (21%)	3 (4%)	10 (20%)
Autologous	19 (83%)	34 (79%)	15 (19%)	40 (80%)
BRCA carrier status				
Yes	3 (13%)	10 (23%)	2 (3%)	9 (18%)
No	20 (87%)	33 (77%)	16 (20%)	41 (82%)

Note: percentages are rounded so might not always sum to 100%.

## Adverse events

Event type	Control no. events (no. patients)	Heated no. events (no. patients)	Total no. events (no. patients)
AR	0 (0)	1 (1)	1 (1)
SAE	10 (7)	20 (15)	30 (22)
SAR	0 (0)	0 (0)	0 (0)
<b>Complication</b>			
Mastectomy Skin-flap necrosis (requiring surgery)	5	2	7
Infection	2	4	6
Haematoma	2	6	8
Re-do anastomosis	0	4	4
Flap failure	1	3	4
Burn	0	1	1

Number of patients shown in brackets as some patients had more than one safety event. AR – Adverse Reaction related to heating protocol, SAE – Serious Adverse Event not related to heating protocol, SAR – Serious adverse reaction related to heating protocol. Note: AE – Adverse events (not serious and not related to heating protocol) were not recorded in the PREHEAT database.