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## Research: Complications

# Infrared thermography and ulcer prevention in the high-risk diabetic foot: data from a single-blind multicentre controlled clinical trial

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### Abstract

**Aim** To assess the usefulness of monthly thermography and standard foot care to reduce diabetic foot ulcer recurrence.

**Methods** People with diabetes ( $n = 110$ ), neuropathy and history of  $\geq 1$  foot ulcer participated in a single-blind multicentre clinical trial. Feet were imaged with a novel thermal imaging device (Diabetic Foot Ulcer Prevention System). Participants were randomized to intervention (active thermography + standard foot care) or control (blinded thermography + standard foot care) and were followed up monthly until ulcer recurrence or for 12 months. Foot thermograms of participants from the intervention group were assessed for hot spots (areas with temperature  $\geq 2.2^\circ\text{C}$  higher than the corresponding contralateral site) and acted upon as per local standards.

**Results** After 12 months, 62% of participants were ulcer-free in the intervention group and 56% in the control group. The odds ratios of ulcer recurrence (intervention vs control) were 0.82 (95% CI 0.38, 1.8;  $P = 0.62$ ) and 0.55 (95% CI 0.21, 1.4;  $P = 0.22$ ) in univariate and multivariate logistic regression analyses, respectively. The hazard ratios for the time to ulcer recurrence (intervention vs control) were 0.84 (95% CI 0.45, 1.6;  $P = 0.58$ ) and 0.67 (95% CI 0.34, 1.3;  $P = 0.24$ ) in univariate and multivariate Cox regression analyses, respectively.

**Conclusions** Monthly intervention with thermal imaging did not result in a significant reduction in ulcer recurrence rate or increased ulcer-free survival in this cohort at high risk of foot ulcers. This trial has, however, informed the design of a refined study with longer follow-up and group stratification, further aiming to assess the efficacy of thermography to reduce ulcer recurrence.

Diabet. Med. 37, 95–104 (2020)

### Introduction

The burden of foot disease for an individual with diabetes and for society is well established [1]. Unhealed foot ulcers precede up to 84% of lower extremity amputations in people with diabetes. Even after healing, the ulcer recurrence rate is high [2–6]. In a recent study, 70% of participants had an

ulcer recurrence within 1 year despite regular podiatry care [7]. There is a need for evidence-based strategies not only to prevent the development of diabetic foot ulcers, but also to reduce their recurrence [8,9].

Measurement of foot skin temperatures has been put forward as a possible tool to identify people at risk of developing foot ulcer. The ability to detect clinically the initial signs of foot ulcers may be limited, and pre-ulcerative inflammation can be missed during routine podiatric assessment. It was Paul Brand who originally suggested the potential benefit of infrared thermography over and above clinical examination in the assessment of the insensate limb,

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**What's new?**

- Areas of the foot with raised skin temperatures may be an indication of pre-ulcerative inflammation in people with diabetes.
- We evaluated the utility of a novel thermal imaging device (the Diabetic Foot Ulcer Prevention System) in reducing foot ulcer recurrence in people with diabetes and history of  $\geq 1$  ulcer. Participants were randomized to intervention (active thermography + standard foot care) or control (blinded thermography + standard foot care) and assessed monthly until they developed a foot ulcer or for 12 months.
- Monthly intervention with thermography did not show a significant reduction in ulcer recurrence rate or increased ulcer-free survival in this cohort at risk of foot ulcers.

documenting that ‘the skin heats up before it breaks down’ [10,11]. Indeed, previous studies have shown that daily home measurement of foot temperatures at six plantar sites with a hand-held thermometer resulted in a significant reduction in ulcer recurrence in individuals at high risk of lower-extremity ulceration and amputation [12–14]. Participants allocated to intervention were one-third to one-tenth less likely to develop a foot ulcer compared to standard therapy alone [12,13]. In a more recent trial, the feasibility of home intervention with a thermometric foot mat for daily assessment of the plantar foot was reported, and an antecedent phase of 37 days from the onset of temperature rise to foot ulcer was reported [15]. Both methods indicated the potential advantage of daily temperature assessment in ulcer prevention [12–15], although, more recently, concerns have been raised regarding self-monitoring as a result of low concordance by study participants [16]. In addition, temperature assessment limited to the sole of the foot would probably miss pre-ulcerative inflammation elsewhere as only half of diabetic foot ulcers develop on the plantar surface [17].

We hypothesized that thermal imaging of all sites of the feet, integrated within the patient’s routine appointment to the foot clinic, could help the podiatrist to identify areas with raised temperature (or ‘hot spots’), which others have reported to be indicative of pre-ulcerative lesions [12–15]. If such lesions are promptly detected and managed in a timely manner, many ulcers can be prevented. To test this hypothesis, a novel prototype of a thermal imaging system for the feet (the Diabetic Foot Ulcer Prevention System) was developed by Photometrix Imaging Ltd in association with the University of South Wales [18]. The application of this device in the assessment of healthy feet, as well as its reliability in temperature assessment of feet, have been previously reported [19,20]. We have now investigated the safety and the performance of this instrument in a clinical

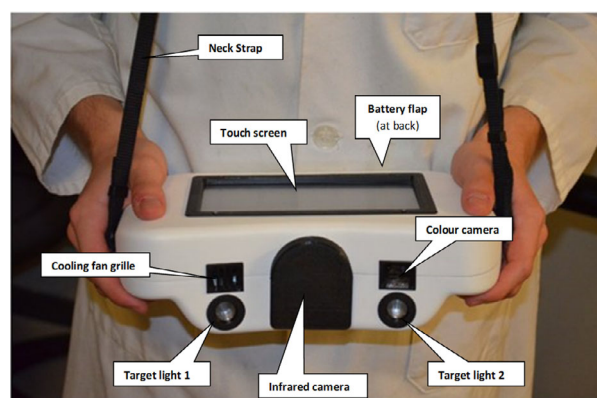
setting. In particular, we aimed to assess the usefulness of this novel thermal imaging system, together with clinical assessment and routine monthly podiatry foot care, in reducing the recurrence of diabetic foot ulcers in people with diabetes.

**Participants and methods****Trial design and participants**

This was a single-blind multicentre clinical trial, performed at three clinical centres in the UK from March 2016 to September 2017. Participants were aged  $\geq 18$  years and had a clinically confirmed diagnosis of type 1 or type 2 diabetes, a history of  $\geq 1$  ulcer, and intact feet (absence of a skin breakdown below the malleoli). To ensure the absence of any bias in the temperature response associated with the process of ulcer healing, we recruited only participants who had been free of foot ulcer for at least 3 months prior to recruitment. They were required to have peripheral neuropathy, palpable foot pulses on both feet (palpable posterior tibial artery pulse or dorsalis pedis artery pulse or both), footwear that, in the opinion of the investigator, was not likely to cause pressure damage [21], and no history of peripheral arterial disease. Individuals were excluded from study participation if they had a foot deformity (such as overriding toes) or a history of foot surgery (such as unilateral minor amputation) that, in the opinion of the investigator, could interfere with the interpretation of the thermal images, or were undergoing casting treatment for an active Charcot neuroarthropathy. Participants with an implantable electronic device were also excluded.

**Study device**

Thermography was carried out with a novel thermal imaging device (Fig. 1) [18]. The thermal imaging device is a portable two-camera battery-operated instrument for imaging plantar, dorsal, medial and lateral sites of each foot. One of the cameras is a standard digital colour camera that works with visible light and allows visual overlay with the other camera



**FIGURE 1** Thermal imaging device.

which is a digital infrared camera that registers the heat emissions from the foot and converts these into a temperature image (thermogram). The device is operated almost entirely via its touch screen. The operating distance is 45 cm, aided by an integrated dual target light projector. The thermal image and visible overlay images are captured simultaneously and are downloaded to computer for subsequent analysis.

All four devices used in the study (one for each centre and one as back-up) were calibrated by the National Physical Laboratory in accordance with the International Organization for Standardization, regulation number 17025, fully traceable to the international temperature scale with an uncertainty of  $0.2^{\circ}\text{C}$  ( $k = 2$ ).

### Procedures and interventions

The study consisted of an initial visit for screening and randomization (if eligible) and then monthly follow-up study visits for 1 year. Investigations at the screening visit included medical history, foot inspection, palpation of foot pulses, assessment of neuropathy and thermography. History of unilateral or bilateral foot ulcers and the number of previously healed foot ulcers were documented. Presence of deformity was recorded for each foot, and graded as no deformity, lesser toe deformities, prominent metatarsal heads, rocker bottom Charcot foot deformity, medial convexity Charcot foot deformity, prominent styloid process of the fifth metatarsal base and pes cavus (high arch, clawed toes, prominent metatarsal heads). Presence of neuropathy was confirmed by impaired sensation, as measured by the neurothesiometer (vibration perception threshold) at the apex of the hallux of  $\geq 25$  volts (V) on one or both feet. A vibration perception threshold  $> 50\text{V}$  was recorded as 50V for the purpose of the analysis.

After reviewing the inclusion/exclusion criteria, individuals who fulfilled the study requirements were randomized, using a simple method based on a computer-generated list, to either an intervention group (active thermography and standard foot care) or a control group (blinded thermography and standard foot care). Study participants were blinded to the group allocation.

For the purpose of blinding, during image acquisition, the thermal imaging device was set up to operate on the visual mode and only the captured visual images were available for viewing on the device. A baseline imaging sequence of all sites of the right and left foot including plantar, dorsal, medial and lateral views was captured after barefoot rest for 10 min on a podiatry chair (10 min post-socks off) and then repeated after 10 min (repeated imaging sequence at 20 min post-socks off). After successful download to a computer, access to the thermal images was granted to the research team at each recruiting centre for only those participants randomized to the intervention group.

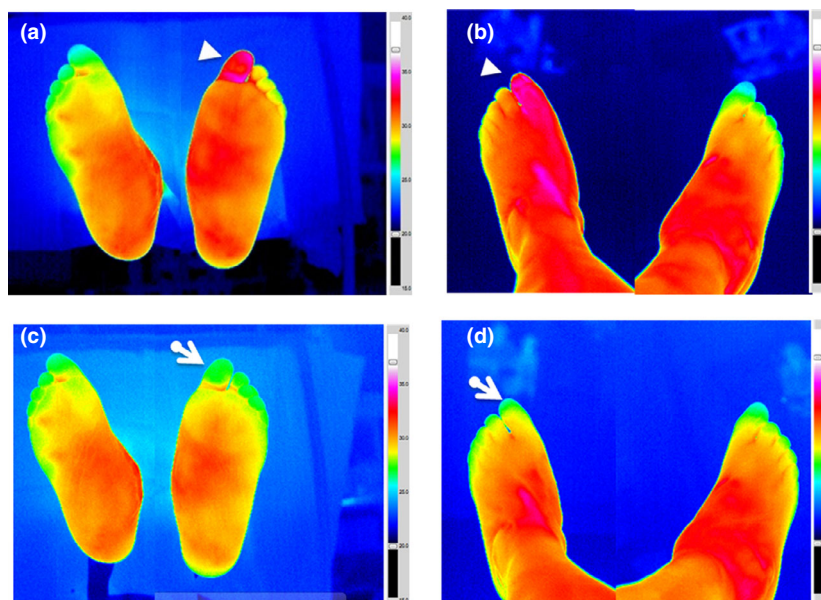
The captured thermal images were reviewed for the presence of hot spots on computers located outside the clinical assessment room. A hot spot was defined as an area with a temperature difference between corresponding sites of feet  $\geq 2.2^{\circ}\text{C}$  [12–14]. If the thermal image showed a hot spot on both sequences (baseline and repeated imaging sequence), which in the opinion of the investigator was potentially indicative of incipient tissue damage (Fig. 2a,b) the participant was advised to reduce daily physical activity and footwear advice was reinforced. The area of the hot spot was monitored and protected as per local standards of care including inspection of the area of concern and the institution of pressure relief (reduction of nail thickness, callus debridement, application of semi-compressed felt or adjustment of insoles as specifically indicated by the thermography). The individual was reassessed at 2 weeks and then followed up every 2 weeks (clinical visits) until the hot spot resolved. Resolution of the hot spot was defined as a temperature difference between corresponding sites of  $< 2.2^{\circ}\text{C}$  (Fig. 2c,d).

In addition to imaging with the thermal imaging device (active or blinded thermography), all participants underwent standard foot care, which included routine callus debridement and pressure offloading (general therapeutic offloading with footwear/insoles according to the guidelines of the International Working Group on the Diabetic Foot) [21], as per local standards of care. Participants were followed up in each recruiting centre until foot ulcer recurrence or up to a period of 12 months. Any ulcer below the malleoli on either foot regardless of the previous ulcer location was measured.

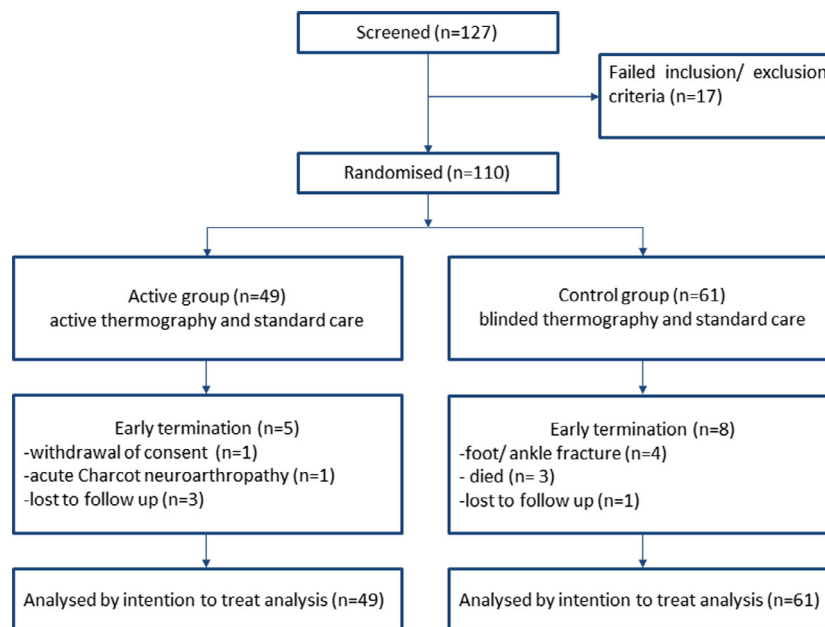
Quality of life was assessed with the EQ-5D-5L instrument at presentation, and then either at the time of ulcer recurrence or at 12 months. Permission for use of the paper version of EQ-5D-5L instrument was granted from the EuroQol Research Foundation. Each participant self-reported their level of mobility, self-care, usual activities, pain/discomfort and anxiety/depression as level 1 (best) to level 5 (worst), and their health status on a visual analogue scale from 0 (worst) to 100 (best).

### Outcome measures

The safety of the thermal imaging device was assessed at each visit by recording device-related adverse events. There were two primary endpoints with respect to evaluating the effectiveness of thermography in addition to standard care in reducing the incidence of diabetic foot ulcers of any type on either foot: a binary indicator for ulcer recurrence at 12 months and the time to ulcer recurrence. The recurrence of ulcer was defined as the full thickness loss of epidermis and dermis or involvement of deeper structures in the foot below the malleoli. The secondary endpoint was participant's quality of life.



**FIGURE 2** (a) Plantar and (b) dorsal thermal images of an individual with a history of healed left foot plantar ulcers (at the medial longitudinal arch and at the third metatarsal head). Thermal imaging revealed a hot spot at the apex of his left big toe noted on the plantar (a) and dorsal (b) thermal images (arrow head). There were no signs of skin breakdown, inflammation, redness or pain at this area. Thermography-guided therapy of the left hallux (callus removal and reduction of nail thickness) resulted in resolution of the hot spot 2 weeks later on both plantar (c) and dorsal (d) thermal images (white arrows).



**FIGURE 3** CONSORT diagram showing the participant flow through the clinical trial.

### Statistical analysis

The likelihood of ulcer recurrence by 12 months and the time to ulcer recurrence, were modelled with logistic and Cox regression analyses, respectively. The ordinal and continuous dimensions of quality of life were modelled with ordinal and linear regressions, respectively. Goodness of fit was run for all statistical models. In order to

adjust for potential confounders, the effect of variables that showed univariate significance  $< 0.20$  was examined in a multivariate model, which included variables that appeared imbalanced at baseline. An intention-to-treat analysis was adopted, with missing data analysis and multiple imputation used to assess the effect of early withdrawals on outcome. STATA v.14 was used for all statistical analysis.



### Sample size calculation

The sample size calculation was based on data from a previous clinical trial assessing the effectiveness of thermometry as adjuvant to standard care, where an odds ratio of 0.30 was obtained [12]. In addition, we estimated 50% to 70% of the participants in the control group to have an ulcer recurrence within 1 year. The rationale for this was clinical and is supported by findings of several studies; Armstrong *et al.* [6], based on a systematic review of 19 studies, reported this proportion to be ~40%, Khalifa [22] reported it as 61.3%, and other studies have reported it to be up to 70% [2–5,7]. Anticipating an ulcer recurrence rate in the control group of ~60%, an effective total sample of 98 participants (49 per treatment group) was sought to detect ulcer odds ratios (of intervention relative to control) of  $\leq 0.30$ , with 80% power, at the 5% significance level. We aimed to recruit a total of 110 participants, among the three clinical centres, to allow for a 10% drop-out rate. This sample size would also provide 80% power to detect hazard ratios of  $\leq 0.55$ , in terms of ulcer-free time and, an effect size of 0.58 in terms of the difference in the change in the quality of life for a visual analogue scale score from baseline.

### Ethics

The trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. It was approved by the London – Surrey Borders Research Ethics Committee (REC reference 15/LO/1940) and registered on the ClinicalTrials.gov website (NCT02579070). Each participant in the study was given an information sheet and all study participants provided written informed consent.

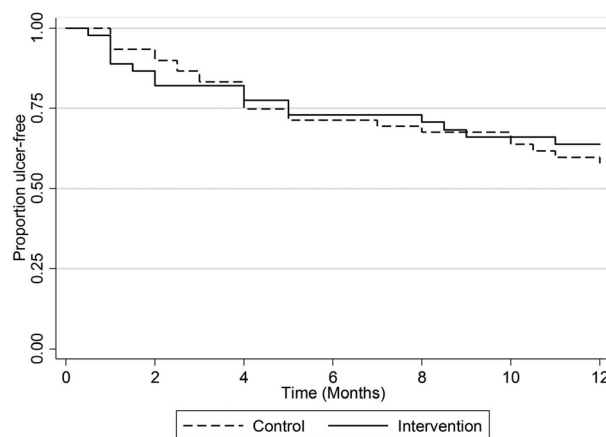
## Results

### Baseline characteristics

Overall, 127 people were screened and 110 were randomized (Fig. 3). Baseline demographic and clinical characteristics for the overall sample and for the control and intervention groups are shown in Table 1. The two groups were similar with regard to their demographic and clinical characteristics, with the exception of imbalance in age and presence of foot deformity (Table 1). The participants in the intervention group were younger and a greater proportion of them had more prominent foot deformities compared with the participants in the control group.

### Modelling of the likelihood of ulcer recurrence at 12 months

Univariate and multivariate modelling of the likelihood of ulcer recurrence at 12 months are shown in Table 2. On a univariate logistic regression, the odds ratio of ulcer



**FIGURE 4** Kaplan–Meier survival curves comparing the proportion of ulcer-free participants between the intervention group and the control group ( $P = 0.58$ ).

recurrence in the intervention group compared with the control group was 0.82 (95% CI 0.38, 1.8;  $P = 0.62$ ). On a multivariate logistic regression, after adjusting for age, history of healed ulcers, mean vibration perception threshold of right and left foot, and presence of foot deformity, the non-statistically significant difference of the effect of treatment between the intervention group and the control group remained (odds ratio 0.55 95% CI 0.21, 1.4;  $P = 0.22$ ). The Hosmer–Lemeshow test signalled a good fit for the logistic regression ( $P = 0.44$ ). These results were consistent when the repeated measures over the 12-month study period were taken into account [odds ratio 0.61 (95% CI 0.31, 1.2);  $P = 0.16$ ].

There were 13 withdrawals: eight from the control and five from the intervention group (Table 3). On logistic regression, the missing mechanism was classified as missing at random. There was an indication that the likelihood of withdrawal was related to type of diabetes and vibration perception threshold. Multiple imputation with 50 imputations was used to simulate the possible scenario if these 13 participants had not left the study. The model estimation was based on the complete case logistic regression (for ulcer) for the withdrawals, and linear regression for the participants with missing age and BMI. The results of the missing data analysis were remarkably consistent with those given by the multiple regression model (Table 2).

### Modelling the time to ulcer recurrence

By the end of the study period, 29 participants (56%) remained ulcer-free in the control group and 27 (62%) in the intervention group (Table 3). In the intervention group, 55.3% of the participants required thermography-guided therapy at least once in response to a hot spot, indicative of incipient tissue damage. A total of 41 participants developed a foot ulcer during the study period. The sites of ulcer recurrence in the control group included 13 plantar and 11

**Table 1** Baseline characteristics for the overall cohort and per treatment group

	Overall sample <i>n</i> = 110	Control group <i>n</i> = 61	Intervention group <i>n</i> = 49
Mean (95% CI) age, years	62 (60, 64)	64 (61, 67)	60 (56, 63)
Men, <i>n</i> (%)	83 (76)	45 (74)	38 (79)
Women, <i>n</i> (%)	26 (24)	16 (26)	10 (21)
Type 1 diabetes, <i>n</i> (%)	29 (27)	13 (21)	16 (37)
Type 2 diabetes, <i>n</i> (%)	81 (73)	48 (79)	33 (67)
Median (25–75 percentile) duration of diabetes, years	18 (10–26)	18 (10–26)	19 (13–24)
Mean (95% CI) BMI, kg/m <sup>2</sup>	31 (29.9, 32.4)	31 (29.5, 33.0)	31 (29.3, 32.8)
Mean (95% CI) vibration perception threshold of both feet	39 (36.8, 40.3)	39 (36, 41)	39 (36.1, 41.4)
Right foot deformities (categorical), <i>n</i> (%)			
No deformity	31 (28.2)	18 (29.5)	13 (26.5)
Lesser toe deformities	53 (48.2)	34 (55.7)	19 (38.8)
Prominent metatarsal heads	6 (5.5)	1 (1.6)	5 (10.2)
Rocker bottom Charcot foot deformity	4 (3.6)	2 (3.3)	2 (4.1)
Medial convexity Charcot foot deformity	6 (5.5)	3 (4.9)	3 (6.1)
Prominent styloid process of 5th metatarsal base	5 (4.6)	1 (1.6)	4 (8.2)
Pes cavus	5 (4.6)	2 (3.3)	3 (6.1)
Right foot deformities (ordinal), <i>n</i> (%)			
No deformity	31 (28.2)	18 (26.5)	13 (26.5)
Lesser toe deformity	53 (48.2)	34 (55.7)	19 (38.8)
More prominent deformities*	26 (23.6)	9 (14.8)	17 (34.7)
Left foot deformities (categorical), <i>n</i> (%)			
No deformity	34 (30.9)	19 (31.2)	15 (30.6)
Lesser toe deformities	56 (50.9)	33 (54.1)	23 (46.9)
Prominent metatarsal heads	5 (4.6)	1 (1.6)	4 (8.2)
Rocker bottom Charcot foot deformity	3 (2.7)	2 (3.3)	1 (2.0)
Medial convexity Charcot foot deformity	6 (5.5)	3 (4.9)	3 (6.1)
Prominent styloid process of 5th metatarsal base	1 (0.9)	0 (0)	1 (2.0)
Pes cavus	5 (4.6)	3 (4.9)	2 (4.1)
Left foot deformities (ordinal), <i>n</i> (%)			
No deformity (0)	34 (31)	19 (31.2)	15 (30.6)
Lesser toe deformity (1)	56 (51)	33 (54.1)	23 (47)
More prominent deformities*	20 (18)	9 (14.7)	11 (22.4)
Right and left feet deformities (ordinal)			
No deformity	25 (22.7)	14 (23)	11 (22.5)
Lesser toe deformity	53 (48.2)	34 (55.7)	19 (38.8)
More prominent deformities	32 (29.1)	13 (21.3)	19 (38.8)
Deformity in either foot (prominent* vs none/lesser-toe deformity), <i>n</i> (%)	32 (29.1)	13 (21.3)	19 (38.8)
Number of healed foot ulcers, <i>n</i> (%)			
1 ulcer	53 (48.2)	34 (55.7)	19 (38.8)
2 ulcers	42 (38.2)	19 (31.2)	23 (46.9)
≥3 ulcers	15 (13.6)	8 (13.1)	7 (14.3)
Past history of ≥ 2 healed ulcers vs 1 ulcer (binary), <i>n</i> (%)	57 (51.8)	27 (44.3)	30 (61.2)
History of unilateral or bilateral healed foot ulcers, <i>n</i> (%)			
Right foot	35 (31.8)	21 (34.4)	14 (28.6)
Left foot	36 (32.7)	22 (36.1)	14 (28.6)
Both feet	39 (35.5)	18 (29.5)	21 (42.8)
History of bilateral vs unilateral healed foot ulcers, <i>n</i> (%)	39 (35.5)	18 (29.5)	21 (42.8)

Prominent deformities (prominent metatarsal heads, rocker bottom Charcot foot deformity, medial convexity Charcot foot deformity, prominent styloid process of the fifth metatarsal base, pes cavus).

non-plantar foot ulcers (eight on the dorsum and three on the medial site of the foot) and only nine out of 21 ulcers recurred at a site of a previously healed foot ulcer. Three participants developed an ulcer in a previously non-ulcerated foot. The sites of ulcer recurrence in the intervention group included nine plantar and eight non-plantar foot ulcers (seven on the dorsum and one on the lateral site of the foot), and only eight out of 17 ulcers recurred at the site of a previously healed ulcer. One participant developed an ulcer on a previously non-ulcerated foot.

The time to ulcer recurrence in the intervention group and control group is presented in Fig. 4. The univariate and multivariate Cox regression models are shown in Table 4.

The unadjusted hazard ratio for time to ulcer recurrence (intervention vs control) was 0.84 (95% CI 0.45, 1.6;  $P = 0.58$ ). On multivariate Cox regression analysis after adjusting for age, history of ≥ 2 healed foot ulcers, mean vibration perception threshold of right and left foot and presence of more prominent foot deformity, the hazard ratio for the time to ulcer recurrence (intervention vs control) was

**Table 2** Univariate and multivariate logistic regressions of the likelihood of ulcer recurrence at 12 months

Outcome: foot ulcer (Yes/No)	Univariate (complete case) <i>N</i> = 110		Multivariate (complete case) <i>N</i> = 96		Multivariate (multiple imputation) <i>N</i> = 110	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Age	0.98 (0.96, 1.02)	0.52	0.99 (0.94, 1.03)	0.40	0.97 (0.93, 1.01)	0.09
Men vs women	0.53 (0.20, 1.4)	0.20				
BMI	1.02 (0.96, 1.1)	0.62				
Type 2 vs type 1 diabetes	1.8 (0.71, 4.6)	0.21				
Duration of diabetes	0.99 (0.97, 1.03)	0.88				
Past history of healed ulcers, $\geq 2$ vs 1	2.9 (1.3, 6.6)	0.01	3.3 (1.3, 8.2)	0.01	1.8 (0.8, 4.1)	0.16
Side of healed ulcers, bilateral vs unilateral	1.7 (0.75, 4.1)	0.20				
VPT, mean right/left foot	1.1 (1.03, 1.1)	0.002	1.1 (1.0, 1.1)	0.01	1.05 (1.0, 1.1)	0.02
Deformity in either foot, prominent vs none/lesser-toe	2.1 (0.91, 4.9)	0.08	1.8 (0.63, 4.8)	0.28	1.0 (0.41, 2.6)	0.96
Treatment intervention vs control	0.82 (0.38, 1.8)	0.62	0.55 (0.21, 1.4)	0.22	0.54 (0.23, 1.17)	0.16

VPT, vibration perception threshold.

**Table 3** Life table to show early terminations and ulcer recurrence in the control group and in the intervention group

Time (months)	Control group ( <i>n</i> = 61)					Intervention group ( <i>n</i> = 49)				
	At risk	Ulcers	Early termination	Ulcer-free	95% CI	At risk	Ulcers	Early termination	Ulcer-free	95% CI
0	61			1		49	2	3	0.96	(0.84, 0.99)
1	61	4	2	0.93	(0.83, 0.97)	44	5	1	0.85	(0.71, 0.92)
2	55	4	0	0.87	(0.75, 0.93)	38	2	0	0.80	(0.66, 0.89)
3	51	2	0	0.83	(0.71, 0.91)					
4	49	5	1	0.75	(0.61, 0.84)	36	2	0	0.76	(0.61, 0.86)
5	43	2	1	0.71	(0.57, 0.81)	34	2	0	0.71	(0.56, 0.83)
6	40	0	1	0.71	(0.58, 0.81)					
7	39	1	1	0.69	(0.56, 0.79)					
8	37	1	1	0.67	(0.54, 0.78)	32	2	0	0.67	(0.51, 0.79)
9						30	1	0	0.65	(0.49, 0.77)
10	35	3	1	0.61	(0.47, 0.73)					
11	31	1	0	0.59	(0.45, 0.71)	29	1	1	0.62	(0.47, 0.75)
12	30	1		0.56	(0.41, 0.68)	27	0		0.62	(0.47, 0.75)

0.67 (95% CI 0.34, 1.3; *P* = 0.24). Based on the Schoenfeld residuals test, the proportionality of hazards assumption of the Cox model was validated in the unadjusted [chi-squared (1 d.f.) = 1.1; *P* = 0.29] and adjusted model [chi-squared (5 d.f.) = 3.65; *P* = 0.60].

### Quality of life

The ordinal regression models for the five dimensions of the EQ-5D-5L instrument (mobility, self-care, usual activities, pain and anxiety/depression) and the linear regression model for the health status (self-reported visual analogue scale) are presented in Table S1. After adjusting for the baseline value of each dimension and health status, at follow-up, there were no significant differences for any of the five dimensions or for the health status between the intervention and control groups (*P* > 0.05 for all dimensions).

### Discussion

The present single-blind multicentre controlled clinical trial showed that monthly intervention with a novel thermal

imaging device in addition to standard care did not lead to significant reduction in the ulcer recurrence rate or a significant increase in ulcer-free survival in people at high risk of diabetic foot. There were no associated device-related adverse events, indicating that thermal imaging with the proposed study device would be safe for the assessment of the diabetic foot.

Previous clinical trials of daily plantar skin foot temperature assessment of diabetic feet have produced variable results. These studies applied the asymmetry approach using a temperature difference of at least 2.2°C between corresponding sites of feet as this is the currently accepted method of identifying participants at risk of foot ulcer [12–14,23,24]. Early studies consistently showed that daily temperature measurement significantly reduced ulcer recurrence in people with neuropathy at increased risk of foot ulcers [12–14], whereas in a more recent study the ulcer recurrence rate was similar between the intervention group and the control group (39% vs 50%, non-significant difference) [25]. The present study was also negative. Although we assessed temperature difference between corresponding sites not only on the



**Table 4** Time to ulcer recurrence: univariate and multivariate Cox's regression models

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	0.98 (0.95, 1.01)	0.19	0.98 (0.96, 1.02)	0.34
Gender (male vs female)	0.56 (0.24, 1.3)	0.19		
BMI	1.02 (0.97, 1.1)	0.48		
Type of diabetes (type 2 vs type 1)	1.6 (0.76, 3.6)	0.21		
Duration of diabetes	1.0 (0.97, 1.02)	0.73		
VPT (mean right and left foot)	1.06 (1.02, 1.1)	0.004	1.04 (1.01, 1.08)	0.02
History of healed ulcers (continuous)	1.2 (0.95, 1.5)	0.12		
Side of healed foot ulcers (bilateral or unilateral)		0.27		
Bilateral vs unilateral healed foot ulcers	1.67 (0.89, 3.1)	0.11		
Number of healed ulcers		0.06		
2 vs 0–1 ulcer	2.2 (1.1, 4.5)	0.02		
≥3 vs 0–1 ulcer	2.2 (0.87, 5.4)	0.10		
Past history of ≥ 2 vs 1 healed ulcers	2.2 (1.15, 4.3)	0.02	2.1 (1.1, 4.2)	0.03
Deformity in either foot		0.22		
Lesser toe vs none	1.0 (0.44, 2.5)	0.91		
Prominent vs none	1.8 (0.75, 2.4)	0.19		
Deformity in either foot (prominent vs none/lesser-toe deformity)	1.8 (0.93, 3.3)	0.08	1.7 (0.84, 3.3)	0.14
Treatment group (intervention vs control)	0.84 (0.45, 1.6)	0.58	0.67 (0.34, 1.3)	0.24

VPT, vibration perception threshold.

plantar foot but also on the medial, lateral and dorsal aspect of the foot, intervention with thermal imaging did not significantly reduce ulcer recurrence rate. This may have been because thermography was carried out only at monthly intervals; however, a recent randomized controlled trial showed that there was no statistically significant difference in ulcer recurrence rate at 1 year whether the interval between podiatric appointments was 2, 4 or 8 weeks [7].

In addition to non-significant difference in ulcer recurrence, there was no significant difference in time to ulceration in the intervention group vs the control group. The Kaplan–Meier plot did not show a significant difference in the time to ulcer recurrence between the groups ( $P = 0.58$ ). It is important to note that the median ulcer-free time was not observable in either group, as in both groups > 50% of participants remained ulcer-free at the end of the study period; thus, a longer follow-up period might have been more informative in comparing the effect of intervention on time to ulcer recurrence.

Unequal allocation may occur as a result of the simple randomization process. Our randomization resulted in 61 participants allocated into the control group and 49 allocated to the intervention group. Although our allocation ratio was only slightly uneven (4:5), we checked that the power of the analysis was not affected. Re-calculating the power, we found that, with the intervention-to-control split that we obtained (0.8:1), the test would still have had the intended power, 80%, to detect the sought difference at the 5% significance level. In addition, we evaluated goodness of fit of the regression models and performed data imputation for the withdrawals. These results were consistent with the complete case analysis and validated the intention-to-treat principle in the present study.

Even though the groups were well matched for demographic and clinical characteristics, participants in the intervention group appeared to be younger and to have more prominent foot deformities compared with the participants in the control group; however, the proportion of participants who remained ulcer-free was similar in both groups (62% in the intervention group and 56% in the control group). Although the overall ulcer recurrence rate in the present study was lower than previously reported, [2–5,7] recurrence was associated with history of two or more healed ulcers and increased vibration perception threshold, consistent with previous observations [6,26,27]. Further research in a larger sample for which the participants would need to be randomized into stratified groups taking into consideration age, type of diabetes and foot deformity with a longer follow-up period (of at least 18 months) is therefore merited.

Recurrence of foot ulcer can be affected by various factors which were difficult to control and these contributed to the limitations of the study. Palpation of pulses does not entirely rule out peripheral arterial disease [28] and participants may have had mild arterial disease which could have affected the rate of ulcer recurrence. Also, when a hot spot was detected, participants were asked to reduce daily physical activity, but we were not able to monitor the physical activity of the participants. Also, the importance of wearing special footwear was stressed, but it is possible that not all study participants wore their prescribed footwear. Applying a plaster cast to a foot with a hot spot may have been an alternative approach to achieve optimum pressure relief. Also, previous studies have used a protocol that required confirmation of a temperature difference the following day rather than 14 days later before instructing the participant to change behaviour and report to a foot care professional [16]. Our protocol was based on a clinic

assessment, however, and it was not practical for participants to return the next day. Using daily temperature monitoring with smart mat technology, Frykberg *et al.* [15] reported an antecedent phase of 37 days from the onset of temperature rise to foot ulcer; thus, our 2-week follow-up would have been within this period. Finally, we selected individuals with a very high baseline risk of ulcer recurrence which may have offset any predictive value of ulcer recurrence that the infrared thermography might have had.

Although the ulcer recurrence rate and ulcer-free survival were not significantly different between the intervention and the control groups, the present trial has informed the design of a refined study to further assess the relative efficacy of thermography. Based on recent observations that ulcer recurrence is not only limited to the plantar foot [6,17], which was confirmed by the present study (50% of ulcers had non-plantar location), a combination of clinical thermography of all sites of the feet in addition to standard podiatric assessment and foot care, supplemented with daily home temperature self-assessment, might increase the effectiveness of this method to predict the development of foot ulcers in people with diabetes.

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#### Competing interests

None declared.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** Quality of life baseline-adjusted regression models to assess treatment difference between the groups (intervention vs control).