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TITLE

Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study

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Glycaemic control for diabetic foot ulcers

ABSTRACT

Introduction One in four diabetes patients will develop a foot ulcer over their lifetime. The role of glycaemic control in diabetic foot ulcer healing is not supported by randomised controlled trial (RCT) data.

Objectives: To determine the feasibility of an RCT of glycaemic control with intensive insulin therapy in diabetic foot ulcer, by assessing: entry criteria; adherence to control regimen; medication satisfaction; sensitivity of different ulcer-healing endpoints to glycaemic control.

Design Two substudies: one cross-sectional, one single-arm prospective.

Setting Single-centre secondary care diabetic foot clinic in New Zealand.

Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy.

Intervention Substudy 1: none. Substudy 2: Intensive insulin therapy with standard podiatry care over 24 weeks.

Outcome measures Substudy 1: Proportion of participants satisfying potential RCT entry criteria; medication satisfaction (DiabMedSat). Substudy 2: Fasting capillary blood sugar (FCBS); index ulcer healing time; index ulcer size; health-related quality of life (HRQoL; EQ-5D-5L and DFS-SF).

Results Proportion in Substudy 1 satisfying all entry criteria was 31% (95% CI 21 to 42). FCBS values decreased between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8), suggesting adherence to control regimen; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBS correlated negatively with medication satisfaction. Ulcer area logarithm was most sensitive to FCBS changes, displaying significant negative correlation with HRQoL outcomes. Detecting a 30%

between-group difference in this outcome (80% power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to study setting.

Conclusions An adequately powered RCT requires co-operation between a large number of centres. Ulcer area logarithm should be primary endpoint.

Trial registration ANZCTR ACTRN12617001414303

Strengths and limitations of this study

- First study in 15 years to examine the feasibility of a definitive randomised controlled trial (RCT) of intensive insulin therapy for diabetic foot ulcers.
- Use of imaging techniques allowed assessment of various ulcer-size-related outcomes as potential primary endpoints for an RCT.
- The target sample size of 20 for Substudy 2, examining the retationship between ulcer healing and glycaemic control, was not achieved during the study period.
- The study was conducted in a single centre in New Zealand, limiting generalisability to other populations and settings with different pathways for diabetes and diabetic complications.

KEYWORDS

Diabetic Foot
Blood Glucose
Wound Healing
Outcome Assessment (Health Care)
Sample Size

Introduction

One in four diabetes patients will develop a foot ulcer in their lifetime [1]. Diabetic foot ulcer is one of the most significant complications of diabetes [1-4] and often responds poorly to treatment, with only one-third of those managed in secondary care healing by 3 months and one-half at 6 months [5]. Non-healing ulcers are an important cause of lower extremity amputation. Most notable causes of foot ulceration are peripheral neuropathy, peripheral vascular disease and structural foot disease [6] [7]. These factors are linked to hyperglycaemia [8-10] and pathological states associated with diabetes.

A meta-analysis of nine randomised controlled trials in nearly 11,000 participants showed that intensive glycaemic control potentially improved the incidence of diabetic foot ulcer, decreased the risk of amputation and improved sensory nerve function compared with less intensive control [11]. As a result, clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers [1].

The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational [11-17]. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing [18]. A previous feasibility study in this area [19] concluded 15 years ago that a definitive randomised trial in this area was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less

stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2). In Substudy 2, presence or absence of peripheral neuropathy, peripheral vascular disease and foot deformities were noted as they were identified factors in the genesis of diabetic foot ulcers. Data on microcirculation in the feet were also collected using novel laser imaging technology. This report focuses on data from Substudy 1 and Substudy 2; the laser imaging data analysis will be reported separately.

The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT. Entry criteria used in the previous feasibility study [19] were revised as follows: removing the requirement for chronic ulcers (>4 weeks); removing the ulcer size criterion (25-2500 mm^2), and including participants with a higher HbA1c (≥58 mmol/mol), renal disease and/or a history of hypoglycaemia. Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication.

In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes (ulcer area, change in ulcer area, and time to complete healing) to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between adherence (using glycaemic control as proxy), as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.

Materials and methods

Setting and Study Design

The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between February and October 2015, with Substudy 2 follow-up to February 2016. Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (Table 1) and treating them with intensive insulin therapy for 24 weeks.

The protocol was approved by the New Zealand Northern A Health and Disability Ethics Committee (ref: 14/NTA/195). All participants provided informed written consent.

Accrual periods and sample size

The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder. To distinguish between recruitment of existing patients and new patients, we prospectively defined two recruitment periods. The first period of recruitment (Period A) was to finish from the moment at which only newly enrolled clinic patients started to be recruited in the study, giving way to Period B.

Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area) with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.

<<Table 1 approximately here>>

Study procedures and outcomes

Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire [20 21]. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed. The following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBS measurement (in mmol/L); medication review; and adverse events assessment. FCBS was used in the analyses as a measure of glycaemic control and as a proxy for adherence. HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. By contrast, fasting capillary glucose or mean daily capillary glucose may provide evidence of acute improvement of glycaemia in a short-term clinical trial [18]. In addition, participants completed three questionnaires at each visit: DiabMedSat [20 21], EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) [22 23] and Diabetic Foot Ulcer Scale-Short Form (DFS-SF) [24].

Intervention

On entry to Substudy 2, intermediate- or long-acting insulin was initiated or adjusted, and given in addition to usual oral hypoglycaemic tablet therapy, consistently with international guidelines [25]. Short-acting mealtime insulin was provided as appropriate. The goal was to maintain FCBS at 4–7 mmol/L, with ≤2 episodes of mild hypoglycaemia per week.

Substudy 2 participants received usual podiatry care at each visit, including ulcer debridement, orthotics prescription and adjustments, antibiotics if indicated and education.

Statistical analyses

Substudy 1

Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment and DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. Models were compared using deviance tests.

Substudy 2

The analysis set for this feasibility study consisted of all participants having initiated treatment. All analyses were carried out on the index ulcers, present at the first visit. All participants had a single index ulcer.

Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm^2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight

management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using all available longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing outcome; between DiabMedSat subscores and FCBS; and between DFS-SF subscores and EQ-5D-5L.

Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.

No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness [26].

Results

Participants

<<Table 2 approximately here.>>

Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 (Table 2). Mean age was 57 years (SD 14). The majority were men and most were of Pacific or European ethnicity. No data were missing for Substudy 1. All participants were identified as having some measure of foot deformity, judged unlikely to affect ulcer healing by the treating podiatrists. However,

no objective measure of foot deformity, to our knowledge, has been assessed for association with ulcer healing.

Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set, assessed on a total of 90 occasions.

Completeness

Two participants with unhealed ulcers did not attend the 24-week visit (13%, 95% CI 2 to 40). Of the 102 scheduled visits, 12 were missed, yielding an attendance proportion of 91% (95% CI 79 to 96), accounting for clustering by participant. Average follow-up time to healing or last visit was 17.6 weeks (SD 7.8). Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DiabMedSat and FCBS) and 85% (ulcer area).

Recruitment rate and entry criteria

Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B.

All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8%, 95% CI 20.8 to 42.2) met all criteria. Removal of any single criteria increased eligibility proportion appreciably only in the case of IC2 (to 37.2%, 95% CI 26.5 to 48.9) and IC5 (to 38.5%, 95% CI 27.7 to 50.2). The probabilities of participants meeting entry criteria differed between periods A and B (Fig. 1); the criterion-period interaction term was significant (P=0.009). The A-to-B rate ratio of eligibility to a full study was 4.1 (95% CI 1.8 to

9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24 to 0.77).

<<Figure 1 approximately here.>>

Diabetes Medication Satisfaction

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 2. Median score for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]). MANOVA demonstrated no significant variation in subscale scores based on ethnicity, sex or diabetes duration, but there was significant variation in the Burden (P = 0.005) and Symptom (P=0.026) scores based on age (generally higher in older participants).

<<Figure 2 approximately here.>>

Glycaemic control

FCBS values during the study indicated that participants were generally adhering to their glycaemic control regimen. Between study end and baseline, the mean difference in FCBS was -3.7 mmol/L (95% CI -6.5 to -0.8) and in HbA1c was -9.4 mmol/mol (95% CI -19.0 to 0.3).

Selection of primary endpoint for RCT

<<Table 3 approximately here.>>

Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer-healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0 to 56.1).The Cox

model showed no significant association between time to ulcer healing and FCBS (Table 3).

Log(ulcer area in cm^2+0.01) (heareafter "log of ulcer area") and ulcer area absolute rate of change were the only ulcer healing outcomes sensitive to change in FCBS (Table 3). The former was selected as most sensitive to changes in FCBS, with effect size of 0.08 per mmol/L increase in FCBS, adjusted for both time and baseline value. Time adjustment was intended to account for non-glycaemia-related improvements and interventions such as podiatric care. Between- and within-participant outcome variances were estimated at 1.3 and 0.4 respectively.

Validation of selected outcome with QOL measures

<<Table 4 approximately here.>>

DFS-SF scores tended to increase over time (i.e. improved HrQOL); increases reached statistical significance for four of the six subscales (Leisure [*P*=0.05], Dependence [*P*=0.01], Negative emotion [*P*=0.001] and Worried about ulcers [*P*=0.04]). All six subscales showed statistically significant, moderate-to-strong negative correlation with log of ulcer area (Table 4).

Participant satisfaction and adherence to intensive insulin therapy

Glycaemia levels displayed weak to moderate negative correlation with the DiabMedSat scores. The correlation of FCBS with the Burden subscale was -0.35 (95% CI -0.59 to -0.09; *P*=0.01), with the Efficacy subscale -0.42 (95% CI -0.61 to -0.18; *P*=0.0009) and with the Symptoms subscale -0.21 (95% CI -0.47 to 0.08, *P*=0.15).

Health-related QOL

The EQ-5D-5L VAS displayed moderate to strong positive correlation with all six DFS-SF subscale scores (Table 4).

Modelling of attendance

The model explaining attendance with smallest AIC involved the DiabMedSat Burden score only, with an attendance odds ratio of 1.78 (95% CI 1.26 to 2.51; *P*=0.001) per 10-point score increase.

Discussion

Key findings

This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) [19]. The study also showed that the primary endpoint of log of ulcer area, with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.

In terms of design and conduct of an RCT of intensive glycaemic control versus standard care in people with diabetic foot ulcers, analysis showed that the largest gains in eligibility from removal of a single criterion would occur by waiving IC2 or IC5. IC5 cannot of course be waived, since participant consent is compulsory in any ethical clinical trial. However if glycaemic control is efficacious in individuals with recently developed diabetes, IC2 could perhaps advantageously be relaxed.

Further findings are indications that acting on the medication burden may improve attendance and that acting on medication satisfaction in general, and satisfaction

with efficacy in particular, may improve adherence to the control regimen. In both cases, however, the evidence obtained is only correlational and not causal.

Relationship to other studies

Ulcer healing data suggested an early beneficial effect of intensive insulin therapy; median healing time was 7 weeks after the initial visit, and by week 21 an estimated 17% of ulcers had not healed. Over a similar timeframe, much lower healing rates have been reported with standard care (e.g. 31% at 20 weeks in a meta-analysis [27]). Even when standard care included insulin, a retrospective study found that only 30% of ulcers had healed after 1.1 months [28]. This result may be due to the high (weekly) frequency of the first four visits in Substudy 2, allowing more opportunities for treatment such as wound debridement, and orthotic or medication adjustments .

Implications for a full study

The log of the ulcer area outcome proved sensitive to glycaemic control even controlling for time since study entry, and was correlated with DFS-SF subscores, corroborating the validity of the measure. Using this measure as primary endpoint, a target reduction in ulcer size of 30% would correspond to a 3 mmol/L average difference in FCBS (corresponding to the difference between the lower bounds of normal glycaemia and a diagnosis of diabetes), with intensive glycaemic control versus standard care. In an RCT, 220 participants per arm would be required to detect a between-group decrease of 30% with 80% power at a 5% significance level. At the differential eligibility rates observed in both periods and assuming a loss to follow-up of 10%, such a number could be achieved within about one year if 15 centres similar to ours were recruiting participants.

Good reductions in FCBS over the first 4 weeks of intensive insulin therapy were seen, but more variable levels observed afterwards. To achieve optimal improvements in glycaemic control over the course of a longer-term RCT more regular visits may be necessary after the first 4-6 weeks of therapy than were used in our feasibility study and more daytime FCBS recordings done to optimise therapy.

The EQ-5D VAS appeared to have good convergent validity with the specialised DFS-SF, indicating its appropriateness as a generic QOL measure in our study population, opening the door to valid economic analyses. We also realise the importance of objective quantification of neuropathy, peripheral vascular disease and foot deformities enabling stratification at randomisation in the larger trial as they are the most notable causative factors of diabetic foot ulceration [29].

Tight glycaemic control relies on long-term patient adherence [1]. Satisfied patients are more likely to adhere to recommendations regarding not only medication use and follow-up visits but also dietary habits and physical activity [30]. Our findings showed that our participants' perception of diabetes medication burden was strongly associated with adherence and attendance, suggesting that intervening on burden may promote attendance.

Limitations

Some limitations temper the interpretation of our results. Firstly, Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT. Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

Conclusion

The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemic control as expressed by FCBS.

This feasibility study is the first since 2005 to investigate issues relevant to the initiation of a definitive RCT evaluating the impact of intensive insulin therapy on ulcer healing in people with diabetes. The results of such a trial would be useful to inform evidence-based clinical practice guidelines. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.

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Contributors A.C.V. and A.D. and designed the study and co-wrote the manuscript. A.D. oversaw the intervention and contributed to the discussion. A.C.V. contributed to data management, data monitoring and analysis planning and conduct. D.P. contributed to statistical analyses. B.M. coordinated the research. R.G. and A.N. provided podiatric care and contributed to discussion. A.D. and A.C.V. take responsibility for the contents of the article, study design, access to data and the decision to submit and publish the results.

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Disclaimer The joint lead authors A.D. and A.C.V. affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted except as noted in the text, and that any discrepancies from the study as planned have been explained.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics approval was given for the study by the New Zealand Northern A Health and Disability Ethics Committee, ethics approval number 14/NTA/195.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data sharing statement Data are available. Please contact corresponding author.

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Figure legends

Figure 1 – Point estimate and confidence interval of probability of each criterion being met by recruitment period. Period A was 0-5 weeks and Period B was 6-35 weeks. FC, full criteria; EC, exclusion criterion; IC, inclusion criterion.

Figure 2 – Histograms of participant scores on the three subscales of the Diabetes Medication Satisfaction questionnaire: (a) Burden, (b) Symptoms and (c) Efficacy subscales. Subscales are scored from 0-100, higher scores indicating greater satisfaction.

Tables

Table 1 Entry criteria assessed in Substudy 1

Criteria	Notation	Description
Inclusion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA1c ≥60 mmol/mol
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

EC, exclusion criteria; HbA1c, glycosylated haemoglobin; IC, inclusion criteria.

Table 2 Characteristics of participants included in both substudies

	Substudy 1 Participants (n=78)	Substudy 2 Participants (n=15)
Median age (IQR), years	58.5 (18.2)	51 (16.5)
Women, *n* (%)	30 (38.5)	6 (40)
Median baseline HbA1c (IQR), mmol/mol	Not collected	94 (44.8)
Median baseline FCBS (IQR), mmol/L	Not collected	9 (9.75)
Ethnicity, *n* (%)		
Asian	5 (6.4)	1 (6.7)
European	27 (34.6)	4 (26.7)
Māori	13 (16.7)	2 (13.3)
Pacific	33 (42.3)	7 (46.7)
Type 1 diabetes mellitus, *n* (%)	12 (15.4)	3 (20.0)
Type 2 diabetes mellitus, *n* (%)	66 (84.6)	12 (80.0)
Duration of diabetes, *n* (%)		
0-10 years	15 (19.2)	3 (20.0)
10-20 years	31 (39.7)	6 (40.0)
20-30 years	22 (28.2)	4 (26.7)
30-40 years	7 (9.0)	2 (13.3)
40-50 years	3 (3.9)	0 (0.0)
Peripheral neuropathy, *n* (%)	Not collected	15 (100.0)
Peripheral vascular disease, *n* (%)	Not collected	1 (6.7)

IQR, interquartile range; HbA1c: glycosylated haemoglobin; FCBS: fasting capillary blood sugar

Table 3 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood sugar

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBS		Equivalent effect size	*P*	
		Estimate	95% CI			
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.011	[-0.019,0.041]	0.01	0.69	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

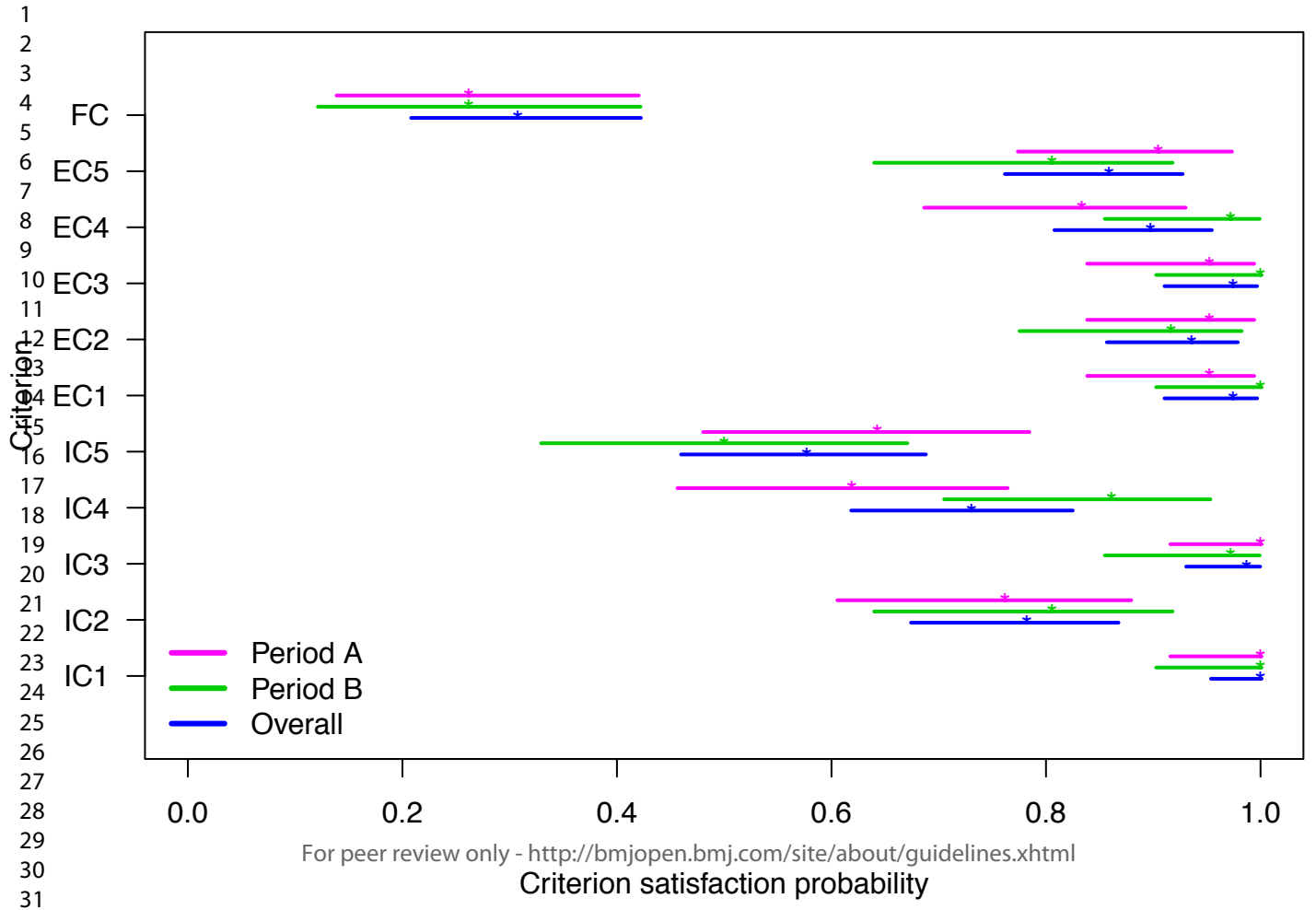
† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBS: fasting capillary blood sugar; CI: confidence interval

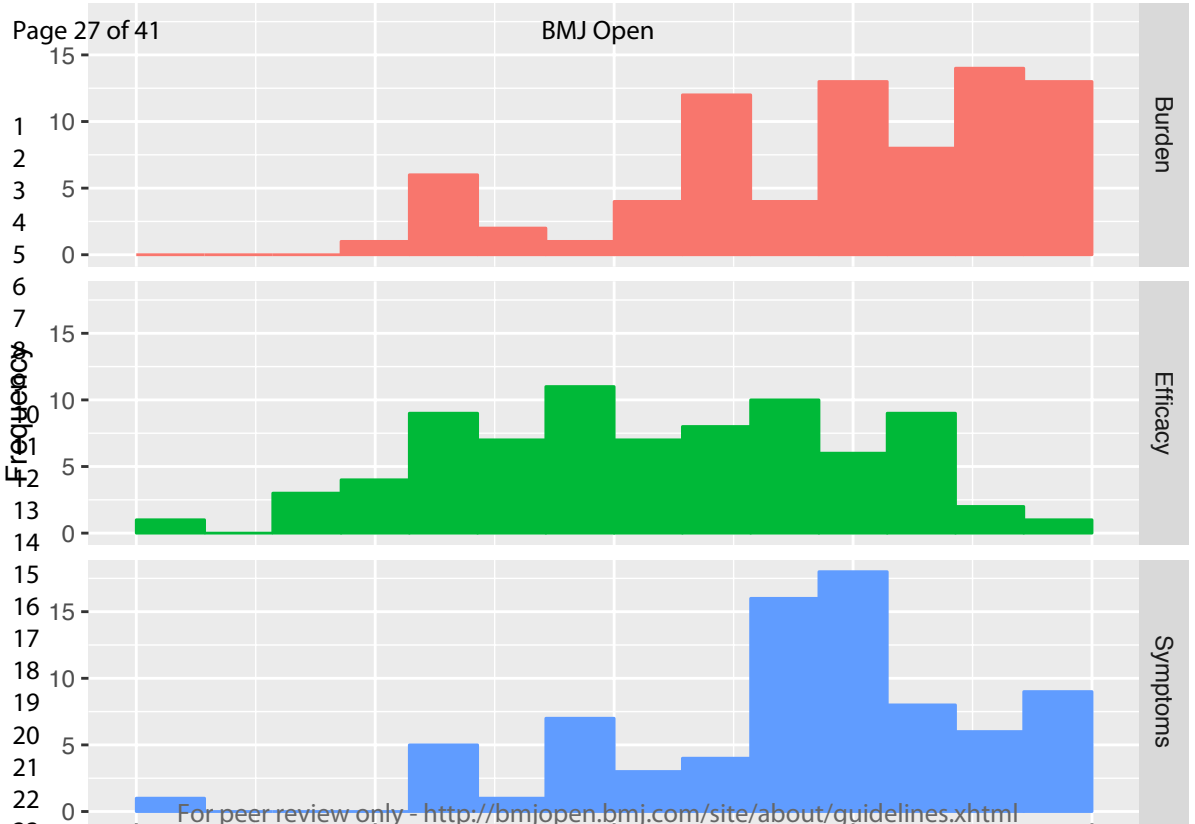
Table 4 Estimated Pearson correlation coefficients between Diabetic Foot Ulcer Scale-Short Form subscale scores and both log(ulcer area+0.01) and EuroQol 5 Dimension 5 Level

Correlates	log(ulcer area+0.01)†				EQ-5D-5L VAS			
DFS-SF subscale	Est.	95% CI	*P*		Est.	95% CI	*P*	
Leisure	-0.48	[–0.66, –0.25]	<0.0001	***	0.50	[0.23, 0.77]	0.0002	***
Physical health	-0.48	[–0.66, –0.26]	<0.0001	***	0.64	[0.44, 0.84]	<0.0001	***
Dependence	-0.54	[–0.71, –0.33]	<0.0001	***	0.58	[0.36, 0.81]	<0.0001	***
Negative emotion	-0.64	[–0.80, –0.42]	<0.0001	***	0.38	[0.04, 0.72]	0.03	*
Worried about ulcers	-0.54	[–0.71, –0.32]	<0.0001	***	0.62	[0.38, 0.86]	<0.0001	***
Bothered by ulcer care	-0.46	[–0.63, –0.24]	0.0001	***	0.36	[0.04, 0.69]	0.03	*

† Area in cm^2.

CI, confidence interval; DFS-SF: Diabetic Foot Ulcer Scale-Short Form; EQ-5D-5L: EuroQol 5 Dimension 5 Level; VAS: visual analogue scale.





STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract	Two substudies: one cross-sectional, one single-arm prospective
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	*What was done:* **Setting** Single-centre secondary care diabetic foot clinic located in New Zealand. Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy. **Intervention** None in Substudy 1. Intensive insulin therapy combined with standard podiatry care over 24 weeks. **Outcome measures** Substudy 1: Proportion of participants satisfying potential entry criteria to the RCT. Substudy 2: Glycaemic control (fasting capillary blood sugar; FCBS); time to index ulcer healing; index ulcer size; medication satisfaction (DiabMedSat scores); and health-related quality of life (HrQOL; EQ-5D-5L and DFS-SF scores).. *What was found:* **Results** Proportion in Substudy 1 fulfilling all entry criteria was 31% (95% CI 21 to 42). FCBS values declined between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8), suggesting adherence to therapeutic regimen; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBS correlated negatively, and weakly-to-moderately, with medication satisfaction. Log(ulcer area in cm2+0.01) was most sensitive to FCBS changes, correlating negatively, and moderately-to-strongly with QOL measures. Detecting a 30% between-group difference in the ulcer area logarithm (80% power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to the study setting.

Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	[…]clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers 1. The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational 11-17. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing 18. A previous feasibility study in this area 19 concluded 15 years ago that a definitive randomised trial in this area was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2)..
Objectives	3	State specific objectives, including any prespecified hypotheses	6	The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT.. […]Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication. In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes […]to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between adherence (using glycaemic control as proxy), as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.
Methods				
Study design	4	Present key elements of study design early in the paper	7	*First paragraph of* Setting and Study Design *section*: Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks.
Setting	5	Describe the setting, locations, and relevant	7-8	*Setting, location and relevant dates, including periods of recruitment, follow-up*:

		dates, including periods of recruitment, exposure, follow-up, and data collection		The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between February and October 2015, with Substudy 2 follow-up to February 2016. […]Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks. *Data collection:* Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7 + Table 1	*Cross-sectional:* Substudy 1 was a cross-sectional study that enrolled all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. *Longitudinal:* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria (Table 1)

Table 1 Entry criteria assessed in Substudy 1 (primary objective)

Criteria	Notation	Description
Inclusion Criterion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA_{1c} ≥60 mmol/mol (≥7.6%)
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion Criterion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full Criteria	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

		EC, exclusion criteria; HbA_{1c}, glycosylated haemoglobin; IC, inclusion criteria.
(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		*Not applicable.*

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	**Study procedures and outcomes** Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, […] [t]he following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBS measurement (in mmol/L); medication review; and adverse events assessment. FCBS was used in the analyses as a measure of glycaemic control and as a proxy for adherence. HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. […]. In addition, participants completed three questionnaires at each visit: DiabMedSat, EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) and Diabetic Foot Ulcer Scale-Short Form (DFS-SF).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*See 7 above. No comparator group is used in this feasibility study.*
Bias	9	Describe any efforts to address potential sources of bias	9	*Substudy 1 – bias due to differential initial and later recruitment:* A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. *Substudy 2 – bias due to confounding by time::* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit […] and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen on the basis of the data to improve the normality of the outcome.) […].Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
			10	*Substudy 2 – bias due to missingness:*

				[The non-survival] analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness. *The relevant sources of bias for the main study (for which this is a feasibility study) is bias due to loss to follow-up or missingness. Accordingly, we have attempted to briefly characterise participant attendance:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression.
Study size	10	Explain how the study size was arrived at	7	**Accrual period and sample size** The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder.[…] Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area) with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10	*Substudy 1:* Descriptive statistics were produced for […] DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. *Substudy 2:* […] Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area, where “log” is the natural logarithm function) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random

				effect. […]The most sensitive outcome was selected by consideration of its time-adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing outcome; between DiabMedSat subscores and FCBS; and between DFS-SF subscores and EQ-5D-5L. (*And before any non-statistical reviewer vociferates that this makes no sense, they should talk to a statistician.)* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	*See 11 above, to which we add:* *Substudy 1:* Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment […]. A Poisson exact test was used to compare recruitment rates over two recruitment periods […]. *Substudy 2:* Time-to-healing was considered as a fifth possible outcome, and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. *Substudy 2 – in regard to confounding:* Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
		(*b*) Describe any methods used to examine subgroups and interactions	9	*Applies to Substudy 1 only:* […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. Models were compared using a deviance test.

		(*c*) Explain how missing data were addressed	10	*(Note: No missing data in Substudy 1).* No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10	*Cross-sectional Substudy 1: not applicable* *Longitudinal Substudy 2:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC. See also 12 (c).
		(*e*) Describe any sensitivity analyses	10	*Arguably, our main analysis for Substudy 2 is a sensitivity analysis:* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate.
Results				
Participants	13*	(a) Report numbers of	10	*Substudy 1:* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1.

		individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		*Substudy 2:* *(page 8):* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria […]. *(page 11):* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 […]. *(page 12 – this is apparently out of order because it is a feasibility result):*. Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. *(page 12):* Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set. *(page 12):* Two participants with unhealed ulcers did not attend the 24-week visit.
		(b) Give reasons for non-participation at each stage	11	*Substudy 2:* One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set.
		(c) Consider use of a flow diagram		*The flow appears to us to be simple enough not to warrant a diagram.*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	*Substudy 1 (see also Table 1)::* Mean age was 57.3 years (SD 14.0). The majority were men and most were of Pacific or European ethnicity. (Table 2). *Substudy 2 – see Table 2*
		(b) Indicate number of participants with missing data for	11	*Substudy 2:* Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DMS and FCBS) and 85% (ulcer area).

		each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11	*Substudy 2:* **Completeness** Of the 102 scheduled visits, 12 were missed […].The average follow-up time to healing or last visit was 17.6 weeks (SD 7.8).
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12	*Substudy 2:* Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0–56.1%). *Table 4 for summary correlations*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	*Substudy 1:* **Recruitment rate and entry criteria** Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B. All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. […] **Diabetes Medication Satisfaction**

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 2. Median score for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]).

Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3

Table 1 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood sugar

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBS: Estimate	95% CI	Equivalent effect size	*P*	
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.011	[-0.019,0.041]	0.01	0.69	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBS: fasting capillary blood sugar; CI: confidence interval

(*b*) Report category boundaries when continuous variables were categorized | *Not applicable.*

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11	*Substudy 1:* The A-to-B rate ratio of eligibility to a full study, however, was 4.1 (95% CI 1.8-9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24-0.77).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		*Not applicable.*
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) 19. The study also showed that the primary endpoint of log(ulcer area+0.01), with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	11	*(No biasing issue was identified, but see 21.)* Some limitations temper the interpretation of our results. Firstly, Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT. Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

		Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16	The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemiccontrol as expressed by FCBS. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.
Generalisability	21	Discuss the generalisability (external validity) of the study results	16	[…] [T]he study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if	17	**Funding** This work was supported by the Health Research Council of New Zealand's Feasibility Study grant number 14/605.

	applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study

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TITLE

Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study

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Glycaemic control for diabetic foot ulcers

ABSTRACT

Introduction One in four diabetes patients will develop a foot ulcer over their lifetime. The role of glycaemic control in the healing of foot ulcers in diabetes patients is not supported by randomised controlled trial (RCT) data.

Objectives: To determine the feasibility of an RCT of glycaemic control with intensive insulin therapy in diabetic foot ulcer, by assessing: entry criteria; adherence to control regimen; medication satisfaction; sensitivity of different ulcer-healing endpoints to glycaemic control.

Design Two substudies: one cross-sectional, one single-arm prospective.

Setting Single-centre secondary care diabetic foot clinic in New Zealand.

Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy.

Intervention Substudy 1: none. Substudy 2: Intensive insulin therapy with standard podiatry care over 24 weeks.

Outcome Substudy 1: Proportion of participants satisfying potential RCT entry criteria; medication satisfaction (DiabMedSat). Substudy 2: Fasting capillary blood glucose (FCBG); index ulcer healing time; index ulcer size; health-related quality of life (HRQoL; EQ-5D-5L and DFS-SF).

Results Proportion in Substudy 1 satisfying all entry criteria was 31% (95% CI 21 to 42). FCBG values decreased between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8), suggesting adherence to control regimen; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBG correlated negatively with medication satisfaction. Ulcer area logarithm was most sensitive to FCBG changes, displaying significant negative correlation with HRQoL outcomes. Detecting a 30%

between-group difference in this outcome (80% power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to study setting.

Conclusions An adequately powered RCT requires co-operation between a large number of centres. Ulcer area logarithm should be primary endpoint.

Trial registration ANZCTR ACTRN12617001414303

Strengths and limitations of this study

- First study in 15 years to examine the feasibility of a definitive randomised controlled trial (RCT) of intensive insulin therapy for diabetic foot ulcers.
- Use of imaging techniques allowed assessment of various ulcer-size-related outcomes as potential primary endpoints for an RCT.
- The target sample size of 20 for Substudy 2, examining the relationship between ulcer healing and glycaemic control, was not achieved during the study period.
- The study was conducted in a single centre in New Zealand, limiting generalisability to other populations and settings with different pathways for diabetes and diabetic complications.

KEYWORDS

Diabetic Foot
Blood Glucose
Wound Healing
Outcome Assessment (Health Care)
Sample Size

Introduction

One in four diabetes patients will develop a foot ulcer in their lifetime [1]. Diabetic foot ulcer is one of the most significant complications of diabetes [1–4] and often responds poorly to treatment, with only one-third of those managed in secondary care healing by 3 months and one-half at 6 months [5]. Non-healing ulcers are an important cause of lower extremity amputation. Most notable causes of foot ulceration are peripheral neuropathy, peripheral vascular disease and structural foot disease [6,7]. These factors are linked to hyperglycaemia [8–10] and pathological states associated with diabetes.

A meta-analysis of nine randomised controlled trials in nearly 11,000 participants showed that intensive glycaemic control potentially improved the incidence of diabetic foot ulcer, decreased the risk of amputation and improved sensory nerve function compared with less intensive control [11]. As a result, clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers [1].

The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational [12–18]. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing [11]. A previous feasibility study in this area concluded 15 years ago that a definitive randomised trial in this area [19] was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less

stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2). In Substudy 2, presence or absence of peripheral neuropathy, peripheral vascular disease and foot deformities were noted as they were identified factors in the genesis of diabetic foot ulcers. Data on microcirculation in the feet were also collected using novel laser imaging technology. This report focuses on data from Substudy 1 and Substudy 2; the laser imaging data analysis will be reported separately.

The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT. Entry criteria used in the previous feasibility study [19] were revised as follows: removing the requirement for chronic ulcers (>4 weeks); removing the ulcer size criterion (25-2500 mm^2), and including participants with a higher HbA1c (≥58 mmol/mol), renal disease and/or a history of hypoglycaemia. Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication.

In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes (ulcer area, change in ulcer area, and time to complete healing) to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between adherence (using glycaemic control as proxy), as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.

Materials and methods

Setting and Study Design

The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between 2 February and 28 September 2015, with Substudy 2 follow-up to 20 February 2016. Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (Table 1) and treating them with intensive insulin therapy for 24 weeks.

The protocol was approved by the New Zealand Northern A Health and Disability Ethics Committee (ref: 14/NTA/195). All participants provided informed written consent.

Accrual periods and sample size

The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder. To distinguish between recruitment of existing patients and new patients, we prospectively defined two recruitment periods. During the first period of recruitment (Period A) all patients attending the diabetic foot clinic were to be recruited. Period A was to finish from the moment patients already attending the clinic were recruited, at which point only newly enrolled clinic patients started to be recruited in the study, giving way to Period B (Figure 1).

<< Figure 1 approximately here. >>

Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area)

with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.

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Patient and Public Involvement

Patients' priorities, experience and preferences were taken into account through the clinical experience of the study team, who devised the research question associated with the intended full study. The participants were not involved in the design of this study; however, one of the objectives of the feasibility study was to obtain feedback from participants that would inform the design of a potential larger study. Patients were not involved in the recruitment or conduct of the study. The participants will be provided access to the research paper. The results of the study will be displayed in the podiatry clinic where the participants attend.

Study procedures and outcomes

Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire [20,21]. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed. The following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBG measurement (in mmol/L); medication review; and adverse events assessment. FCBG was used in the analyses as a measure of glycaemic control [22] and as a proxy for adherence [23]. HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. By contrast, fasting capillary glucose or mean daily capillary glucose may provide evidence of acute improvement of

glycaemia in a short-term clinical trial[22]. In addition, participants completed three questionnaires at each visit: DiabMedSat [20,21], EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) [24,25] and Diabetic Foot Ulcer Scale-Short Form (DFS-SF) [26].

Intervention

On entry to Substudy 2, intermediate- or long-acting insulin was initiated or adjusted, and given in addition to usual oral hypoglycaemic tablet therapy (first line metformin, second line sulphonylurea). In addition participants received cholesterol lowering medication, anti-hypertensives and aspirin to prevent cardiovascular disease consistent with international guidelines [27]. Short-acting mealtime insulin was provided as appropriate. The goal was to maintain FCBG at 4–7 mmol/L, with ≤2 episodes of mild hypoglycaemia per week. Within these parameters the choice of regimen was determined by the Diabetes Nurse Specialist.

Substudy 2 participants received usual podiatry care at each visit, including ulcer debridement, orthotics prescription and adjustments, antibiotics if indicated and education.

Statistical analyses

Substudy 1

Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment and DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first

model, and interacting with period in a second model. Models were compared using deviance tests.

Substudy 2

The analysis set for this feasibility study consisted of all participants having initiated treatment. All analyses were carried out on the index ulcers, present at the first visit. All participants had a single index ulcer.

Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm^2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint has been previously validated as a surrogate marker of ulcer healing [28] was chosen based on the data to improve the normality of the outcome.) FCBG was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBG, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using all available longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing

outcome; between DiabMedSat subscores and FCBG; and between DFS-SF subscores and EQ-5D-5L.

Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBG, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.

No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness [29].

Results

Participants

<<Table 2 approximately here.>>

Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 (Table 2). Mean age was 57 years (SD 14). The majority were men and most were of Pacific or European ethnicity. No data were missing for Substudy 1. All participants were identified as having some measure of foot deformity, judged unlikely to affect ulcer healing by the treating podiatrists. However, no objective measure of foot deformity, to our knowledge, has been assessed for association with ulcer healing.

Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set, assessed on a total of 90 occasions.

Completeness

Two participants with unhealed ulcers did not attend the 24-week visit (13%, 95% CI 2 to 40). Of the 102 scheduled visits, 12 were missed, yielding an attendance proportion of 91% (95% CI 79 to 96), accounting for clustering by participant. Average follow-up time to healing or last visit was 17.6 weeks (SD 7.8). Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DiabMedSat and FCBG) and 85% (ulcer area).

Recruitment rate and entry criteria

Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B.

All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8%, 95% CI 20.8 to 42.2) met all criteria. Removal of any single criteria increased eligibility proportion appreciably only in the case of IC2 (to 37.2%, 95% CI 26.5 to 48.9) and IC5 (to 38.5%, 95% CI 27.7 to 50.2). The probabilities of participants meeting entry criteria differed between periods A and B (Figure 2); the criterion-period interaction term was significant (P=0.009). The A-to-B rate ratio of eligibility to a full study was 4.1 (95% CI 1.8 to 9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24 to 0.77).

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Diabetes Medication Satisfaction

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 3. Median score

for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]). MANOVA demonstrated no significant variation in subscale scores based on ethnicity, sex or diabetes duration, but there was significant variation in the Burden (P = 0.005) and Symptom (P=0.026) scores based on age (generally higher in older participants).

<<Figure 3 approximately here.>>

Glycaemic control

FCBG values during the study indicated that participants were generally adhering to their glycaemic control regimen. Between study end and baseline, the mean difference in FCBG was -3.7 mmol/L (95% CI -6.5 to -0.8) and in HbA1c was -9.4 mmol/mol (95% CI -19.0 to 0.3). The fasting blood glucose of participants of Substudy 2 over time are shown in Figure 4.

<< Figure 4 approximately here. >>

Selection of primary endpoint for RCT

<<Table 3 approximately here.>>

Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer-healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0 to 56.1).The Cox model showed no significant association between time to ulcer healing and FCBG (Table 3).

Log(ulcer area in cm^2+0.01) (hereafter “log of ulcer area”) and ulcer area relative rate of change were the only ulcer healing outcomes sensitive to change in FCBG (Table 3). The former was selected as most sensitive to changes in FCBG, with effect size

of 0.08 per mmol/L increase in FCBG, adjusted for both time and baseline value. Time adjustment was intended to account for non-glycaemia-related improvements and interventions such as podiatric care. Between- and within-participant outcome variances were estimated at 1.3 and 0.4 respectively.

Validation of selected outcome with QOL measures

<<Table 4 approximately here.>>

DFS-SF scores tended to increase over time (i.e. improved HrQOL); increases reached statistical significance for four of the six subscales (Leisure [*P*=0.05], Dependence [*P*=0.01], Negative emotion [*P*=0.001] and Worried about ulcers [*P*=0.04]). All six subscales showed statistically significant, moderate-to-strong negative correlation with log of ulcer area (Table 4).

Participant satisfaction and adherence to intensive insulin therapy

Glycaemia levels displayed weak to moderate negative correlation with the DiabMedSat scores. The correlation of FCBG with the Burden subscale was -0.35 (95% CI -0.59 to -0.09; *P*=0.01), with the Efficacy subscale -0.42 (95% CI -0.61 to -0.18; *P*=0.0009) and with the Symptoms subscale -0.21 (95% CI -0.47 to 0.08, *P*=0.15).

Health-related QOL

The EQ-5D-5L VAS displayed moderate to strong positive correlation with all six DFS-SF subscale scores (Table 4).

Modelling of attendance

The model explaining attendance with smallest AIC involved the DiabMedSat Burden score only, with an attendance odds ratio of 1.78 (95% CI 1.26 to 2.51; *P*=0.001) per 10-point score increase.

Discussion

Key findings

This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) [19]. The study also showed that the primary endpoint of log of ulcer area, with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.

In terms of design and conduct of an RCT of intensive glycaemic control versus standard care in people with diabetic foot ulcers, analysis showed that the largest gains in eligibility from removal of a single criterion would occur by waiving IC2 (type 1 or type 2 diabetes for greater than one year with an HbA1c of >60mmol/mol) or IC5. IC5 cannot of course be waived, since participant consent is compulsory in any ethical clinical trial. However, if glycaemic control is efficacious in individuals with recently developed diabetes, IC2 could perhaps advantageously be relaxed. Those with recent onset diabetes maybe different to those with long standing diabetes in ways that impact upon ulcer healing. On the other hand, those with recently diagnosed diabetes will likely have years of exposure to risk factors they share with those with long standing diabetes that predispose them to ulcer formation also [30]. Further findings are indications that acting on the medication burden may improve attendance and that acting on medication satisfaction in general, and satisfaction with efficacy in particular, may improve adherence to the control regimen. In both cases, however, the evidence obtained is only correlational and not causal.

Relationship to other studies

Ulcer healing data suggested an early beneficial effect of intensive insulin therapy; median healing time was 7 weeks after the initial visit, and by week 21 an estimated 17% of ulcers had not healed. Over a similar timeframe, much lower healing rates have been reported with standard care (e.g. 31% at 20 weeks in a meta-analysis [31]). Even when standard care included insulin, a retrospective cohort study found that only 30% of ulcers had healed after 1.1 month [32]. The baseline mean HbA1c was lower in the participants of that study (7.9% or 63mmol/mol) compared to our own (10.8% or 94mmol/mol). While this finding is promising, a randomised controlled trial is needed to confirm that this is the effect of intensive blood glucose control. There are other factors that may account for more rapid ulcer healing in our study such as the high (weekly) frequency of the first four visits in Substudy 2, allowing more opportunities for treatment such as wound debridement, and orthotic or medication adjustments.

Implications for a full study

The log of the ulcer area outcome proved sensitive to glycaemic control even controlling for time since study entry, and was correlated with DFS-SF subscores, supporting the use of this measure. This is consistent with prior validation of log ulcer area as a surrogate end point for ulcer healing [28]. Using this measure as primary endpoint, a target reduction in ulcer size of 30% would correspond to a 3 mmol/L average difference in FCBG (corresponding to the difference between the lower bounds of normal glycaemia and a diagnosis of diabetes), with intensive glycaemic control versus standard care. In an RCT, 220 participants per arm would be required to detect a between-group decrease of 30% with 80% power at a 5% significance level. At the differential eligibility rates observed in both periods and assuming a loss

to follow-up of 10%, such a number could be achieved within about one year if 15 centres similar to ours were recruiting participants.

Good reductions in FCBG over the first 4 weeks of intensive insulin therapy were seen, but more variable levels observed afterwards. To achieve optimal improvements in glycaemic control over the course of a longer-term RCT more regular visits may be necessary after the first 4-6 weeks of therapy than were used in our feasibility study and more daytime FCBG recordings done to optimise therapy.

The EQ-5D VAS appeared to have good convergent validity with the specialised DFS-SF, indicating its appropriateness as a generic QOL measure in our study population, opening the door to valid economic analyses. We also realise the importance of objective quantification of neuropathy, peripheral vascular disease and foot deformities enabling stratification at randomisation in the larger trial as they are the most notable causative factors of diabetic foot ulceration [11].

Tight glycaemic control relies on long-term patient adherence [1]. Satisfied patients are more likely to adhere to recommendations regarding not only medication use and follow-up visits but also dietary habits and physical activity [33]. Our findings showed that our participants' perception of diabetes medication burden was strongly associated with adherence (as determined by the surrogate marker FCBG) and attendance, suggests, although does not prove, that intervening on burden may promote attendance.

Limitations

Some limitations temper the interpretation of our results. The most important limitation was that Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT.

Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

Another limitation of this study is that FCBG was the only surrogate for medication adherence. The addition of other surrogates such as a record of whether prescriptions had been filled would. Furthermore, in a study aiming to evaluate the four times a day blood glucose testing is preferable to FCBG and HbA1c.

Non-adherence to standard care was an exclusion criterion of this study. This was included so that the impact of glycaemic control would be the focus of this study. However, this criterion limits the application of the study to the real world as non-adherence is a major issue in most real-life clinical settings.

Conclusion

The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemic control as expressed by FCBG.

This feasibility study is the first since 2005 to investigate issues relevant to the initiation of a definitive RCT evaluating the impact of intensive insulin therapy on ulcer healing in people with diabetes. The results of such a trial would be useful to inform evidence-based clinical practice guidelines. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.

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Contributors A.C.V. and A.D. and designed the study and co-wrote the manuscript with V.B. A.D. oversaw the intervention and contributed to the discussion. A.C.V. contributed to data management, data monitoring and analysis planning and conduct. D.P. contributed to statistical analyses. B.M. coordinated the research. R.G. and A.N. provided podiatric care and contributed to discussion. A.D. and A.C.V. take responsibility for the contents of the article, study design, access to data and the decision to submit and publish the results.

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Disclaimer The joint lead authors A.D. and A.C.V. affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted except as noted in the text, and that any discrepancies from the study as planned have been explained.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics approval was given for the study by the New Zealand Northern A Health and Disability Ethics Committee, ethics approval number 14/NTA/195.

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Figure legends

Figure 1 – Substudy 1 recruitment flow diagram

Figure 2 – Point estimate and confidence interval of probability of each criterion being met by recruitment period. Period A was 0-5 weeks and Period B was 6-35 weeks. FC, full criteria; EC, exclusion criterion; IC, inclusion criterion.

Figure 3 – Histograms of participant scores on the three subscales of the Diabetes Medication Satisfaction questionnaire: (a) Burden, (b) Symptoms and (c) Efficacy subscales. Subscales are scored from 0-100, higher scores indicating greater satisfaction.

Figure 4. Fasting capillary blood glucose against time from study entry during intensive insulin therapy in the 15 participants of substudy 2

Tables

Table 1 Entry criteria assessed in Substudy 1

Criteria	Notation	Description
Inclusion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA1c ≥60 mmol/mol
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

EC, exclusion criteria; HbA1c, glycosylated haemoglobin; IC, inclusion criteria.

Table 2 Characteristics of participants included in both substudies

	Substudy 1 Participants (n=78)	Substudy 2 Participants (n=15)
Median age (IQR), years	58.5 (18.2)	51 (16.5)
Women, *n* (%)	30 (38.5)	6 (40)
Mean baseline HbA1c (SD), mmol/mol	Not collected	93 (29)
Mean baseline FCBG (SD), mmol/L	Not collected	11.3 (5.7)
Ethnicity, *n* (%)		
Asian	5 (6.4)	1 (6.7)
European	27 (34.6)	4 (26.7)
Māori	13 (16.7)	2 (13.3)
Pacific	33 (42.3)	7 (46.7)
Type 1 diabetes mellitus, *n* (%)	12 (15.4)	3 (20.0)
Type 2 diabetes mellitus, *n* (%)	66 (84.6)	12 (80.0)
Duration of diabetes, *n* (%)		
0-10 years	15 (19.2)	3 (20.0)
10-20 years	31 (39.7)	6 (40.0)
20-30 years	22 (28.2)	4 (26.7)
30-40 years	7 (9.0)	2 (13.3)
40-50 years	3 (3.9)	0 (0.0)
Peripheral neuropathy, *n* (%)	Not collected	15 (100.0)
Peripheral vascular disease, *n* (%)	Not collected	1 (6.7)

IQR, interquartile range; HbA1c: glycosylated haemoglobin; FCBG: fasting capillary blood glucose

Table 3 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood glucose

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBG		Equivalent effect size	*P*	
		Estimate	95% CI			
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.009	[-0.014,0.032]	0.01	0.70	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

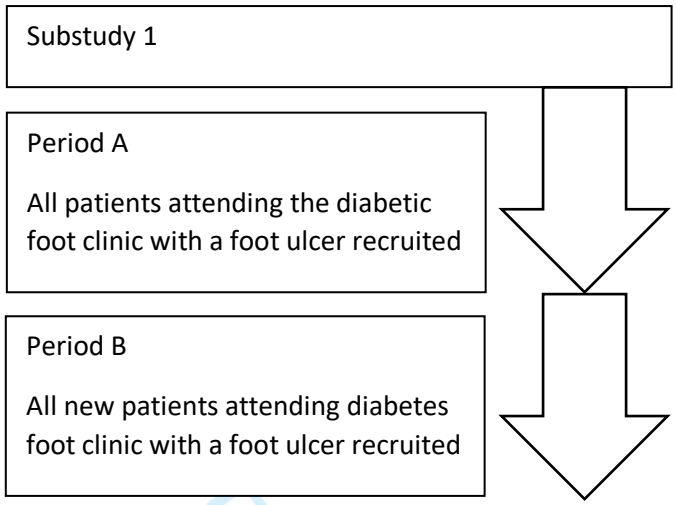
† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBG: fasting capillary blood glucose; CI: confidence interval

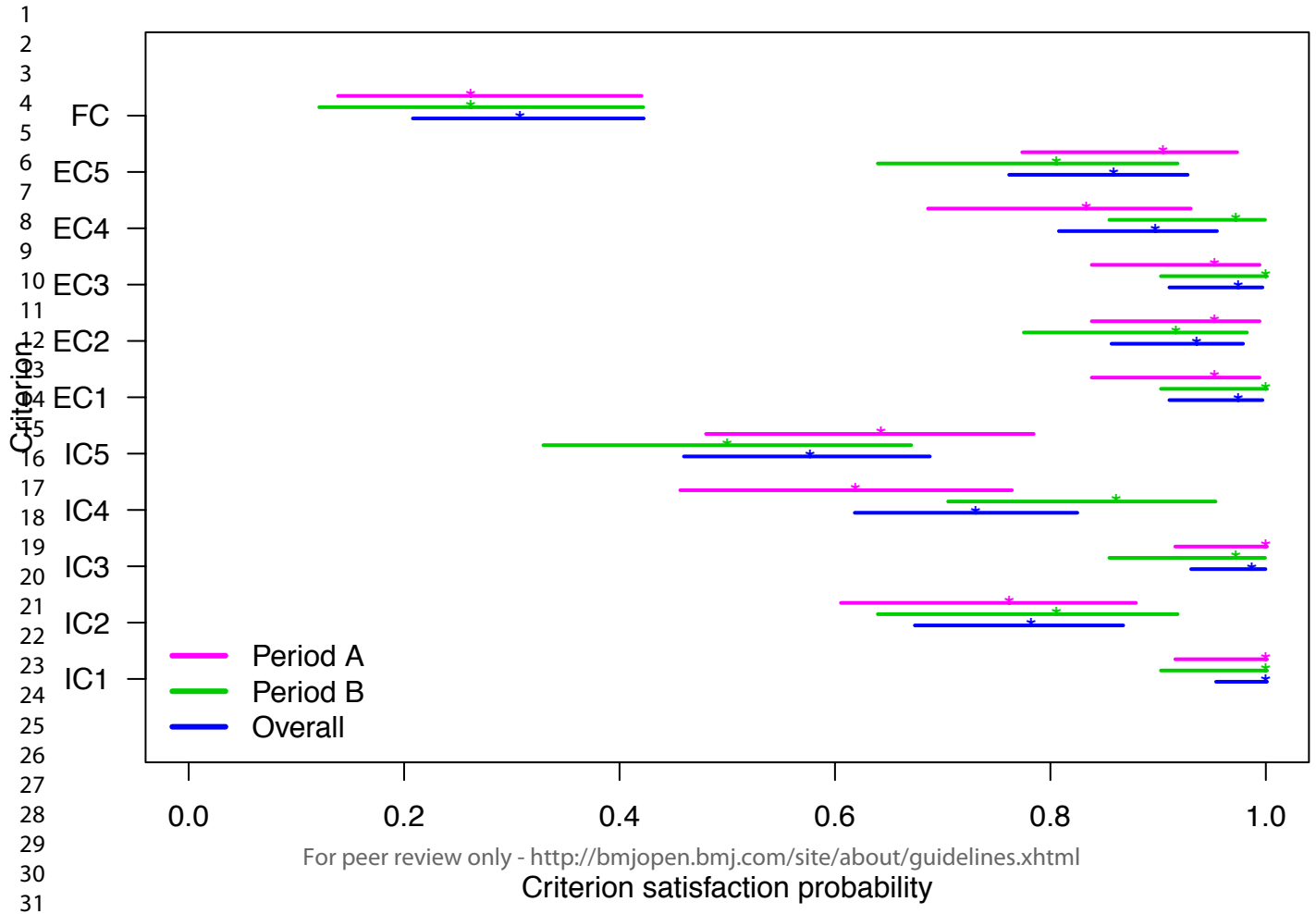
Table 4 Estimated Pearson correlation coefficients between Diabetic Foot Ulcer Scale-Short Form subscale scores and both log(ulcer area+0.01) and EuroQol 5 Dimension 5 Level

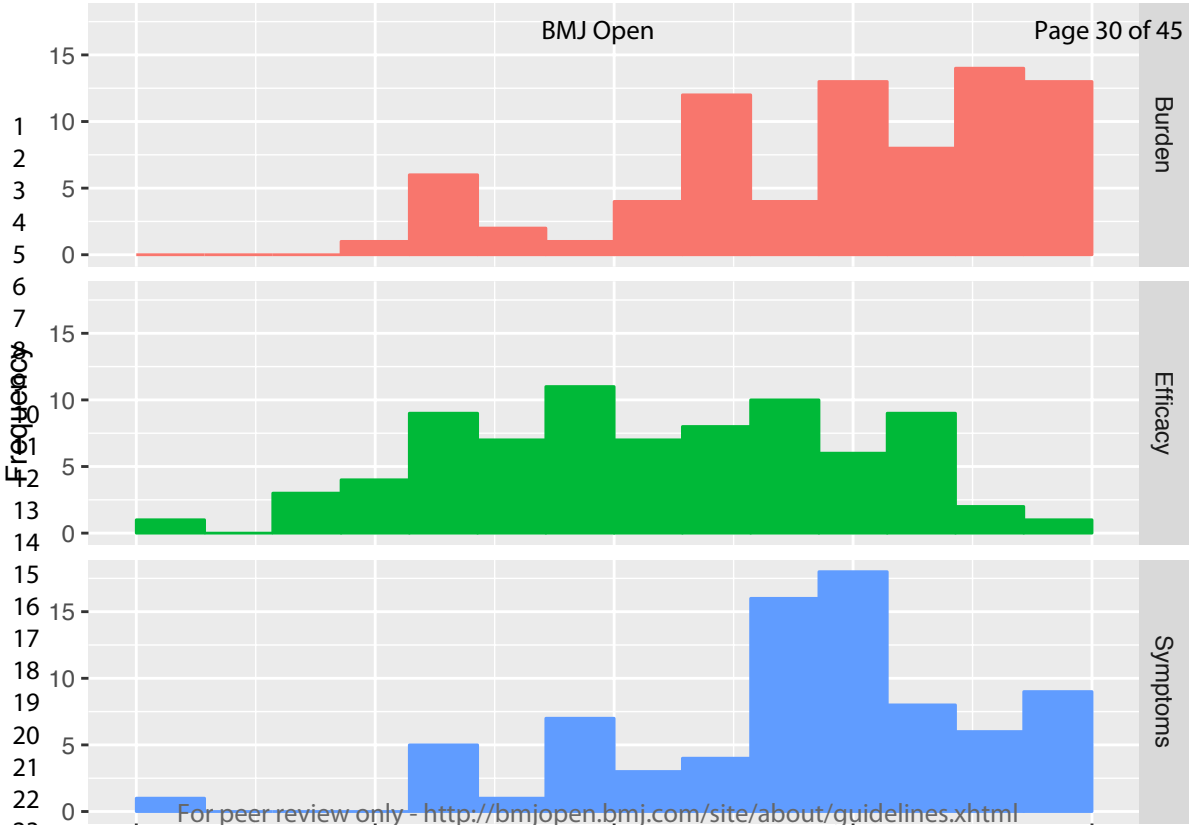
Correlates	log(ulcer area+0.01)†				EQ-5D-5L VAS			
DFS-SF subscale	Est.	95% CI	*P*		Est.	95% CI	*P*	
Leisure	-0.48	[–0.66, –0.25]	<0.0001	***	0.50	[0.23, 0.77]	0.0002	***
Physical health	-0.48	[–0.66, –0.26]	<0.0001	***	0.64	[0.44, 0.84]	<0.0001	***
Dependence	-0.54	[–0.71, –0.33]	<0.0001	***	0.58	[0.36, 0.81]	<0.0001	***
Negative emotion	-0.64	[–0.80, –0.42]	<0.0001	***	0.38	[0.04, 0.72]	0.03	*
Worried about ulcers	-0.54	[–0.71, –0.32]	<0.0001	***	0.62	[0.38, 0.86]	<0.0001	***
Bothered by ulcer care	-0.46	[–0.63, –0.24]	0.0001	***	0.36	[0.04, 0.69]	0.03	*

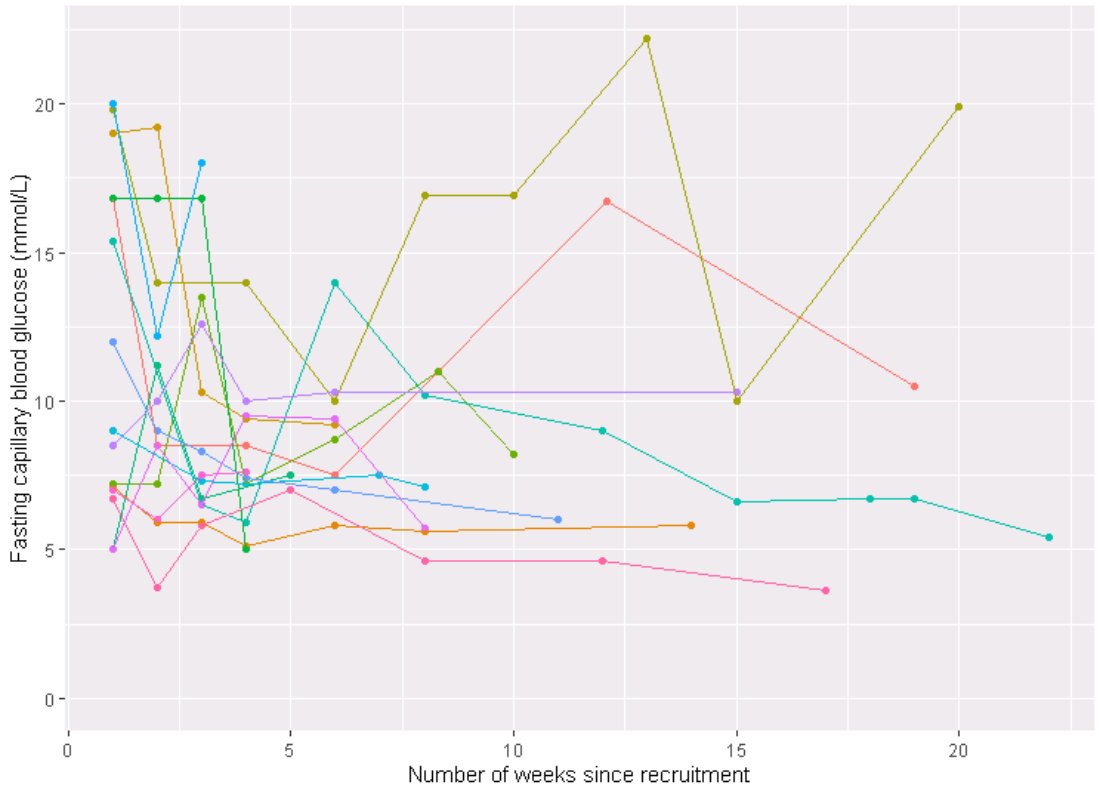
† Area in cm^2.

CI, confidence interval; DFS-SF: Diabetic Foot Ulcer Scale-Short Form; EQ-5D-5L: EuroQol 5 Dimension 5 Level; VAS: visual analogue scale.









STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract	Two substudies: one cross-sectional, one single-arm prospective
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	*What was done:* **Setting** Single-centre secondary care diabetic foot clinic located in New Zealand. Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy. **Intervention** None in Substudy 1. Intensive insulin therapy combined with standard podiatry care over 24 weeks. **Outcome measures** Substudy 1: Proportion of participants satisfying potential entry criteria to the RCT. Substudy 2: Glycaemic control (fasting capillary blood sugar; FCBS); time to index ulcer healing; index ulcer size; medication satisfaction (DiabMedSat scores); and health-related quality of life (HrQOL; EQ-5D-5L and DFS-SF scores).. *What was found:* **Results** Proportion in Substudy 1 fulfilling all entry criteria was 31% (95% CI 21 to 42). FCBS values declined between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8), suggesting adherence to therapeutic regimen; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBS correlated negatively, and weakly-to-moderately, with medication satisfaction. Log(ulcer area in cm2+0.01) was most sensitive to FCBS changes, correlating negatively, and moderately-to-strongly with QOL measures. Detecting a 30% between-group difference in the ulcer area logarithm (80% power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to the study setting.

Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	[…]clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers 1. The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational 11-17. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing 18. A previous feasibility study in this area 19 concluded 15 years ago that a definitive randomised trial in this area was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2)..
Objectives	3	State specific objectives, including any prespecified hypotheses	6	The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT.. […]Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication. In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes […]to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between adherence (using glycaemic control as proxy), as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.
Methods				
Study design	4	Present key elements of study design early in the paper	7	*First paragraph of* Setting and Study Design *section*: Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks.
Setting	5	Describe the setting, locations, and relevant	7-8	*Setting, location and relevant dates, including periods of recruitment, follow-up*:

		dates, including periods of recruitment, exposure, follow-up, and data collection		The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between February and October 2015, with Substudy 2 follow-up to February 2016. […]Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks. *Data collection:* Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7 + Table 1	*Cross-sectional:* Substudy 1 was a cross-sectional study that enrolled all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. *Longitudinal:* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria (Table 1)

Table 1 Entry criteria assessed in Substudy 1 (primary objective)

Criteria	Notation	Description
Inclusion Criterion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA_{1c} ≥60 mmol/mol (≥7.6%)
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion Criterion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full Criteria	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

		EC, exclusion criteria; HbA_{1c}, glycosylated haemoglobin; IC, inclusion criteria.
(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		*Not applicable.*

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	**Study procedures and outcomes** Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, […] [t]he following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBS measurement (in mmol/L); medication review; and adverse events assessment. FCBS was used in the analyses as a measure of glycaemic control and as a proxy for adherence. HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. […]. In addition, participants completed three questionnaires at each visit: DiabMedSat, EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) and Diabetic Foot Ulcer Scale-Short Form (DFS-SF).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*See 7 above. No comparator group is used in this feasibility study.*
Bias	9	Describe any efforts to address potential sources of bias	9	*Substudy 1 – bias due to differential initial and later recruitment:* A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. *Substudy 2 – bias due to confounding by time::* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit […] and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen on the basis of the data to improve the normality of the outcome.) […].Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
			10	*Substudy 2 – bias due to missingness:*

				[The non-survival] analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness. *The relevant sources of bias for the main study (for which this is a feasibility study) is bias due to loss to follow-up or missingness. Accordingly, we have attempted to briefly characterise participant attendance:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression.
Study size	10	Explain how the study size was arrived at	7	**Accrual period and sample size** The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder.[…] Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area) with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10	*Substudy 1:* Descriptive statistics were produced for […] DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. *Substudy 2:* […] Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area, where “log” is the natural logarithm function) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random

				effect. […]The most sensitive outcome was selected by consideration of its time-adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing outcome; between DiabMedSat subscores and FCBS; and between DFS-SF subscores and EQ-5D-5L. (*And before any non-statistical reviewer vociferates that this makes no sense, they should talk to a statistician.)* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	*See 11 above, to which we add:* *Substudy 1:* Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment […]. A Poisson exact test was used to compare recruitment rates over two recruitment periods […]. *Substudy 2:* Time-to-healing was considered as a fifth possible outcome, and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. *Substudy 2 – in regard to confounding:* Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
		(*b*) Describe any methods used to examine subgroups and interactions	9	*Applies to Substudy 1 only:* […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. Models were compared using a deviance test.

		(*c*) Explain how missing data were addressed	10	*(Note: No missing data in Substudy 1).* No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10	*Cross-sectional Substudy 1: not applicable* *Longitudinal Substudy 2:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC. See also 12 (c).
		(*e*) Describe any sensitivity analyses	10	*Arguably, our main analysis for Substudy 2 is a sensitivity analysis:* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate.
Results				
Participants	13*	(a) Report numbers of	10	*Substudy 1:* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1.

		individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		*Substudy 2:* *(page 8):* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria […]. *(page 11):* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 […]. *(page 12 – this is apparently out of order because it is a feasibility result):*. Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. *(page 12):* Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set. *(page 12):* Two participants with unhealed ulcers did not attend the 24-week visit.
		(b) Give reasons for non-participation at each stage	11	*Substudy 2:* One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set.
		(c) Consider use of a flow diagram		*The flow appears to us to be simple enough not to warrant a diagram.*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	*Substudy 1 (see also Table 1)::* Mean age was 57.3 years (SD 14.0). The majority were men and most were of Pacific or European ethnicity. (Table 2). *Substudy 2 – see Table 2*
		(b) Indicate number of participants with missing data for	11	*Substudy 2:* Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DMS and FCBS) and 85% (ulcer area).

		each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11	*Substudy 2:* **Completeness** Of the 102 scheduled visits, 12 were missed […].The average follow-up time to healing or last visit was 17.6 weeks (SD 7.8).
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12	*Substudy 2:* Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0–56.1%). *Table 4 for summary correlations*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	*Substudy 1:* **Recruitment rate and entry criteria** Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B. All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. […] **Diabetes Medication Satisfaction**

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 2. Median score for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]).

Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3

Table 1 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood sugar

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBS: Estimate	95% CI	Equivalent effect size	*P*	
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.011	[-0.019,0.041]	0.01	0.69	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBS: fasting capillary blood sugar; CI: confidence interval

(*b*) Report category boundaries when continuous variables were categorized | *Not applicable.*

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11	*Substudy 1:* The A-to-B rate ratio of eligibility to a full study, however, was 4.1 (95% CI 1.8-9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24-0.77).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		*Not applicable.*
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) 19. The study also showed that the primary endpoint of log(ulcer area+0.01), with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	11	*(No biasing issue was identified, but see 21.)* Some limitations temper the interpretation of our results. Firstly, Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT. Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

		Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16	The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemiccontrol as expressed by FCBS. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.
Generalisability	21	Discuss the generalisability (external validity) of the study results	16	[…] [T]he study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if	17	**Funding** This work was supported by the Health Research Council of New Zealand's Feasibility Study grant number 14/605.

	applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study

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TITLE

Does intensive glycaemic control promote healing in diabetic foot ulcers? A feasibility study

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Glycaemic control for diabetic foot ulcers

ABSTRACT

Introduction One in four diabetes patients will develop a foot ulcer over their lifetime. The role of glycaemic control in the healing of foot ulcers in diabetes patients is not supported by randomised controlled trial (RCT) data.

Objectives: To determine the feasibility of an RCT of glycaemic control with intensive insulin therapy in diabetic foot ulcer, by assessing: entry criteria; fasting capillary blood glucose (FCBG) medication satisfaction; sensitivity of different ulcer-healing endpoints to glycaemic control.

Design Two substudies: one cross-sectional, one single-arm prospective.

Setting Single-centre secondary care diabetic foot clinic in New Zealand.

Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy.

Intervention Substudy 1: none. Substudy 2: Intensive insulin therapy with standard podiatry care over 24 weeks.

Outcome Substudy 1: Proportion of participants satisfying potential RCT entry criteria; medication satisfaction (DiabMedSat). Substudy 2: Fasting capillary blood glucose (FCBG); index ulcer healing time; index ulcer size; health-related quality of life (HRQoL; EQ-5D-5L and DFS-SF).

Results Proportion in Substudy 1 satisfying all entry criteria was 31% (95% CI 21 to 42). FCBG values decreased between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8),; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBG correlated negatively with medication satisfaction. Ulcer area logarithm was most sensitive to FCBG changes, displaying significant negative correlation with HRQoL outcomes. Detecting a 30% between-group difference in this outcome (80%

power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to study setting.

Conclusions An adequately powered RCT requires co-operation between a large number of centres. Ulcer area logarithm should be primary endpoint.

Trial registration ANZCTR ACTRN12617001414303

Strengths and limitations of this study

- First study in 15 years to examine the feasibility of a definitive randomised controlled trial (RCT) of intensive insulin therapy for diabetic foot ulcers.
- Use of imaging techniques allowed assessment of various ulcer-size-related outcomes as potential primary endpoints for an RCT.
- The target sample size of 20 for Substudy 2, examining the relationship between ulcer healing and glycaemic control, was not achieved during the study period.
- The study was conducted in a single centre in New Zealand, limiting generalisability to other populations and settings with different pathways for diabetes and diabetic complications.

KEYWORDS

Diabetic Foot
Blood Glucose
Wound Healing
Outcome Assessment (Health Care)
Sample Size

Introduction

One in four diabetes patients will develop a foot ulcer in their lifetime [1]. Diabetic foot ulcer is one of the most significant complications of diabetes [1–4] and often responds poorly to treatment, with only one-third of those managed in secondary care healing by 3 months and one-half at 6 months [5]. Non-healing ulcers are an important cause of lower extremity amputation. Most notable causes of foot ulceration are peripheral neuropathy, peripheral vascular disease and structural foot disease [6,7]. These factors are linked to hyperglycaemia [8–10] and pathological states associated with diabetes.

A meta-analysis of nine randomised controlled trials in nearly 11,000 participants showed that intensive glycaemic control potentially improved the incidence of diabetic foot ulcer, decreased the risk of amputation and improved sensory nerve function compared with less intensive control [11]. As a result, clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers [1].

The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational [12–18]. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing [11]. A previous feasibility study in this area concluded 15 years ago that a definitive randomised trial in this area [19] was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less

stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2). In Substudy 2, presence or absence of peripheral neuropathy, peripheral vascular disease and foot deformities were noted as they were identified factors in the genesis of diabetic foot ulcers. Data on microcirculation in the feet were also collected using novel laser imaging technology. This report focuses on data from Substudy 1 and Substudy 2; the laser imaging data analysis will be reported separately.

The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT. Entry criteria used in the previous feasibility study [19] were revised as follows: removing the requirement for chronic ulcers (>4 weeks); removing the ulcer size criterion (25-2500 mm^2), and including participants with a higher HbA1c (≥60 mmol/mol), renal disease and/or a history of hypoglycaemia. Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication.

In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes (ulcer area, change in ulcer area, and time to complete healing) to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between improved glycaemic control as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.

Materials and methods

Setting and Study Design

The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between 2 February and 28 September 2015, with Substudy 2 follow-up to 20 February 2016. Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (Table 1) and treating them with intensive insulin therapy for 24 weeks.

The protocol was approved by the New Zealand Northern A Health and Disability Ethics Committee (ref: 14/NTA/195). All participants provided informed written consent.

Accrual periods and sample size

The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder. To distinguish between recruitment of existing patients and new patients, we prospectively defined two recruitment periods. During the first period of recruitment (Period A) all patients attending the diabetic foot clinic were to be recruited. Period A was to finish from the moment patients already attending the clinic were recruited, at which point only newly enrolled clinic patients started to be recruited in the study, giving way to Period B (Figure 1).

<< Figure 1 approximately here. >>

Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area)

with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.

<<Table 1 approximately here>>

Patient and Public Involvement

Patients' priorities, experience and preferences were taken into account through the clinical experience of the study team, who devised the research question associated with the intended full study. The participants were not involved in the design of this study; however, one of the objectives of the feasibility study was to obtain feedback from participants that would inform the design of a potential larger study. Patients were not involved in the recruitment or conduct of the study. The participants will be provided access to the research paper. The results of the study will be displayed in the podiatry clinic where the participants attend.

Study procedures and outcomes

Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire [20,21]. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed. The following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBG measurement (in mmol/L); medication review; and adverse events assessment. FCBG was used in the analyses as a measure of glycaemic control [22] HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. By contrast, fasting capillary glucose or mean daily capillary glucose may provide evidence of acute improvement of glycaemia in a short-term clinical trial[22]. In

addition, participants completed three questionnaires at each visit: DiabMedSat [20,21], EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) [23,24] and Diabetic Foot Ulcer Scale-Short Form (DFS-SF) [25].

Intervention

On entry to Substudy 2, intermediate- or long-acting insulin was initiated or adjusted, and given in addition to usual oral hypoglycaemic tablet therapy (first line metformin, second line sulphonylurea). In addition participants received cholesterol lowering medication, anti-hypertensives and aspirin to prevent cardiovascular disease consistent with international guidelines [26]. Short-acting mealtime insulin was provided as appropriate. The goal was to maintain FCBG at 4–7 mmol/L, with ≤2 episodes of mild hypoglycaemia per week. If > 2 episodes of mild hypoglycaemia occurred the target FCBG was raised. Within these parameters the choice of regimen was determined by the Diabetes Nurse Specialist.

Substudy 2 participants received usual podiatry care at each visit, including ulcer debridement, orthotics prescription and adjustments, antibiotics if indicated and education.

Statistical analyses

Substudy 1

Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment and DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first

model, and interacting with period in a second model. Models were compared using deviance tests.

Substudy 2

The analysis set for this feasibility study consisted of all participants having initiated treatment. All analyses were carried out on the index ulcers, present at the first visit. All participants had a single index ulcer.

Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm^2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint has been previously validated as a surrogate marker of ulcer healing [27] was chosen based on the data to improve the normality of the outcome.) FCBG was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBG, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using all available longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing

outcome; between DiabMedSat subscores and FCBG; and between DFS-SF subscores and EQ-5D-5L.

Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBG, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.

No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness [28].

Results

Participants

<<Table 2 approximately here.>>

Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 (Table 2). Mean age was 57 years (SD 14). The majority were men and most were of Pacific or European ethnicity. No data were missing for Substudy 1. All participants were identified as having some measure of foot deformity, judged unlikely to affect ulcer healing by the treating podiatrists. However, no objective measure of foot deformity, to our knowledge, has been assessed for association with ulcer healing.

Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set, assessed on a total of 90 occasions.

Completeness

Two participants with unhealed ulcers did not attend the 24-week visit (13%, 95% CI 2 to 40). Of the 102 scheduled visits, 12 were missed, yielding an attendance proportion of 91% (95% CI 79 to 96), accounting for clustering by participant. Average follow-up time to healing or last visit was 17.6 weeks (SD 7.8). Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DiabMedSat and FCBG) and 85% (ulcer area).

Recruitment rate and entry criteria

Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B.

All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8%, 95% CI 20.8 to 42.2) met all criteria. Removal of any single criteria increased eligibility proportion appreciably only in the case of IC2 (to 37.2%, 95% CI 26.5 to 48.9) and IC5 (to 38.5%, 95% CI 27.7 to 50.2). The probabilities of participants meeting entry criteria differed between periods A and B (Figure 2); the criterion-period interaction term was significant (P=0.009). The A-to-B rate ratio of eligibility to a full study was 4.1 (95% CI 1.8 to 9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24 to 0.77).

<<Figure 2 approximately here.>>

Diabetes Medication Satisfaction

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 3. Median score

for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]). MANOVA demonstrated no significant variation in subscale scores based on ethnicity, sex or diabetes duration, but there was significant variation in the Burden (P = 0.005) and Symptom (P=0.026) scores based on age (generally higher in older participants).

<<Figure 3 approximately here.>>

Glycaemic control

FCBG values during the study indicated that participants were generally adhering to their glycaemic control regimen. Between study end and baseline, the mean difference in FCBG was -3.7 mmol/L (95% CI -6.5 to -0.8) and in HbA1c was -9.4 mmol/mol (95% CI -19.0 to 0.3). The fasting blood glucose of participants of Substudy 2 over time are shown in Figure 4.

<< Figure 4 approximately here. >>

Selection of primary endpoint for RCT

<<Table 3 approximately here.>>

Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer-healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0 to 56.1).The Cox model showed no significant association between time to ulcer healing and FCBG (Table 3).

Log(ulcer area in cm^2+0.01) (hereafter “log of ulcer area”) and ulcer area relative rate of change were the only ulcer healing outcomes sensitive to change in FCBG (Table 3). The former was selected as most sensitive to changes in FCBG, with effect size

of 0.08 per mmol/L increase in FCBG, adjusted for both time and baseline value. This corresponds to a 30% reduction in ulcer area with a 3mmol/L improvement in FCBG. Time adjustment was intended to account for non-glycaemia-related improvements and interventions such as podiatric care. Between- and within-participant outcome variances were estimated at 1.3 and 0.4 respectively.

Validation of selected outcome with QOL measures

<<Table 4 approximately here.>>

DFS-SF scores tended to increase over time (i.e. improved HrQOL); increases reached statistical significance for four of the six subscales (Leisure [*P*=0.05], Dependence [*P*=0.01], Negative emotion [*P*=0.001] and Worried about ulcers [*P*=0.04]). All six subscales showed statistically significant, moderate-to-strong negative correlation with log of ulcer area (Table 4).

Participant satisfaction and improvement of fasting capillary blood glucose

Glycaemia levels displayed weak to moderate negative correlation with the DiabMedSat scores. The correlation of FCBG with the Burden subscale was -0.35 (95% CI -0.59 to -0.09; *P*=0.01), with the Efficacy subscale -0.42 (95% CI -0.61 to -0.18; *P*=0.0009) and with the Symptoms subscale -0.21 (95% CI -0.47 to 0.08, *P*=0.15).

Health-related QOL

The EQ-5D-5L VAS displayed moderate to strong positive correlation with all six DFS-SF subscale scores (Table 4).

Modelling of attendance

The model explaining attendance with smallest AIC involved the DiabMedSat Burden score only, with an attendance odds ratio of 1.78 (95% CI 1.26 to 2.51; *P*=0.001) per 10-point score increase.

Discussion

Key findings

This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) [19]. The study also showed that the primary endpoint of log of ulcer area, with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.

The mean HbA1c of substudy group 2 prior to the intervention was 93 mmol/mol and the mean FCBG was 11.3 mmol/L. Depending on the model used to estimate HbA1c from FCBG there may appear to be a discrepancy. However, this is explained by the small number of participants, and the variability of contribution between FCBG and post-prandial capillary blood glucose between individuals especially at higher HbA1c concentrations [22].

In terms of design and conduct of an RCT of intensive glycaemic control versus standard care in people with diabetic foot ulcers, analysis showed that the largest gains in eligibility from removal of a single criterion would occur by waiving IC2 (type 1 or type 2 diabetes for greater than one year with an HbA1c of >60mmol/mol) or IC5. IC5 cannot of course be waived, since participant consent is compulsory in any ethical clinical trial. However, if glycaemic control is efficacious in individuals with

recently developed diabetes, IC2 could perhaps advantageously be relaxed. Those with recent onset diabetes maybe different to those with long standing diabetes in ways that impact upon ulcer healing. On the other hand, those with recently diagnosed diabetes will likely have years of exposure to risk factors they share with those with long standing diabetes that predispose them to ulcer formation also [29]. Further findings are indications that acting on the medication burden may improve attendance and that acting on medication satisfaction in general, and satisfaction with efficacy in particular, may improve adherence to the control regimen. In both cases, however, the evidence obtained is only correlational and not causal.

Relationship to other studies

Ulcer healing data suggested an early beneficial effect of intensive insulin therapy; median healing time was 7 weeks after the initial visit, and by week 21 an estimated 17% of ulcers had not healed. Over a similar timeframe, much lower healing rates have been reported with standard care (e.g. 31% at 20 weeks in a meta-analysis [30]). Even when standard care included insulin, a retrospective cohort study found that only 30% of ulcers had healed after 1.1 month [31]. The baseline mean HbA1c was lower in the participants of that study (7.9% or 63mmol/mol) compared to our own (10.8% or 94mmol/mol). While this finding is promising, a randomised controlled trial is needed to confirm that this is the effect of intensive blood glucose control. There are other factors that may account for more rapid ulcer healing in our study such as the high (weekly) frequency of the first four visits in Substudy 2, allowing more opportunities for treatment such as wound debridement, and orthotic or medication adjustments.

Implications for a full study

The log of the ulcer area outcome proved sensitive to glycaemic control even controlling for time since study entry, and was correlated with DFS-SF subscores, supporting the use of this measure. This is consistent with prior validation of log ulcer area as a surrogate end point for ulcer healing [27]. Using this measure as primary endpoint, a target reduction in ulcer size of 30% would correspond to a 3 mmol/L average difference in FCBG (corresponding to the difference between the lower bounds of normal glycaemia and a diagnosis of diabetes), with intensive glycaemic control versus standard care. In an RCT, 220 participants per arm would be required to detect a between-group decrease of 30% with 80% power at a 5% significance level. At the differential eligibility rates observed in both periods and assuming a loss to follow-up of 10%, such a number could be achieved within about one year if 15 centres similar to ours were recruiting participants.

Good reductions in FCBG over the first 4 weeks of intensive insulin therapy were seen, but more variable levels observed afterwards. To achieve optimal improvements in glycaemic control over the course of a longer-term RCT more regular visits may be necessary after the first 4-6 weeks of therapy than were used in our feasibility study and more daytime FCBG recordings done to optimise therapy.

The EQ-5D VAS appeared to have good convergent validity with the specialised DFS-SF, indicating its appropriateness as a generic QOL measure in our study population, opening the door to valid economic analyses. We also realise the importance of objective quantification of neuropathy, peripheral vascular disease and foot deformities enabling stratification at randomisation in the larger trial as they are the most notable causative factors of diabetic foot ulceration [11].

Tight glycaemic control relies on long-term patient adherence [1][32]. Satisfied patients are more likely to adhere to recommendations regarding not only medication use and follow-up visits but also dietary habits and physical activity [33]. Our findings showed that our participants' perception of diabetes medication burden was strongly associated with fasting capillary blood glucose and attendance, suggests, although does not prove, that intervening on burden may promote attendance.

Limitations

Some limitations temper the interpretation of our results. The most important limitation was that Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT. Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

Another limitation of this study is that FCBG was the only surrogate for medication adherence. The addition of other surrogates such as a record of whether prescriptions had been filled would. Furthermore, in a study aiming to evaluate the four times a day blood glucose testing is preferable to FCBG and HbA1c.

Non-adherence to standard care was an exclusion criterion of this study. This was included so that the impact of glycaemic control would be the focus of this study. However, this criterion limits the application of the study to the real world as non-adherence is a major issue in most real-life clinical settings.

Conclusion

The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemic control as expressed by FCBG.

This feasibility study is the first since 2005 to investigate issues relevant to the initiation of a definitive RCT evaluating the impact of intensive insulin therapy on ulcer healing in people with diabetes. The results of such a trial would be useful to inform evidence-based clinical practice guidelines. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.

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Contributors A.C.V. and A.D. and designed the study and co-wrote the manuscript with V.B. A.D. oversaw the intervention and contributed to the discussion. A.C.V. contributed to data management, data monitoring and analysis planning and conduct. D.P. contributed to statistical analyses. B.M. coordinated the research. R.G. and A.N. provided podiatric care and contributed to discussion. A.D. and A.C.V. take responsibility for the contents of the article, study design, access to data and the decision to submit and publish the results.

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Disclaimer The joint lead authors A.D. and A.C.V. affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted except as noted in the text, and that any discrepancies from the study as planned have been explained.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics approval was given for the study by the New Zealand Northern A Health and Disability Ethics Committee, ethics approval number 14/NTA/195.

Provenance and peer review Not commissioned; externally peer-reviewed.

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Figure legends

Figure 1 – Substudy 1 recruitment flow diagram

Figure 2 – Point estimate and confidence interval of probability of each criterion being met by recruitment period. Period A was 0-5 weeks and Period B was 6-35 weeks. FC, full criteria; EC, exclusion criterion; IC, inclusion criterion.

Figure 3 – Histograms of participant scores on the three subscales of the Diabetes Medication Satisfaction questionnaire: (a) Burden, (b) Symptoms and (c) Efficacy subscales. Subscales are scored from 0-100, higher scores indicating greater satisfaction.

Figure 4. Fasting capillary blood glucose against time from study entry during intensive insulin therapy in the 15 participants of substudy 2

Tables

Table 1 Entry criteria assessed in Substudy 1

Criteria	Notation	Description
Inclusion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA1c ≥60 mmol/mol
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

EC, exclusion criteria; HbA1c, glycosylated haemoglobin; IC, inclusion criteria.

Table 2 Characteristics of participants included in both substudies

	Substudy 1 Participants (n=78)	Substudy 2 Participants (n=15)
Median age (IQR), years	58.5 (18.2)	51 (16.5)
Women, *n* (%)	30 (38.5)	6 (40)
Mean baseline HbA1c (SD), mmol/mol	Not collected	93 (29)
Mean baseline FCBG (SD), mmol/L	Not collected	11.3 (5.7)
Ethnicity, *n* (%)		
Asian	5 (6.4)	1 (6.7)
European	27 (34.6)	4 (26.7)
Māori	13 (16.7)	2 (13.3)
Pacific	33 (42.3)	7 (46.7)
Type 1 diabetes mellitus, *n* (%)	12 (15.4)	3 (20.0)
Type 2 diabetes mellitus, *n* (%)	66 (84.6)	12 (80.0)
Duration of diabetes, *n* (%)		
0-10 years	15 (19.2)	3 (20.0)
10-20 years	31 (39.7)	6 (40.0)
20-30 years	22 (28.2)	4 (26.7)
30-40 years	7 (9.0)	2 (13.3)
40-50 years	3 (3.9)	0 (0.0)
Peripheral neuropathy, *n* (%)	Not collected	15 (100.0)
Peripheral vascular disease, *n* (%)	Not collected	1 (6.7)

IQR, interquartile range; HbA1c: glycosylated haemoglobin; FCBG: fasting capillary blood glucose

Table 3 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood glucose

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBG		Equivalent effect size	*P*	
		Estimate	95% CI			
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.009	[-0.014,0.032]	0.01	0.70	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

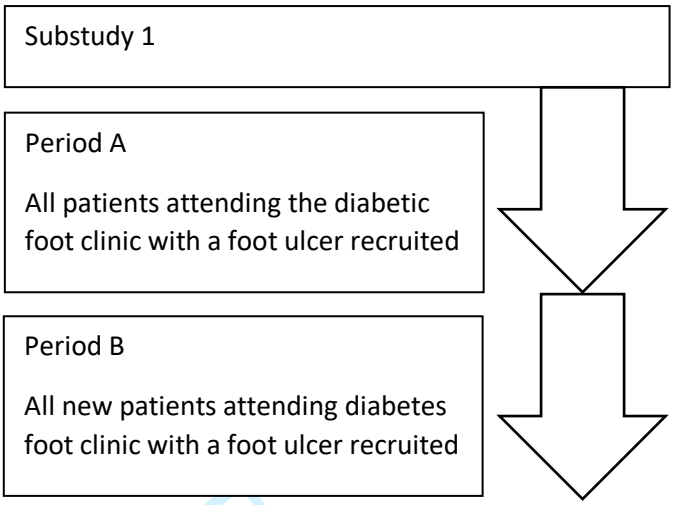
† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBG: fasting capillary blood glucose; CI: confidence interval

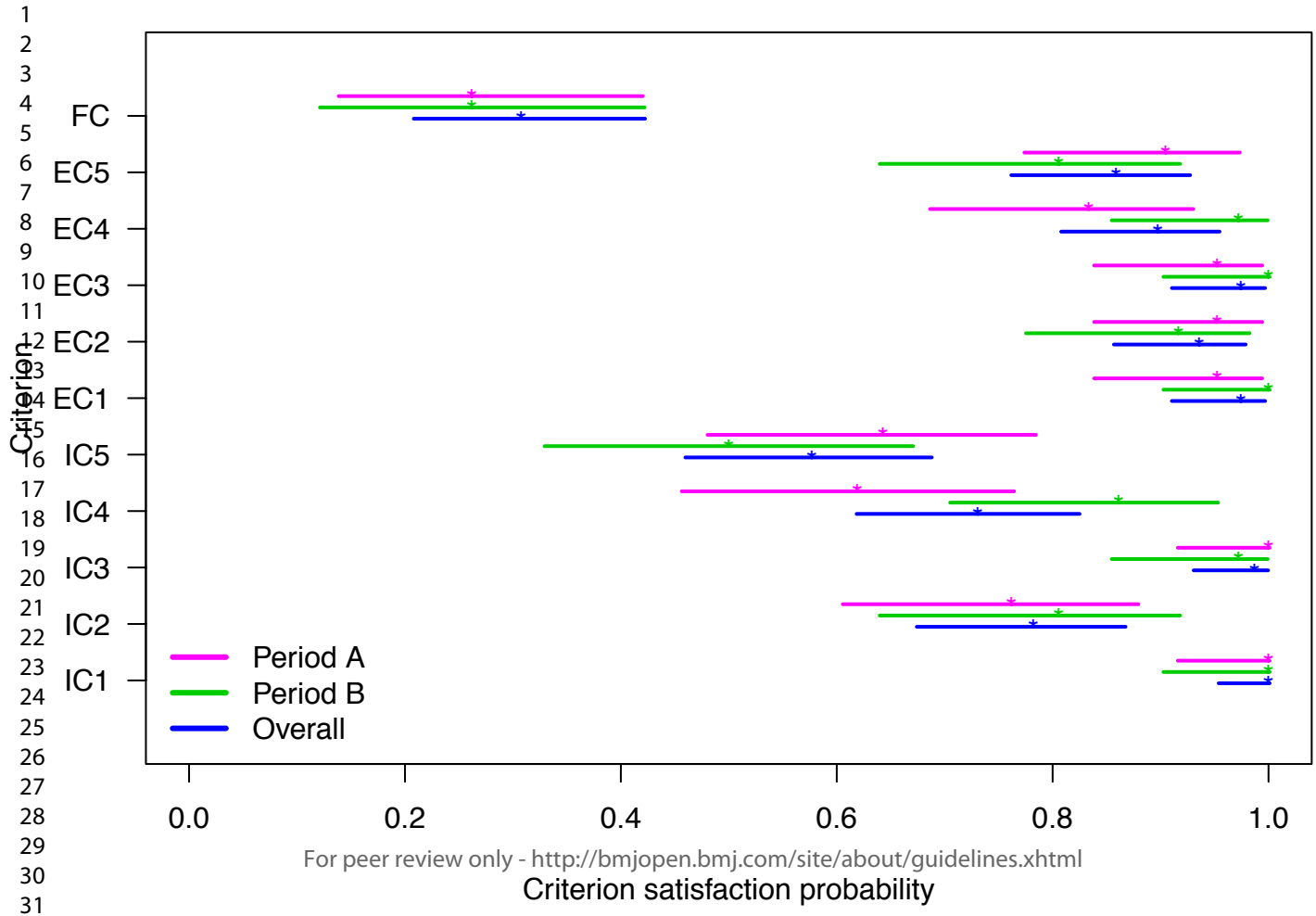
Table 4 Estimated Pearson correlation coefficients between Diabetic Foot Ulcer Scale-Short Form subscale scores and both log(ulcer area+0.01) and EuroQol 5 Dimension 5 Level

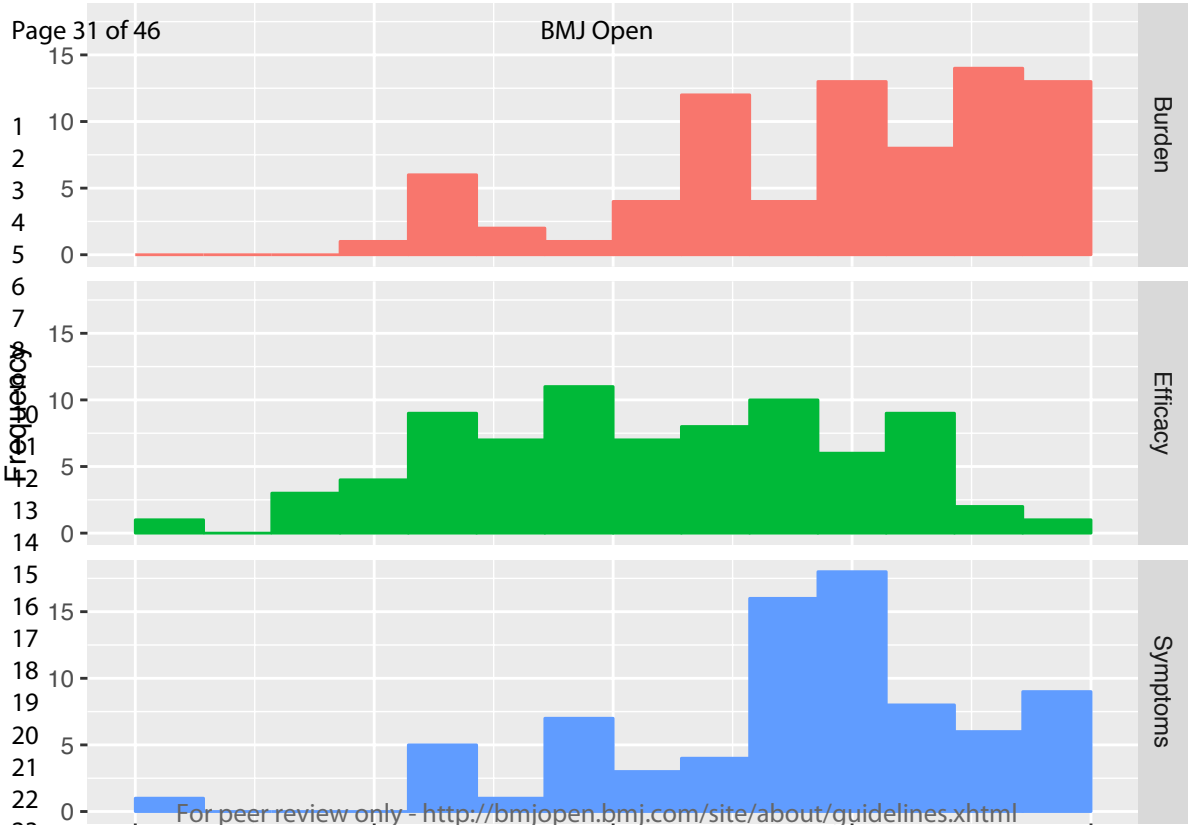
Correlates	log(ulcer area+0.01)†				EQ-5D-5L VAS			
DFS-SF subscale	Est.	95% CI	*P*		Est.	95% CI	*P*	
Leisure	-0.48	[–0.66, –0.25]	<0.0001	***	0.50	[0.23, 0.77]	0.0002	***
Physical health	-0.48	[–0.66, –0.26]	<0.0001	***	0.64	[0.44, 0.84]	<0.0001	***
Dependence	-0.54	[–0.71, –0.33]	<0.0001	***	0.58	[0.36, 0.81]	<0.0001	***
Negative emotion	-0.64	[–0.80, –0.42]	<0.0001	***	0.38	[0.04, 0.72]	0.03	*
Worried about ulcers	-0.54	[–0.71, –0.32]	<0.0001	***	0.62	[0.38, 0.86]	<0.0001	***
Bothered by ulcer care	-0.46	[–0.63, –0.24]	0.0001	***	0.36	[0.04, 0.69]	0.03	*

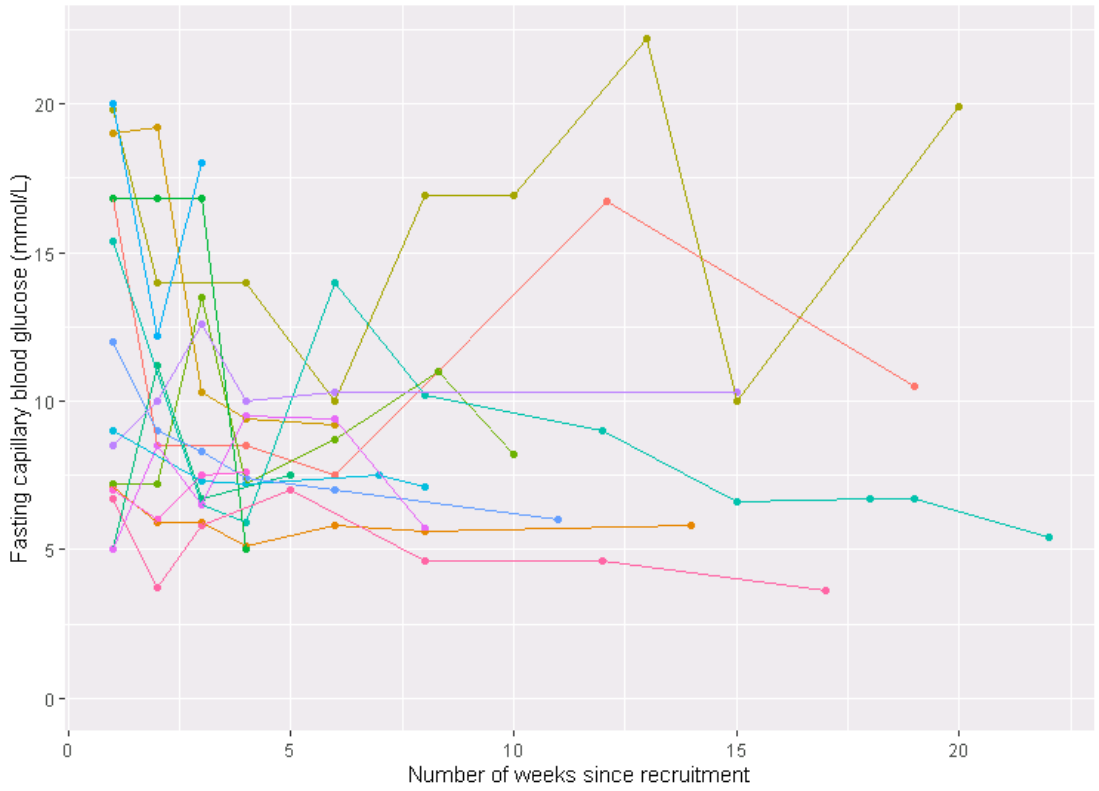
† Area in cm^2.

CI, confidence interval; DFS-SF: Diabetic Foot Ulcer Scale-Short Form; EQ-5D-5L: EuroQol 5 Dimension 5 Level; VAS: visual analogue scale.









STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract	Two substudies: one cross-sectional, one single-arm prospective
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	*What was done:* **Setting** Single-centre secondary care diabetic foot clinic located in New Zealand. Participants Substudy 1: 78 participants consisting of all people ≥18 years with a diabetic foot ulcer presenting to the clinic over 35 weeks in 2015. Substudy 2: 15 participants from Substudy 1 consenting to intensive insulin therapy. **Intervention** None in Substudy 1. Intensive insulin therapy combined with standard podiatry care over 24 weeks. **Outcome measures** Substudy 1: Proportion of participants satisfying potential entry criteria to the RCT. Substudy 2: Glycaemic control (fasting capillary blood sugar; FCBS); time to index ulcer healing; index ulcer size; medication satisfaction (DiabMedSat scores); and health-related quality of life (HrQOL; EQ-5D-5L and DFS-SF scores).. *What was found:* **Results** Proportion in Substudy 1 fulfilling all entry criteria was 31% (95% CI 21 to 42). FCBS values declined between baseline and study end (difference -3.7 mmol/L, 95% CI -6.5 to -0.8), suggesting adherence to therapeutic regimen; 83% (95% CI 44 to 95) of ulcers healed by 24 weeks. FCBS correlated negatively, and weakly-to-moderately, with medication satisfaction. Log(ulcer area in cm2+0.01) was most sensitive to FCBS changes, correlating negatively, and moderately-to-strongly with QOL measures. Detecting a 30% between-group difference in the ulcer area logarithm (80% power, α=5%) requires 220 participants per arm, achievable within 1 year with 15 centres similar to the study setting.

Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	[…]clinical practice guidelines from the Society for Vascular Surgery, American Podiatric Medical Association, and Society for Vascular Medicine now recommend adequate glycaemic control (glycosylated haemoglobin [HbA1c] <53 mmol/mol) to reduce the incidence of diabetic foot ulcers 1. The evidence that improved glycaemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation remains observational 11-17. There is no randomised trial evidence that tight glycaemic control improves ulcer wound healing 18. A previous feasibility study in this area 19 concluded 15 years ago that a definitive randomised trial in this area was not feasible, possibly due to exacting entry criteria. To investigate further whether a randomised controlled trial (RCT) evaluating the efficacy of intensive insulin therapy on diabetic foot ulcer healing is possible, this two-part feasibility study sought appropriate but less stringent trial entry criteria to improve accrual rates (Substudy 1) and sought appropriate endpoints for such a trial (Substudy 2)..
Objectives	3	State specific objectives, including any prespecified hypotheses	6	The primary objective of Substudy 1 was to estimate the proportion of participants satisfying the entry criteria for the planned RCT.. […]Secondary objectives were to estimate the length of the recruitment period for the intended RCT, and determine participant satisfaction with their diabetes medication. In Substudy 2, the main objective was to determine a primary endpoint for the RCT by analysing sensitivity of ulcer healing-related outcomes […]to glycaemic control accounting for standard podiatry care. The ulcer healing outcome measure with the best association with glycaemic control was to be assessed for convergent validity with an established foot ulcer scale. Secondary objectives included examining the relationship between adherence (using glycaemic control as proxy), as well as attendance, and satisfaction with diabetes medication, and evaluating health-related quality of life (HrQOL) measures in this population.
Methods				
Study design	4	Present key elements of study design early in the paper	7	*First paragraph of* Setting and Study Design *section*: Substudy 1 was a cross-sectional study enrolling all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks.
Setting	5	Describe the setting, locations, and relevant	7-8	*Setting, location and relevant dates, including periods of recruitment, follow-up*:

		dates, including periods of recruitment, exposure, follow-up, and data collection		The study was conducted at the Counties Manukau Health (CMH) Diabetes Foot Clinic in Auckland, New Zealand between February and October 2015, with Substudy 2 follow-up to February 2016. […]Substudy 2 was a single-arm interventional study enrolling Substudy 1 participants meeting all entry criteria (below) and treating them with intensive insulin therapy for 24 weeks. *Data collection:* Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, visits occurred weekly between weeks 1 (baseline) and 4, then at 6, 8, 12, 16, 20 and 24 weeks, or until the index ulcers healed.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7 + Table 1	*Cross-sectional:* Substudy 1 was a cross-sectional study that enrolled all people aged ≥18 years with diabetes and a current foot ulcer presenting at the CMH Diabetes Foot Clinic over a period of 24 weeks. *Longitudinal:* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria (Table 1)

Table 1 Entry criteria assessed in Substudy 1 (primary objective)

Criteria	Notation	Description
Inclusion Criterion	IC1	Male or female aged ≥18 years
	IC2	Type 1 or Type 2 diabetes mellitus for more than one year with an HbA_{1c} ≥60 mmol/mol (≥7.6%)
	IC3	Incident foot ulcer(s) located below the level of the malleoli
	IC4	Able and willing to undertake home blood glucose monitoring and administer insulin up to 4 times daily under the supervision of the diabetes nurse specialist
	IC5	Able and willing to provide informed consent to participate in the study
Exclusion Criterion	EC1	Ulcers with radiological features of osteomyelitis
	EC2	Significant peripheral vascular disease under consideration for re-vascularisation
	EC3	Significant bone deformity as determined by the investigator which may delay wound healing
	EC4	Non-adherence to standard care
	EC5	Any other disease or condition in the opinion of the investigator could make them unsuitable for entry
Full Criteria	FC	All inclusion criterion satisfied (5-Yes) and all exclusion criterion satisfied (5-No)

		EC, exclusion criteria; HbA_{1c}, glycosylated haemoglobin; IC, inclusion criteria.
(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		*Not applicable.*

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	**Study procedures and outcomes** Substudy 1 participants completed a Diabetes Medication Satisfaction (DiabMedSat) questionnaire. Their foot wound(s) (index ulcers) were inspected, and entry criteria status (Table 1) and demographic data recorded. In Substudy 2, […] [t]he following were undertaken at each visit: ulcer examination: digital photographic planimetry of ulcer area (using the SilhouetteStar camera, ARANZ Medical, New Zealand); FCBS measurement (in mmol/L); medication review; and adverse events assessment. FCBS was used in the analyses as a measure of glycaemic control and as a proxy for adherence. HbA1c was assessed at baseline and at the end of trial, providing an assessment of chronic hyperglycaemia. […]. In addition, participants completed three questionnaires at each visit: DiabMedSat, EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) and Diabetic Foot Ulcer Scale-Short Form (DFS-SF).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*See 7 above. No comparator group is used in this feasibility study.*
Bias	9	Describe any efforts to address potential sources of bias	9	*Substudy 1 – bias due to differential initial and later recruitment:* A Poisson exact test was used to compare recruitment rates over two recruitment periods and mixed logistic regression used to compare differences in entry criteria fulfilment between the periods. *Substudy 2 – bias due to confounding by time::* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit […] and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen on the basis of the data to improve the normality of the outcome.) […].Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
			10	*Substudy 2 – bias due to missingness:*

				[The non-survival] analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness. *The relevant sources of bias for the main study (for which this is a feasibility study) is bias due to loss to follow-up or missingness. Accordingly, we have attempted to briefly characterise participant attendance:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression.
Study size	10	Explain how the study size was arrived at	7	**Accrual period and sample size** The accrual period for Substudy 1 (35 weeks) was selected as long as possible while respecting contractual obligations with the study funder.[…] Substudy 2 aimed to recruit 20 participants. Assuming 10% attrition, this number is sufficient to estimate the standard deviation of a continuous variable (e.g. ulcer area) with a coefficient of variation inferior to 0.2. This criterion is consistent with the goal of identifying a sensitive primary endpoint endowed with good precision.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10	*Substudy 1:* Descriptive statistics were produced for […] DiabMedSat subscores. Multivariate analysis of variance (MANOVA) was used to detect differences in subscores based on demographic or participant characteristics. […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. *Substudy 2:* […] Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area, where “log” is the natural logarithm function) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random

				effect. […]The most sensitive outcome was selected by consideration of its time-adjusted observed significance level and its equivalent Cohen's effect size where appropriate. To estimate correlations and their 95% confidence intervals (CI) using longitudinal data, we fitted outcomes jointly using a heterogeneous compound symmetry covariance model, and using only intercepts as fixed effects. We thus obtained correlations between DFS-SF subscores and selected ulcer healing outcome; between DiabMedSat subscores and FCBS; and between DFS-SF subscores and EQ-5D-5L. (*And before any non-statistical reviewer vociferates that this makes no sense, they should talk to a statistician.)* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	*See 11 above, to which we add:* *Substudy 1:* Descriptive statistics were produced for participant demographic characteristics, recruitment rate, entry criteria fulfilment […]. A Poisson exact test was used to compare recruitment rates over two recruitment periods […]. *Substudy 2:* Time-to-healing was considered as a fifth possible outcome, and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. *Substudy 2 – in regard to confounding:* Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways.
		(*b*) Describe any methods used to examine subgroups and interactions	9	*Applies to Substudy 1 only:* […] [M]ixed logistic regression [was] used to compare differences in entry criteria fulfilment between the periods. Indicators of criterion satisfaction were fitted jointly by themselves in a first model, and interacting with period in a second model. Models were compared using a deviance test.

		(*c*) Explain how missing data were addressed	10	*(Note: No missing data in Substudy 1).* No data were missing for time-to-healing analyses. Other analyses all involved mixed models on longitudinal data, known to alleviate selection bias due to missingness
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10	*Cross-sectional Substudy 1: not applicable* *Longitudinal Substudy 2:* Descriptive statistics were produced on completed follow-ups (defined as healing before 24 weeks or attending the 24-week visit) and attended visits. Attendance probability was regressed on the most recently available FCBS, measure of ulcer area and DiabMedSat subscores using mixed logistic regression. The final attendance model was selected using AIC. See also 12 (c).
		(*e*) Describe any sensitivity analyses	10	*Arguably, our main analysis for Substudy 2 is a sensitivity analysis:* Linear mixed models were used to determine the relationship between four different ulcer area-related outcomes at each visit (ulcer area in cm2, log[ulcer area+0.01], absolute and relative rates of change in ulcer area) and glycaemic control. (The value of 0.01 in the logarithmic endpoint was chosen based on the data to improve the normality of the outcome.) FCBS was the fixed effect and participant the random effect. Time-to-healing was considered as a fifth possible outcome. A Kaplan-Meier estimate of ulcer persistence probability was produced and Cox regression used to estimate the hazard ratio of ulcer healing under changes in FCBS, taken as a time-dependent covariate. Time- and/or baseline ulcer area-adjusted estimates, as well as unadjusted estimates, were produced to assess potential confounding, as tight management in a foot clinic may promote ulcer healing in several ways. The most sensitive outcome was selected by consideration of its adjusted observed significance level and its equivalent Cohen's effect size where appropriate.
Results				
Participants	13*	(a) Report numbers of	10	*Substudy 1:* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1.

		individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		*Substudy 2:* *(page 8):* Substudy 2 was a single-arm interventional study that enrolled Substudy 1 participants meeting all entry criteria […]. *(page 11):* Seventy-eight participants (all unique clinic visitors during the recruitment period) were enrolled in Substudy 1 […]. *(page 12 – this is apparently out of order because it is a feasibility result):*. Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. *(page 12):* Seventeen participants entered Substudy 2. One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set. *(page 12):* Two participants with unhealed ulcers did not attend the 24-week visit.
		(b) Give reasons for non-participation at each stage	11	*Substudy 2:* One withdrew consent after Visit 1 and another was healed on Visit 1, leaving 15 participants in the analysis set.
		(c) Consider use of a flow diagram		*The flow appears to us to be simple enough not to warrant a diagram.*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	*Substudy 1 (see also Table 1)::* Mean age was 57.3 years (SD 14.0). The majority were men and most were of Pacific or European ethnicity. (Table 2). *Substudy 2 – see Table 2*
		(b) Indicate number of participants with missing data for	11	*Substudy 2:* Clinical constraints or patient choice prevented some measurements from being taken, yielding completeness proportions for specific outcomes between 78% (DMS and FCBS) and 85% (ulcer area).

		each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11	*Substudy 2:* **Completeness** Of the 102 scheduled visits, 12 were missed […].The average follow-up time to healing or last visit was 17.6 weeks (SD 7.8).
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12	*Substudy 2:* Twelve Substudy 2 participants experienced complete healing between weeks 3 and 24; the remaining three had unhealed ulcers at the time of their last visit on or before week 24. Median ulcer healing time was 7 weeks. The Kaplan-Meier estimate of the proportion of ulcers not healing by week 24 was 16.7% (95% CI 5.0–56.1%). *Table 4 for summary correlations*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	8	*Substudy 1:* **Recruitment rate and entry criteria** Period A (as defined earlier) finished after 6 weeks, and was the most active with 42 participants recruited compared with 36 participants over the remaining 29 weeks, forming Period B. All participants satisfied criterion IC1, 78.2% met IC2, 98.7% met IC3, 73.1% met IC4 and 57.7% met IC5.Twenty-four participants (30.8% [95% CI 20.8, 42.2]) met all criteria. […] **Diabetes Medication Satisfaction**

Higher scores on the DiabMedSat subscales indicate increased satisfaction for all three subscales. The subscale histograms are displayed in Figure 2. Median score for the Efficacy subscale was 63.3 (interquartile range [IQR] 26.7), and was numerically lower than those of the Burden (81.8 [IQR 22.8]) and Symptom subscales (80.0 [IQR 16.0]).

Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 3

Table 1 Unadjusted and adjusted regression results for five ulcer-healing endpoints against fasting capillary blood sugar

Ulcer outcome	Adjustment status	Change in outcome per 1 mmol/L increase in FCBS: Estimate	95% CI	Equivalent effect size	*P*	
Ulcer area (cm^2) †	Unadjusted	0.010	[–0.041,0.062]	0.004	0.69	
	Adjusted§	0.004	[-0.024,0.032]	0.001	0.77	
Log(ulcer area+0.01) †	Unadjusted	0.134	[0.049,0.214]	0.10	0.002	**
	Adjusted§	0.114	[0.020,0.194]	0.08	0.0145	*
Rate of absolute change (cm^2/week) †	Unadjusted	0.011	[-0.018, 0.041]	0.01	0.45	
	Adjusted¶	0.011	[-0.019,0.041]	0.01	0.69	
Rate of relative change (%/$week^{-1}$) †	Unadjusted	5.7	[1.1, 10.3]	0.06	0.015	*
	Adjusted¶	5.7	[1.1,10.3]	0.06	0.015	*
Hazard ratio‡	Unadjusted	0.90	[0.74,1.10]	N/A	0.31	
	Adjusted † †	0.88	[0.71,1.08]	N/A	0.21	

† Mixed linear regression, additive change reported ‡ Cox regression, multiplicative change reported
§ Adjusted for baseline value and time since Visit 1. ¶ Adjusted for time since Visit 1 only.
† † Adjusted for baseline ulcer area
FCBS: fasting capillary blood sugar; CI: confidence interval

(*b*) Report category boundaries when continuous variables were categorized | *Not applicable.*

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11	*Substudy 1:* The A-to-B rate ratio of eligibility to a full study, however, was 4.1 (95% CI 1.8-9.2). The eligibility rate in period B was 0.45 participant per week (95% CI 0.24-0.77).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		*Not applicable.*
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	This feasibility study showed that by using less stringent entry criteria, more people with diabetic foot ulcers attending our foot clinic (30%) may be eligible for a proposed RCT investigating the efficacy of an intensive insulin regimen on diabetic foot ulcer healing than reported in a previous feasibility study (0.5% [1/200]) 19. The study also showed that the primary endpoint of log(ulcer area+0.01), with ulcer area measured using digital photographic planimetry, may be sensitive enough to glycaemic control to base an RCT on in this population.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	11	*(No biasing issue was identified, but see 21.)* Some limitations temper the interpretation of our results. Firstly, Substudy 2 did not reach the target sample size of 20. This shortfall was largely due to availability of personnel and funder timelines. These issues, particularly around staffing, have the potential to affect any future RCT. Moreover, the study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.

		Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16	The study has produced evidence of moderate quality that tight glycaemic control may be beneficial for ulcer healing, and that an outcome derived from ulcer area could be sensitive to glycaemiccontrol as expressed by FCBS. However, we have also demonstrated that a reasonably powered trial would require the involvement of a large number of centres, increasing the complexity of such an undertaking.
Generalisability	21	Discuss the generalisability (external validity) of the study results	16	[…] [T]he study was conducted at a single centre in New Zealand, limiting generalisability to other populations and settings with different care pathways for diabetes and diabetic complications.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if	17	**Funding** This work was supported by the Health Research Council of New Zealand's Feasibility Study grant number 14/605.

	applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.