North Cumbria Integrated Care NHS Foundation Trust

ODIN (Observation of DIabetic Neuropathy) study:

A prospective cohort study screening for presence and progress of diabetic neuropathy in type II diabetes mellitus patients, using MEDIPIN pinprick and monofilament devices.

V1.0, dd 15 October 2024

Chief Investigator's Statement of Ownership and Content.

I, Dr Stacey Fisher, confirm that this protocol is my work and is owned by me. The protocol conforms to standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):_____Dr Stacey Fisher_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	**A prospective cohort study screening for presence and progress of diabetic neuropathy in type II diabetes mellitus patients, using MEDIPIN pinprick and monofilament devices.**
Short title:	ODIN (Observation of DIabetic Neuropathy) study
IRAS number	342532
Device description	CE-marked neuropathy test device: Medipin (MHRA No. 1321) Medipin is a single-use precision instrument designed to optimise cutaneous pinprick perception. Medipin's protected point is designed to significantly enhance pinprick acuity to achieve useful stimulation and reduce risk of damaging delicate skin. The protective annulus inhibits depth of penetration and protects against self-inflicted "needle stick" injury.
Study design	Prospective, single-centre, controlled, non-randomised, evaluative screening cohort study
Primary objective	The rationale for the study follow-up time is based on the suggestion Laudadio and colleagues (1998), who found that an 18-month follow-up period for detection of diabetic neuropathy progression is an insufficiently long period. Description of the rate of progression observed in study population, with progression being either sharp->dull or dull->no sensation step-change. Follow-up period of 3 years, and presented with Kaplan-Meier survival graph.
Secondary objectives	Concordance between Medipin and 10g monofilament test (dorsal application, 'Canadian method') results. Multiple binary logistic regression and Cox logistic regression to investigate if any variables (eg patient sex, age, BMI, HbA1c control, blood pressure, diabetes and cardiovascular medication use) are significantly associated with presence of diabetic neuropathy and/or progression.
Inclusion & Exclusion criteria	Inclusion criteria: - Adult patients aged ≥ 18 years - Patients with type II diabetes mellitus (in accordance with NICE guidelines, Oct 2023) Exclusion criteria: - Aged < 18 years - Confirmed complete diabetic neuropathy (patients can be consented if this is not known beforehand, but will then not be included in diabetic neuropathy progression analysis)

	- Any reasons for the patient being unable to follow the protocol, including lack of mental capacity to consent to taking part in the study (examples include dementia, severe learning disability). - The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives (examples include receiving palliative care, active cancer treatment, medical condition that contraindicates giving routine blood samples) - Amputation of hallux, foot, or complete lower limb (at baseline) - Confirmed and ongoing foot wound / ulcer (at baseline)
Sample size	Observed incidences of new diabetic neuropathy (or progression of existing DN) at 80% power (beta) and 5% significance (alpha), and 40% dropout/withdrawal/lost to follow-up rate. The Keio University Japan source, https://nshi.jp/en/js/ , was utilised to determine sample size for 'survival' (ie measuring incidence of a DN progression) in a single cohort (Nagashima et al, 2021). The minimum required number of patients to be recruited, is therefore: 178 x 1.4 (withdrawal rate) = 250 participants. Assuming two-thirds of participants report a sharp sensation when tested with the MEDIPIN device at baseline, depending on accrual success this sub-cohort of patients can be assessed separately. For this purpose, the required sample size can be increased to 250 x 1.5 = 375 participants.
Manufacturer & provider of material	Medipin Ltd, Barry Jacobs 24 Chiltern Ave, Bushey WD23 4QB clinical@medipin.net
Chief Investigator	Dr Stacey Fisher, Research GP, North Cumbria Integrated Care NHS Foundation Trust, stacey.fisher@ncic.nhs.uk
Co-investigators	Dr Leon Jonker PhD, Science & Innovation Manager, North Cumbria Integrated Care NHS Foundation Trust Leon.jonker@ncic.nhs.uk
Sponsor and organisation where research will take place	North Cumbria Integrated Care NHS Foundation Trust R&D department Ann Burrow Thomas Centre Workington, CA14 2ED
Planned timeline	Recruitment start date (first patient, first visit): 1 August 2024, Recruitment end date (last patient, first visit): 31 August 2025 Follow-up end date (last patient, last visit): 31 August 2028 Study end date: 31 October 2028
Protocol version, date	Version 1.0, dd 15 October 2024

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Lay Summary

Diabetic neuropathy (DN) is a complication related to diabetes. This loss of protective sensation (LOPS) occurs because of nerve damage and can lead to further complications such as foot ulcers. The frequency of screening of patients for presence of DN is once yearly in clinical guidelines but the rationale and exact method for this is not clear; perhaps as a result of this, testing practices vary in clinical practice. DN diagnosis is complicated by the fact that different medical devices test for functioning of slightly different nerve types, either small or large fibre. Currently the NHS mainly uses a monofilament which checks predominantly large fibre function. However, there is evidence that small fibre nerves are damaged earlier in DN. A recent trial with a pinprick Medipin device – which targets mainly small fibres because it looks for a pain response – confirms this.

In this ODIN trial the aim is to utilise both the Medipin and monofilament devices to describe the development and potential progression of DN in diabetes patients. The main objective is to see how many patients' status may go from 'no neuropathy' (sharp sensation with Medipin) to 'reduced sensation' (dull sensation), and from 'reduced sensation to no sensation' (complete absence of sensation). A minimum total of 214 patients with no neuropathy at baseline visit will be involved in the study. By using one group (cohort) of patients and following them up for three years, a clearer picture should emerge on the profile of DN and also if it is affected by other factors such as blood pressure and blood glucose control. The eventual results may inform how and when DN should be tested for, and may form foundation for future research into the potential treatment of DN.

1 BACKGROUND AND RATIONALE

In developed countries, type 2 diabetes mellitus (T2DM) is a very common condition associated with poor diet and sedentary lifestyle. T2DM can lead to multiple complications affecting various organs, including of the lower limbs (Chatterjee et al, 2017). Initial nerve damage in the patient's foot results in loss of protective sensation (LOPS), diagnosed as diabetic neuropathy (DN). Due to reduced sensation in the feet, patients may not notice footwear being too tight or loose and may not realise feet are damaged; this can then result in ulceration (Feldman et al, 2019). Poor healing associated with diabetes – because of vascular damage – can then lead to infection and ultimately amputation. This is also costly in terms of healthcare provision: costs for foot ulcer care were £300m in 2005-06 and had risen to ~£900m in 2014–15 (Posnett & Franks 2008; Kerr et al, 2019). In the United States, neuropathy is implicated in up to 80% of >50,000 amputations (Smieja et al, 1999).

Large studies conducted in Europe in the mid-90s estimated a prevalence of diabetic neuropathy of circa 25% (Young et al, 1993; Tesfaye et al 1996; Cabezas-Cerrato et al 1998). In a more recent study where 10g monofilament testing was utilised, 11.7% of women with normal fasting glucose, 14.4% of women with impaired fasting glucose (IFG), and 18.3% of women with diabetes had LOPS (Ylitalo et al, 2013). Interim data from a study conducted by the ODIN study investigators - involving the Medipin pinprick test - gave the following prevalence numbers: 3.6% patients with complete diabetic neuropathy (ie absence of sensation in large toe), 27% with degree of diabetic neuropathy (dull instead of sharp sensation), and 70% responded normally to a pinprick challenge. See Figure 2 for distribution of these outcomes when a 10-com visual display score is applied. It is imperative to ensure DN is diagnosed early in diabetes patients

and that they are educated to look after their feet, thereby minimising the risk of further costly and serious complications.

In regular clinical practice, the use of a 10g monofilament is the mainstay for DN diagnosis. The 10g relates to the amount of g-force applied to the skin with the nylon strand attached to a handheld stick. More sensitive tests are available, including nerve conduction tests and biopsy of skin tissue, but monofilaments are used since they are relatively effective in detecting DN and because the test is affordable, plus straightforward to apply and interpret. Two types of nerves are present in the skin, and diabetes related damage can lead to a) large fibre neuropathy: manifests with the loss of joint position and vibration sense and sensory ataxia, and b) small fibre neuropathy: manifests with the impairment of pain, temperature and autonomic functions. Monofilament application, akin of stroking the skin, tests predominantly for large fibre DN. This means that small fibre damage is usually not specifically tested for. There is evidence that small fibre damage develops before large fibre damage manifests, which may be of value if early intervention and prevention for DN is the goal (Malik et al, 2011; Ponirakis et al, 2014; Breiner et al, 2014). Recently, Burgess et al (2021) stated "DN is diagnosed at a late, often pre-ulcerative stage due to a lack of early systematic screening and the endorsement of monofilament testing which identifies advanced neuropathy only".

Screening with a pin-prick device offers an alternative to monofilament testing. Medipin Ltd has developed a purpose-design pin-prick that allows for rapid screening for diabetic neuropathy in clinic (Jacobs 2006a; Jacobs 2006b). Interim results from an ongoing research project (MANDARIN study) appraising the performance of screening for DN with the Medipin shows that a pinprick test does not give the same results as a monofilament test. Firstly, unlike the monofilament test which tests with application of pressure, the Medipin test allows for a sensory grading. Figure 1 shows the distribution of the type of sensation felt by the patients and how this correlates with a score on a 10cm visual display scale. Applying Medipin on the forearm before applying it to the hallux gives a reference for type ('sharp') and score (5 out of 10). The accompanying median score for a sharp sensation is 6 and for dull it is 3; in absence of any sensation, the scores were 0. Secondly, Medipin testing compared to monofilament testing indicates that a pinprick test detects LOPS earlier. Figure 2 summarises interim data from the MANDARIN study; monofilament testing was done in accordance with a method from Canadian Journal Diabetes (2018). That monofilament method involves applying the monofilament four times to the left and right hallux, also with the forearm used as the reference sensation. Relatively more patients score 'dull' with Medipin when the monofilament result deems there is no DN pathology present. Table 1 shows that the correlation (Kendall's Tau ranked correlation) in test outcomes is only modest when Medipin is compared to a dorsal monofilament test, supporting the notion that they test for slightly different nerve fibre types. Taken together, these results suggest that Medipin pinprick testing is a suitable tool to screen for DN.

Figure 1, Distribution of Medipin test results for Type II Diabetes Mellitus patients (MANDARIN study interim results)

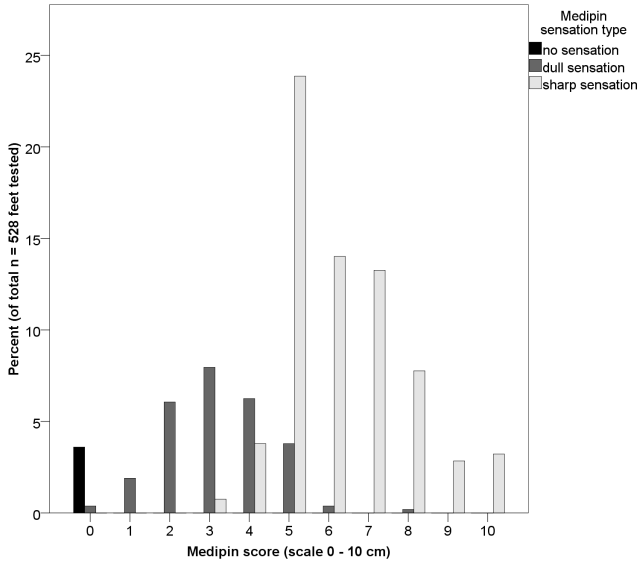

Figure 2, Comparison of Medipin and monofilament results in Type II Diabetes Mellitus patients (MANDARIN study interim results)

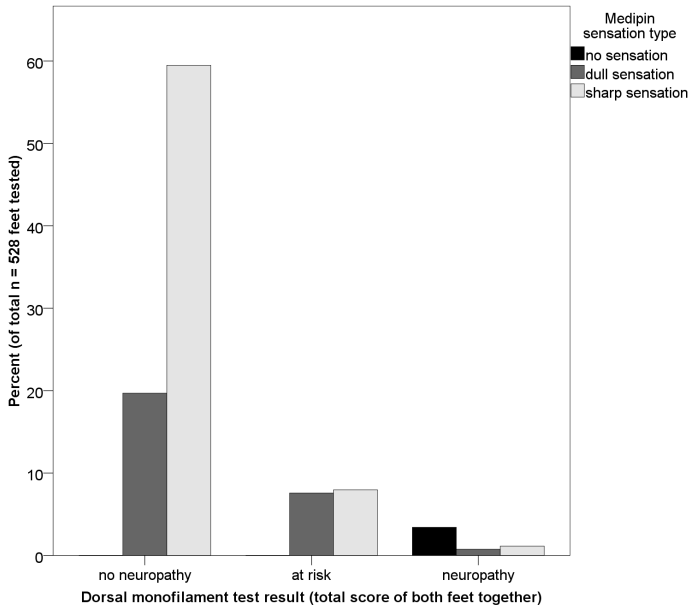

Table 1, Kendall's Tau correlation analysis between Medipin and dorsal monofilament results in Type II Diabetes Mellitus patients (MANDARIN study interim results, n = 528 feet from 264 patients)

		Medipin score (0-10 VDS scale)	Monofilament result (neuropathy, risk of neuropathy, no neuropathy)	Monofilament raw score (0-8 points)
Medipin sensation type (absent, dull, sharp)	Correlation Coefficient	0.65	0.28	0.26
	p-value	<0.001	<0.001	<0.001
Medipin 0-10 VDS scale score	Correlation Coefficient		0.27	0.26
	p-value		<0.001	<0.001

The use of a pinprick has been advocated in the past and utilized in research studies (Abbott et al,2002; Boulton et al 2008). In those studies, it was shown that inability to perceive the pinprick challenge is significantly associated with a risk of developing ulcers. However, the test does not tend to feature in current NHS guidance on screening for DN. One reason may be that in the past very rudimentary or home-made pinprick device were utilized in the absence of a fit-for-purpose device. For example, one research group developed an in-house weighted pinprick device involving a hypodermic needle (Chan et al, 1992). This kind of solution is carries too much risk of needle injury for both patient and clinician. To further illustrate past suboptimal practice, in one paper by Smieja et al (1999) the following approach was taken: "Pinprick sensation was tested with a sterile or unused safety pin over the plantar aspect of the distal first, third, and fifth toe of each foot with the stimulus applied once per site." Unlike with testing for large fibre nerve damage using the reusable monofilament device, testing for small fibre damage requires more force and therefore should always be conducted using a single use disposable device that cannot pierce the skin. A device like Medipin meets that design brief.

In addition to variation in test methodology for DN screening, the rate of progression of DN is currently not a focal point in primary care. However, having an understanding of DN progression and any factors that may be associated with this progression may be useful for managing, monitoring, and educating patients. Even in research studies where nerve function was a primary outcome measure and assessed with more quantitative methods like measurement of sensory nerve conduction velocity with electrodes, follow-up is often limited to a year or less. One interventional trial to try and treat DN followed patients up for only six months (Ekberg et al, 2007). Laudadio and colleagues (1998) suggested that even an 18-month follow-up period in their clinical trial was insufficient. There have been reports on the incidence of diabetic neuropathy over time in cohorts followed up for longer periods but these studies had limitations or involved type I diabetes patients. In one study T2DM patients were followed up for 10 years, but the sample size was small and diabetic neuropathy status was obtained from medical records; no distinction was made between no DN, elevated risk of DN (where there is reduced sensation but not complete absence of sensation), and complete DN (no sensation) (Tomah et al, 2023). Another study compared patients who did or did not have DN and looked at risk factors associated with its diagnosis, but did not explore progression despite this being mentioned in the article's title (Huang et al, 2021). The type of test

can influence the overall prevalence of DN seen in a population. Compared to questionnaire-based screening, monofilament testing resulted in a lower prevalence of DN (Pfannkuche et al 2020).

Taken together, there is a lack of evidence concerning the rate of diabetic neuropathy progression in a real-world community setting; this is particularly the case in terms of comparing small and large nerve function assessment. This study will determine the prevalence of diabetic neuropathy using both the Medipin pin-prick and monofilament devices. By following up and testing patients over three years, the presence of and progression rate of diabetic neuropathy can be determine. The findings of this present ODIN study may potentially help to inform a) how diabetic neuropathy tests are done in the future, b) the frequency of screening for diabetic neuropathy in a primary care/community setting, and c) give a better overview of the nature of diabetic neuropathy. Overall, any obtained results may be useful reference data for any future efforts to treat diabetic neuropathy.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE AND OUTCOME MEASURES

Description of the rate of diabetic neuropathy progression observed in study population, with main objective being the progression from sharp->dull sensation or dull->no sensation as determined with Medipin test. Follow-up period of 3 years, and presented with Kaplan-Meier survival graph. Sample designed to be powerful enough to reflect representation of general T2DM population.

2.2 SECONDARY OBJECTIVES AND OUTCOME MEASURES

- Comparison of rate of progression between Medipin and monofilament test results (clinic observations at baseline, 18 months, and 36 months)
- Evaluation of possible relationship of variables (blood pressure, blood glucose control [HbA1c], medication use for diabetes and cardiovascular disease) with prevalence and rate of progression of diabetic neuropathy.

3 INVESTIGATIONAL PLAN

3.1 TRIAL DESIGN AND TIMELINE

Prospective, single-centre, controlled, non-randomised, evaluative screening cohort study

Table 3 shows the anticipated timeline for the study. For this study, appropriately trained staff will conduct the Medipin and monofilament tests.

During the study period, all patients can continue to be managed and receive their standard treatment regime by their usual clinical team. Therefore, management of participants' diabetes is not affected by participating in this present study. If signs of diabetic neuropathy are identified then the patient's GP will be notified by means of a GP notification letter. In relation to the baseline visit, and the patients being

recruited, a GP letter will be sent out that also contains the screening results. For the other two follow-up visits, at 18 and 36 months, the results will be uploaded directly onto the patient's GP medical records. The regular GP and/or diabetes practice nurse can then decide the next course of action in relation to those findings, should they deem this necessary.

Table 3, Anticipated study timeline

Month	Setup	Cohort	Analysis
June 2024	Submission to NRES and HRA		
	NIHR portfolio adoption		
July 2024	HRA and Trust approval		
Aug 2024		Start recruitment	
Aug 2025		Finish all recruitment	
Aug 2028		Last follow-up appt	
Oct 2028			Finalise analysis & report

4 PARTICIPANTS

4.1 TRIAL PARTICIPANTS & LOCATIONS

Patients will be recruited from the adult population managed in one of 16 different GP practices, see Table 4. The GP practices will act as Patient Identification Centres, and the study activities will take place in the clinic spaces of North Cumbria Integrated Care NHS.

Table 4, List of participating GP practices

ODS CODE	name	POSTCODE	patient list (Jan2023)
A82016	Carlisle Healthcare	CA1 3UB	37516
A82047	James Street Group Practice	CA14 2DL	32999
A82044	Fellview Healthcare	CA28 7QE	24021
A82020	Eden Medical Group	CA2 7AJ	16330
A82041	Lowther Medical Centre	CA28 7RG	14343
A82045	Wigton Group Medical Practice	CA7 9QD	8980
A82654	Warwick Square Group Practice	CA1 1LB	7777
A82055	Aspatria Medical Group	CA7 3HH	6869
A82013	Upper Eden Medical Practice	CA17 4RB	6680
A82024	Seascale Health Centre	CA20 1PN	5878
A82038	Temple Sowerby Medical Practice	CA10 1RW	4882
A82037	Silloth Group Medical Practice	CA7 4AH	4328
A82631	Court Thorn Surgery	CA4 0HP	3690
A82029	The Croft Surgery	CA7 5JH	3479
A82004	Alston Medical Practice	CA9 3QX	2236
A82620	Glenridding Health Centre	CA11 0PD	932

Identification of potentially eligible diabetes patients will be done by the Investigator/GP. Therefore, the patient will be approached initially by the clinical team caring for them. An invite letter and patient information sheet is sent out to the eligible patients and they then return a reply slip via Freepost if they are interested in participating. The patient is then contacted – they will have indicated how they prefer to be contacted on the reply slip – and they will attend a one-off study visit. The researchers will obtain written informed consent from the patients after talking them through the patient information sheet. Then the tests for diabetic neuropathy and questionnaires will be conducted.

4.2 INCLUSION & EXCLUSION CRITERIA

Inclusion criteria:

- Adult patients aged ≥ 18 years
- Patients with type II diabetes mellitus (diagnosed in accordance with NICE guidelines, Oct 2023)

Exclusion criteria:

- Aged < 18 years
- Confirmed complete diabetic neuropathy (patients can be consented if this is not known beforehand, but will then not be included in diabetic neuropathy progression analysis)
- Any reasons for the patient being unable to follow the protocol, including lack of mental capacity to consent to taking part in the study (examples include dementia, severe learning disability).
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives (examples include receiving palliative care, active cancer treatment, medical condition that contraindicates giving routine blood samples)
- Amputation of hallux, foot, or complete lower limb (at baseline)
- Confirmed and ongoing wound / ulcer located on the foot (at baseline). This may impede ability to conduct the DN tests (ie wound and dressing/bandage covering the hallux [big toe])

5 STUDY PROCEDURES

5.1 INFORMED CONSENT

Before being recruited to the clinical evaluation, the patient must have consented to participate, after the nature, scope and possible consequences of the evaluation have been explained in an understandable form.

For all eligible patients, an initial invite letter and patient information leaflet will be provided to the patient via post. If patients are interested, they then return a reply slip and during the study visit the patient will provide written informed consent. Consent to take part in this research is obtained from adult patients, where they possess mental capacity.

During the consent procedure the following information will be outlined in writing, which will also be relayed verbally: a) The evaluation involves research, a description of the aims of the evaluation and how

it will be organised and the expected duration of the patient's participation; b) Any potential risks and benefits of taking part; c) The freedom to ask for further information, and to withdraw from the study, at any time; d) The extent to which confidentiality of records identifying the patients will be maintained and that the Regulatory Authorities may inspect the records.

A slightly alternative approach is allowed for any patients who have participated in the MANDARIN study. This study also involved the same Medipin and monofilament tests as to be conducted for the ODIN study. Therefore, baseline data is already available for those patients. MANDARIN participants who are eligible for the ODIN study will receive a specific invite lette, explaining that they will join ODIN at the 18 month time point if they are indeed interested in participating. The patient information leaflet and informed consent form will also be adapted for those who have previously participated in the MANDARIN study.

The staff will be trained in obtaining informed consent as part of professional development, members of staff involved in the consent process will also have current ICH Good Clinical Practice training (even though this officially does not fall under the remit of Good Clinical Practice requirements).

5.2 STUDY PROCEDURES

After completing informed consent, information on relevant clinical parameters and demographics will be collected. See Table 5 for an overview of the activities conducted at the single research visit. The Medipin assessment is an added investigation, whereas the other activities are all regular elements of a diabetes (foot) review.

Table 5, Overview of study activities for study participants at single study visit.

Visits	*Activities*

Baseline ('0 months')
 	
And
 	
18 months (+/- 3 months where possible; file note if outside this period)
 	
And
 	
36 months (+/- 3 months where possible; file note if outside this period)
 	
(All in-person, in clinic)
	• Complete informed consent form (baseline visit only).
	• Answer medical/general information questions (e.g. height, weight, medication) if not in medical notes (baseline visit only)
	
	• Latest blood pressure, HbA1c glucose level (from medical notes)
	• Two questionnaires, one on quality of life and one on diabetic neuropathy symptoms
	  o EQ-5D-5L (Herdman et al, 2011)
	  o Michigan Neuropathy Screening Instrument symptom questionnaire (Moghtaderi et al, 2006)
	• Medipin test, done by researcher (sharp/dull scoring as per Boulton et al, 2008)
	• Monofilament test on dorsal side of hallux, done by researcher (Canadian Journal Diabetes, 2018)

5.3 Description of tests for DN

10g Monofilament test: four applications on dorsal side of hallux, proximal to toenail, on both left and right foot

A reference from Canadian Diabetes is used for this purpose,
https://www.canadianjournalofdiabetes.com/article/S1499-2671(17)30866-3/fulltext

1. Touch patient with monofilament on the forearm to establish that sensation is understood
2. Instruct patient to say 'yes' every time stimulus is felt. Answer can be 'yes, less than forearm' or 'yes, same or more as forearm'.
3. With patient's eyes closed, apply the monofilament to the dorsal area of the great proximal to the nail bed. Apply monofilament for one second each time, bending the filament. Ask patient where possible to identify and grade the quantity of deficit between them and the 'control' area as per point 2.
4. Perform the stimulus a total of 4 times, each time having the patient score the test (if sensation felt)
5. Total of 8 applications, and score can be 0 if stimulus not perceived, 0.5 if perceived substantially less than on forearm and score of 1 if perceive same or more as on forearm. Score below 3.5 means DN present, score of 3.5 to 5 means risk of DN within next four years, and score 5.5 or higher means low risk of neuropathy.

Figure 1. Application of monofilament on dorsal side of hallux

Medipin test: application on dorsal side of hallux, proximal to toenail, five times each on left and right foot respectively.

1. Break tab to expose point - avoid contact with fingers.

2. Grasp device between thumb and index finger lightly enough to permit slight axial slippage if required - utilize textured surface to facilitate control.

3. Apply to skin at a perpendicular to standardize point pressure for improved test consistency and optimize annular contact to generate a 'centre surround' field of enhanced acuity. Establish a control area in an unaffected region (forearm) with an 'average' stimulation level by making several quick applications around the same locality for about 5-10 seconds. Press firmly but carefully using a repetitive, percussive contact.

Avoid high amplitude or ‘stabbing’ actions - penetration is checked by the annulus but never assumed ‘impossible’. Instruct your patient this “normal” area represents a ‘sharp’ sensation and that this equates to a score of 5 out of 10 (on a 10cm scale).

4. With patient’s eyes closed, apply the Medipin five times to the dorsal area of the great proximal to the nail bed (random locations within this anatomical site). Ask patient where possible to identify and grade the quantity of deficit between them and the ‘control’ area. Answer can be ‘no’ sensation, ‘dull’ sensation, and ‘sharp’ sensation. Patient will also score the sensation on a 10cm visual analogue scale.

5. To prevent re-use destroy point by compression against a hard surface and/or dispose of in a biohazard container.

Figure 2. Medipin device.

5.4 DEFINITION OF END OF STUDY

For participants the study involves a three year follow-up, and three in-person clinic visits during that time (0, 18, 36 months). Once the 36-month follow-up visit has been completed, all study involvement is complete. The study itself therefore ends once the last participant has been seen in person for the third time.

5.5 DISCONTINUATION OR WITHDRAWAL OF PARTICIPANTS

Each participant has the right to withdraw from the study at any time. Any data already collated as part of the study will be retained if a subject withdraws from the study. Participants do not need to give a reason for study withdrawal and their normal clinical care will not be affected should they decide to discontinue participating in the study. A partial withdrawal is allowed if a participant initially opted to do the home testing with the Medipin device but wishes to stop doing those. They can then still continue with the in-person scheduled visits. Participants cannot withdraw from the in-person visits and continue with the at-home tests.

5.6 SOURCE DATA

Source data will include patient's GP records and the Case Record Form for the results of the neuropathy detection test results. Medipin Ltd will have no access to patient data other than pseudo-anonymised data for the test results.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study number.

6 EVALUATION PRODUCT

6.1 DESCRIPTION OF MEDIPIN MEDICAL DEVICE

CE-marked neuropathy test device: Medipin (MHRA No. 1321). Medipin is a single-use precision instrument designed to optimize cutaneous pinprick perception. Medipin's protected point is designed to significantly enhance pinprick acuity to achieve useful stimulation and reduce risk of damaging delicate skin. The protective annulus inhibits depth of penetration and protects against self-inflicted "needle stick" injury.

6.2 DISTRIBUTION & ACCOUNTABILITY

Delivery of kits to the centre will be arranged by Medipin Limited. Records will be retained for kits received and on which dates.

7 SAFETY

7.1 SAFETY DEFINITIONS

For the purpose of this study, the only safety reporting that is indicated is strictly only when there is an adverse event during the diagnostic testing with the Medipin and monofilament. Over the course of the study, any other clinic incidents (eg hospital admissions, falls and other emergencies) are not reported on.

Table 5, Description of different adverse event reporting definitions.

Adverse Event (AE)	Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.
Serious Adverse Event	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening - requires inpatient hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.2 PROCEDURES FOR RECORDING ADVERSE EVENTS

All SAEs need to be reported to the sponsor/host Trust R&D immediately and within no more than 24 hours of the investigator team becoming aware of them.

The only devices to be in contact with the patient is the Medipin device and also the 10g monofilament device. These are both minimally-invasive devices, the patient’s skin is not pierced through or damaged in proceedings.

7.3 CAUSALITY

The relationship of each adverse event to the trial must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from Medipin device application. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

8 Statistical consideration and data analysis plan

8.1 GENERAL AND BASELINE CHARACTERISTICS

The numbers of patients entering the study will be recorded, as will be number of any study withdrawals. Adverse events will also be recorded – adverse events are only included if the event occurs during the actual study clinic visit. Any preceding or subsequent events will not be considered an adverse event.

In order to describe the sample and facilitate analysis of objectives, the following characteristics and parameters will be collated, either from the patient or the patients’ records (using EMIS patient clinical record system), see also accompanying Case Report Forms for 0m , 18m and 36m study visits:

- Patient demographics, including age, sex and body mass index
- Pre-existing co-morbidities, including peripheral arterial disease, medical treatment for high blood pressure, and foot/toe malformations.
- Any use of diabetes related medication
- Recent blood pressure and HbA1c results. No new measures or tests will be conducted as part of the ODIN study. Only readily available data will be utilised. Where possible these measurements will have been taken within 6 months of the specific study visit.

8.2 SAMPLE SIZE CALCULATION

The rationale for the study follow-up time is based on the suggestion Laudadio and colleagues (1998), who found that an 18-month follow-up period is insufficiently long.

Sample size determined on basis of single-arm Kaplan-Meier survival analysis, based on 3 year follow-up of participants. Observed incidences of diabetic neuropathy (progression) at 80% power (beta) and 5% significance (alpha). A 40% dropout/withdrawal/lost to follow-up rate is anticipated.

An event in this instance is the change from a sharp to a dull sensation or a change from a dull sensation to absence of sensation ('no' sensation), as measured with a Medipin pinprick test.

The Keio University Japan source, https://nshi.jp/en/js/ , was utilised to determine sample size for 'survival' (ie measuring incidence of a DN progression) in a single cohort (Nagashima et al, 2021)

The minimum required number of patients to be recruited, taking into account withdrawal is therefore:

178 x 1.4 (withdrawal rate) = 250 participants.

In the MANDARIN study, which involved the same testing as for the ODIN study, approximately two-thirds of participants reported a sharp sensation when tested with the MEDIPIN device. Depending on accrual rates and patient willingness to be part of this long-term ODIN study, there is potential scope to also focus on progression rates in patients who report a sharp sensation at baseline. For this purpose, the sample size can be increased to 250 x 1.5 = 375 participants to ensure a sample size with sufficient power is obtained.

8.3 PRIMARY OUTCOME STATISTICS

Description of the rate of diabetic neuropathy progression observed in study population, with main objective being the progression from either sharp->dull sensation or dull->no sensation as determined with Medipin test. Follow-up period of 3 years, and presented with Kaplan-Meier survival graph. Sample is designed to be powerful enough to reflect representation of general T2DM population.

Table 6, Definition and score cut-offs for different DN tests.

Test (both left and right foot tested, one single result)	**Score indicating *absence of* Diabetic Neuropathy**	**Score indicating *risk* of Diabetic Neuropathy / degree of *loss of protective sensation***	**Score indicating *presence of* Diabetic Neuropathy**
10g Monofilament test (four applications on dorsal side of hallux, both feet)	Score of 5.5 or higher (out of 8).	Score of 3.5 to 5 (out of 8)	Score of 3 or lower (out of 8)
Medipin test (five applications on dorsal side of hallux, each foot)	Sharp sensation in both feet (average of applications)	Dull sensation in one or both feet (average of applications)	Absence of sensation in one or both feet (average of applications)

8.4 SECONDARY OUTCOME STATISTICS

- Overview of Medipin result and monofilament results (either dorsal or plantar outcome) will be presented with descriptive statistics to show percentage of patients with LOPS / DN. This will be done for baseline 0 months, 18 months and 36 month time-point respectively.

- Comparison of rate of progression between Medipin and monofilament test results (clinic observations at baseline 0 months, 18 months and 36 months)

- Evaluation of possible relationship of variables (blood pressure, blood glucose control [HbA1c], medication use for diabetes and cardiovascular disease) with prevalence and rate of progression of diabetic neuropathy.

The patient's age, diabetes chronicity, smoking status, blood pressure medication and diabetes medication, foot malformations, presence of peripheral arterial disease, general quality of life (EQ-5Q-DL), and MNSI symptom questionnaire score are primarily used to define the cohort on which the DN screening has been conducted. Parameters collated at the clinic visit will be recorded and presented in a tabulated format.

Kendall's Tau concordance value will be calculated to assess level of concordance between Medipin and monofilament tests (using the three possible outcomes in Table 6).

Cox proportional hazards models will be run to calculate hazard ratios for both prevalence and progression of DN (dichotomizing the incidence and progression point of DN at each time point over the 10-year). A standalone model will be evaluated as well as a model that includes abovementioned variables (anthropomorphic and disease-related variables).

- Further evaluation, in follow-up to MANDARIN study, to apply a a (Likert) numerical scale for Medipin in relation to degree of neuropathy, as opposed to standard yes/no quantification and no sensation/dull sensation/sharp sensation distribution

Mann-Whitney U-test will be used to compare median 10-point score between those with present and absent DN respectively (ie yes/no groups), to determine if the median value differs. Similarly, Kruskall-Wallis test will be used to compare median score between the two groups of no sensation/dull sensation/sharp sensation.

No identifiable data will be presented, only averages and totals. Analysis will be performed on complete datasets, with incomplete data for participants who have missed one or two follow-up clinic visits excluded from final analysis. Data will first be collated in Microsoft Excel, followed by analyses performed using SPSS v24.

9 Data handling and Monitoring

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who will work on Trust premises and see patients, and does not have a substantive contract with NCIC, will need to apply for a letter of access via the NIHR research passport scheme.

Participants will be pseudo anonymised by allocating a study ID to each of them. Patient identifiable data will only be used within North Cumbria Integrated Care NHS Foundation Trust; if applicable, only anonymised data are shared with the wider members of the study team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP training.

All paper data will be held in secure locked environments in the office of the Research & Development department in Wigton Hospital, Cross Lane, Wigton CA7 9DD, Wigton, North Cumbria Integrated Care NHS Foundation Trust. Electronic data will be saved on the patient management system such as EMIS, and also a password protected research database. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 10 years in line with local archiving policy and procedures.

Direct access to anonymised data only will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Final data, will be shared with Medipin Ltd company in pseudo-anonymised form.

10 Governance of study

10.1 APPROVALS

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures.

10.2 SPONSOR & INDEMNITY

North Cumbria Integrated Care NHS Foundation Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Medipin Ltd has provided a grant for this study by means of provision of the Medipin test kits free of charge.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are ideally seen when they attend their regular clinical appointment.

11 Publication and data-sharing policy

The results of this study will potentially be disseminated through:

- Peer-reviewed scientific journal
- Internal report

A summary of the main findings can be supplied to participants on request and this will be stated in the patient information leaflet.

12 References and Further Reading

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