NORMALISED SPINAL CORD AREA MEASUREMENT IN MONITORING DIABETIC NEUROPATHY

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Short title:	**Sp**inal **I**maging in **N**europathy of **D**iabetes: **L**ongitudinal **E**valuation
Acronym:	SpINDLE
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SYNOPSIS

Title	Normalised Spinal Cord Area Measurement in Monitoring Diabetic Neuropathy
Acronym	SpINDLE
Short title	Spinal Imaging in Neuropathy of Diabetes: Longitudinal Evaluation
Chief Investigator	Prof Cris S Constantinescu MD PhD FRCP
Objectives	1. To determine the utility of normalised spinal cord area measurement in monitoring diabetic neuropathy using a novel sensitive method; and compare it to standard monitoring methods (serial vibration perception thresholds and neurophysiology) 2. To compare spinal cord atrophy (or changes) in patients with diabetes with and without neuropathy, other neuropathies, multiple sclerosis (MS) and healthy volunteers 3. To correlate spinal cord area with neuropathic pain, quality of life, depression, and inflammatory, metabolic, and genetic markers in blood (and urine if applicable)
Trial Configuration	Observational with a cross-sectional and a longitudinal component
Setting	Secondary and Tertiary care
Sample size estimate	Based on previous data showing differences at 1.5T between diabetes with and without neuropathy at and healthy controls with n=10, and our own data in healthy controls at 3T we estimate we need 20-30 per group to detect a significant reduction ($p<0.05$) in upper spinal cord area at 3T over 1 year with 80% power.
Number of participants	115
Eligibility criteria	5 groups: 1. Diabetes without diabetic peripheral neuropathy (DM-DPN); 2. DM+DPN; 3. Healthy volunteers; 4. MS. 5. Other peripheral neuropathies (OPN). Age 18-75; No contraindications to MRI; Able to speak and understand English language.
Description of interventions	MRI imaging. Nerve conduction studies, Blood sampling, Urine collection
Duration of study	start date: 1 March 2017, completion date: 1 December 2023 12-24 months per participant
Randomisation and blinding	No randomisation but primary assessment will be blinded. MRI will be analysed by a researcher blind to the patient's clinical condition
Outcome measures	Upper cervical cord area (UCCA); normalised brain volume

Statistical methods	Man Whitney test; repeated measures ANOVA

ABBREVIATIONS

AE Adverse Event

CI Chief Investigator

CNS Central Nervous System

CRF Case Report Form

DM Diabetes Mellitus

DMC Data Monitoring Committee

DPN Diabetic Peripheral Neuropathy

DSP Distal Symmetric Polyneuropathy

GCP Good Clinical Practice

HSMN Hereditary Sensory Motor Neuropathy

ICF Informed Consent Form

MRI Magnetic Resonance Imaging

MS Multiple Sclerosis

NHS National Health Service

NUH Nottingham University Hospitals

OPN Other Peripheral Neuropathy

P/GIS Parent / Guardian Information Sheet

PI Principal Investigator

PIS Participant Information Sheet

PN Peripheral Neuropathy

QMC Queen's Medical Centre, Nottingham

REC Research Ethics Committee

R&D Research and Development department

SPMIC Sir Peter Mansfield Imaging Centre

SAE Serious Adverse Event

UCCA Upper Cervical Cord Area

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Diabetes mellitus (DM) affects almost 400 million people worldwide and about 4.6% of the United Kingdom population. This prevalence is expected to increase significantly. Diabetes is typically irreversible. Its late complications cause decreased life expectancy and major medical, social and financial burdens.

The most frequent nervous system involvement is the diabetic distal symmetric polyneuropathy (DSP), commonly called “diabetic (peripheral) neuropathy, DPN”. DM is the most common cause of peripheral neuropathy in the western world. DSP can be complicated by foot ulcers and is the leading non-trauma cause of lower limb amputation.

There is evidence of central nervous system (CNS) involvement in DM. In addition to brain atrophy, memory deficits, and higher risk of dementia, pathological studies revealed degeneration of spinal cord dorsal columns.

In a study using 1.5 Tesla magnetic resonance imaging (MRI), Tesfaye and colleagues showed cervical and thoracic spinal cord atrophy in male patients with DSP, even in preclinical stages, but no atrophy in DM without DSP or hereditary purely demyelinating neuropathy (Hereditary Sensory Motor Neuropathy (HSMN) type I)[1].

While this cross-sectional study provides strong evidence for spinal cord involvement in DSP, the longitudinal use of MRI measurements for DSP monitoring is questionable, because of high cord area estimation error by insufficient correction for partial volume averaging, particularly at 1.5T MRI. Having expertise in spinal cord MRI and histopathology (e.g.[2-5]), we have performed one of very few longitudinal studies of cord atrophy in multiple sclerosis (MS), and monitored the effect of interferon beta[6]. We have optimised the technique for high field (3T) imaging and have dramatically reduced variance at all cord levels by correcting for height and gender[7].

This study proposes a longitudinal evaluation of spinal cord imaging in DM, focusing on normalised upper cervical cord area (UCCA) measurement and assessing the utility of UCCA in the monitoring of DPN.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The Purpose of the study is to determine the longitudinal course of spinal cord atrophy in diabetic neuropathy (DPN) using a sensitive and reliable measurement method we developed. In addition, the method will be applied to other neuropathies and to diabetes without neuropathy and to MS (as positive control).

PRIMARY OBJECTIVE

The primary objective is to assess the degree and rate of atrophy of the UCCA over 1 year in DM+DPN and its correlation with the other measures of DM+DPN (clinical and electrophysiological).

SECONDARY OBJECTIVES

The secondary objectives are:

1. Assessment of rate of atrophy of the UCCA in the other groups (DM-DPN; Healthy volunteers; MS. Other peripheral neuropathies (OPN).
2. Correlate atrophy of the UCCA with other cord regions, with brain atrophy, other measures of progression of DM and DPN (e.g. electrophysiology), quality of life, depression, and inflammatory, metabolic, and genetic markers.

DETAILS OF PRODUCT(S)

No specific products will be used. Patients will receive their usual treatment for their condition. Wherever possible patients will be included after being stable on medication for > 3 months and any changes during the study will be recorded. Medication will be taken into account in sensitivity analysis of the results.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This is an observational study with a cross-sectional and a longitudinal component

Primary endpoint

UCCA at baseline and correlation with severity of DM and DPN; change in UCCA over time

Secondary endpoint

Correlation of UCCA with other cord region areas and with brain atrophy

Safety endpoints

AEs during this observational study will be recorded.

Stopping rules and discontinuation

Patients will not be asked to return for the follow up visit if they are too unwell. We do not anticipate discontinuation of the whole trial unless serious recruitment problems are encountered.

RANDOMIZATION AND BLINDING

There is no randomization. The MRI measurements and electrophysiological studies will be performed by researchers unaware of the patient's clinical diagnosis. The patients will have a study number and the diagnosis will be matched with the MRI and electrophysiology results

TRIAL/STUDY MANAGEMENT

The PI and researchers will meet at least every 3 months to discuss the trial recruitment and other issues.
The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: We plan to complete the study in 6.5 years maximum.

Participant Duration: Each participant will be in the study for up to 24 months. We plan to obtain a baseline MRI followed by an MRI 12-24 months later.

End of the Trial

This will be the last visit of the last recruited participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

We plan to recruit:

1- 40 patients with clinical or subclinical DPN (diagnosed by nerve conduction studies (NCS))
2- 20 with DM without DPN
3- 20 with other neuropathies (HSMN, cryptogenic, and chronic inflammatory polyneuropathy (confirmed by NCS))
4- 15 MS, relapsing remitting and progressive, positive control patients (atrophy rates predictable from our studies). Subjects will be matched for gender and DM type (I and II).
5- 20 healthy volunteers will be recruited from the University/Nottingham University Hospitals (NUH) environment using displays in relevant areas (bulletin boards etc). The healthy control subjects will be invited to contact the PI or the Research Fellow to discuss the study.

20 historical controls from our recent MRes student study using the novel technique will be used for normative values (consent was obtained). Sample size estimation is inferred from our MS longitudinal study and from differences in age and disease duration between subclinical and clinical DSP in Tesfaye's cross sectional study[1]. Subjects will be recruited from diabetes (Page, Gazis), neuropathy (Wills) and MS (Constantinescu, Evangelou) clinics.

The initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinical areas.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

Due to the necessity of being able to communicate safely with patients during MRI scan for example (which involves essential safety communications), we will not recruit anyone with special communication needs for this study. This includes patients who do not speak English language.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

There will be 5 groups:
1. Diabetes without diabetic peripheral neuropathy (DM-DPN)
2. DM+DPN
3. Healthy volunteers
4. MS
5. Other peripheral neuropathies (OPN)

Inclusion criteria

1. Age 18-75
2. Ability to give informed consent
3. Ability to speak and understand English language
4. Diagnosis consistent with one of the groups 1-5, with initial symptoms having preceded the inclusion into the study by 12 months or and condition stable for 2 months or more.

Exclusion criteria

1. Extensive cardiovascular and/or cerebrovascular comorbidity (Treatment for angina or peripheral vascular disease constitutes a contraindication).
2. Other comorbidities, in particular neurological diseases, that in view of the researcher may interfere with the study.
3. Significant spinal or spinal cord disease (other than MS in the MS control group).
4. Contraindications for MRI including but not restricted to pacemaker, orbital foreign body, certain aneurysm clips, claustrophobia, and un-removable piercings.
5. Pregnancy or planning for pregnancy.

Expected duration of participant participation

Study participants will be participating in the study for 12-24 months

Removal of participants from therapy or assessments/Participant Withdrawal

Participation may be withdrawn from the study under certain circumstances such as: safety reasons (e.g pregnancy, new contraindication for MRI e.g. pacemaker, recent metal implant), failure of participant to adhere to protocol requirements, disease progression that may preclude lying in MRI scanner for 30 min-1 hr, and withdrawal of consent.

Participants must be withdrawn from study if consent is withdrawn – however, data up to the point of withdrawal cannot be destroyed.

Participants will only be accepted as lost to follow-up if phone calls, and up to two letters to the participant have been fruitless.

Withdrawn participants may be replaced if the withdrawal is during the recruitment period (the first 24 months).

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY COURSE AND REGIMEN

This is an observational study with a cross-sectional and a longitudinal component. After informed consent, participants fulfilling the inclusion criteria will undergo a brief general physical and neurological examination, a review of their medical history, social and family history. Medication will be documented. The BMI will be calculated. The participant assessment will take place in the Division of Clinical Neurosciences, Section of Clinical Neurology, Queen's Medical Centre (QMC), or in the examining area of Sir Peter Mansfield Imaging Centre (SPMIC) MRI unit at QMC. Alternatively, it could be done in the outpatients clinics with the questionnaires completed at the patients' leisure provided this is done within 2 weeks of the MRI.

For subjects who fail screening due to a transient problem, rescreening will be possible 2 months or more after the problem is solved (for example, worsened diabetes control or MS exacerbation).

To rule out neuropathy in the non-PN control groups, a brief examination of the feet with completion of the Michigan Neuropathy Screening Instrument will be performed in all subjects. The assessment including relevant history is estimated to take 20 minutes.

All patients with DPN and those with PN of other causes will have had NCS as part of their routine NHS care. NCS for DPN and other symmetrical PN are performed according to a standard protocol. The measurements of NCS (latency, velocity, amplitude) will be available from the patients' neurophysiology report and will be recorded in the clinical report forms (CRF). At the time of the visit the patients will complete a series of generic questionnaires and questionnaires related to their condition. All subjects will complete three generic quality of life (QoL) questionnaires and a screening test for depression (approx. 30 minutes):

EQ-5D
SF-36
VAS
HADS

Participants with DM and those with MS will complete additionally the D-QoL (Diabetes QoL) and PAID (Problem Areas in Diabetes) Questionnaire and MuSiQoL/MS-QoL-54 questionnaire, respectively.

To quantify neuropathic pain, patients with diabetes and those with neuropathy will complete the Neuropathic Pain Scale (NPS) and LANSS questionnaires and all subjects will complete the DN4 questionnaire (as it has been validated for MS both in the literature and in our MS clinic through a recent audit).

The examination of the MS patients will include estimation of the Expanded Disability Status Scale (EDSS) score and the patients will also complete the MSIS-29 assessment.

All subjects will undergo vibration perception threshold testing (5 minutes) using a Harwood Neurothesiometer.

MRI scanning will be performed in the University of Nottingham SPMIC MRI facility at QMC. This facility has been designed for studies involving NHS patients, and uses clinical MRI scanners fully compliant with all standards required for imaging patient populations. Following standard MRI safety checks, participants will undergo spinal cord imaging including T1-weighted and T2-weighted sequences. Spinal cord cross-sectional area (CCA) will be measured at 3 levels using an edge detection technique. Normalised brain volume will be obtained using standard approaches from T1-weighted volumetric brain images. It is anticipated that the MRI scan acquisition will last 40 minutes. Allowing for transfer of the participant onto and off the MRI scanner table, MRI scan set-up, and re-positioning of the participant mid-scan to allow both brain and spine to be imaged, the participant will in the MRI scanner room for up to one hour. During this time the participant will be able to communicate with the scanner operator via a two way intercom, and will have a hand-held alarm buzzer to alert the operator to any discomfort or problems during the scan. Mean upper cervical cord area (MUCCA), a potential outcome measure in MS, will be calculated.

Blood (maximum of 30 ml tubes) will be collected. HbA1c, triglycerides, cholesterol, eGFR will be measured if results not available within the previous 2 months. 2-3 ml blood will be collected in paxgene tubes for measurement of inflammatory/metabolic markers (including IL1-33, TNF, Osteopontin, MMP). 5-10 ml will be obtained for serum measurements of some of these markers. 2-3 ml blood will be saved for DNA for genetic polymorphisms associated with MS, DM, and brain and spinal cord atrophy to detect common genetic predisposing factors. The DNA portion of the study will be optional.

Urine will be obtained for protein and validation of some biomarkers (e.g. osteopontin, sTLR).

All of the above assessments and sample collections will be performed at baseline and after 18 months (or as close to 18 months as possible). The samples will be saved in the licenced freezer in the laboratory of Prof Constantinescu under the Human Tissue Act 2004.

Compliance

Compliance will represent attending the visits as part of the study protocol.

Criteria for terminating trial

It is unlikely that the study will be terminated. However, stopping as a whole may occur as a result of a formal or informal interim analysis and based on overwhelming evidence of efficacy/inefficacy, major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). These problems are not anticipated. The investigators will make efforts to minimise these risks and maintain recruitment rates.

Unused trial materials (e.g. monofilaments) will be retained for clinical use within the NHS. Any surplus biological samples will either be safely disposed of as per the laboratory's SOP under the HTA (2004) regulations or retained with participants' informed consent (optional) for future ethically approved studies of DM, PN, MS, biomarkers.

N.B. research data will not be destroyed (it will be archived according to the archiving section below).

TRANSPORT AND STORAGE OF THE TISSUES

Blood and urine samples will be obtained at the location of the patient assessment. If this is in the Clinical Neurology Trial Unit the samples will be taken immediately to the laboratory in the same unit. If the collection occurs elsewhere (e.g. HILF) the samples will be transported safely (in racks, on ice if needed, in polystyrene containers) to the laboratory of Prof Constantinescu. Each sample will be labelled with the unique study number assigned to the participant and the date of collection. Samples will be stored in a linked anonymised format and labelled using a combination of study reference, unique study identifier and cross referenced with location code numbers to permit accurate linkage to study data and the consent form. The linked participant identifiable information which will be available only to the investigator and stored safely on a university computer by the investigator under password protection.

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

720 blood samples (including serum and paxgene) representing 3 tubes per patient on 2 occasions, and 240 urine samples (1 tube per patient on 2 occasion) will be collected and stored in aliquots if feasible, at -80 degrees centigrade.

The master database will be held by Prof Constantinescu in a password encrypted file.

The analysis of samples will take place at the University of Nottingham within the Division of Clinical Neuroscience. The samples will be stored during the study in the licenced freezer in the laboratory of Prof Constantinescu in accordance with the competencies of the Human Tissue Act 2004 and under Research Ethics Committee favourable opinion.

Remaining samples will be stored within the Research Tissue Bank for future research (DI Dr William Dunn - Licence Number 12265) if participants are agreeable and sign the optional clause on the consent form.

Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2004.

LABORATORY ANALYSES

ELISA for inflammatory/biomarkers, DNA for SNP for genes linked with MS, Diabetes and brain and spinal cord atrophy –optional, RNA for inflammatory/biomarkers (All will be done in Prof Constantinescu's laboratory by trained personnel).

STATISTICS

Methods

Differences in Upper CCA (UCCA) between groups 1-5 will be the primary outcome measure. Differences in UCCA between baseline and year 1 will be the secondary outcome measures. Correlation between UCCA and inflammatory markers and presence and severity of neuropathy, neuropathic pain will be exploratory outcome measures. Multiple regression analysis will identify factors associated with spinal cord atrophy.

The groups will be compared by ANOVA for repeated measurements.

Sample size and justification

Sample size for this observational study where there are pilot data was estimated based on our preliminary results on normalised UCCA in healthy volunteers and in MS patients and from Edwards et al in DM.

20 subjects per group will give an 80% power to reveal a correlation with a correlation coefficient r of 0.7 between NRS score.

Assessment of efficacy

Efficacy as such is not an endpoint in this study. The trend in UCCA over time and the differences between groups are main endpoints.

Assessment of safety

Safety will be monitored as in all observational studies but as there is no therapeutic intervention safety in itself is not an outcome.

Procedures for missing, unused and spurious data

The analysis of data will be cross-sectional (between groups and correlative between MRI, clinical, neurophysiological and biological measurements) and longitudinal over 1 year. For missing year 1 data we will only do cross-sectional analysis.

Definition of populations analysed

We will have a cross-sectional (baseline) and a longitudinal (baseline and year 1) population.

ADVERSE EVENTS

a) Risk of MRI scanning: MRI uses radio waves similar to those used in radio and TV transmission. These have a much lower energy than X-rays and as such are considered biologically safe. We will be following strict national safety guidelines

which are designed to prevent the potential hazards of MRI which are burns and electric shocks. Preventable accidents like skin burn at the contact point have never occurred in our imaging centre and have only very rarely occurred elsewhere in the UK. Participants will undergo safety questionnaires at the time of the screening, consent and just prior to scanning to ensure there are no contraindications to them being scanned. During an MRI scan, certain types of tattoos may heat up if they are inside the region being scanned; in exceptional conditions burning may occur around the tattoo (in extreme cases leading to blistering). For people with facial or genital tattoos or large tattoos (greater than 7.5cms across), such burning could be inconvenient or uncomfortable and may require medical care. People may feel tingling at the site of the tattoo during scanning if it is going to heat up; this provides a warning of a potential problem. MRI can also evoke feelings of claustrophobia due to its small size.

b) Finding unexpected MRI results: There is a small chance that we will find something unexpected on the brain scan. The chief investigator will arrange for the patient to be assessed appropriately in a clinic or inpatient setting depending on the findings. Patient's GP will be informed.

c) Time inconvenience: Participants will be warned of the time needed for each visit prior to consent, both verbally and in written information sheet.

d) Blood sampling: Brief mild discomfort and slight bruising are not uncommon and participants will be warned prior to the procedure. Experienced staff will perform the procedure to minimise this.

e) Nerve conduction studies: Mild to moderate discomfort is not uncommon and participants will be warned prior to the procedure. Experienced staff will perform the procedure to minimise this.

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Trial Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The data will be presented at international meetings and published in peer reviewed scientific journals. It will also be presented to patient groups.

USER AND PUBLIC INVOLVEMENT

There is strong public involvement in diabetes research. The applicants (Dr Gazis in particular) have been strongly involved with patient groups and monitoring neuropathy is a priority. The proposal has been reviewed and funded by the NUH charity which has a strong public participation.

STUDY FINANCES

Funding source

This study is funded by NUH Charity

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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