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Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution (FINESSE) Statistical Analysis Plan

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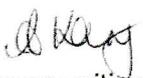
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FINESSE study statistical analysis plan summary of changes from version 1 to 2

Page/section	Changed text	Comments/Rationale
2.3 Sample size	"moderately severe to severe" changed to "moderate to severe"	Correction of typographical error in version 1
4.4 Baseline characteristics 5.1 Outcome definitions Appendix 1	Neuropathy assessment "total neuropathy score" changed to "modified total neuropathy score"	Adjective added to accurately represent the tool as specified in the protocol
2.2 Randomisation 5.2 Analysis methods	Maximum score of TNS changed from 32 to 28. As the modified TNS does not include vibration, the maximum score is 28.	The study protocol specifies the use of a modified Total Neuropathy Score. The specific modification is the exclusion of the vibration domain. The consequence is that the total possible score in FINESSE is 28.
5.1 Exploratory analyses	Physical examination (pin sensitivity, strength, tendon reflexes)	"Vibration' removed in accordance with use of modified TNS as described above
5.1 Exploratory analyses	Repeat primary and appropriate secondary analyses using original (not modified) Total Neuropathy Score.	Addition of sensitivity testing using original Total Neuropathy Score
Appendix 1	Vibration row removed from table Interpretation severe neuropathy changed from "25-32" to "25-28"	As above
5.1 Secondary outcomes	Added text: 1. The intent of secondary outcome 1b is to evaluate the proportion of people with asymptomatic disease in each group. To allow each assessment to be categorised as either asymptomatic or symptomatic, we have specified a definitive mathematical range for each category, 0-8 and 9-28 respectively. The 0-8 range represents the 'asymptomatic' range which we are more accurately describing here as 'no or minor neuropathy'.	Footnote added to explain change in definition of no/minor disease, and terminology between protocol and SAP.
5.1 Outcome definitions	Under inter-rate reproducibility added "and neurophysiologists" "Neurologists" changed to "assessors"	All endpoint assessors were trained neurologists or neurophysiologists.

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1   Introduction

1.1   Background and Rationale

Uraemic neuropathy is a common complication of end stage kidney disease (ESKD), affecting 60-100% of patients receiving dialysis therapy[1-3]. It is a sensorimotor progressive polyneuropathy causing pain, loss of sensation, weakness and muscle wasting, and leading to disability and poor quality of life. The pathophysiology is believed to be the result of accumulated metabolic toxins. A small cross-sectional study suggested improved nerve excitability in patients undergoing haemodiafiltration, which provides greater clearance of small and middle molecules, compared to high flux standard haemodialysis[4]. No previous randomised trials have reported the effect of haemodiafiltration versus high flux haemodialysis on neuropathy[5].

1.2   Objective

We aimed to determine the effect of haemodiafiltration compared to high flux standard haemodialysis on the occurrence and progression of uraemic neuropathy in recipients of maintenance haemodialysis therapy.

2   Study Methods

2.1   Trial Design

The Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution (FINESSE) study is a parallel 2-arm, multi-centre, open-label, randomised controlled trial of haemodiafiltration versus standard high flux haemodialysis for uraemic neuropathy in patients with ESKD. All participants received routine medical care and monitoring including the recommendation of a multivitamin[6].

2.2   Randomization

Participants were randomised to receive either haemodiafiltration or standard high flux haemodialysis. Participants were randomised in a 1:1 fashion with stratification by baseline neuropathy score. Strata 1 was defined as TNS score 0-8 (no to minor neuropathy) and strata 2 as TNS score 9-28 (moderate to severe neuropathy). The allocation sequence was based on blocks of 4 and generated centrally by an independent statistician who had no other involvement in the study. To ensure allocation concealment, randomisation was performed by an independent university employee based in a physically separate site with no other involvement in the study. The randomisation schedule was known only to the independent university employee, the generating statistician and the unblinded statistician.

2.3   Sample Size

Total Neuropathy Score was selected to measure the primary endpoint as it met the requirements for neuropathy assessment as articulated in the 2005 Consensus Statement[7]. However, at the time the study was designed, *there were no available results for Total Neuropathy Score assessments in dialysis patients*. Accordingly power calculations were made using information on Neuropathy Symptom Score grades and sural nerve conductions values that were available when the study was designed[3, 8, 9]. Using assumptions based on those studies FINESSE was calculated as having more than 90% power to detect a reduction in moderate to severe neuropathy from 80% in the control arm to 48% prevalence in the treatment arm (absolute difference of 32%) with a sample size of 120 (with alpha=0.05), including an allowance for 20% combined drop-out and loss to follow-up

(n=96 in the final analysis). We also calculated that with 90% power (with alpha=0.05) the study could detect an absolute difference of 2.6mcV in the mean response of sural nerve sensory amplitudes between the treatment groups (assuming a standard deviation of 3.9).

Since developing the original protocol, studies have been conducted that provide data on the Total Neuropathy Score from an external cohort of dialysis patients (Krishnan, personal communication). In 49 dialysis patients, the mean TNS was 9.2 (SD: 7.8) with 42% (20/48) having a TNS score of 17-32 (moderate to severe neuropathy). Using these assumptions, FINESSE has 90% power to detect a mean difference of 5.2 in TNS between treatment arms at the end of the study and 80% power to detect a mean difference of 4.5.

2.4   Timing of Outcome Assessments

Data on neuropathy outcomes were collected at baseline, 1, 2, 3 and 4 years after randomization. Data on all other study endpoints were collected at baseline and 6 monthly follow-up visits until 4 years from randomization. Assessments may be conducted at other time points for participant or assessor reasons. If this occurs, the results will be allocated to the nearest unmeasured outcome assessment time point.

2.4.1. Data Linkage

Data linkage offers a means of ascertaining differences in mortality and late clinical events while minimising the trial demands on participants and sites. Participants consented to data linkage beyond the 48 month duration of the study to the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) to gather information on vital status and technique survival. The ANZDATA information will establish the durability of each intervention and medium-term effects on participant survival.

Participants also consented to long term follow-up through data linkage to the Department of Human Services Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS).

The analysis of linked data and long-term follow-up outcomes will be the subject of a separate Statistical Analysis Plan.

3   Statistical Principles

3.1   Confidence intervals and p values

All tests are two-sided and the nominal level of alpha will be 5%. P-values will not be adjusted for multiplicity.

3.2   Analysis populations

All analyses will be conducted on an intention-to-treat (ITT) basis. All randomized participants will contribute to the final study analyses and will be analysed in the group to which they were assigned regardless of protocol violations. The only exception would be where a participant withdraws consent for participation and use of their data.

3.3   Subgroup analysis

Sub-groups will be limited, are pre-specified and described below in Section 5.2.1.

4   Trial Population

4.1   Eligibility

Participants were recruited from hospital or satellite centres with the capacity to offer haemodiafiltration and standard high flux haemodialysis.

All adult patients with ESKD who meet the inclusion and no exclusion criteria were considered eligible for this study.

Participants were eligible for INCLUSION in the study if ALL the following criteria are met:

1. Incident or prevalent patients requiring maintenance haemodialysis therapy for ESKD

2. Aged 18 years or older

3. Suitable for either haemodiafiltration or standard dialysis in the view of the treating physician

4. Agreeable to randomisation

Patients were EXCLUDED from the study if, in the opinion or knowledge of the responsible clinician the following criterion is present:

1. Life expectancy less than 6 months

2. Definite plans to undergo renal transplantation, transfer to a non-study site, transfer to peritoneal dialysis or transfer to home haemodialysis within 12 months of entry to the study

3. Receiving haemodiafiltration

4. Unable or unwilling to complete neuropathy staging, including nerve conduction studies.

4.2 Recruitment

Flow of patients through the study will be displayed in a CONSORT flow diagram. We will report the number of screened patients who met study inclusion criteria, the number randomised into the study, and the number available for the primary analysis (Figure 1). The reasons for exclusion will be documented at each step in the diagram.

4.3 Participant Follow-up and Withdrawal

All participants were asked to participate in an intervention phase that lasted from randomisation until the earliest of:

- Completion of 48 months in the trial from randomisation, or

- In-centre/ satellite haemodialysis therapy was no longer required (eg patient receives a kidney transplant, transfers to peritoneal dialysis, transfers to home haemodialysis), or

- Transfer to a dialysis unit not able to offer both study interventions, or

- Withdrawal of consent by the participant, or

- Participant death.

Participants withdrawn from the randomised treatment for any reason (either by choice or on advice from their physician) will be followed-up according to the study follow-up schedule and analysed according to the intention-to-treat principle, providing they consent to such follow-up.

The level of withdrawal (to intervention and/or follow-up), timing and reasons for withdrawal will be recorded and presented by treatment group.

4.4 Baseline Characteristics

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated in the list below. Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation and/or median and quantile points at 0.25, 0.5 and 0.75 where appropriate. Free text entries for fields collecting both categorical and free text information (eg ethnicity) will be assessed and assigned to a category if appropriate. No testing will be performed for differences in baseline characteristics between treatment arms, as per CONSORT.

Demographics
- Sex
- Age
- Ethnicity (ethnicities constituting 10% or more of the study population will be listed)

Medical History
- Primary cause of Renal disease (Categorized as Diabetic Nephropathy, Hypertension/ Vascular Nephropathy, Glomerulonephritis, Polycystic Kidney Disease, Other)
- Co-morbidities:
  - Diabetes Mellitus – type 1, type 2, nil
  - Hypertension
  - Ischaemic heart disease (Angina, Acute MI, Previous Coronary Artery Bypass/ Percutaneous Transluminal Coronary Angioplasty)
  - Congestive Heart Failure (NYHA classification)
  - Cerebrovascular Disease (rapid or focal neurological deficit lasting > 24 hours)
  - Peripheral Vascular Disease (requiring or having required peripheral re-vascularisation of carotid or peripheral artery, or amputation related to peripheral vascular disease)
  - Parathyroidectomy surgery
  - Previous fracture (Pathological fracture, Stress fracture, Traumatic fracture)
  - Carpal tunnel surgery
  - Other surgery on nerves
  - Peripheral neuropathy
  - Ovarian disease or bilateral oophorectomy (women only)
  - Menopausal status (women only)
- Smoking status (Categorized as Current smoker, Former smoker or Non-smoker)
- Dialysis
  - Site: home, centre (hospital and satellite)
  - Dialysis vintage (from ANZDATA)
  - Dialysis in last week: number of hours/session, number of sessions/week, number of hours/week
  - Timing of dialysis: day/night/combination of both
  - Access: native AVF, synthetic graft, tunnelled catheter, non-tunnelled catheter, other
  - Mode of access: buttonhole cannulation, rope ladder cannulation, Dialysis catheter, other
  - Anticoagulation (heparin, enoxaparin, nil or other and dose)
  - Dialysate composition: Sodium, Potassium, Calcium, Glucose

- - - Dialysis parameters: blood flow rate, dialysate flow rate, membrane, machine brand and model, dialysate temperature
  - Medications
    - Phosphate binders, number and dose

Physical Examination
- Pre-dialysis blood pressure, average of 3 if available
- Height, weight, dialysis ideal body weight, BMI (derived from height and ideal body weight)
- Waist circumference, Hip circumference, Waist:hip circumference (derived from waist and hip circumferences)

Laboratory Measures
- Haematology: Haemoglobin, Total white blood cell count, Platelet count
- Biochemistry: Sodium, Potassium, Chloride, Glucose, Bicarbonate, Creatinine, Calcium (using corrected calcium formula[a]), Phosphate (pre-dialysis), Calcium phosphate product (derived from calcium and phosphate), Albumin, C-reactive protein, Parathyroid Hormone
- Pre dialysis and post dialysis Urea, Small molecular clearance reported as either Urea Reduction Ratio or Kt/V
- β_2-microglobulin levels (pre and post dialysis)
- Total cholesterol, Triglycerides
- Ferritin, Transferrin saturation
- HbA1c (if diabetic)
- Troponin (if available)
- B natriuretic peptide (if available)

[a]The corrected calcium will be calculated according to the following formula:

corrected calcium (in mmol/l) = measured calcium (in mmol/l) + ((40-albumin (g/l))x0.02)

Quality of Life Scores
- EQ-5D
- KDQOL SF-1.3
- KDRL

Neuropathy assessment (Appendix 1)
- Modified Total Neuropathy Score and stratification
- Neuropathy symptom score and Neuropathy symptom score stage, derived from neuropathy symptom score

5 Analysis

5.1 Outcome Definitions

Primary Outcome

The primary end-point for this study is the difference in the mean change in modified total neuropathy score (TNS) from baseline between the two groups.

Mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach (MRMM). Analyses will include the fixed, categorical effects of treatment, visit (unstructured), and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. We will test a range of covariance structures (autoregressive(1), heterogeneous autoregressive(1), unstructured, compound symmetry structure) and select the structure with

the lowest AIC (best fit). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Analyses will be implemented using SAS/Stat 14.2.

The primary comparison will be the average of the contrast between treatment groups across all time points in the study, with each observed time-point weighted equally.

Secondary Outcomes

These will follow the same plan approach for the primary outcome (MRMM), with different comparisons and distributions for the outcomes as appropriate.

1) Neuropathy outcomes. Analyses will include:

a) Difference between groups in mean change from baseline in modified TNS at years 1, 2, 3, 4 with the same method as the primary analysis

b) Difference between treatment groups in proportion of participants with modified TNS 0-8 (no or minor neuropathy) overall (time-points weighted equally) and at 1, 2, 3 and 4 years, using a generalised linear mixed model with a binomial distribution and a logit link.[1]

c) Difference between groups in mean change from baseline in NSS overall (as per main outcome), and at 1, 2, 3 and 4 years with the same method as the primary analysis.

d) Difference between treatment groups in proportion of participants with no or asymptomatic neuropathy on NSS (NSS stage 0-1) overall, and at 1, 2, 3 and 4 years using a generalised linear mixed model with a binomial distribution and a logit link .

e) Difference between treatment groups in change in sural nerve sensory amplitude (mV) from baseline overall, and at 1, 2, 3 and 4 years with the same method as the primary analysis.

1. The intent of secondary outcome 1b is to evaluate the proportion of people with asymptomatic disease in each group. To allow each assessment to be categorised as either asymptomatic or symptomatic, we have specified a definitive mathematical range for each category, 0-8 and 9-28 respectively. The 0-8 range represents the 'asymptomatic' range which we are more accurately describing here as 'no or minor neuropathy'.

To limit the number of comparisons and risk of Type I error we will only test for differences in binary outcomes where there has been a difference detected ($p<0.05$) in the analysis of the continuous variable, i.e. analysis of 1b will only proceed if there is a difference in a time point in 1a, and 1d proceeds if we find a difference in 1c.

2) Safety outcomes. Analyses will include:

a) Time to access failure, defined as thrombosis or fistula requiring revision

b) Number of discrete episodes of access failure, defined as above.

c) Episodes of septicaemia defined as blood culture positive septic episode without defined source.

d) Mortality

e) Cardiovascular events (composite of: cardiovascular death or any of the following requiring or occurring during a hospital admission: acute myocardial infarction, cerebrovascular event, percutaneous coronary or cerebrovascular revascularisation, or surgical coronary or cerebral revascularisation)

f) Surgery for carpal tunnel syndrome

g) Parathyroidectomy surgery

h) Fractures requiring or occurring during a hospital admission

3) Durability:

Durability is defined as adherence to the intervention at each time point

4) Ranked composite endpoint combining mortality and TNS

5) Follow-up of long term events.

    a) Long-term survival at 24, 36 and 48 months following the conclusion of individual's intervention period

    b) Durability of the intervention at 12, 24, 36 and 48 months following the conclusion of individual's intervention period

These events will be analysed during the post-intervention cohort observation period and will be subject to a later Statistical Analysis Plan.

Exploratory analyses:
1) By components of modified TNS: Mean change in score from baseline to end of study for:
   a. Clinical symptoms (sensory and motor symptoms)
   b. Physical examination (pin sensitivity, strength, tendon reflexes)
   c. Nerve conduction study (sural and tibial amplitudes)
2) Quality of life measures were collected at baseline and during the follow-up period. The analysis of quality of life measures will be part of a later Statistical Analysis Plan.
3) Repeat primary and appropriate secondary analyses using original (not modified) Total Neuropathy Score.

Inter-rater reproducibility of TNS:
Neuropathy assessments were undertaken by qualified neurologists and neurophysiologists and supervised by Arun Krishnan, who performed the measurements in the vanguard phase of the trial. Assessors were blinded to participant treatment allocation. Arun Krishnan duplicated neuropathy assessments for 5 patients to allow assessment of inter-rater reliability. Inter-rater reliability will be estimated using the Spearman's rank correlation coefficient with a 95% CI as was performed by Cornblath et al in the original description of TNS[10].

Neuropathy assessment

Neuropathy will be assessed in all participants using two validated scoring systems that incorporate clinical symptoms, examination findings and results of nerve conduction studies:

(1) Modified Total Neuropathy Score (TNS), a validated measure of peripheral nerve function[10]. (Appendix 1)

(2) Neuropathy Symptom Score (NSS) which, in conjunction with nerve conduction findings, will be used to calculate a neuropathy stage[8, 11]. (Appendix 1)

The neuropathy scores will be obtained at baseline, annually and, where possible, at anticipated transfer to another modality of renal replacement therapy (transplant, peritoneal dialysis or home haemodialysis) or transfer to a non-study centre that cannot offer both interventions, by treatment group.

Intervention: Dialysis Treatment

The adherence to the treatment allocation (haemodiafiltration versus standard high flux) at each time point will be reported and analysed.

Achieved dialysis parameters will be reported in each allocation group, including:

- Blood flow rates and dialysate flow rates
- Convection volumes (for participants randomized to haemodiafiltration)
- Pre-dialysis systolic and diastolic blood pressure
- Dialysis prescription: number of hours/session, number of sessions/week, number of hours/week
- Dialysis site: in-centre/ hospital or satellite
- Dialysis access: native AV fistula, synthetic graft, tunnelled catheter, non-tunnelled catheter, other
- Dialysate composition: Sodium, Potassium, Calcium, Glucose, addition of phosphate

Variables will be presented as percentages for each group at baseline and 1, 2, 3 and 4 years.

5.2 Analysis methods

Subgroup analyses

The following pre-specified subgroup analyses will be conducted:

1. Baseline TNS: 9-28 vs 0-8
2. Diabetic vs not diabetic
3. Gender: M/ F
4. Baseline access type: AVF vs other (including graft/ catheter)
5. Dialysis vintage at randomisation: <12 months v ≥12 months

The access type will be separated into AVF verses other as the clear majority of participants (78%) were using an AVF at baseline. Baseline blood flow rate was considered for subgroup analysis but discarded as there was little variation across the cohort (baseline blood flow rate

median 300, 5th percentile 300, 95th percentile 330). Sub-group analyses will be completed by including an interaction between each sub-group and the treatment variable.

5.2. Secondary/SAEs outcomes

A summary of each secondary or safety endpoint will be provided. Continuous outcomes will be summarised by their mean (SD), while binary outcomes will be summarised by percentages.

Continuous: All continuous secondary endpoints without repeated measurements will be analysed using linear regression adjusted with its baseline counterpart. This applies to the exploratory analyses

Continuous repeated measurements: All secondary outcomes repeatedly measured over time (Secondary outcomes 1a, 1c, 1e) will be modelled using a Linear Mixed model including random intercept, randomisation and time categories as per the analysis of the main outcome (5.1). The Linear Mixed model will be formulated to use Direct Likelihood, which will allow for data that is missing at random.

Binary repeated measurement: will be analysed using generalised linear mixed model with a logit link and a binary distribution (logistic regression), for Secondary outcomes 1b and 1d.

Count: Count secondary endpoints, such as number of reported access-related AEs, will be modelled using a Poisson regression model, and a negative binomial model if there is overdispersion (>1.3). This will apply for secondary outcomes 2b, 2c, 2e, 2f, 2g, 2h.

Survival time: Survival curves and estimated median survival time will be generated according to the Kaplan-Meier method. Log-rank test will be used to assess the difference between the two survival curves by secondary endpoint. The hazard ratio between two treatments will be estimated with a Cox Proportional Hazards model is the PH assumption is met. This will apply for Secondary outcomes 2a and 2d.

Composite Rank Score: A rank-based procedure combining mortality and functional neuropathy score will be used (Secondary outcome 4). Patients who die before the 48 month follow-up will be ranked from lowest (poorest outcome) to highest on their survival time (less survival time=lower rank). Then, those who alive at the final follow-up with a TNS will be ranked from least to most favourable change in TNS from baseline (TNS follow-up – TNS baseline) . If participants are alive but do not have a valid TNS then they will be censored (Shortest Survival < Longest Survival < Lowest TNS change < Highest TNS change). Ranks between treatment groups will be compared with a log-rank test, and hazard ratio (with 95% confidence intervals) will be estimated with Cox proportional hazards regression. The main assumption underlying the composite ranking is that death at any time is worse than the greatest increase in TNS.

Sensitivity test for missing data in the main outcome: A sensitivity analysis of the missing at random assumption in the main outcome will be made with a delta-adjustment tipping point analysis. If a significant difference is found between the groups we will use a marginal delta adjustment method with a tipping point. We will impute missing visits (using a non-monotone MCMC method), then add a constant (delta) to the imputed data until the difference is no longer significant (p>0.05). If the value of delta required to overturn significant results is implausible then we will consider the results to be robust.

Further analyses: Further analyses for the cohort phase of the study will be subject to a separate report when data is available.

Serious adverse event outcomes:
Serious adverse event outcomes will be independently categorized by two authors into the following groups (as defined above):
- Access failure
- Septicaemia
- Cardiovascular event
- Surgery for carpal tunnel syndrome
- Parathyroidectomy surgery
- Fractures requiring or occurring during a hospital admission
- Other

5.3   Missing Data

If data points are missing no imputation will be performed. The direct likelihood method used in the longitudinal mixed model (4.1) is robust to the Missing at Random assumption. Percentages will be calculated according to the number of patients for whom data are available and the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. A sensitivity test of the primary outcome will be conducted as follows: If the main outcome is significantly different between treatment groups, we will then impute the missing values with adjustment (delta) such that the imputed data is 'missing not at random' with differential pattern between treatments. This is iterated until the main outcome is no longer significantly different between treatment groups (the 'tipping point') and we then report the delta needed to reach this point, and whether it is realistic or not.

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Appendices

Appendix 1: Neuropathy Assessment scales

Modified Total Neuropathy Score[1]

	Score				
Parameter	**0**	**1**	**2**	**3**	**4**
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Sural amplitude[2]	Normal/reduced to <5% LLN	76 to 95% LLN	51 to 75% LLN	26 to 50% LLN	0 to 25% LLN
Tibial amplitude[3]	Normal/reduced to <5% LLN	76 to 95% LLN	51 to 75% LLN	26 to 50% LLN	0 to 25% LLN

[1] The Modified TNS as specified in the FINESSE protocol omits the vibration domain. The original TNS is shown below.

[2] Lower limit of normal range for sural amplitude by age group (age range (years), amplitude (μV)): 0-20, 12 μV; 21-40, 9 μV; 41-60, 7μV; 61-80, 6μV.

[3] Lower limit of normal range for tibial amplitude: 3 mV

Interpretation:

Strata	Score	Descriptive terminology
1	0-8	No to minor
	2-8	Minor
2	9-16	Moderate
	17-24	Moderately severe

	25-28	Severe

Original Total Neuropathy Score

The original Total Neuropathy Score will be used in exploratory analyses.

	Score				
Parameter	**0**	**1**	**2**	**3**	**4**
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Sural amplitude[2]	Normal/reduced to <5% LLN	76 to 95% LLN	51 to75% LLN	26 to 50% LLN	0 to 25% LLN
Tibial amplitude[3]	Normal/reduced to <5% LLN	76 to 95% LLN	51 to75% LLN	26 to 50% LLN	0 to 25% LLN

Strata	Score	Descriptive terminology
1	0-8	No to minor
	2-8	Minor
2	9-16	Moderate
	17-24	Moderately severe
	25-32	Severe

Modified Neuropathy Symptom Score

	Score 1 point for presence of a symptom
Symptoms of muscle weakness	
Symptoms of limb muscle weakness	Shoulder girdle and upper arm
	Hand
	Glutei and thigh
	Legs
Sensory disturbances	
Negative symptoms	Difficulty identifying objects in mouth
	Difficulty identifying objects in hands
	Unsteadiness in walking
Positive symptoms	"Numbness," "part of your body is asleep," "like having been given local anaesthetic," "pins and needles", "prickling," – at any site
	Pain – burning, deep aching, tenderness – at any location

Neuropathy Symptom Score (NSS) stages

Stage	Definition		
	NSS score (max 9)	NCS	'Disabling' neuropathic symptoms
0 No neuropathy	< 2	Normal	No
1 Asymptomatic	0	Abnormal	No
2 Symptomatic	≥ 2	Normal	No
	≥ 1	Abnormal	No
3 Disabling	≥ 2	Normal	Yes
	≥ 1	Abnormal	Yes