Investigating the psychometric properties of patient reported outcome measures in individuals with chronic diabetic neuropathic pain: Prospective longitudinal cohort study protocol

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Abstract

Background: The prevalence of Diabetes in New Zealand is estimated to be 7% of the total population. And higher incidence rates of peripheral Neuropathic Pain (NeP) in diabetic population have been estimated (between 3% and 25%). A range of outcome measures (OMs), are used to evaluate a change following an intervention, in diabetic NeP clinical trials, but very few have adequate psychometric properties (PMPs) for key dimensions. This study aims to investigate the remaining PMPs (which have not been investigated so far) of established specific pain intensity and physical functional OMs in adults (≥18 years) with chronic diabetic NeP.

Methods and analysis: This prospective longitudinal cohort study aims to recruit a total of 80 adults with Diabetic NeP in Dunedin, Otago region, New Zealand, from November 2013. Outcomes include two questionnaires: Pain outcome measure: modified Brief Pain Inventory-Diabetic Peripheral Neuropathy item scale; and Physical functional outcome measure: Screening of Activity Limitation and Safety Awareness scale. To capture the reliability and validity of these measures two follow up assessments (1 and 3 month after the baseline assessment) will be scheduled. For test-retest reliability, 'Intraclass Correlation Coefficient', and to find out the correlation between two measures, 'Pearson Correlation Coefficient' will be calculated. To investigate responsiveness, 'Minimally Clinically Important Change' scores will be calculated.

Ethics and Dissemination: Full Final ethical approval from University of Otago Human Ethics Committee has been obtained: Ethical Committee reference number H13/041. Maori Research Consultation through the Ngāi Tahu Research Committee has also been undertaken. **Trial registration:** The Australian New Zealand Clinical Trials Registry: ACTRN12613000748718.

Key words: Diabetic Neuropathy; pain intensity outcome measure; physical functioning outcome measure; psychometric properties; reliability; validity; responsiveness

Background:

Diabetic Neuropathic Pain is defined as- "*pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes"* (International Association for the Study of Pain).[1,2] Diabetic neuropathic pain is considered to be a multi-disabling condition, affecting 15% or more diabetic patients.[3] For those with diabetic neuropathic pain, pain is considered a risk factor for, as well as a cause of disability.[4] According to the International Classification of Functioning, Disability and Health, functioning is described as a complex interaction of body functions, body structures, activities and participation, environmental and personal factors, and has provided a theoretical framework for evaluating functioning and disability.[5] In order to achieve the aims of complete rehabilitation, evaluation of pain along with subjective interaction of pain and comorbidities should be assessed.

A range of pain assessment guidelines have been developed including the, Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)[6] along with assessment guidelines from the European Federation of Neurological Sciences (EFNS),[7, 8] and the Neuropathic Pain Special Interest Group (NeuPSIG).[9] These guidelines recommend outcome measures (OMs) that evaluate a range of issues associated with neuropathic pain, such as- pain, quality of life, mood, sleep, and functional capacity (physical, cognitive, emotional, and social).[8, 9] Since numerous other OMs are also available, justification for selection for clinical practice or clinical trials must be based on the extent of established psychometric property (ies). The various domains of psychometric properties include reliability, validity, and dimensionality. Reliability is a measure of stability, consistency, and homogeneity; whereas validity involves multiple forms of measures that include content, construct, criterion, and face validity. Responsiveness is considered a validity measure and involves the accurate reflection of change within the tool when a clinically meaningful change has occurred within the respondent. Related to responsiveness is interpretability, which is the

interpretation of the extent of change necessary for clinical importance. Dimensionality is a psychometric property that involves the assessment of one or more specific latent constructs.[10]

The Brief Pain Inventory (BPI) is a widely used and validated numeric rating scale that measures severity of pain and its interference with daily functions.[11] The modified form of BPI-modified Brief Inventory for Diabetic Peripheral Neuropathy (mBPI-DPN), is a patient-completed numeric rating scale specifically designed for diabetic peripheral neuropathy, which includes a four item pain severity scale, and a seven item pain interference scale. Initially formal validation of BPI in neuropathic pain was not conducted, though it was used widely in clinical trials of neuropathic pain.[12] The initial validation of this tool was done in a herpes zoster population,[13] followed by the establishment of other psychometric properties.[14] Due to fluctuations of neuropathic pain over time, mBPI-DPN scale assessing average pain by measuring the "pain at its worst", "pain as its least", and "pain right now" have been recommended to assess pain and disability in patients with diabetic neuropathy. Both scales of the mBPI-DPN outcome measure (pain severity scale, and pain interference scale) have been established for their internal consistency (high Cronbach's alpha α= 0.90; and criterion validity) as the mean pain severity scale was highly correlated with Bodily Pain from the Medical Outcome Study short form-12 version 2 (Spearman correlation coefficient r= 0.63, P< 0,001), the Pain/Discomfort item in the Euro-QoL (Spearman correlation coefficient r= 0.58, P< .001), and a verbal rating scale measure of pain severity (Spearman correlation coefficient r= 0.74, P< .001).[14] Individual mBPI-DPN interference domains have been found to moderately correlate (Spearman correlation coefficient r's> 0.5, P< .001) with analogous measures, and the Sleep Interference item had a high, significant association with the three primary Medical Outcome Study-Sleep scale subscales (Spearman correlation coefficient r's= 0.66 –71, P< .001).[15, 16] However no further published evidence for the other forms of psychometric properties, i.e. test-retest reliability, and responsiveness/interpretability form of validity has been found. To make the further recommendations for the future use of this measure, there is a need to establish these remaining psychometric properties in the underline population.

The original Screening of Activity Limitation and Safety Awareness (SALSA) scale is a 374 items questionnaire, comprising different 19 sections of self-care, around the house, reading and writing, getting around, leisure, child care, working with tools etc. Twenty items from this original 374-item questionnaire were selected and approved by the SALSA collaborative study group to be applied in diabetic neuropathic pain and Leprosy populations.[17] This tool has been shown to discriminate between people with and without activity limitation in these populations. The short form SALSA questionnaire has been established for its high reliability coefficient (Cronbach's alpha $\alpha = 0.884$) and a strong association found between the SALSA score and the score assigned to the respondents by the independent experts (Spearman correlation coefficient r's= 0.70, P< 0.0001); thus this scale has been found to be sensitive to the changes in the diabetic neuropathic population. However, the validation of this scale should be considered as preliminary, as its sensitivity to change has not been assessed to date in further clinical trials. The test-retest reliability of short form SALSA has been determined only in a leprosy population.[18] Additionally, no published evidence for the other forms of psychometric properties, i.e. test-retest reliability in diabetic neuropathic pain population, and responsiveness/interpretability form of validity, has been found. Since, for clinical and research purposes, it is imperative that psychometric properties are established for these OMs, the proposed research aims to investigate the test-retest reliability, responsiveness, and interpretability (Minimally Clinically Important Change- MCIC) of pain intensity (mBPI-DPN) and physical functioning (SALSA) OMs in adults with chronic diabetic neuropathic pain. Psychometrically sound instruments are essential to assist healthcare professionals to accurately measure and monitor changes in patient health, to assess the efficacy of interventions and to facilitate goal settings for therapeutic interventions. Since the severity of pain and its impact on daily life (including disability) should also be explored, the study further aims to assess the relationship between these two measures.

Methods:

Study design:

This prospective longitudinal cohort study aims to recruit diabetic participants with nerve pain, from New Zealand, initiating in March 2014.

Sample size estimation:

We are aiming to recruit n= 80 adults for the study. Following the Donner and Eliasziw's equation[19] for the calculation of sample size, considering two possible observations per subject, level of significance; α= 0.05, a type II error; β= 0.20, ρ_0= 0.5, ρ_1= 0.7, sample size for the reliability study was estimated to be 63 participants,[20 21] (Null Hypothesis= ρ_0= minimal acceptable level of reliability, and Alternate hypothesis= $\rho_1 > \rho_0$). N= 80 sample size was decided after considering the 10-15% attrition rate because of withdrawal and discontinuity of participants during the study. Further the current sample size is also in recommendations of the Consensus-based Standards for the selection of Health Measurement Instruments (COSMIN)[22] checklist, developed by an international group of experts. According to COSMIN guidelines,[23] a sample size between 50 to 99 is considered to be a good sample size as they recognize the need for precision in the overall estimates.

Participant recruitment:

For recruitment, advertisement flyers/posters will be circulated to health care centres, physiotherapy clinics, and University premises. Other sources of advertisements such as public media (e.g. local newspapers), public noticeboards (e.g. public library and community local boards), University newsletter, and social networking sites (Facebook invitations to diabetes New Zealand; Peripheral neuropathy New Zealand etc.) will also be considered. Invitation letters to General Physicians and Diabetes NZ branches will also be posted requesting them to refer potential patients to participate in the study. A snowball sampling technique (Exponential non- discriminative) as a chain referral will be followed.[24] Under such a methodology, participants who enter into the study will be asked to provide assistance to help identify additional people with similar characteristics.

Adults with a history of diabetes and chronic pain, who are interested in volunteering for the study, will be requested to contact the research administrator (telephonically or by electronic mail) at the Centre for Health, Activity, and Rehabilitation Research (CHARR), University of Otago. The research team will contact volunteers (telephonically) and screen for eligibility using a standardized procedure. Participants will be asked a set of questions from the Leeds Assessment of Neuropathic Symptoms and Signs: self-complete questionnaire (S-LANSS) in a telephonic interview by the primary investigator (PI). Participants scoring ≥12 on the S-LANSS, which has been suggestive of pain of predominantly nerve origin,[25] will be eligible to participate in the study. Eligible participants will then be provided with their first appointment with the primary investigator at the CHARR. After obtaining written informed consent, a unique identification code will be assigned to each participant. Figure 1 summarizes the procedure to be adopted.

Selection criteria:

Inclusion criteria: Adults (18 years and over) either with a confirmed diagnosis of diabetes by a general physician, associated with chronic (defined as- pain duration for ≥3 months)[26] neuropathic pain and a score of ≥12 on the S-LANNS will be eligible to participate. Participants should be able to understand English and provide informed consent to participate. Exclusion criteria: Participants who are unable to comprehend and record OM data will be excluded.

Measurements:

Data will be collected at baseline, followed by four weeks intervals, and twelve weeks intervals. After patients sign an informed consent document, they will be asked to answer a baseline questionnaire, stating their demographic details, various historical (diabetic, drug etc.) questions followed by the physical measurements (height, weight, waist circumference, and hip circumference). The Charlson Comorbidity Index will be used to assess the presence of other associated illnesses in included participants.[27] [28] [29] The New Zealand Physical Activity Questionnaire:

Short Form- Version 1 will also be incorporated to assess the level of physical activity of the participants.[30] Followed by demographic information, each participant will be requested to complete two questionnaires: the modified Brief pain Inventory- Diabetic Peripheral Neuropathy item scale (mBPI-DPN), and the short form Screening of Activity Limitation and Safety Awareness scale (SALSA). The Patient Global Impression of Change scale (PGIC) scale will be used as an external criterion at the follow up visits.

The modified Brief pain Inventory- Diabetic Peripheral Neuropathy item scale:

The mBPI-DPN: pain severity scale, and pain interference scale is a patient-completed numeric rating scale. Each BPI item uses a 0-10 rating anchored at zero for "no pain" and 10 for "pain as bad as you can imagine" for severity, and a 0-10 scale to measure interference from 0 "does not interfere" to 10 "completely interferes". The participants will be asked to report the level of pain experienced at different occasions. To distinguish between pain due to diabetic peripheral neuropathy and pain due to other causes, the following phrase is added to all items 'due to your diabetes' (as already used in the prior study).[14]

The short form Screening of Activity Limitation and Safety Awareness scale:

The short form SALSA is also a patient-completed physical functional scale. For the purpose of scoring, participants will be asked whether a particular activity was ever carried out by the respondent. If the response is NO, then the item is graded as zero. However if the response is a YES, grading is provided by asking further questions, such as: whether this was perceived as easy: Grade 1, whether it was perceived as a little difficult: Grade 2, whether it was very difficult: Grade 3, and if patient indicates that this activity was physically impossible or avoided because of a perceived risk of injury: Grade 4, indicating advanced degree of activity limitation.

The Patient Global Impression of Change scale:

The PGIC is a patient-completed numeric rating scale. The participant will be instructed to write down their present chief complaint followed by the question: '*Since beginning this study, how you would describe the change (if any) in activity limitations, symptoms, emotions, and overall Quality of Life, related to your painful condition*'?, (adapted from previous study).[31] A seven point Likert scale will be employed where zero indicates No change (or condition has got worse) and seven indicates A great deal better, and a considerable improvement that has made all the difference. Participants will be instructed to circle the number which matches most closely with their degree of change since participating in this study for the above stated chief complaint.

Procedures:

Baseline assessment

On Assessment one, each participant will be requested to complete two questionnaires (mBPI-DPN, and SALSA) at the CHARR. Any questions about the project will be answered to participant's satisfaction prior to the study, and participants will be free to request further information at any stage. Study participants will be offered a gift voucher at the baseline assessment as a reimbursement for their time to participate in the study.

Re-assessments:

Re-assessment-1 will be conducted following four weeks from the baseline assessment. Questionnaires (Pain OM: mBPI-DPN; Physical functional OM: SALSA) including the PGIC scale will be sent with detailed instructions to all participants (either electronically or by mail). The PGIC will serve as an external criterion for overall participant improvement.[31] The self-report data collected at re-assessment-1 will be used to evaluate the test-retest reliability of the chosen OMs.

Reassessment-2 will be conducted following twelve weeks from the baseline assessment. Again, both OMs including the PGIC will be completed by all participants. The self-report data collected at re-assessment-2 will be used to evaluate the responsiveness component of validity.

Participants will be instructed to re-send their completed forms via e-mail or priority stamped enclosed envelopes to the CHARR within two weeks of receipt. To increase the response rate, modified Dillman's respondent contact strategies will be adopted.[32] Following this strategy, if no response is received after two weeks, follow-up reminders (telephonic call or e-mail) will be made by the PI. Replacement questionnaires will be mailed to the non-respondents, if required, in case of missing mail.

Statistical Considerations:

Demographic data of the study sample will be presented with descriptive statistics. For statistical analysis of the mBPI-DPN scale: mean pain scores for the individual items (4 pain severity items and 7 interference items), mean pain scores for the individual indexes (pain severity index; and pain-related interference index), and mean pain scores for the complete mBPI-DPN unit (pain severity index and pain-related interference scale) will be calculated. Further, the SALSA scale subtotal score for individual item: 20 questions (S1; S2; S3; S4; S5; and S6) and a complete SALSA score by adding up all subtotal scores (S1+S2+S3+S4+S5+S6) will be calculated.

To handle missing data, initially a 'follow-up' strategy will be adopted.[33] Participants who either failed to report on second and/or third assessments, or failed to fill any section of the questionnaires, will be contacted telephonically, or via e-mail to obtain their readings. However, if this strategy is not feasible, then the 'Last observation carried forward' method will be preferred.[33] Here the participant's last data point before dropping out or at prior assessment will be used as the OM.

Test-retest reliability:

To check out the *relative form of test-retest reliability*, Intraclass Correlation Coefficient ($ICC_{2,k}$) will be calculated.[34] ICC values ≥ 0.75 will be considered as good reliability; values from 0.50 to <0.75 will indicate moderate reliability; and values <0.50 will indicate poor reliability.[15] For the

absolute form of reliability changes in mean, measurement variability i.e. standard error of measurement (SEM), and smallest real difference (SRD) will be calculated.[35]

Validity:

The MCIC scores for mBPI-DPN and SALSA scale will be calculated using three different variations of the 'Anchor based approach': "sensitivity and specificity" approach, "within patients" score change, and "between patients" score change. The PGIC will be used as an external criterion based on the patient's subjective perception of improvement.[31] Based on previous studies,[36] a score of 5-7 will be considered as a significant, favourable change and a 1-4 score will be considered as no significant change. For the sensitivity and specificity approach, receiver operating characteristic curves (ROC) at 95% CIs will be used to discriminate between 'major improvement' and 'unimportant change'. The area under the ROC curve will be interpreted as the probability that scores have correctly identified the patients classified as having 'major improvement' to 'unimportant change' by the external criterion.[15] The "within patients" change will be calculated as the mean change score (Assessment 3 minus Assessment 1) for mBPI-DPN and SALSA, corresponding to the patients defined as achieving significant favourable change (score of 5-7 on PGIC). The "between patients" change score will be calculated as the difference in the change score of 'significant favourable change' (a score of 5-7 on PGIC) and 'no significant change' (a score of 1-4 on PGIC).[15]

Correlation:

The 'Pearson Correlation Coefficient' will be used to investigate the correlation between pain (mBPI-DPN) and physical functional (SALSA) OMs.[37] A coefficient of +1 indicates that the variables (pain and physical functioning) are perfectly positively correlated, and thus that as the scores for pain intensity increase, the Physical functional limitation also increases commensurately. The 'Scatter plot Method' will be used to illustrate these findings; this will provide information about

the variables-: whether there is any relationship between the two variables? What kind of relationship it is, negative or positive? And whether any cases are markedly different from the others? The following criteria will be used to assess the strength of associations: 0.00 to 0.25 little or no correlation; 0.25 to 0.50 fair relationship; 0.50 to 0.75 moderate to good relationship; and above 0.75 good to excellent relationship.[15]

Ethics and Dissemination:

Ethical approval from the University of Otago Human Ethics Committee has been obtained for this study: Ethical Committee reference number H13/041. Maori Research Consultation through the Ngāi Tahu Research Committee has also been undertaken. This trial has been registered with the Australian New Zealand Clinical Trials Registry: ACTRN12613000748718; the Universal Trial Number (UTN): U1111-1145-2867.

There are no potential risks for participants taking part in this study. All the participants will provide written informed consent to participate and will have all the rights to withdraw from participation in the project at any time without any disadvantage to them of any kind. This study will establish benchmark OMs that are originally constructed to measures pain and physical functioning status in individuals with diabetic neuropathic pain. This research will investigate whether relationships exist between pain perception and physical activity threshold in a diabetic neuropathic pain population. Further the results will add to our knowledge of what amount of change in pain intensity or physical functioning level might be considered as beneficial for the diabetic neuropathic pain participants. This will also be useful for clinicians and researchers to evaluate a change in pain and physical functioning status in individuals with diabetic neuropathic pain following interventions, thus better informing appropriate management to minimize the risks of comorbidities and disabilities.

Trial Status:

At the time of submission of this study protocol, we are recruiting participants for the study.

Abbreviations:

mBPI-DPN, The modified Brief pain Inventory- Diabetic Peripheral Neuropathy item scale; CIs, Confidence intervals; COSMIN, The COnsensus based Standards for the selection of health status Measurement INstruments guidelines; EFNS, The European Federation of Neurological Sciences; IASP, The International Association for the Study of Pain; ICC, Intraclass Correlation Coefficient; IMMPACT, The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials; MCIC, Minimally Clinically Important Change; NeuPSIG, The Neuropathic Pain Special Interest Group; OMs, Outcome Measures; PGIC, The Patient Global Impression of Change scale; PI, Primary investigator; RCTs, Randomized controlled trials; ROC, Receiver operating characteristic curve; SALSA, The Screening of activity limitation and safety awareness scale; SEM, Standard Errors of Measurement; S-LANSS, The Leeds Assessment of Neuropathic Symptoms and Signs: self-complete Questionnaire; WHO, The World Health Organization

Competing Interests:

This project is supported by Centre for Health, Activity, and Rehabilitation Research, University of Otago, Dunedin, New Zealand, internal grant and the Mark Steptoe Memorial Trust, School of Physiotherapy; University of Otago, Dunedin, New Zealand. All authors declare that there exist no conflicts of financial or non-financial competing interests associated with the current study.

Author's Contributions:

PM drafted the manuscript. LC, RM, PH, and GDB critically revised the manuscript. All authors have been involved in the design of the study. All authors have read and approved the final manuscript.

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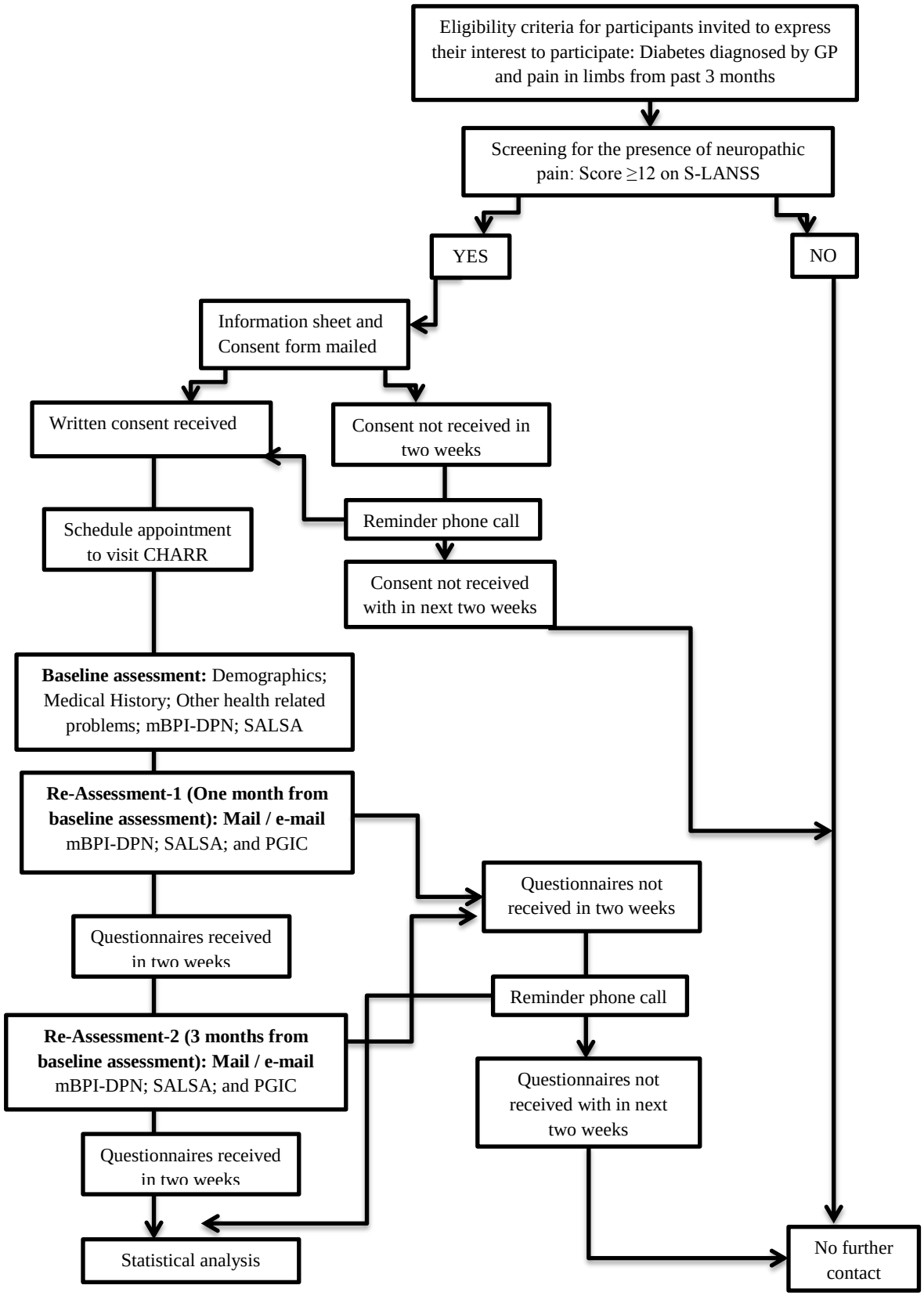
Figure 1 Flow diagram summarising the participant recruitment and procedure followed


Eligibility criteria for participants invited to express their interest to participate: Diabetes diagnosed by GP and pain in limbs from past 3 months
Screening for the presence of neuropathic pain: Score ≥12 on S-LANSS
YES
NO
Information sheet and Consent form mailed
Written consent received
Consent not received in two weeks
Reminder phone call
Schedule appointment to visit CHARR
Consent not received with in next two weeks
Baseline assessment: Demographics; Medical History; Other health related problems; mBPI-DPN; SALSA
Re-Assessment-1 (One month from baseline assessment): Mail / e-mail mBPI-DPN; SALSA; and PGIC
Questionnaires not received in two weeks
Questionnaires received in two weeks
Reminder phone call
Re-Assessment-2 (3 months from baseline assessment): Mail / e-mail mBPI-DPN; SALSA; and PGIC
Questionnaires not received with in next two weeks
Questionnaires received in two weeks
Statistical analysis
No further contact