Medicines and Technologies Programme
Adoption Scoping Report

MT318 The Neuropad test for inadequate sweat gland function in the early detection of diabetic foot neuropathy (DPN)

SUMMARY – for MTAC1 meeting

Contributors to this report familiar with Neuropad, have experience of use from a trial or research perspective within an NHS setting and not routine clinical use.

Contributors thought that sweat production is a good marker of diabetic peripheral neuropathy. All reported that Neuropad could be used as part of a comprehensive foot assessment and in conjunction with sensory testing.

Adoption Levers

- Good clinician confidence: contributors felt that Neuropad was a better test than the sensory tests currently used.
- Minimal clinician training required.
- Potential to improve patient education.
- High patient acceptance.

Adoption Barriers

- Capacity: the test takes 15 minutes to prepare for, carry out and produce a result.
- Device cost.

1. Introduction

The Adoption team has collated information from healthcare professionals who have experience of undertaking sensory testing within NHS diabetes services. Feedback from clinicians familiar with Neuropad has come from a trial or research perspective within an NHS setting, and not routine clinical use.

This adoption scoping report includes some of the benefits, considerations and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

Current practice as reported by contributors

Foot examinations/assessments for people with diabetes are carried out in a range of primary, secondary and social care settings by various health professionals (GPs, practice nurses, podiatrists, and diabetologists). Frequency of foot assessments is likely to be based on risk category (as per recommendation 1.3.6 in NICE guidance on diabetic foot problems: prevention and management and ranges from every six weeks to annually. Annual assessments were reported as being the minimal frequency for low risk people, however the 2015 National Diabetes Audit reported that 27.6% of people with type 1, and 13.3% of people with type 2 diabetes had not achieved this standard. The foot assessment should include assessment of; skin (usually using the Young Townson FootSkin scale), peripheral circulation (palpable pulses), physical abnormalities, loss of power and peripheral neuropathy (10g monofilament or calibrated tuning fork).

General awareness of peripheral neuropathy, competence in conducting sensory testing and clinician confidence in testing was reported to be low resulting in foot assessments, interpretation of tests (if tests are carried out) and acting on results may not always be done well. Recording foot assessments is currently a QOF indicator which aims to improve practice within primary care. All contributors thought that adding Neuropad to the foot assessment process as an adjunct test may be useful in certain populations/settings.

Currently, there is no standard test in use for identifying autonomic neuropathy via detection of inadequate sweat production.

2. Use of Neuropad in practice

The MTEP analyst requested intelligence on patient selection and particular subgroups and settings within which contributors would prioritise use of Neuropad.

Contributors said:

- It would be useful to recommend Neuropad in a specific population in the first instance, due to its cost, to see how well it works and to establish if use helps to prevent hospital visit/admission, ulcer and amputation rates.

- Neuropad may be particularly useful for people with cognitive issues or in those with a language barrier as other methods of sensory testing require a level of understanding and communication from the patient.

- Older people or those with mobility issues may benefit from screening using this test as it can easily be applied at home. Mobility issues would need to be considered if asking people to apply themselves.

- One contributor suggested that use of Neuropad should be prioritised in high risk people within a diabetic foot care clinic.

- One contributor thought that use in primary care, as an early screening test to direct referral and frequency of assessment, would be useful.

3. Reported benefits

The benefits of adopting Neuropad, as reported to the Adoption team by the healthcare professionals with expertise in this area are:

- Easy to use and interpret with little training requirements. Provides an objective result.
- Can be carried out easily where the personresides rather than requiring patients to attend a healthcare setting.
- May be used as an early screening test to prompt referral for comprehensive foot assessment. This test may detect a problem before any visual problems are apparent.
- The visual nature of this test may have high educational value for people with diabetes and help them to appreciate there is a problem and therefore motivate them to make changes to their lifestyle and foot care regimen.
- Sensory testing can be difficult to carry out and there is a lot of subjectivity involved. This test offers a simple objective adjunct test to the foot assessment process.
- This test may be useful for monitoring progression of diabetic peripheral neuropathy at annual foot assessments.

4. Levers and barriers to adoption

The key considerations for adoption highlighted through discussions with expert contributors are:

Capacity

The most significant adoption challenge reported was time. Neuropad takes 10 minutes to produce a result once it has been applied. Feet should ideally be exposed to the air for 5 minutes to ensure they are dry before application. Contributors said this may not be easy to perform in a busy NHS clinic or podiatry treatment session. However, they did highlight that there are ways of dealing with this e.g. applying Neuropad at the start of the assessment and leaving in situ whilst completing the rest of the assessment or applying whilst the patient is waiting for their appointment.

One contributor's trust has reconfigured their diabetes screening clinics to reduce capacity required. Here people attend an annual eye screening assessment which is followed by a foot assessment/examination (including application of Neuropad) and required blood tests. This reduces the number of appointments attended from 3 to 1. Attendance is reported to be high for these clinics as people are more motivated to look after their eyes. Previous to this reconfiguration, this contributor reported that 20% of people with diabetes had not had their feet looked at/assessed at all.

Resource impact

The cost of Neuropad may present an issue as this is an additional cost and is more expensive than current sensory tests. However, contributors reported that if use leads to a reduction in hospital visit/amputation, ulceration and future amputations, savings could be substantial.

Clinician confidence

Four contributors reported that Neuropad was a better test than the sensory tests currently used in practice (10 g monofilament, calibrated tuning fork testing) as interpretation of the result is subjective (so much so that one contributor estimates that a third of sensory tests carried out are not accurate). Another contributor has recently completed an audit of screening for neuropathy/nerve damage in the feet of over 100 older (aged 70-94) inpatients and care home residents and found that

Neuropad frequently reported abnormal results when the monofilament test result was reported as normal.

Contributors stated that sweat production is a good marker of diabetic peripheral neuropathy. All reported that Neuropad should be used in conjunction with comprehensive foot assessment and sensory testing and that it is important to maintain and improve the clinical skills required to do a comprehensive foot assessment.

Training and education

Minimal training is required and therefore this, with the potential to improve patient education, may act as an adoption lever.

Four contributors highlighted the powerful education potential of this technology. Some people who have lost sensation in their feet can struggle to understand that there is a problem. The visual nature of this test's result can help people to appreciate there is a problem and take action to prevent damage.

Clear instructions will need to be given if allowing people with diabetes to apply the test independently.

There are wider education and training needs associated with the whole foot assessment process including acting upon the outcome of this.

Patient acceptance

Feedback from people with diabetes has been that they like this test and that it aids their understanding and acceptance of the fact they may have diabetic peripheral neuropathy.

5. Comparators

One contributor also uses SUDOSCAN. This contributor works at the trust where they have reconfigured screening services for people with diabetes.

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT318 The Neuropad test for the early detection of diabetic peripheral neuropathy

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

<table>
<tr><th>Submission Document Section/Sub-section number</th><th>Question / Request
Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</th><th>Response
Attach additional documents provided in response as Appendices and reference in relevant cells below.</th></tr>
<tr><td>Clinical section</td><td>Initial questions sent to manufacturer 10.05.17
1. Can the manufacturer provide the full outline of their search strategy for all the databases they searched? Sections 7 and 10 do not provide any information about how published and unpublished studies were found.
2. Can the sponsor provide detail on the following for clinical evidence, economic evidence and resource identification, measurement and valuation (published and unpublished studies)?
• which databases they searched
• the date the search(es) took place
• the date limits of the search
• the search strategies used
• inclusion and exclusion criteria
• data abstraction strategy
3. The unpublished study by Tentolouris, et al (“The Neuropathy Disability Score and the indicator plaster test Neuropad predict foot ulceration in diabetes”) is described as ‘in-press’ but this study is not listed on medical</td><td>Responses received from manufacturer 15.05.17

1. Report the numbers of published studies included and excluded at each stage in an appropriate format. A search was performed for ‘neuropad’ as there is no generic equivalent to the test and it is a device. Date and time search performed: 30.01.2017 at 15.13. No date limit set.
We then re-ran the same search for ‘neuropad’ with the following results.
Report Information from ProQuest Dialog. May 13 2017 12:23. No date limit set. Databases: Derwent Drug File, Embase®, MEDLINE®

Search Strategy:
<table><tr><th>Set#</th><th>Searched for</th><th>Results</th></tr><tr><td>S1</td><td>neuropad</td><td>193°</td></tr></table>
After removing all irrelevant results including many referencing a device also called neuropad used to diagnose certain illnesses affecting children’s brains (137 including duplicate records), we were then left with 56 studies. After removing duplicate records (4), case reviews (2) and product reviews (7) and studies involving patients with cardiovascular autonomic neuropathy (1) and a study involving the use of a novel algorithm to produce a continuous output for Neuropad (1) there were 41 studies remaining which matches the original search we conducted on the 30th of January 2017.

Please note that both searches resulted in the identification of no economic studies involving Neuropad which is why we are providing a de novo model.

Please also note that the 2 unpublished studies are known to the manufacturer as they were originally presented as posters at the European Association for the Study of Diabetes though in different years.

2. Please see 1. Above.</td></tr>
</table>

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	databases and cannot be found through Google searching. Can the sponsor provide more detail about the origin of this paper? In which journal is this paper in press? 4. Does the manufacturer know when the ongoing studies plan to be published/fully analysed? 5. Can the sponsor provide details of how they searched for adverse events i.e. the search strategy used in MHRA or FDA (MAUDE)? 6. Can the manufacturer confirm that no quality appraisal was carried out (see section 7.6)? Was there a reason for this? 7. Meta-analysis (section 7.9) – was any quality assessment carried out on the independent meta-analysis (Tsapas et al. 2014)? What was the reason for excluding the papers from this meta-analysis from the clinical evidence search? Can the manufacturer provide a summary of the paper? 8. Does the technology function the same between the populations with type 1 or type 2 diabetes?	3. For clarification, we have now established that the manuscript, a copy of which has been provided with our clinical submission, is still in preparation and has not yet been submitted for publication. The authors intend to submit for peer-review and publication to either Diabetes Care or Diabetic Medicine in 2017. The delay is because this is a multi-centre prospective study and the manuscript requires analysis and consensus from all participating centres. 4. For Tentolouris et al, please see point 3 above. Concerning Sanz et al, this is unknown currently. 5. From Neuropad's launch in 2006 to date there have been no adverse events reported. In Germany, manufacturers are obliged to report any adverse event to the German medicines and medical devices regulator BfArM and this is also an essential requirement of German and EU law such as Medical Devices Directive equirements (Council Directive 93/42/EEC of 14 June 1993) and the Medizinproduktegesetz (MPG), Medical de Vigilance System (MEDDEV), Medizinprodukte-Sicherheitsplanverordnung (MPSV). Neuropad is also distributed by the global pharmaceurical company Sanofi SA in Germany, Switzerland, Austria and Australia, as such Sanofi, and in fact all distributors are obliged to report immediately any adverse events to the national relevant regulator and the manufacturer. Since there is no comparator to Neuropad the search of adverse events associated with the technology in national regulatory databases is not applicable. In Germany, the quality management team performs active market surveillance, including the searching of the MHRA, but this is again limited to Neuropad because of the lack of comparative technologies. However, we have subsequently run a wide search with no date range specified on 12 May 2017 at 16:06 looking specifically for adverse events (AEs) in all databases to which we have access. The search found only 3 reports, none of which are AEs relating directly to Neuropad. We have in this instance provided a copy of the three reports obtained including the search strategy which

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	9. In section 7.1 the submission notes that "choice of standard tests used to compare against Neuropad varied according to the choice of the authors. The generally accepted gold standard test is the intraepidermal nerve fibre density measurement (IENFD)." Were there specified criteria, or literature used to select the standard tests or was this a subjective judgement? Did the authors choosing comparators include clinical experts? What are the sources suggesting that IENFD is the gold standard for detecting sudomotor dysfunction? Would the manufacturer also suggest that this is the gold standard for diabetic peripheral neuropathy detection? 10. Is there only one version of the Neuropad? Have there been others in the past? 11. In selection criteria tables B1 and B2 (in 7.1 and 7.2) the intervention section states that Neuropad is a test for "diabetic autonomic neuropathy" (which can affect any organ in the body). Should this say "diabetic	was run against a subset of the original 193 neuropad documents. (See AEs Report Information from ProQuest Dialog.) We have provided additional evidence in the form of the MPSV process (in German), the EU MEDDEV for a medical devices vigilance system, which the manufacturer follows and recent email correspondence from Sanofi confirming that no AEs have been reported. 6. This is not the case but at the time of compiling the clinical submission we did not understand what was required. For clarification, Neuropad is a CE Class I medical device manufactured to a high standard and is fully compliant with good manufacturing practice. Quality appraisal of the Neuropad manufacturing process is carried out regularly and to national, EU and global standards and practices. Further supporting evidence is provided comprising a copy of the manufacturer's internal quality control procedures (in German). 7. On the 21st of March 2017 we asked the following question of the evaluation team via Jae Long, Project Manager, MTEP, NICE, and received directly the below reply from Paul Dimmock, Senior Technical Analyst (Evaluations), NICE. John Simpson, Neuropad: "We are fortunate enough to have a recently published meta-analysis which includes data from 18 pooled studies. Will NICE accept this paper rather than the paper plus all 18 individual studies in addition? We feel that including all 18 of these studies will increase significantly the volume of data we would have to present. We prefer to include the meta-analysis plus other relevant studies not included in the meta-analysis. Is this acceptable?" Paul Dimmock, NICE: "Yes, please do just stick to the meta-analysis."

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	peripheral neuropathy" (which affects the extremities)? Could you clarify the association between the 2 terms? We assume the Neuropad does not rule-out large fibre neuropathy, please could the manufacturer confirm? 12. In section 7.10, the manufacturer states that the "clinical efficacy of Neuropad has been determined in over 40 clinical studies, involving more than 1000 diabetic patients", however the submission includes 7 published studies, and the meta-analysis (Tsapas et al.) includes 18 studies with 3470 participants. Could the manufacturer please explain the difference between this claim and the studies presented?	As the meta-analysis is an important document within our submission we would rather that it were examined in its entirety and subject to NICE/KiTEC critical appraisal if required. We do not feel that we are adequately qualified to appraise it nor that is appropriate for the sponsor to carry out an appraisal of it. The meta-analysis also includes detailed information on the searches that the authors performed for eventual study selection. 8. The Neuropad test functions in precisely the same way for all patient populations with any form of diabetes. 9. This information is provided within the published papers that we have provided. The studies' authors are experts in diabetes and diabetic neuropathy. The manufacturer had no influence on which secondary care test was used as a comparator and secondary care specialists do not all use the same test. In addition, some secondary care tests were not available or licensed at the time the studies took place and may now have been replaced with other forms such as corneal confocal microscopy (CCM). Secondary care tests were used as comparators to demonstrate the efficacy of Neuropad rather than in most cases common primary care tests such as the SWME using 10g monofilament. 10. There is just one version and there have been no previous versions. 11. Diabetic peripheral neuropathy is more properly referred to as distal symmetric polyneuropathy and comprises three sub-types: motor, sensory and autonomic diabetic neuropathies. In this instance it may be more appropriate to use the term diabetic peripheral neuropathy. From Malik R. Neuropad: early diagnostic test for diabetic peripheral neuropathy. Prescriber. 42-5. 19th November 2008 (copy provided):

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		"Diabetic peripheral neuropathy is traditionally subdivided into lesions affecting the somatic (sensory and motor nerves) and the autonomic nervous systems. Sensory neuropathy leads to a loss of sensation initially in the toes but progressing more proximally to the entire foot and lower leg, which can predispose patients to unperceived trauma and facilitate the development of foot ulceration. Motor neuropathy contributes to muscle atrophy and deformities, which leads to abnormally high forces and shear stress – both precursors to wound formation. Both large- and small-diameter nerve fibres are implicated in neuropathy. Sensory neuropathy is mediated by large nerve fibres, and small fibres not only mediate pain but also play a vital role in the pathogenesis of foot ulceration via their function within the peripheral autonomic nervous system. Autonomic innervation of sweat glands and dermal blood vessels alters tissue hydration and blood flow, both important in the genesis of breakdown of skin integrity that leads to ulceration." We have also provided 5 additional clinical papers concerning sudomotoric dysfunction and small and large fibre innervation in relation to DPC. (Faeman I et al 1982, Hoeldtke RD et al 2001, Malik RA et al 2005, Malik RA et al 2011, Quattrini C et al 2004) 12. The statement that "clinical efficacy of Neuropad has been determined in over 40 clinical studies, involving more than 1000 diabetic patients" was intended to be an *aide memoire* while the submission was being prepared and it should have been removed. It is a direct quotation taken from a review in Prescriber journal published in 2008 and authored by Professor Rayaz Malik FRCP. The reference to >40 studies in 2008 in fact is un-referenced so we were unable to validate the statement which is why it should have been removed. As you have correctly pointed out, Neuropad has now been studied in >3,400 patients.

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Clinical evidence section	**Minutes of TC sent to manufacturer 18.05.17 (see appendix 1)**	**Response from manufacturer 18.05.17** Dear Joanne Thank you for your email and for the copy of the minutes. It was very helpful of you. Though it's early evening, I don't expect you to receive this email and to respond if you need to until tomorrow morning, so if you do read it this evening please don't feel the need to reply! Concerning the Sanz et al poster (P53 presented at an EASD subgroup meeting on the diabetic foot in September 2016), Dr Sanz Corbalan's email address is: iresanzcorbalan@hotmail.com. However, to expedite matters I have already taken the liberty of writing to her to ask for her help on your behalf and the following is a copy of the email that I wrote to her. It's in Spanish but I hope it's helpful and of course I can provide a translation is you require it: Estimada Sra. Dr Sanz Corbalán, Soy John Simpson, jefe ejecutivo de Neuropad UK (SkyRocket Phytopharma (UK) Ltd), compañía que ha desarrollado una prueba diagnóstica del pie diabético del que soy consciente que eres conocedora, Neuropad. Estamos actualmente trabajando con NICE (National Institute for Health and Care Excellence), organismo encargado en el Reino Unido de la aprobación de tecnologías sanitarias y la posterior recomendación de su uso dentro del Sistema Nacional de Salud, y KiTEC (http://kitec.co.uk/) para que Neuropad sea recomendado por NICE como herramienta para el diagnóstico del pie diabético. A lo largo de la elaboración del informe pertinente, uno de los estudios que nos ha sido de apoyo ha sido el estudio realizado por usted conjuntamente con José Luis Lázaro y Esther García Morales sobre la eficacia de Neuropad como objeto de su tesis de máster. Querría saber, ya que KiTEC también me ha preguntado sobre ello, si dicho estudio está pendiente de publicación.

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		Muchas gracias por adelantado. **E-mail from manufacturer 30.05.17** So far we've had no response from Dr Irene Sanz Corbalan. Via a colleague at the University of Madrid we will see if we can contact her internally rather than via email. I will let you know if we are able to establish if she has plans to submit her poster as a clinical study to a peer-reviewed journal.
Clinical section	**E-mail sent to expert advisers 23.05.17** 1. What are the main guidelines used in the UK relevant to the diagnosis of diabetic peripheral neuropathy (DPN)? Do these align with the clinical pathway for diagnosis of DPN? 2. What are the standard peripheral neuropathy screening tests in the UK? In which settings are these carried out? Is practice standardised or is there local variation in the UK? What about non-UK countries?	**Response from James Holt (Consultant Neurologist) 31.05.17** What are the main guidelines used in the UK relevant to the diagnosis of diabetic peripheral neuropathy (DPN)? Do these align with the clinical pathway for diagnosis of DPN? *Its a clinical diagnosis, based on history and examination.* 2. What are the standard peripheral neuropathy screening tests in the UK? In which settings are these carried out? Is practice standardised or is there local variation in the UK? What about non-UK countries? *I suspect there is regional variation, perhaps between specialties. For example, diabetologists, who often diagnose diabetic neuropathy may do things differently to neurologists, but I don't know; I can only speak for neurologists to say there is no rule book. Nerve conduction studies are useful for diagnosis, but may not be required in straightforward cases of diabetic neuropathy on clinical assessment.*

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	3. Does diabetic peripheral neuropathy always lead to sudomotor dysfunction? How does DPN relate to diabetic autonomic neuropathy (DAN) – is DPN as subcategory of DAN? 4. How would the Neuropad fit into the current pathway in different settings? 5. If a patient is diagnosed with DPN, will they continue to be screened? 6. Is it possible that a patient has DPN detected on one occasion and not another? If this does happen, how is it communicated to a patient? 7. What are confounding factors that may affect results of the Neuropad test? E.g. different patient characteristics, testing environment, room temperature, positioning on foot, left vs right foot. 8. Would you regard the Neuropad as suitable or useful for home use by the patient or carer and why? 9. Reliability of the Neuropad: the objectivity of the test is a key benefit cited by the manufacturer, however can you explain the possible influence of subjective interpretation?	3. Does diabetic peripheral neuropathy always lead to sudomotor dysfunction? How does DPN relate to diabetic autonomic neuropathy (DAN) – is DPN as subcategory of DAN? *No! DAN is a subcategory of DPN. Autonomic involvement is usually present in DPN to a variable extent, and sometime it may be the dominant problem, where it could be labelled as DAN.* 4. How would the Neuropad fit into the current pathway in different settings? *It may help with small fibre neuropathy, where signs and neurophysiology may not confirm a problem. Not all cases would need this however as many can be diagnosed confidently with small fibre neuropathy on history alone. I am not too sure that screening would be worthwhile as not much can be done about it beyond ensuring good diabetic control.* 5. If a patient is diagnosed with DPN, will they continue to be screened? *No.* 6. Is it possible that a patient has DPN detected on one occasion and not another? If this does happen, how is it communicated to a patient? *Nerve tests may give ambiguous results and clinical assessment most useful.* 7. What are confounding factors that may affect results of the Neuropad test? E.g. different patient characteristics, testing environment, room temperature, positioning on foot, left vs right foot. *I would need to revise original information provided and my reply to answer this.*

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	10. Would the Neuropad assess problems with large fibre neuropathy? Presumably small fibre neuropathy always precedes large fibre neuropathy. 11. Is a person diagnosed as prediabetic impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) considered to be diabetic?	8. Would you regard the Neuropad as suitable or useful for home use by the patient or carer and why? *I cannot see why it would be useful to have in the home.* 9. Reliability of the Neuropad: the objectivity of the test is a key benefit cited by the manufacturer, however can you explain the possible influence of subjective interpretation? *I would need to revise original information provided and my reply to answer this.* 10. Would the Neuropad assess problems with large fibre neuropathy? Presumably small fibre neuropathy always precedes large fibre neuropathy. *Small fibre involvement is common with large fibre neuropathy (and is reflected most accurately by the degree of distal burning pain patients report), but small fibre neuropathy can occur in isolation, or as a prelude to large fibre neuropathy. We have nerve conduction studies to assist in large fibre neuropathies but we lack objective tests for small fibre neuropathy. This is not always needed in straightforward cases, as many diabetic neuropathies are, but could be very useful for unusual cases in the neurology clinic, assuming it were validated.* 11. Is a person diagnosed as prediabetic impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) considered to be diabetic? *No.*
Clinical section		**Response from Antonin Gechev (Consultant Neurologist) 05.06.17** 1. What are the main guidelines used in the UK relevant to the diagnosis of diabetic peripheral neuropathy (DPN)? Do these align with the clinical pathway for diagnosis of DPN? **Answer:**

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		British Society for Clinical Neurophysiology: *Guidelines: Generalised Peripheral Neuropathy* *These guidelines are widely accepted for the Neurophysiology Departments in UK.* *I am not sure about current published UK Neurology Association guidelines of DPN.* 2. What are the standard peripheral neuropathy screening tests in the UK? In which settings are these carried out? Is practice standardised or is there local variation in the UK? What about non-UK countries? **Answer:** *Clinical:* *- Neurological Exam* *- Monofilament test (SWMT)* *- 128 Hz standard tuning fork* *Instrumental:* *Neurophysiology assessment* *Routine: NCS; EMG; Sympathetic Skin Response; Quantitative Sensory Test (QST); Research: Contact Heat Evoked Potential; Small fibre near nerve stimulation* *New: Vibratip* *According to my experience the routine UK clinical practice is standardised.* 3. Does diabetic peripheral neuropathy always lead to sudomotor dysfunction? How does DPN relate to diabetic autonomic neuropathy (DAN) – is DPN as subcategory of DAN? **Answer:** *Large fibre Diabetic Peripheral Neuropathy and Diabetic Autonomic Neuropathy affect different organs and systems and have different relationship to the increased risk of subsequent complications. DPN is not a subcategory of DAN.*

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		4. How would the Neuropad fit into the current pathway in different settings? **Answer:** *Neuropad could be used in Endocrinology; Neurology; Neurophysiology and Rehabilitation Clinics when an autonomic dysfunction is clinically suspected.* 5. If a patient is diagnosed with DPN, will they continue to be screened? **Answer:** *This would depend on the clinical course of the disease. It is a deteriorating condition and needs to be monitored.* 6. Is it possible that a patient has DPN detected on one occasion and not another? I f this does happen, how is it communicated to a patient? **Answer:** *DPN is a multifactorial condition and presents in different forms; degrees and patterns. The clinicians are aware of that and could communicate the individual situations to the patient.* 7. What are confounding factors that may affect results of the Neuropad test? E.g. different patient characteristics, testing environment, room temperature, positioning on foot, left vs right foot. **Answer:** *This concerns the standardisation of the technique. If we have a control measurement for example palm/hand at the same time as foot assessment that might decrease the variation for the same patient.* 8. Would you regard the Neuropad as suitable or useful for home use by the patient or carer and why? **Answer:** *Neuropad would be safe and suitable for home use by the patient or perhaps better from the carer if measurement is performed according to the instructions. Of course it would be difficult to verify and*

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		standardise all conditions. 9. Reliability of the Neuropad: the objectivity of the test is a key benefit cited by the manufacturer, however can you explain the possible influence of subjective interpretation **Answer:** *Since the assessment is based upon color changes of the pad, impairment of examiner's color vision could have some impact* 10. Would the Neuropad assess problems with large fibre neuropathy? Presumably small fibre neuropathy always precedes large fibre neuropathy. **Answer:** *Neuropatd could not be used as a sensitive study of large fibre peripheral neuropathy.* *Small fibre peripheral neuropathy could precede large fibre peripheral neuropathy and vice versa.* 11. Is a person diagnosed as prediabetic impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) considered to be diabetic? **Answer:** *The World Health Organisation recognizes Pre-diabetes as not a clinical term. The American Diabetes Association has set a level for pre-diabetes as blood glucose measurements of HbA1C 5.7% (39 mmol/mol). I am not aware of UK defined criteria for pre-diabetes.*
Clinical section		**Notes from phone call with Prof Solomon Tesfaye (Consultant Physician and Honorary Professor of Diabetic Medicine) 30.05.2017**

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		1. What are the main guidelines used in the UK relevant to the diagnosis of diabetic peripheral neuropathy (DPN)? Do these align with the clinical pathway for diagnosis of DPN? Shoes and socks removed first – normal practice. Standard tests are monofilament, pulses and circulation examination. The nerve and neuro examination using bed side instruments incl. monofilament. Press for one sec with monofilament, ask 'can you feel this?' with patients eyes close. If they feel can feel it, no NP. Flawed due to subjectivity. Reliant on patient being unimpaired, concerns for use in elderly or those with Alzheimer's. Maybe tuning fork for vibration as well as monofilament. Also circulation tests. Way to diagnose NP. Flawed – diagnoses at a time when it is irreversible, already have foot ulcers. Standard tests detect the disease very late, when it is already not reversible. Advanced NP. Good detector for high risk of foot ulceration, not good for use at early stages of progression. Healthcare professionals will do the tests differently. Normally done by non-expert nurses with no specific training, not trained to do specific neurological examinations. Already burdened. Ideally this should be done by a trained podiatrist. At his hospital in Sheffield, patients attending a diabetic eye test also get foot tests for earlier diagnosis. Combined eye, kidney and foot test would be best practice for early detection. 20 locations in Sheffield do this in primary care. All patients come for eye screening 95% attendance. Fewer attend for foot, so this strategy increases uptake for foot tests. Amputations are on the rise. 2. What are the standard peripheral neuropathy screening tests in the UK? In which settings are these carried out? Is practice standardised or is there local variation in the UK? What about non-UK countries? Monofilament (sometimes tuning fork) – primary care.

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		3. Does diabetic peripheral neuropathy always lead to sudomotor dysfunction? How does DPN relate to diabetic autonomic neuropathy (DAN) – is DPN as subcategory of DAN? Diabetic NP as a whole is not one entity. There are two groups. Focal NP – affects one side/area of the body. DFU, thigh amyotrophy, one eye closing. Carpal tunnel syndrome. Symmetrical NP. Affect both sides, eg both hands. Also called Distal symmetrical NP or DPN. This is more common! Affects nerve endings in feet and legs first, then hands later. Onset is related to cardiac NP. If there is DPN, then there will be cardiac NP as well. Focal is not related to cardiac. US diabetic society – Guidance states all T2 patients should have a foot and cardiac screening every year. For T1, every year after the first 5yrs from diagnosis. This does not happen in the UK. 4. How would the Neuropad fit into the current pathway in different settings? If there is a partial colour change or no colour change then more testing is required – such as monofilament or tuning fork. Full colour change then no further testing for another year, then repeat Neuropad. Use by patient in home – patients that do not/cannot attend surgery or are in care homes or have no tests done, these can have neuropad sent to them on an annual basis with instructions for use. If normal, no further tests needed that year. Abnormal, then they will need to attend an outpatient's clinic. Outpatient –don't need neuropad, standard tests are proficient – monofilament, tuning fork, foot pulse. These are prompted within GP IT system (SystmOne). If the above is not completed, neuropad could be used to assess (eg in a care home) so that they are not disadvantaged by not attending.

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		Currently, it appears neuropad will be used when a patient requests it themselves or goes to a pharmacy etc. to obtain neuropad. Whereas, it should be the responsibility of the GP, not the patient – who is unaware of such options. Neuropad should be part of the drop down of tests available. If others are completed, then it is not necessary. However, if they are not completed, the GP should consider neuropad being sent to the patient for self-testing in the home. Giving the patient choice of treatment and convenience. 5. If a patient is diagnosed with DPN, will they continue to be screened? Retested annually 6. Is it possible that a patient has DPN detected on one occasion and not another? If this does happen, how is it communicated to a patient? 7. What are confounding factors that may affect results of the Neuropad test? E.g. different patient characteristics, testing environment, room temperature, positioning on foot, left vs right foot. Callused feet affects result? Yes, it would. Must apply to place with no callus. This is mentioned in the instructions. Same as monofilament – not on callus. 8. Would you regard the Neuropad as suitable or useful for home use by the patient or carer and why? Untrained testing at home – As long as instructions are followed (shoes and socks off 10mins before..) then temp and other factors will not significantly influence the outcome of the test. As long as patient follows instructions, it is fine. This assumes the patient can read and is compos mentis. 9. Reliability of the Neuropad: the objectivity of the test is a key benefit cited by the manufacturer, however can you explain the possible influence of subjective interpretation?

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		10. Would the Neuropad assess problems with large fibre neuropathy? Presumably small fibre neuropathy always precedes large fibre neuropathy. Large and small fibre np sometimes develop at the same time. Sometimes small is first. Recent study from Germany showed that they do develop around the same time. Neuropad will not be the gold standard, it should be used as a fail-safe. Vulnerable people will end up having ulceration, amputations if no fail-safe is available to patients. Therefore neuropad prevents things from getting worse. In 1-3 years' time, point of care devices will prevent more negative outcomes. Diabetes is no longer the main cause of working age blindness. Effect of amputations on patients is devastating physically and emotionally. Earning capacity decreases and people tend to die within 2 years of receiving an amputation. The cost of an amputation is around £40,000, far higher than costs associated with early diagnosis. Need more handheld diagnostics done by a trained podiatrist to prevent amputations. 11. Is a person diagnosed as prediabetic impaired glucose tolerance (IGT), or impaired fasting glucose (IFG) considered to be diabetic? IGT and IFG are classed as prediabetic; a fasting blood glucose 7-11. This is not diabetes. Below 7 is diabetic. Cut-off for diabetes is when a patient will develop eye disease. Neuropathy precedes retinopathy, therefore NP can occur in prediabetes. Dictating a necessity for earlier testing. However, clinically checks for np in prediabetics does not occur. In the future, it is likely prediabetics will be tested for signs of NP. This is because NP is not just caused by an inability to control blood glucose, but also due to effects of high blood pressure, cholesterol and obesity which are all independent factors causing NP in diabetes/prediabetes.

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Clinical and economic sections	**Additional questions to expert advisers – 07.06.17** 1. We are assuming that people who already have foot ulceration are presumed to have peripheral neuropathy – is this correct? If people already had ulceration our assumption is that they would be automatically placed under more intense management where screening tests like the Neuropad (or monofilament) would not be used – is this also correct? 2. Would BMI or the presence of peripheral arterial occlusive disease have a significant direct impact on DPN results? 3. Many studies we are finding assess the Neuropad against a reference standard of the Neuropathy Disability Score – when/where would the NDS be typically used? 4. For the 10g monofilament – how many uses can you get per monofilament? How often does it need to be rested? 5. If the screening test indicates an abnormal result (either true or false positive), what would be the next step in the care pathway?	**Response from James Holt 10.06.17** 1. We are assuming that people who already have foot ulceration are presumed to have peripheral neuropathy – is this correct? Not necessarily, they may have foot ulceration due to peripheral vascular disease, also common in diabetic patients. Often they have a mix of neuropathy and vascular disease when there is foot ulceration. Foot ulceration is uncommon in neuropathy without concurrent vascular disease, but often occurs in vascular disease without neuropathy If people already had ulceration our assumption is that they would be automatically placed under more intense management where screening tests like the Neuropad (or monofilament) would not be used – is this also correct? If they have foot ulceration due to vascular disease then this may compromise Neuropad testing and I do not think this or any other testing of nerves with tests would be appropriate in that circumstance. 2. Would BMI or the presence of peripheral arterial occlusive disease have a significant direct impact on DPN results? I don't understand this question, if it is about whether Neuropad results may be affected by vascular disease or obesity then I would have thought they could be, though I would need to revise how the device works. 3. Many studies we are finding assess the Neuropad against a reference standard of the Neuropathy Disability Score – when/where would the NDS be typically used? Neurologists don't use this I have no experience of it. 4. For the 10g monofilament – how many uses can you get per monofilament? How often does it need to be rested? Neurologists don't use this I have no experience of it. 5. If the screening test indicates an abnormal result (either true or false positive), what would be the next step in the care pathway? What screening test, do you mean using the Neuropad or clinical examination? I presume they would then provide advice, but best to ask a diabetologist wha they do. 6. If the screening test indicates a normal result (either true or false negative), would the patient carry on with routine management such as annual foot checks? Yes.

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	6. If the screening test indicates a normal result (either true or false negative), would the patient carry on with routine management such as annual foot checks? 7. Do clinicians have any way of telling if the test result is potentially a false one (positive or negative) e.g. would contextual factors such as history be considered as an indication of whether the result is accurate and potentially overrule the screening test? 8. Is the 10g Monofilament or 128hz tuning fork more likely to be used as a screening test? If both are used, what would be the usual test order? If the Neuropad is included and results are abnormal would there be a monofilament test following Neuropad, and then followed by a tuning fork?	7. Do clinicians have any way of telling if the test result is potentially a false one (positive or negative) e.g. would contextual factors such as history be considered as an indication of whether the result is accurate and potentially overrule the screening test? Examination supports history, which is nearly always more important. 8. Is the 10g Monofilament or 128hz tuning fork more likely to be used as a screening test? If both are used, what would be the usual test order? If the Neuropad is included and results are abnormal would there be a monofilament test following Neuropad, and then followed by a tuning fork? Neurologist don't use monofilaments. We do use pins (Neurotips), but vibration testing with a 128 Hz tuning fork is more sensitive for detecting neuropathy.
Clinical and economic sections		**Response from Antonin Gechev – 12.06.17** We are assuming that people who already have foot ulceration are presumed to have peripheral neuropathy – is this correct? If people already had ulceration our assumption is that they would be automatically placed under more intense management where screening tests like the Neuropad (or monofilament) would not be used – is this also correct? **Answers:** *People who have foot ulcerations might also preset with peripheral neuropathy, but it would not be always the case. I could not give you precise evidence at the moment, but in this scenario the distal lower*

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		limb peripheral nerves might be affected by the local trophic factors, not necessary as a part of more widespread neuropathy. Monofilament or Neuropad would be difficult to use in this cases. 2. Would BMI or the presence of peripheral arterial occlusive disease have a significant direct impact on DPN results? **Answer:** *Body Mass Index (BMI) would have impact on some instrumental DPN results such as Nerve Conduction Studies.* *Peripheral arterial occlusive disease as a macro-angiopathy should not have direct impact on DPN results on the basis of its pathophysiology. Of course in advanced cases local trophyc factors could have some impact.* 3. Many studies we are finding assess the Neuropad against a reference standard of the Neuropathy Disability Score – when/where would the NDS be typically used? **Answer:** *Neuropathy Disability Score could be retrieved form the Clinical Neurological Examination. Technically it could be used every time a neurological examination is performed.* 4. For the 10g monofilament – how many uses can you get per monofilament? How often does it need to be rested? **Answer:** *Perhaps this depends on the manufacturer. Usually Monofilament should not be used to test more than 10 patients in one session and should be left to "rest" at least 24 hours.* 5. If the screening test indicates an abnormal result (either true or false positive), what would be the next step in the care pathway?

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		Answer: *As a Clinical Neurophysiologist I could not give precise details on the clinical care pathway in this situation* 6. If the screening test indicates a normal result (either true or false negative), would the patient carry on with routine management such as annual foot checks? **Answer:** *Similarly to the previous question as a Clinical Neurophysiologist I could not give precise answer.* 7. Do clinicians have any way of telling if the test result is potentially a false one (positive or negative) e.g. would contextual factors such as history be considered as an indication of whether the result is accurate and potentially overrule the screening test? **Answer:** *All instrumental tests results should be put in the clinical context despite their indication of accuracy. Whether a test result is potentially false (positive or negative) depends on the given "gold" standard to which it is compared against.* 8. Is the 10g Monofilament or 128hz tuning fork more likely to be used as a screening test? If both are used, what would be the usual test order? If the Neuropad is included and results are abnormal would there be a monofilament test following Neuropad, and then followed by a tuning fork? **Answer:** *As part of the routine neurological examination 10g Monofilament and 128 Hz Tuning fork could be used as screening test. Usually light touch assessment (monofilament test) is used before the vibratory sensitivity assessment (tuning fork). If the Neuropad is included in the examination I think*

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		it should be after the first two. It give us information abut different nerve fibres type involved in comparison with Monofilament and Tuning fork.
Economic section	**Additional questions to manufacturer – 07.06.17** 1. No search strategy or results are provided for Section C (8. Existing economic evaluations). Was any search done (for instance PUBMED) to arrive at the conclusion that there was no economic evidence for Neuropad ? If so, could the sponsor share the search strategy? 2. The model has a time horizon of 3 years? The justification provided is that Neuropad has a shelf life of 3 years. However, the shelf life of the product has no implication for the disease progression in the model. Is there any other reason for the time horizon of 3 years? 3. Transition probabilities have been taken from 2 papers (Ortegon 2004) and Ragnarson (2001). How did the sponsor arrive at the conclusion that	**Response from manufacturer – 08.06.17** I have some positive news concerning the Sanz-Corbalan study/poster (P53) first presented at the EASD foot care study group last year. It has now been confirmed to us that the study is being submitted for publication and is being peer-reviewed currently. Please see below for the correspondence between the various parties and please also feel free to contact Professor Martinez (head of the diabetic foot unit at Complutense University of Madrid) directly if you need any further confirmation. I hope this is of assistance. In the meantime, we are just double-checking the answers that we have compiled to KiTEC's questions concerning our de novo healthcare economic model and this will be with you shortly. We have also sought further expert opinion from Professor Alan Sinclair. **Response from manufacturer – 08.06.17** 1. No search strategy or results are provided for Section C (8. Existing economic evaluations). Was any search done (for instance PUBMED) to arrive at the conclusion that there was no economic evidence for Neuropad ? If so, could the sponsor share the search strategy? There are no economic studies analysing the cost-effectiveness of Neuropad, which we were already aware of, and we confirmed so by doing a literature search. We used EconLit, Medline and Google Scholar to run such review on economic analysis of Neuropad. The key words that we used were "Neuropad", "costs", "costs analysis", "economic analysis", "economic consequences" and "cost-effectiveness analysis"

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	these are the best possible evidence for transition probabilities? Did the sponsor systematically search for all evidence? If so, can the search strategy be shared with the EAC? 4. Both Ortegon 2004) and Ragnarson (2001) have transition probabilities available for death state too. Why did the sponsor not include 'death' state in the model? The sponsor does allude to diabetic neuropathy leading to death in the long run (section 9.1.2)? How does the sponsor define 'long run' and on what basis? 5. The model appears to assume that all patients who test positive for neuropathy have the same risk of foot ulceration regardless of whether the test result is a true or false positive. Is this correct? 6. The positive predictive value of Neuropad and SWME is calculated but does not appear to be applied in the model. Is this the case?	2. The model has a time horizon of 3 years? The justification provided is that Neuropad has a shelf life of 3 years. However, the shelf life of the product has no implication for the disease progression in the model. Is there any other reason for the time horizon of 3 years? One of the papers used in the report, the one by Green and Taylor (2016), aimed to assess the cost-effectiveness of a device to control insulin regimen in people at high risk of diabetic foot problems. It is the most recent paper that has been found aiming to assess the cost-effectiveness of an intervention (medical device, screening test, etc.) for diabetic neuropathy. They also used a time horizon of 3 years in their Markov model. 3. Transition probabilities have been taken from 2 papers (Ortegon 2004) and Ragnarson (2001). How did the sponsor arrive at the conclusion that these are the best possible evidence for transition probabilities? Did the sponsor systematically search for all evidence? If so, can the search strategy be shared with the EAC? Ragnarson (2001) transition probabilities were used in the paper by Ortegon (2004), who updated some of them. Those were the only ones found in the literature that clearly reported transition probabilities between the health states considered in our Markov model. The literature search conducted was through Medline, EconLit and Google Scholar. Instead of running the literature search focusing only on Neuropad economic evidence, we searched for any economic analysis on any diabetic neuropathy intervention. The key words that we used were "diabetic neuropathy", "diabetic foot", "costs", "costs analysis", "economic analysis", "economic consequences" and "cost-effectiveness analysis" 4. Both Ortegon 2004) and Ragnarson (2001) have transition probabilities available for death state too. Why did the sponsor not include 'death' state in the model? The sponsor does allude to diabetic neuropathy leading to death in the long run (section 9.1.2)? How does the sponsor define 'long run' and on what basis?

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	7. A transition probability from no neuropathy to infected foot ulcer is calculated but does not appear to be applied in the model. Further, the model appears to assume that patients testing negative for neuropathy do not get a foot ulcer regardless of whether the result is a true or false negative? Is this correct? 8. How is the cost of infected ulcer derived (£11,848.07)? Does this cost include inpatient care as well as primary and community care? Does the sponsor assume that every infected foot will require hospitalization?	Following the assumption made by Green and Taylor (2016), we assume that there is no discernible difference between tests with regards to risk of death. Mortality could then be neglected within the 3-year time period. 5. The model appears to assume that all patients who test positive for neuropathy have the same risk of foot ulceration regardless of whether the test result is a true or false positive. Is this correct? It is indeed correct. We took into account the possible progression of the disease applying the transition probabilities and the joint probability of Neuropad for getting a positive result, regardless of whether it is a true or false positive. 6. The positive predictive value of Neuropad and SWME is calculated but does not appear to be applied in the model. Is this the case? In the economic model, we considered the possible pathways of the disease along the life cycle and the joint probability of Neuropad and SWME for getting a positive result, regardless of whether it is a true or false positive, which refer to the predictive probabilities of each diagnostic test. 7. A transition probability from no neuropathy to infected foot ulcer is calculated but does not appear to be applied in the model. Further, the model appears to assume that patients testing negative for neuropathy do not get a foot ulcer regardless of whether the result is a true or false negative? Is this correct? It is correct. As we take into account the joint probabilities of Neuropad and SWME, we assume that, once a negative result is obtained, the individual is healthy (no neuropathy) and will remain in the same health state during the rest of the time horizon of the model. As it has been stated in the assumptions, Neuropad and SWME will only be used in the first cycle of the model. Hence, if the person does not get a positive result in the first cycle, no test will be taken during the 3-year time model horizon and s/he will have no neuropathy during that period.

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		8. How is the cost of infected ulcer derived (£11,848.07)? Does this cost include inpatient care as well as primary and community care? Does the sponsor assume that every infected foot will require hospitalization? The cost of infected foot ulcer is taken from the report on the economic impact of diabetic foot care in England, taking into account both primary and community care (£8,620.8) and inpatient care (£8,620.8). It might not be the case that every patient receives both types of care, but, since we do not have data on that information, we assume the worst-case scenario. However, as the sensitivity analysis shows, when costs of infected foot ulcer are diminished, Neuropad would still be the optimal test for diabetic neuropathy.
Economic section	**E-mail sent to manufacturer 15.06.17** 1. Would you confirm that the Neuropad test is currently indicated for use as an adjunctive test with sensation tests, primarily the monofilament, in primary care or home settings as part of the diagnostic process? Our assumption is that it will not routinely be used in secondary care in conjunction with neuropathy scoring systems or specialist neuropathy tests (which are more confirmatory tests) – is this correct? 2. The submission states that "Tests could be provided easily and cheaply through direct patient contact via GP practices requesting that patients	**Response from manufacturer 15.06.17** 1. Would you confirm that the Neuropad test is currently indicated for use as an adjunctive test with sensation tests, primarily the monofilament, in primary care or home settings as part of the diagnostic process? Our assumption is that it will not routinely be used in secondary care in conjunction with neuropathy scoring systems or specialist neuropathy tests (which are more confirmatory tests) – is this correct? Yes, this is correct. Neuropad may be used in a specialist secondary care setting to confirm an earlier positive Neuropad test though its high reproducibility (~100%) would make the need for re-testing with a Neuropad unlikely. Confirmation is more likely with IENFD which requires biopsy and specialist interpretation. Furthermore, Neuropad can also be deployed on frail elderly patients who cannot respond to SWME testing due to cognitive or other impairment. Neuropad is a categorical test and does not require a patient response; SWME is a subjective test and requires a patient response.

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	either collect a Neuropad test pack from the GP practice where they are registered as a patient or take an official letter along to a community (high street or local) pharmacist to collect a test pack." Would the provision of the Neuropad be prompted by the GP or other healthcare professional? Or would the patient ask for the Neuropad test? In the latter situation, what would be the trigger for this?	2. The submission states that "Tests could be provided easily and cheaply through direct patient contact via GP practices requesting that patients either collect a Neuropad test pack from the GP practice where they are registered as a patient or take an official letter along to a community (high street or local) pharmacist to collect a test pack." Would the provision of the Neuropad be prompted by the GP or other healthcare professional? Or would the patient ask for the Neuropad test? In the latter situation, what would be the trigger for this? We do not believe that patients should have to request a Neuropad test, which would be a reactive way of deploying it and not very productive in terms of identifying patients at future risk of ulceration. Neuropad has been designed principally but not exclusively for self-testing at home. The triggers would be (a) as part of the annual diabetes foot test as specified in NG19, as a routine adjunct to SWME with the Neuropad test being provided to all diabetes patients before they attend for an annual foot test bringing their results along with them and (b) speculatively in newly diagnosed patients or those patients with diabetes that a HCP may have specific concerns about for reasons such as overall poor glycaemic control. A key additional important issue is reaching the 400,000 or so people with diabetes in England who do not have an annual foot test and don't attend when requested to do so for whatever reason. This potentially high-risk cohort of patients could be more easily reached we believe if they are either sent a Neuropad test pack as part of e.g. a CCG or STG initiative or they are provided with a letter from their registered GP practice requesting that they pick a test up from their local community pharmacy, take the rest and return the result card to their GP or even community pharmacist who would then forward the result to the relevant GP surgery. Those at greatest risk can then be followed up and triaged. Currently, these patients are not being reached by conventional means.
Economic section	**E-mail send to expert advisors 23.06.17** We currently understand that if the monofilament and Neuropad are carried out in	**Reply from Antonin Gechev 28.06.17** Since I am not directly involved in patients' treatment process, the answer might not be complete:

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	primary care and the patient is deemed to have moderate to advanced neuropathy, the patient will be referred on to a foot protection service. Once the patient is referred, is a confirmatory test for neuropathy then carried out? If so what test would this typically be?	Usually we receive neurophysiology assessment referrals for that group of patients either from Neurologists or Endocrinologists. I am not sure if podiatrist could refer patients directly for neurophysiology studies. Since neither Mono-filament nor Neuropad could assess motor nerve functions a routine Nerve Condition studies (NCS) and/or Electromyography would be necessary to verify and scale the degree of large fibre peripheral neuropathy.
Economic section		**Reply from James Holt 28.06.17** NeuroPad could be used to help decide who might benefit from a foot care service if there was evidence it was better than clinical assessment (which may include monofilament testing) alone. Nerve conduction studies would be the 'confirmatory test', but I do not think this would be necessary in straightforward length-dependent diabetic polyneuropathy.

Appendix 1

Minutes of teleconference with sponsor 15.05.17:

MT318 Neuropad_sponsor

Appendix 2 [Insert additional appendices as required]

Attachments received in e-mail from sponsor dated 15.10.15:

EU MEDDEV 2.12-1 rev 08 140408 dr.pdf

Faerman I et al 1982.pdf

Malik RA et al 2005.pdf

Manufacturer QC 710 AA Meldung vor

Neuropad - Prescriber article - n

Hoeldtke RD et al 2001.pdf

Malik RA et al 2011.pdf

MPSV 170512 dr.pdf

Quattrini C et al 2004.pdf

Sanofi Bestätigung April AEs.pdf

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre report factual check

MT318 Neuropad test for the early detection of diabetic foot neuropathy

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from KiTEC to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **17th July 2017** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

[10 July 2017]

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The following sentence from the Conclusion of the EAC report (page 117) is an excellent summary of the rationale for Neuropad. "The Neuropad assesses sudomotor dysfunction, which may be the earliest manifestation of small fibre neuropathy. Theoretically, this indicates that the Neuropad may be able to detect neuropathy at an earlier stage than the monofilament." Furthermore, on page 120 of the report, the Conclusion continues in the same positive vein: "Experts noted that the Neuropad could be useful if used for annual foot checks in the home setting with people who could not attend clinic or with people with cognitive or communication impairments – if the results were normal (indicating no DPN), then no further tests would be required that year. Unfortunately, the impact of this further excellent summary statement is immediately negated by the following text: "However, the Neuropad is currently used as an adjunctive screening test and current guidance notes the annual foot check requirement with the use of a monofilament, therefore the monofilament would not be	We request that the following text is removed from the report as it is incorrect: "However, the Neuropad is currently used as an adjunctive screening test and current guidance notes the annual foot check requirement with the use of a 10g monofilament, therefore the monofilament would not be replaced on this basis." In addition, there are a further 6 incorrect uses of the word 'adjunctive' with reference to the Neuropad test. For the avoidance of any further confusion, what is important is that Neuropad is not intended as a replacement for the monofilament. It can either be used as a stand-alone test or as an additional test to go alongside the monofilament. We request that these comparisons be removed as they are not relevant.	Factually incorrect. Requires rectification. Not relevant.	*The NICE briefing note and published final scope describe the Neuropad as an adjunctive test "Neuropad is intended to be used in conjunction with standard neuropathy tests, such as the 10g monofilament to improve the detection of diabetic foot neuropathy". In the sponsor submission the intended use was unclear, therefore further clarification was sought from the sponsor, including the following question: "Would you confirm that the Neuropad test is currently indicated for use as an adjunctive test with sensation tests, primarily the monofilament, in primary care or home settings as part of the diagnostic process?" The sponsor stated that this assumption was correct.* *As the sponsor is now more clearly stating that Neuropad is also intended as a standalone test, there is still the issue of what would be done on the basis of the result. There is a paucity of evidence for assessing and managing early DPN. The decision point to refer for further care after screening is currently based, in part, on the monofilament result. In addition, there is a lack of evidence for Neuropad's effectiveness on patient-important outcomes and cost-*

replaced on this basis." This latter statement is completely incorrect and represents a fundamental error of fact that may have been caused by the EAC's misinterpretation of previous answers to questions raised of the sponsor. For absolute clarity, Neuropad is intended either as stand-alone test or in combination with monofilament testing as it is complementary and the sponsor has most certainly not proposed Neuropad as a replacement a replacement for the monofilament or any other test for DPN in the primary care setting. Its whole rationale is based on its ease of use in the home by the patient or their carer, its categorical and objective results, its low cost, and, most importantly as noted, the potential for early diagnosis. Much of the report dwells on comparisons between Neuropad and other tests for sudomotor dysfunction. This is irrelevant as Neuropad is not intended as a replacement for any other tests. It should be viewed solely as a low cost, early warning, self-administered, objective test for the home setting. As such, it is a unique device with the potential to reach currently disenfranchised patients who do not have an annual diabetes foot check.			*effectiveness of implementation in the diagnostic pathway compared with the standard clinical examination. The EAC is not making a judgement of the adequacy of current guidance, but making an objective observation about gaps in the pathway and also gaps in the evidence to support pathway changes.* *Based on the recent clarification from the manufacturer, references to replacing the monofilament have either been amended or removed (please see the following pages in the revised report: 11, 15, 16, 17-20). Due to the lack of evidence and guidance in key areas (such as effectiveness in home care settings and in certain patient subgroups) and on early DPN assessment and management there is still uncertainty about the impact of the Neuropad result in these situations.* *The EAC notes that contrary to the response from the sponsor that "the sponsor has most certainly not proposed Neuropad as a replacement for the monofilament or any other test for DPN in the primary care setting", the sponsor implies that "128MHz tuning fork and other vibration perception tests may no longer be required as these devices also help identify patients with sensory deficits which may be carried out using the standard 10g*

			monofilament test." (section 3.7 of sponsor's submission, and page 19 of EAC AR).
On page 120 of the EAC report it states: "The sponsor claims that Neuropad may also be particularly useful in patients with communication or language difficulties who may not respond accurately to tests such as monofilament", however, no clear evidence was found to support the claim for benefits in this subgroup."	We feel that the final sentence comprising the words: "however, no clear evidence was found to support the claim for benefits in this subgroup." is an unnecessary addition.	Neuropad provides a visual (colour change) result with no requirement for any verbal communication. Thus any language or communication difficulties are irrelevant. The test could be carried out perfectly well on a blind, deaf, dumb, demented, or non-English speaking patient. This is obvious and hardly needs supporting evidence.	The EAC did not find evidence of the performance of Neuropad in these populations. The EAC can only comment on the evidence presented. As noted, the EAC has speculated that these populations may benefit, but cannot draw firm conclusions without supporting evidence. Evidence in these populations would be particularly helpful to support the sponsor's claims, that these are key populations that may benefit. As it stands there is a lack of evidence for patient outcomes and cost effectiveness (the EAC is clearly not equating this to evidence of no benefit or disbenefit).
On pages 120-121 the report states that "The manufacturer claimed that the Neuropad is a "non-subjective test". One study assessed the reliability of the Neuropad, finding that there was a "very good" overall agreement between the patient and the heathcare professional. Though the study supports the sponsor's claims, the EAC notes that this is limited evidence." It is not factual to claim that a study provides 'limited evidence' as this is merely an opinion and has not been substantiated.	We request that the following sentence be replaced with the alternative immediately following below: "Though the study supports the sponsor's claims, the EAC notes that this is limited evidence." Replacement sentence: "One study assessed the reliability of the Neuropad, finding that there was a "very good" overall agreement between the patient and the healthcare professional. The study appears to support the sponsor's claims."	It is clear that Neuropad, which displays its results as a colour change, is objective and not subjective since no opinion has to be given – the colour has either changed or it has not. Yes, there was only one study which confirmed this but there were none that did not confirm it so there is no need to add the 'spoiler' comment about 'limited evidence'. This is evident from the fact that there was just one study.	The objectivity of the Neuropad is a key benefit claimed by the sponsor. If this is the case it would be helpful to have more evidence to assess the reliability/ inter-observer agreement to validate this claim (and also potentially assessment of external factors that may impact results). The EAC notes that one study found "very good" inter-observer agreement and highlights this and that this was carried out in the home setting, but does mention that more evidence is required to provide stronger support of this claim. The EAC notes there was no power calculation associated with the agreement measure, and

			that 20.5% of patients requested help for self-testing. More evidence may answer questions such as the following: How will patients or carers infer the colour change? Will they relay the right answer back? There is also the recall issue of how patients will recall the results of the test. In addition, one NICE expert mentioned that the assessor's colour vision may impact the result interpretation. Environmental factors may also impact the Neuropad results (Mendivil et al. 2016) (e.g. temperature, humidity), therefore evidence would be useful to assess environmental impacts, particularly if the test is intended to be carried out in non-controlled home settings. The EAC has amended the sentence "One study assessed the reliability of the Neuropad, finding that there was a "very good" overall agreement between the patient and the healthcare professional. Though evidence is limited, the study appears to support the sponsor's claims."
Concerning the de novo economic model, the report states that only the cost and resource consequences need to be modelled. Utilities need not be included to estimate the net benefit. This is justified according to a NICE approach established in 2011	The sponsor believes that when evaluating health technologies, health gains should also be considered and therefore not only the costs. The sponsor has also included health gains derived from each intervention in their analysis, contrary	The EAC report incorrectly states that the sponsor did not include health gains from each intervention when in fact the opposite is the case. We wish to request that this is corrected in the EAC report and that then EAC acknowledges that it did	The EAC has followed the approach based on Medical Technology methods guide – See section 7.3(NICE 2011). To change the NICE approach is not within the remit of the EAC.

for the evaluation of medical technologies.	to what the EAC has reported. Moreover, the EAC mentions in their conclusions that "The no-testing strategy, whilst cheaper than the alternative tests, is likely to deliver inferior outcomes…" It should also be noted that the Neuropad plus monofilament testing saves money by increasing specificity at the slight loss of sensitivity. As such a strategy of 'no testing' may deliver poorer health outcomes than either the Neuropad or monofilament test alone." But the EAC does not provide any estimation on utilities or health gains. Hence, including the analysis of utilities would be appropriate.	not include any estimation on utilities or health gains.	The inclusion of the 'no testing' strategy as a subgroup analysis (not the main analysis) is just to represent a scenario of patients who are routinely not tested. In the report, the EAC has cautioned the interpretation of the results of the no testing strategy, since only costs are modelled.
The EAC considers that the 6-month cost of community & primary care for patients with neuropathy as £1,855, taken from Kerr (2017), is on the high side. They suggest using other estimate of the cost of a foot care (McCabe et al (1998)). After adjusting for current prices, it is £325 over 6 months, which the EAC thinks is more reasonable to be used in the model.	The sponsor believes that even though the 6-month cost of £1,855 is on the high side, it is nevertheless based on reliable and recent data taken from the NHS. The estimate proposed by the EAC, even after adjusting for current prices, comes from an old source.	The EAC has used data older than that used by the sponsor. Out of date data cannot responsibly be substituted with more recent and therefore up to date data. This EAC's data needs to be updated and the report and model amended accordingly.	The estimate (£1855) used by the sponsor is taken from Kerr (2017) who reports a weekly cost of £77 for primary, community and outpatient care for patients who have ulcers with no infection or relatively mild infection. The cost includes dressing, medications and off-loading devices (orthotics). The EAC thinks this estimate is on the high side, since many patients with neuropathy will not have ulcers. The only reliable UK estimate of a diabetic foot programme is McCabe et al (1998). The EAC agrees that it is a limitation to use an older study. However, since the Kerr (2017) estimates are more relevant for people with ulcers with no infection or relatively mild infection, the EAC thinks it does not appropriately represent a diabetic

			foot programme cost. To address the uncertainly, the cost used by the EAC was varied in sensitivity analysis, and it did not alter the cost savings conclusion; Neuropad was not cost saving. Even with the sponsor's estimate used in the EAC model, Neuropad is highly cost incurring.
The EAC calculates the cost of the SWME 10g monofilament tool as £0.80, considering that it would only include the cost per examination and that it could have a useful life of 200 patients.	The sponsor included a cost of £16.80 (the purchaser price to the NHS) for the 10g monofilament instrument according to the NICE briefing note for Neuropad. The consumable costs reach £14.28 plus cleaning for consumables and holder plus trained healthcare professional time to perform test. These costs would me more than the £0.80 stated by the EAC. Moreover, according to the same NICE briefing note, it is unclear how many times a 10g monofilament can be used before a replacement is required.	In an independent UK study by Booth J et al (2000) the authors concluded that longevity and recovery testing suggest that a monofilament will survive usage on 10 patients before needing a recovery time of 24 hours before further use. The sponsor feels that the comparison with monofilament is unfair and unbalanced. (Diabetes Care 23:984–988, 2000). We would like the above to be included in the EAC report as currently the assumption is that 10g monofilament may be more reliable and reproducible than it actually is particular when used in isolation.	The EAC has given more weight to the MTEP evaluation of VibraTip (Willits et al 2015), as it is evidence driven. The EAC would like to highlight that the monofilament needs to be rested (rather than replaced) after every 10 patients. A useful life of 200 tests reported by Willits et al (2015) was the best available estimate of the monofilament lifetime. The EAC varied on the cost of the 10g monofilament in sensitivity analysis and it did not change the cost savings conclusions.
The EAC calculates the cost of Neuropad as £8, including nurse costs and the purchaser price of £7.28	Neuropad requires minimal training as it has been very specifically designed to be capable of self-administration by the patient or even an un-trained assistant in primary care or the community so it does not require highly trained health care professional intervention. The objective of Neuropad is to identify those people at early and elevated risk of developing diabetic	The sponsor believes that the addition of an extra £0.62 to the costs associated with Neuropad testing to be unjustified.	The EAC model is based on the scenario that the Neuropad will be used during the annual diabetic check to reflect practice in UK. So, some time will be required for the application and interpretation, which the EAC estimates to be a minute and hence an extra cost of £0.62. The EAC believes that mailing the test to patients to complete at home prior to their annual check-up is likely

	neuropathy who are not routinely tested for diabetic foot problems. No administration costs should then be included.		to generate distribution costs equivalent or greater than the additional cost of £0.62 estimated for inclusion of the test during the annual diabetic check. The EAC undertook sensitivity analysis on the cost of Neuropad; even after excluding any cost other than an acquisition cost of £7.28, Neuropad is not cost saving compared to monofilament.
The EAC includes "No testing" as one of the strategies included in the analysis.	The sponsor finds the inclusion of a 'No testing' strategy to be unjustified and should not have been included in their analysis. It is obvious that no testing will be less costly than any intervention. However, a strategy of no testing could be included in the analysis but only if health gains were also considered in order to demonstrate that costs would be lower, but of course there would be no health gains and indeed health losses may be possible.	As no health gains were provided in the EAC's healthcare economic model and no health losses the flawed strategy should be removed.	The inclusion of the 'no testing' strategy as a subgroup analysis (not the main analysis) is undertaken to allow comparison of the costs of Neuropad in patients with communication difficulties for whom 10g monofilament would be inappropriate. In the report, the EAC has cautioned the interpretation of the results of the no testing strategy, since only costs are modelled.
In Conclusions. Section 5.1 the EAC report states that "The included evidence does not strongly support the sponsor's claims that Neuropad has been validated against both primary and secondary care tests (section 7.10 of the sponsor submission). Only 2 studies were found that validated the Neuropad against the 10g SWME monofilament. The results were inconclusive (1 study showed higher sensitivity but lower specificity for the	This is not a true reflection of the facts presented in the sponsor's clinical and evidence submission. Significant evidence was presented that Neuropad has been validated against secondary care tests which are superior to the 10g SWME including a 'gold-standard' test for early neuropathy, intraepidermal nerve fibre density (IENFD). The Quattrini (2008) study included investigators at the University of Mancester and involved 57 patients	As 10g SWME monofilament is a sensory test and the sponsor is not advocating its replacement there should be greater emphasis with respect to Neuropad's performance against established and more accurate secondary care tests in the clinical setting. The word 'inconclusive' should be deleted from the EAC's report.	The EAC maintains that the Neuropad has not been assessed in a significant number of studies against primary care comparators or in the home setting which these are the most directly relevant comparators and settings. The results from the two studies comparing Neuropad with monofilament against a reference standard. The EAC has amended the sentence (removing the term "inconclusive" to more clearly reflect

Neuropad and 1 study showed similar accuracies)."	who underwent skin biopsy and IENFD assessment. The sensitivity of an abnormal Neuropad test response in detecting clinical neuropathy (neuropathy disability score ≥5) was 85% (negative predictive value 71%) and the specificity was 45% (positive predictive value 69%). P=0.02. Specialist secondary care tests such as IENFD are clearly superior to monofilament testing which as a recent systematic review (Dros J, 2009) concluded cannot be relied upon alone to diagnose diabetic peripheral neuropathy. (Ann Fam Med 2009;7:555-558. doi:10.1370/afm.1016) Selectively comparing Neuropad with 10g SWME monofilament which may identify innervation of the large nerve fibres which affect mainly sensation is highly questionable when Neuropad testing identifies earlier innervation of small nerve fibres and therefore sudomotoric damage rather than insensation. These two tests measure entirely different things. The sponsor does not understand why the EAC appears to have disregarded important evidence concerning the efficacy of Neuropad testing. The EAC's conclusion that the results were 'inconclusive' is not correct and should properly take into account the comparative studies in secondary care. Indeed, in Section 7 Implications for research, the EAC makes the		that the two studies appear to show Neuropad has a higher sensitivity but lower specificity than the monofilament (difference in the latter appears more pronounced): "studies indicated that overall, the Neuropad has a higher sensitivity but a much lower specificity than the monofilament (one study carried out statistical analysis noting that the difference was not significant for sensitivity but significant for specificity)." The sponsor and EAC note that the meta-analysis was carried out using the NDS (primarily a research tool and commonly used as a reference standard for assessing DPN in the studies retrieved) as reference standard therefore to state that the EAC has disregarded evidence on the efficacy of Neuropad testing against secondary care tests is inaccurate. The lack of validation in primary care tests, the EAC believes, is still true and the sentence has been amended to the following: "The included evidence does not strongly support the sponsor's claims that Neuropad has been validated against primary care tests (section 7.10 of the sponsor submission)." The EAC would note that the results from these secondary tests (as outlined in the sponsor's feedback e.g. sensitivity of 85% and specificity

	statement that 'The review of clinical evidence found adequate evidence of the accuracy of Neuropad against a reference standard (as carried out in secondary and tertiary care settings). This requires clarification and correction as it is on the whole supportive of our clinical submission and therefore a strong affirmative conclusion.		of 45%) tend to indicate a relatively similar sensitivity but lower specificity compared with sensitivity and specificity estimates for monofilament for a UK population available from the MTEP VibraTip evaluation (Willits et al 2015) (84% and 83% respectively).
In the conclusion, the EAC report states that 'The sponsor claims that "as Neuropad may detect neuropathic deficits before monofilament and vibration perception testing, it has potential as a screening test for early neuropathy and referral onward to specialist podiatry care. The sponsor claims that Neuropad may also be particularly useful in patients with communication or language difficulties who may not respond accurately to tests such as monofilament", however, no clear evidence was found to support the claim for benefits in this subgroup."	As the monofilament requires application by a healthcare professional trained in its use and a subjective response by the person being tested it cannot be carried out on people who are unable to respond. On the other hand, it is abundantly clear that the Neuropad test being a simple categorical device involving a simple colour change and not requiring a subjective response provides a very real opportunity to screen patients that are currently not having their feet examined or tested at all because of physical and mental illness including dementia and communication problems such as deafness. The sponsor requests that the words 'however, no clear evidence was found to support the claim for benefits in this subgroup.' should be withdrawn.	The benefits of a categorical and objective test in patients with language or communication difficulties are obvious since there is either a colour change or there is not, and no communication with the patient is necessary.	The EAC understands that this, in theory, is the case but found only one study to support the reliability of the test in a home setting (which did so positively), and no evidence into the use of the Neuropad in the key populations as outlined by the sponsor. The EAC believes this is an objective statement of fact. Nowhere does the EAC state that the Neuropad is unsuitable for the home setting (this is not the same as a lack of evidence). The EAC has, however, now added that, "this in theory is a benefit of the Neuropad, however, no evidence was …." (page 122).
The Neuropad assesses sudomotor dysfunction, which may be the earliest manifestation of small fibre	The advantage of detecting nerve fibre damage early is IMPORTANT – the use of the Neuropad would	We request that the word 'Theoretically' is removed as the remainder of the sentence is already	The EAC has removed the word "theoretically". The EAC understands that these are potential benefits of

neuropathy. Theoretically, this indicates that the Neuropad may be able to detect neuropathy at an earlier stage than the monofilament. It unclear whether the Neuropad will have any impact on treatment or management decisions within current clinical guidelines as action is triggered if moderate or advanced foot risk is identified; if there is no change in action based on the Neuropad result in isolation (normal or abnormal) the benefit of the test is unclear. More evidence is also required on the reliability of the test to adequately conclude that the test is objective enough to be used by carers or patients at home.	increase the momentum for changing clinical guidelines which are not particularly developed or regularly updated – once moderate to severe neuropathy is present (detected only by current screening tests such as the monofilament) , it becomes very difficult to alter the natural history of the condition. This has not been taken into account and requires clarification. The second sentence from the extract quoted in the 'Description' box begins 'Theoretically…' The writers of the document seem determined to qualify many of the good points of Neuropad (see Issue 1 – 'However…'). We feel this qualification is unnecessary and presents an unfair negativity.	sufficiently cautious – '*Neuropad **may** be able to detect…'*	the test, but the aim of the assessment report is, in fact, to qualify these benefits. If there is a paucity of evidence, this has to be highlighted (for example as an area of further research [see section 7 of the report]). As noted, there is currently a paucity information around how DPN assessment is or should be carried out and managed. The EAC notes that NICE NG19 states that "The evidence surrounding different referral criteria for those at risk of, or who have developed diabetic foot problems was limited." Further research is recommended to indicate "When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?" Therefore, if further research indicates that people with earlier stage DPN (irrespective of loss of protective sensation) should be referred, the Neuropad may prove to be of clearer benefit (see also page 16 of the AR). The sponsor notes the importance of early detection, something that is not disputed by the EAC. The EAC notes, however, that in the unpublished Tentolouris et al. study (2017) no significant difference was found in the chance of a shorter ulcer-free interval whether the results of both the NDS and Neuropad were normal (indicating no disease) or the

			NDS was normal and the Neuropad abnormal (indicating early DPN). In addition, the EAC notes that the lack of evidence for changes to the clinical pathway is an issue in section 7 (Implications for research): "Further research may investigate the effectiveness of interventions at early stage foot neuropathy (for example a foot care education programme) to further understand what the benefits of tests into early DPN may be." The EAC has added a sentence to further clarify this point: "More research may be carried out to further develop and update clinical guidelines, in particular to aid diagnosis and management of early DPN."
The EAC report states that 'There was no published economic evidence on Neuropad, and the de novo model submitted by the sponsor had limitations which required rectification. The revised EAC model showed that Neuropad is not a cost saving option compared to other strategies, which is quite contrary to the sponsor's conclusion; i.e Neuropad is the optimal strategy.	The sponsor does not agree that its model is as flawed as the EAC claim and that in addition the EAC's own model has limitations as admitted to in the report, therefore we believe that it is unfair and incorrect of the EAC to dismiss the sponsor's Markov economic model Perhaps, in view of what the sponsor considers to be a controversy rather than as the EAC believes is a statement of fact, the optimal strategy is to combine Neuropad with the 10g monofilament test in view of the costs savings on the basis that the tests are complementary (looking at different aspects of nerve damage and associated time points) and	The sponsor believes that the EAC have been unjustifiably critical of the sponsor's de novo economic model taking into account the EAC's own flawed model. We believe that the sponsor's model is equally pertinent as a response to the NICE scoping document. We request that the EAC give greater credence to the sponsor's Markov economic model and that this is reflected in the report.	The limitations of the sponsor's model are detailed by the EAC in its report. The EAC undertook its own modelling to address these limitations. The EAC has stated the assumptions underpinning the revised model. These assumptions reflect the limitations of the available data. Where possible, the EAC has examined the impact of its assumptions through sensitivity analysis. The EAC model considers the use of Neuropad in addition to monofilament. The EAC finds that a combined testing strategy in which a positive result on **both** tests is required to confirm DPN and refer

	therefore providing an opportunity for earlier detection of nerve damage and the implementation of preventative measures such as improved patient education, medicine optimisation and e.g. adding hypoglycaemic agents to achieve tighter blood glucose control which is a major contributory factor in the development of nerve fibre damage in the feet of people with diabetes.		the patient to a foot care programme is cost saving. However, the interpretation of this result requires extreme caution, since the strategy has applied sensitivity and specificity values assuming the two tests are completely independent. There is insufficient clinical evidence to confirm such an assumption.
The sponsor claims that the Neuropad is a categorical and objective test and that a main benefit of the Neuropad test is that it can be used by the patient or carer at home. More evidence about the repeatability/inter-observer agreement of results is required to verify the accuracy of results in this setting.	Whilst the sponsor is cogniscent that additional evidence would be helpful, it is in fact obvious that Neuropad is a categorical and objective colour change test that is intended for self-testing in a home environment which is most certainly not the case with 10g SWME which is subjective and requires the intervention of someone with training to carry out the test. It is simply not practical to expect patients at home to use a monofilament. The following sentence is unnecessary and unjustified and should be deleted from the EAC's report: 'More evidence about the repeatability/inter-observer agreement of results is required to verify the accuracy of results in this setting.'	The criticism is unjustified and unfair.	Please also see the response to Issue 3. The EAC does not use this sentence as a criticism of the test but to highlight that additional evidence would be helpful to support a key claim (given one study is presented). The EAC is clearly not stating that the Neuropad is unreliable, but that, as a key benefit claimed by the sponsor, it would be helpful to have more evidence to provide stronger support for this. The EAC has amended the sentence to reflect that there was one study found that looked at inter-observer agreement in the home setting: "One study was found that indicated that the Neuropad had "very good" reliability in the home setting. More evidence about the repeatability/inter-observer agreement of results would provide further support to verify the accuracy of results in this setting."

In the conclusion, the EAC makes the point that 'It is unclear where Neuropad would complement the current clinical pathway as there is a significant paucity of information around how early DPN assessment is or should be carried out and managed.'	The sponsor is of the opinion that the current clinical pathway is indeed flawed and provides no opportunity for the primary care clinician to detect DPN early therefore the pathway does not meet the criterion of preventative action.	It is abundantly clear how Neuropad can complement existing practice and that it provides an excellent opportunity for earlier identification of small fibre neuropathy allowing earlier interventions to be carried out in order to prevent more serious complications from developing. The sponsor requests that the EAC appraise the current pathway rather than attempt a somewhat vague defence of something that may need to change to improve earlier diagnosis.	The sponsor notes that the clinical pathway is flawed. In a similar vein, the EAC notes the lack of evidence around how early DPN should be assessed and managed: "It is unclear where Neuropad would complement the current clinical pathway as there is a significant paucity of information around how early DPN assessment is or should be carried out and managed." The sponsor asks that the EAC assesses the clinical pathway (see Issues 14 and 15). An in-depth assessment of the evidence surrounding the current clinical pathways and their potential gaps is beyond the scope of this work. However, the EAC has noted in 7. Implications for research, that: "More research may be carried out to further develop and update clinical guidelines, in particular to aid diagnosis and management of early DPN. Further research may investigate the effectiveness of interventions at early stage foot neuropathy (for example a foot care education programme) to further understand what the benefits of tests into early DPN may be." The EAC has added the following sentence to the section 6 summary to reflect the possible conditions for a change in the clinical pathway: "Currently there is insufficient evidence for effectiveness on patient-

			important outcomes and cost-effectiveness of implementation in the diagnostic pathway compared with the standard clinical examination. An addition or change to the pathway may be considered on this basis."
The EAC report states 'that more investigation is needed regarding where in the clinical pathway the test would usefully fit, and about its clinical utility. For example, further investigation may be carried out into what kind of consequent decisions and actions the results of the Neuropad could usefully influence. Experts noted that the Neuropad could be useful if used for annual foot checks in the home setting with people who could not attend clinic or with people with cognitive or communication impairments – if the results were normal (indicating no DPN), then no further tests would be required that year.'	The EAC assumes that the existing clinical pathway is correct and intimates that it should be adhered to. The sponsor states argue that because Neuropad not only complements 10g SWME monofilament testing when used together or prior to the annual diabetes foot checks by patients self-testing at home that it may help identify patients at early risk for the development of later sensory neuropathy which would provide primary care clinicians with an earlier opportunity to intervene on behalf of their patients, addressing poor glycaemic, lipid and blood pressure control for example which may all contribute to the development of diabetic peripheral neuropathy. Indeed, it its concluding remarks the EAC report states: 'The evaluation has highlighted a lack of evidence on the effectiveness and cost-effectiveness of foot care programmes.'	In NG19 Diabetic foot problems: prevention and management section 1.3.10 states "Give advice about, and provide, skin and nail care of the feet." As NG19 in fact mentions skin care of the feet there is clearly an existing need for a test that measures the moisture content of the skin. The sponsor requests that the EAC more accurately reflect the requirement in NG19 for a foot skin assessment.	The EAC is not assuming that the current clinical pathway is "correct". As the sponsor notes in this comment, the report states: "The evaluation has highlighted a lack of evidence on the effectiveness and cost-effectiveness of foot care programmes", in addition this is included a point for further research in section 7. The EAC considers the evidence for Neuropad in the current context of care and has made some suggestions about where there may be future research to address gaps in the evidence for a pathway. The pathway cannot be changed without an evidence base. NG19 mentions skin care of the feet, however it may be an extrapolation to suggest this would involve testing the moisture content of the feet. The guidance mentions calluses, but no mention is made of moisture content. The online Diabetes UK patient guidance for foot care also does not explicitly mention skin moisture.

Overall, the EAC review of the Neuropad test lacks a real clinical perspective for the benefits in those older adults with diabetes who are demented, have language problems, have visual loss, are housebound, or reside in care homes where there is a high percentage of dementia, frailty and comorbidity. Early detection of nerve damage may save feet in those with an already limited life expectancy and bring about a sustained level of quality of life for the remaining years. The sponsor believes that the EAC report is limited in scope and lacks sufficient clinical insight into these vulnerable group of older people despite their consultations with clinical experts.	The EAC report is limited in scope and lacks relevant clinical insight into these vulnerable groups of older people. The EAC report should have included greater clinical focus than it does. Although external clinical guidance was sought, the sponsor notes that no primary care general practitioners nor care of the elderly specialists with an interest in diabetes were consulted and that this fundamental error needs to be addressed. The sponsor wishes to draw to the attention of the EAC the paper by Quattrin et al (2004) which states 'In conclusion, an accurate assessment of small fiber damage in the skin of diabetic patients has not evolved in parallel with that of large fiber damage. While the latter is the primary predisposing factor in foot ulceration, recent findings have suggested that small nerves are of paramount importance in regulating cutaneous neurobiology. Quattrini C, Jeziorska M, Malik RA.Small fiber neuropathy in diabetes: clinical consequence and assessment. Int J Low Extrem Wounds. 2004 Mar;3(1):16-21.	The EAC report requires a greater clinical focus and a proper understanding of diabetic peripheral neuropathy. In addition, Completely absent from the EAC's report are the UK costs (>£1 billion, Kerr 2017)) of treating people with diabetes who have foot ulcers or who experience ulceration and the burden on patients and the people who care for them. There appears a determination that 'doing nothing' is preferable to doing something. May we remind the EAC that >400,000 people with diabetes in England never have an annual diabetic foot check as specified in NG19. What the sponsor finds astonishing is that the EAC seems determined to dismiss evidence that doesn't meet the current guidelines or practices. May we ask what significant progress has been made since the following editorial appeared in The Lancet in 1991? Is there anything we can do for neuropathy? Do we just diagnose it and commiserate with the patient? Editorial Lancet 1991; 338; 1496-7.	The EAC understands that theoretically the patient subgroups outlined may particularly benefit from a test such as the Neuropad, however claims have to be supported by evidence and studies into these populations have neither been presented by the sponsor in their submission nor retrieved by the EAC. In no way is the EAC recommending that "do nothing" is the preferable situation, however this may be the most cost saving route, particularly in light of the relatively low specificity.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: MT318 The Neuropad Test

Sponsor: Skrocketphytopharma (UK) Ltd

Date sections A and B submitted: 03/05/2017

Date section C submitted: 25/05/2017

August 2011 (Version 1.1)

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Glossary of terms

Abbreviation or acronym	Meaning
AN	Autonomic neuropathy
CAN	Cardiovascular autonomic neuropathy
CCM	Corneal confocal microscopy
DAN	Diabetic autonomic neuropathy
DFS	Diabetic foot syndrome
DPN	Diabetic peripheral neuropathy
DSPN	Diabetic sensori-motor polyneuropathy
IENF	Intraedipdermal nerve fibre
IENFD	Intraedipdermal nerve fibre density
LFN	Large fibre neuropathy
NCS	Nerve conduction studies
NDS	Neuropathy disability score
NSS	Neuropathy symptom score
PAN	Peripheral autonomic neuropathy
QST	Quantitative sensory testing
QSART	Quantitative sudomotor axon reflex testing
SFN	Small fibre neuropathy
SFT	Sudomotor function test

SSR	Sympathetic skin response
SWME	Semmes Weinstein monofilament examination
T1D	Type 1 diabetes
T2D	Type 2 diabetes
VPT	Vibration perception threshold

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People with diabetes undergoing routine foot-care checks by health care workers in primary and secondary care settings and/or undertaking a DPN self-test in the home		
Intervention	Neuropad		
Comparator(s)	• 10 g monofilament • Other sensation tests used in primary care (e.g. Vibratip, Neurotip, tuning fork, biothesiometer, Ipswich Touch Test) • Standard neuropathy scoring systems used in primary care (e.g. Neuropathy Disability Score) • Specialist small fibre neuropathy tests used in secondary care (nerve conduction tests, intraepidermal nerve fibre density biopsy, quantitative sudomotor axon reflex test (QSART), Sudoscan, corneal confocal microscopy, NC-stat DPN check) (see also 'Cost analysis' below)	Note: the 10g monofilament test also known at the Semmes Weinstein monofilament examination (SWME) is the only test that NICE recommend for routine use in primary care.	
Outcomes	The outcome measures to consider include: • Sensitivity and specificity in identifying diabetic peripheral neuropathy (DPN) compared to reference standard (standard neuropathy scoring or specialist secondary care tests) • Patient experience and ease of use by patients and clinicians • Reliability and reproducibility of use by patients and clinicians • Total time to carry out test and obtain result • Rates of GP surgery or hospital attendance • Incidence of foot ulceration and/or amputation • Device-related adverse events.		

Cost analysis	Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	• People in community settings • People with communication difficulties or cognitive impairment		
Special considerations, including issues related to equality	Diabetes is a chronic condition that is covered under the Equality Act 2010. DPN is more common with increasing age and men may develop DPN earlier than women, but neuropathic pain causes more morbidity in women than in men. More secondary complications from DPN have been shown to occur in people of Hispanic or African American family origin. The Neuropad test may be easier to use for people with communication difficulties, as it is an objective test that does not require assessment of subjective patient responses, unlike the vibration tests. This may allow for improved detection of diabetic neuropathy in children, people with mental health disabilities or people who have problems communicating. People with visual impairments may need help to administer the Neuropad, so self-testing at home may not be possible in this subgroup.		

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Neuropad 10-minute screening test comprising two (2) Neuropad plasters in one packet.What is the principal mechanism of action of the technology?

2.2 What is the principal mechanism of action of the technology?

Cobalt chloride, in its dry (anhydrous) state, is blue. In contact with moisture, it takes up water molecules and undergoes a colour change to pink. Neuropad is a small adhesive pad impregnated with anhydrous cobalt chloride. When applied to the sole of the foot, any moisture present as a result of normal sweat production will initiate the colour change from blue to pink. A partial change, (Fig 1b) or no change at all (Fig 1a), indicates an inadequate level of sweat production which acts as a surrogate for peripheral autonomic neuropathy. A visible result is obtained in 10 minutes.

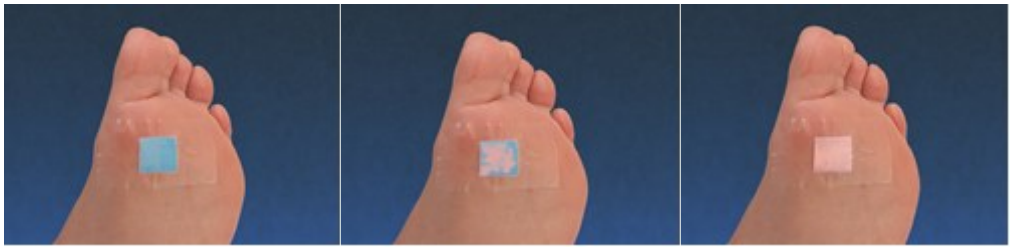


Fig 1a Fig 1b Fig 1c

Figure 1. In the presence of normal levels of sweat production, Neuropad will undergo a blue (Fig 1a) to pink (Fig 1c) colour change. In patients with a degree of nerve damage, insufficient sweat levels will fail to trigger the complete colour change (Fig 1b). More serious degrees of nerve damage will result in no colour change at all (Fig 1a).

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

In the UK, an estimated 4.5 million people have diabetes: this is predicted to rise to 5 million people by 2025. Diabetic peripheral neuropathy (DPN) is a common long-term complication, where high blood glucose levels damage the small blood vessels supplying the nerves to the hands and feet. DPN affects up to 50% of people with diabetes, with chronic, painful neuropathy affecting up to 26%, which increases the risk of foot ulceration and subsequent amputation. In England, around 2.5% of people with diabetes have foot ulcers at any given time (approximately 86,000 people) and there were around 7,400 lower limb amputations due to DPN in 2015/2016.

Diabetes UK Facts and Stats October 2016

https://www.diabetes.org.uk/Documents/Position%20statements/DiabetesUK_Facts_Stats_Oct16.pdf

DPN may involve large nerve fibres, small nerve fibres, or both, affecting different sensation modalities. *Boulton et al., (2004).* Large fibres affect motor function and sensation function for vibration and temperature. Small fibres constitute 80–91% of peripheral nerve fibres and control pain perception and autonomic sudomotor function. Small fibre neuropathy is the most common type of neuropathy in people over 50 years; it typically affects the lower limbs and often precedes large fibre neuropathy. Sudomotor dysfunction is indicative of diabetic autonomic neuropathy, which can result in foot ulceration. A lack of sweating can cause the skin to crack, leading to an increased risk of infection; if untreated, this can cause sepsis and gangrene with the need for amputation."

According to data from Public Health England's 2014 report:

"In England, the rising prevalence of obesity in adults has led, and will continue to lead, to a rise in the prevalence of type 2 diabetes. This is likely to result in increased associated health complications and premature mortality, with people from deprived areas and some minority ethnic groups at particularly high risk. Modelled projections indicate that NHS and wider costs to society associated with overweight, obesity and type 2 diabetes will rise dramatically in the next few decades."

Regarding economic impact, the report goes on to state that:

"It is estimated that in 2010-11 the cost of direct patient care (such as treatment, intervention and complications) for those living with type 2 diabetes in the UK was £8.8 billion and the indirect costs (such productivity loss due to increased death and illness and the need for informal care) were approximately £13 billion. Prescribing for diabetes accounted for 9.3% of the total cost of prescribing in England in 2012-13."

https://www.gov.uk/government/publications/public-health-england-annual-report-and-accounts-2014-to-2015

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

Current published guidelines:

Diabetic foot problems: prevention and management: NICE guideline [NG19]
Published date: August 2015. Last updated: January 2016
https://www.nice.org.uk/Guidance/NG19
https://pathways.nice.org.uk/pathways/foot-care-for-people-with-diabetes

NG19 specifies the frequency of and methods for carrying out a foot assessment

Frequency of risk assessments
"For children with diabetes who are under 12 years, give them, and their family members or carers (as appropriate), basic foot care advice.
For young people with diabetes who are 12–17 years, the paediatric care team or the transitional care team should assess the young person's feet as part of their annual assessment, and provide information about foot care. If a diabetic foot problem is found or suspected, the paediatric care team or the transitional care team should refer the young person to an appropriate specialist.

"For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times:

- When diabetes is diagnosed, and at least annually thereafter (see managing the risk in this pathway).
- If any foot problems arise.
- On any admission to hospital, and if there is any change in their status while they are in hospital."

Current guidelines recommendations for the assessment of the feet of people with diabetes are as follow:

Assessing the risk

"When examining the feet of a person with diabetes, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following risk factors:

- Neuropathy (use a 10 g monofilament as part of a foot sensory examination). How to conduct the test.

http://www.northdevonhealth.nhs.uk/wp-content/uploads/2014/06/how_to_use_a_10_monofilament.pdf

http://www.rdehospital.nhs.uk/docs/patients/services/diabetes/use-of-the-10g-monofilament-in-the-screening-of-the-diabetic-foot.pdf

- Limb ischaemia (see the NICE pathway on lower limb peripheral arterial disease).
- Ulceration.
- Callus.
- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy.

Use ankle brachial pressure index in line with the NICE pathway on lower limb peripheral arterial disease. Interpret results carefully in people with diabetes because calcified arteries may falsely elevate results.
Assess the person's current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification:

Low risk:

- no risk factors present except callus alone.

Moderate risk:

- deformity or neuropathy or non-critical limb ischaemia.

High risk:

- previous ulceration or
- previous amputation or
- on renal replacement therapy or
- neuropathy and non-critical limb ischaemia together or
- neuropathy in combination with callus and/or deformity or
- non-critical limb ischaemia in combination with callus and/or deformity.

Active diabetic foot problem:

- ulceration or spreading infection or
- critical limb ischaemia or
- gangrene or
- suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain."

Managing the risk

Low risk

For people who are at low risk of developing a diabetic foot problem, continue to carry out annual foot assessments, emphasise the importance of foot care, and advise them that they could progress to moderate or high risk.

Moderate or high risk

Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service.

The foot protection service should assess newly referred people as follows:

- Within 2–4 weeks for people who are at high risk of developing a diabetic foot problem.
- Within 6–8 weeks for people who are at moderate risk of developing a diabetic foot problem.

For people at moderate or high risk of developing a diabetic foot problem, the foot protection service should:

- Assess the feet.
- Give advice about, and provide, skin and nail care of the feet.
- Assess the biomechanical status of the feet, including the need to provide specialist footwear and orthoses.
- Assess the vascular status of the lower limbs.
- Liaise with other healthcare professionals, for example, the person's GP, about the person's diabetes management and risk of cardiovascular disease.
- Depending on the person's risk of developing a diabetic foot problem, carry out reassessments at the following intervals:
- Annually for people who are at low risk.
- Frequently (for example, every 3–6 months) for people who are at moderate risk.
- More frequently (for example, every 1–2 months) for people who are at high risk, if there is no immediate concern.
- Very frequently (for example, every 1–2 weeks) for people who are at high risk, if there is immediate concern.
- Consider more frequent reassessments for people who are at moderate or high risk, and for people who are unable to check their own feet.
- People in hospital who are at moderate or high risk of developing a diabetic foot problem should be given a pressure redistribution device to offload heel pressure. On discharge they should be referred or notified to the foot protection service."

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

NG28 Type 2 diabetes in adults: management

Identifying and managing complications in adults with type 2 diabetes

https://pathways.nice.org.uk/pathways/foot-care-for-people-with-diabetes/reducing-the-risk-of-developing-a-diabetic-foot-problem#content=view-index&path=view%3A/pathways/foot-care-for-people-with-diabetes/managing-a-diabetic-foot-problem.xml

Managing the risk

Low risk

For people who are at low risk of developing a diabetic foot problem, continue to carry out annual foot assessments, emphasise the importance of foot care, and advise them that they could progress to moderate or high risk.

Moderate or high risk

Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service.

The foot protection service should assess newly referred people as follows:

Within 2–4 weeks for people who are at high risk of developing a diabetic foot problem.

Within 6–8 weeks for people who are at moderate risk of developing a diabetic foot problem.

For people at moderate or high risk of developing a diabetic foot problem, the foot protection service should:

Assess the feet

Give advice about, and provide, skin and nail care of the feet.

Assess the biomechanical status of the feet, including the need to provide specialist footwear and orthoses.

Assess the vascular status of the lower limbs.

Liaise with other healthcare professionals, for example, the person's GP, about the person's diabetes management and risk of cardiovascular disease.

Depending on the person's risk of developing a diabetic foot problem, carry out reassessments at the following intervals:

Annually for people who are at low risk.

Frequently (for example, every 3–6 months) for people who are at moderate risk.

More frequently (for example, every 1–2 months) for people who are at high risk, if there is no immediate concern.

Very frequently (for example, every 1–2 weeks) for people who are at high risk, if there is immediate concern.

Consider more frequent reassessments for people who are at moderate or high risk, and for people who are unable to check their own feet.

People in hospital who are at moderate or high risk of developing a diabetic foot problem should be given a pressure redistribution device to offload heel pressure. On discharge they should be referred or notified to the foot protection service.

Quality standards

Diabetic foot problems: prevention and management (2015 updated 2016) NICE guideline NG19

https://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults#path=view%3A/pathways/type-2-diabetes-in-adults/identifying-and-managing-complications-in-adults-with-type-2-diabetes.xml&content=view-node%3Anodes-neuropathy

Autonomic neuropathy

Think about the possibility of contributory sympathetic nervous system damage for adults with type 2 diabetes who lose the warning signs of hypoglycaemia.

Think about the possibility of autonomic neuropathy affecting the gut in adults with type 2 diabetes who have unexplained diarrhoea that happens particularly at night.

When using tricyclic drugs and antihypertensive drug treatments in adults with type 2 diabetes who have autonomic neuropathy, be aware of the increased likelihood of side effects such as orthostatic hypotension.

Investigate the possibility of autonomic neuropathy affecting the bladder in adults with type 2 diabetes who have unexplained bladder-emptying problems.

In managing autonomic neuropathy symptoms, include specific interventions indicated by the manifestations (for example, for abnormal sweating or nocturnal diarrhoea).

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Improved screening and earlier identification of patients at risk of developing the diabetic foot syndrome (DPN) offers an excellent opportunity for patients with diabetes to make behavioural changes to reduce the risk of unperceived trauma and identify those patients who should undergo more intense intervention including improved glycaemic, blood pressure and lipid control and, if at particularly high risk, referral to multidisciplinary foot care teams *Gaede et al., (1999); Gaede et al., (2008).*

It has been estimated that in 2014-2015, the NHS in England spent an estimated £972 million–£1.13billion, equivalent to 0.72–0.83% of its entire budget, on relating to foot ulceration and amputation. Around two thirds of this expenditure was on care in primary, community and outpatient settings for ulceration.

Diabetic Foot Care in England: An Economic Study. Marion Kerr, Insight Health Economics, January 2017

Not all people with diabetes receive an annual foot test. Variation in diabetes patients receiving foot surveillance in NHS England for the period 2011-12 was as follows:

Type 1 - 73% received an annual foot test

Type 2 – 87.1% received an annual

Combined – 85.4% of people with any form of diabetes had an annual foot test

In 2015, 2,913,538 people in England had a recorded diagnosis of diabetes

Type 1 diabetes accounts for 10% of all cases (291,353)

Type 2 diabetes accounts for 90% of all cases (2,622,184)

Applying the percentages above:

78,665 people with Type 1 diabetes in England do not receive at least an annual foot test

338,261 people with Type 2 diabetes in England do not receive at least an annual foot test

For all people with diabetes that equates to 416,926 people at risk of developing motor, sensory or autonomic neuropathy with an annual incidence of between 1-4% which equates to between 4,169 and 16,640. If, due to lack of early diagnosis this cohort of patients first present with an ulcer, the annual cost of treating these patients would be in the region of £29 million - £116 million.

QOF and National Diabetes Audit

National Diabetes Footcare Audit 2014-15 Published March 2016

http://content.digital.nhs.uk/searchcatalogue?productid=20582&q=national+diabetes+footcare+audit&sort=Relevance&size=10&page=1#top

Variation by Clinical Commissioning Group:

There is significant regional variation. In the worst performing region only 47% of patients with diabetes receive an annual foot test, whilst in the best performing region 87% receive an annual diabetic foot test

http://fingertips.phe.org.uk/profile/atlas-of-variation

Accuracy of monofilament testing:

'The accuracy of foot risk assessment tools to predict ulceration requires evaluation in randomized controlled trials with concurrent economic evaluations.' *Crawford et al., (2011).*

'There is great variation in the current literature regarding the diagnostic value of the Semmes Weinstein monofilament examination (SWME) as a result of different methodologies. To maximize the diagnostic value of SWME, a three site test involving the plantar aspects of the great toe, the third metatarsal, and the fifth metatarsals should be used. Screening is vital in identifying DPN early, enabling earlier intervention and management to reduce the risk of ulceration and lower extremity amputation.' *Feng et al., (2009).*

‘Despite the frequent use of monofilament testing, little can be said about the test accuracy for detecting neuropathy in feet without visible ulcers. Optimal test application and defining a threshold should have priority in evaluating monofilament testing, as this test is advocated in many clinical guidelines. Accordingly, we do not recommend the sole use of monofilament testing to diagnose peripheral neuropathy. *Dros et al., (2009)*

‘Data show extremely low diagnostic utility for standard screening methods (tuning fork and 10-g monofilament) but acceptable utilities for biothesiometry and finer (1 g) monofilaments. Data on the diagnostic utility should be used to inform national and international guidelines on diabetes management.’ *Hirschfeld et al., (2014)*

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

Neuropad test screening offers a number of potential advantages to the NHS:

As a significant percentage of people with diabetes never have an annual foot test, there is an opportunity through home testing and the provision of tests by post to identify people at risk that would otherwise not be diagnosed.. Tests could be provided easily and cheaply through direct patient contact via GP practices requesting that patients either collect a Neuropad test pack from the GP practice where they are registered as a patient or take an official letter along to a community (high street or local) pharmacist to collect a test pack. Results recorded on an accompanying card can then either be handed in to the patients' primary care practice or to the community pharmacist who originally provided the test or by post or even email. As Neuropad is a categorical and objective test, there are only three possible outcomes available for patients to record results after 10 minutes:

Indicator pad remains blue: report test results to GP who may administer monofilament test and depending on his/her clinical judgement send for referral.

Indicator pad turns partially blue/pink: as above

Indicator pad turns completely pink: report test result to GP who may, depending on clinical judgement, advise annual review and repeat of test.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Significant changes to current practice are unlikely. Although the Neuropad test has been designed primarily for home testing it can also be applied in-clinic by healthcare professionals either highly trained or relatively un-skilled. The test can therefore be used as part of the annual primary care initiated diabetes foot test and deployed in clinic or either provided to patients to self-test at home before they attend for an annual foot test or afterwards by either being handed a Neuropad test pack or being asked to pick a test up from their local pharmacy. In addition, any patient with diabetes not having been recorded as having a recent (at least annual) foot test should either be provided with a Neuropad test for home testing or requested to collect one from either community pharmacy or their primary care practice. As the

test is simple, non-invasive, low-risk and with results that are easy to interpret, it is anticipated that take up of the test by patients testing at home may be high unlike some other screening tests for other conditions that have more complex requirements.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Neuropad is the only self-testing device for sudomotor function available for use in a primary care or the home setting. More specialist tests are used in secondary care to detect small fibre neuropathy. Neuropad is a screening test with good sensitivity and variable though reasonable specificity. Therefore for a firm diagnosis of diabetic autonomic neuropathy (DAN), patients identified as at potential risk should be referred to secondary care where further hospital-based tests may be carried out to confirm the diagnosis.

Secondary care tests include:

Nerve conduction studies (NCS)

Vibration perception threshold (VPT)

Intraepidermal nerve fibre density (IENFD)

Quantitative sudomotor axon reflex test (QSART)

Corneal confocal microscopy (CCM)

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None identified

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

128MHz tuning fork and other vibration perception tests may no longer be required as these devices also help identify patients with sensory deficits which may be carried out using the standard 10g monofilament test. Using the Neuropad test plus the 10g monofilament test and a foot examination by a suitably qualified healthcare professional combined would assess for distal symmetric polyneuropathy comprising motor, sensory and autonomic neuropathy in clinic.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

There is currently no alternative test for diabetic neuropathy that that is suitable for patients to self test. By encouraging patients with diabetes to monitor their foot health using Neuropad by deploying the test at home, self testing would reduce the need for patients to attend for a foot examination and free up more time in the clinic or GP surgery. Longer term, by reducing the incidence of ulcers and amputations, the NHS would require fewer wound care specialists and surgeons and these could be deployed elsewhere. It would also save considerably on dressings, medications, antibiotics and post-operative care.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with

relevant dates (for example, date of application and/or expected approval dates).

Neuropad is a CE marked Class I medical device. Legal classification: CE medical device Class I, Annex I + VII, Directive 93/42 EEC.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Neuropad is approved for use across the entire European Union. Neuropad is currently distributed in Germany, Switzerland and Austria by Sanofi SA and in various other EU countries by Menarini Diagnostics.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Neuropad has been available and listed on the NHS Drugs Tariff since 2008 and is currently available.

4.5 If the technology has been launched in the UK provide information on the use in England.

Neuropad is listed on the NHS Drugs Tariff and has been used in a number of secondary care specialist settings including at Manchester Royal Infirmary by Professors Boulton and Malik and colleagues.

http://research.bmh.manchester.ac.uk/ena/techniques/Neuropadtest/

Neuropad is also being deployed nationally as part of a diabetic foot care screening programme offered by the UK private podiatry service Shuropody.

Neuropad is being promoted by the IDDT charity via their web site (www.iddt.org).

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

An audit of frail elderly people with diabetes using Neuropad to assess diabetic peripheral neuropathy was carried out in care homes and amongst inpatients in hospital in 2016. An initial analysis of this data has been performed but it is the study authors' intention to increase the size of the cohort of patients by at least 100% and, subsequently, to submit data for publication.

Post-marketing safety surveillance conducted by the manufacturer of Neuropad has produced zero case studies regarding safety concerns.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

None planned. Recently submitted for assessment by the NHS Innovation Accelerator (NIA) with positive feedback received.

In 2016 Neuropad was submitted for consideration by the NHS Innovation Accelerator programme and was shortlisted by a panel of assessors which included NHS national clinical directors, Academic Health Science Network representatives, charities, patient representatives as well as commercial experts drawn from the public and private sectors. It was shortlisted on the basis that Neuropad is 'a good, patient-centred innovation that has the potential to improve screening for foot problems in people with diabetes and therefore reduce preventable foot ulceration and amputation, which are expensive for the NHS and devastating for patients.' Significantly, 'clinical assessors were strongly in support of this innovation.'

Following shortlisting, a decision making panel, chaired by Professor Sir Bruce Keogh and made up of the 11 AHSN partners, patient representatives and the Health Foundation provided the following final feedback:

Neuropad is a 'simple, inexpensive product addressing a clear need that was supported by the panel' and a 'great innovation.'

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

None identified or known

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None identified or known

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

N/A

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published research comparing Neuropad to standard methods for assessing sudomotor dysfunction

The Neuropad test has been evaluated against established standard tests in 43 international studies (41 published; 2 unpublished). The choice of standard tests used to compare against Neuropad varied according to the choice of the authors. The generally accepted gold standard test is the intraepidermal nerve fibre density measurement (IENFD). IENFD and other hospital based tests may require expensive equipment, trained staff and time to perform.

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

N/A

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

N/A

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format

41 studies in literature search for Neuropad

Exclusions: studies already included in the meta analysis (12), studies not in English (2), review studies (3), study on Neuropad foam (1), and studies not relevant to the current application (15) = 33 exclusions.

8 studies remaining after exclusions

Meta analysis (1), studies dealing with small fibre neuropathy and sudomotor dysfunction (4), a prospective study (1), and studies dealing with self examination and DFS (2)

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients with diabetes
Interventions	Neuropad test for identification of sudomotor dysfunction and diabetic autonomic neuropathy
Outcomes	Positive or negative test result
Study design	N/A
Language restrictions	English language or at least English abstract
Search dates	2005 onwards
Exclusion criteria	
Population	Non-diabetic patients
Interventions	Studies dealing with Neuropad foam; studies dealing with conditions other than sudomotor dysfunction
Outcomes	
Study design	Studies included in the meta analysis
Language restrictions	Non-English abstract
Search dates	2005 onwards

7.3

Unpublished studies

7.3.1 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients with diabetes
Interventions	Neuropad test for idenitification of sudomotor dysfunction and diabetic autonomic neuropathy
Outcomes	Positive or negative test
Study design	N/A
Language restrictions	English language or English abstract only
Search dates	2005 onwards
Exclusion criteria	
Population	Non-diabetic patients
Interventions	Studies dealing with Neuropad foam; studies dealing with conditions other than sudomotor dysfunction
Outcomes	N/A
Study design	N/A
Language restrictions	English language or English abstract only
Search dates	N/A

7.3.2 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

2 studies included; none excluded

7.4 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.4.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies

Primary study reference	Study name	Population	Intervention	Comparator
Ishibashi et al (2014)	Correlation between sudomotor function, sweat gland duct size and corneal nerve fibre pathology in patients with type 2 diabetes mellitus.	78 type 2 diabetic patients and 28 age-matched non-diabetic control participants.	Neuropad test result	a) Corneal CM b) CM of Sweat Gland Ducts
Quattrini et al (2008)	The Neuropad test: a visual indicator test for human diabetic neuropathy	57 diabetic patients (20 type 1 and 37 type 2) 15 age and sex matched non-diabetic control individuals	Neuropad test result	a) (CASE) IV quantitative sensory assessment b) IENFD Skin biopsies
Tomesova et al (2013)	Differences in Skin microcirculation on the upper and lower extremities in Patients with diabetes mellitus: Relationship of diabetic neuropathy and skin microcirculation	52 patients with type 2 diabetes	Neuropad test result	Microvascular reactivity was measured by laser Doppler iontophoresis, using 1% acetylcholine chloride (ACH) and 1% sodium nitroprusside.
Ponirakis et al (2014)	The diagnostic accuracy of Neuropad® for assessing large and small fibre diabetic neuropathy	127 diabetic patients (68 with Type 1 diabetes and 59 with Type 2 diabetes)	Neuropad test result	Large nerve fibre assessments: NDS, vibration perception threshold, peroneal motor nerve CV Small nerve fibre assessments: Diabetic Neuropathy Symptoms score (corneal nerve fibre length and warm perception threshold).
Tentolouris et al (2008)	Evaluation of the self-administered Indicator plaster Neuropad for the diagnosis of neuropathy in diabetes	156 diabetic patients	Neuropad test result	NDS & Questionnaires for Self examination Evaluation.
Tentolouris et al (2010)	Moisture status of the skin of the feet assessed by the visual test Neuropad correlates with foot ulceration in diabetes	379 diabetic patients	Neuropad test result	NSS, NDS, VPT to DP with and without foot ulceration.
.Papanas et al (2010)	A prospective study on the use of the indicator test Neuropad for the early diagnosis of peripheral neuropathy in type 2 diabetes	109 type 2 diabetic patients	Neuropad test result	Neuropathy Disability Score (NDS)
Tsiapas et al (2014)	A simple plaster for screening for diabetic neuropathy: a diagnostic test accuracy systematic review and meta-	3470 diabetic patients	Neuropad test result	Full analysis to meta analysis chapter

	analysis.			

Table B4 List of relevant unpublished studies

Data source	Study name	Population	Intervention	Comparator
Tentolouris et al. (in press)	The Neuropathy Disability Score and the indicator plaster test Neuropad predict foot ulceration in diabetes	221 patients with diabetes	Neuropad test result	Prospective results For incidence of foot ulceration NDS.
Sanz et al 2016)	Utility of sudomotor function test (Neuropad) as a clinical tool in risk stratification system of diabetic patient.	221 patients with diabetes	Neuropad test result	Prospective results For incidence of foot ulceration NDS.

7.4.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

Studies dealing with non-relevant topics such as Neuropad foam or non foot-related neuropathies and product reviews

7.5 Summary of methodology of relevant studies

Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

No RCTs have been conducted.

Table B5 Summary of methodology for randomised controlled trials

Study name
Objectives
Location

Design
Duration of study
Sample size
Inclusion criteria
Exclusion criteria
Method of randomisation
Method of blinding
Intervention(s) (n =) and comparator(s) (n =)
Baseline differences
Duration of follow-up, lost to follow-up information
Statistical tests
Primary outcomes (including scoring methods and timings of assessments)
Secondary outcomes (including scoring methods and timings of assessments)

Table B6 Summary of methodology for observational studies

Study title	**Correlation between sudomotor function, sweat gland duct size and corneal nerve fibre pathology in patients with type 2 diabetes mellitus. Ishibashi F, Kojima R, Kawasaki A, Yamanaka E, Kosaka A, Uetake H. Diabetes Invest., Sep;5(5):588-96 (2014)**
Objective	To study the correlation between sudomotor function, sweat gland duct size and corneal nerve fibre pathology in type 2 diabetes. Sudomotor function was quantified by the Neuropad test.
Location	Hiroshima, Japan
Design	Cross-sectional.
Duration	Not given
Patient population	78 patients with type 2 diabetes with or without staged severity of diabetic neuropathy and 28 age-matched non-diabetic control participants
Sample size	n = 106
Inclusion criteria	Patients with type 2 diabetes with or without staged severity of diabetic neuropathy, diagnostic criteria proposed by the Diabetic Neuropathy Study Group in Japan.
Exclusion criteria	Age < 30 or > 65 years, peripheral arterial disease, allergy to metals, skin diseases (neurodermatitis, psoriasis, Raynaud's syndrome and hyperhydrosis), drug therapy (corticosteroids, B-blocker, antihistaminic and psychoactive drugs, which may affect sweating), chronic alcohol abuse, thyroid disease and lumbar spine disorders or any other causes of peripheral neuropathy.
Intervention(s)	Stages of DN SI 23 SII 28 SIII 20 SIV+V 7 (n=78) and comparator(s) (n =28) Control subjects Neuropad test time complete colour change (CCC), sweat gland duct size, Corneal Confocal Microscopy (CCM) defining corneal nerve fibre (CNF) changes.

Baseline differences	Assessment of diabetic neuropathy (DN): Stage I - no neuropathy, which includes patients who do not meet the diagnostic criteria for DN (n = 23); Stage II - asymptomatic DN, in which patients have no subjective symptoms, but meet the diagnostic criteria for DN (n = 28); Stage III - subjective symptoms are positive, but either ankle reflex or vibration sense is within the normal range (n = 20); Stage IV - patients show clinically manifested autonomic neuropathy, such as orthostatic hypotension. Motor neuropathy appears at stage V. Because small numbers of patients were classified into stage IV and V, the investigators combined (stage IV with stage V (IV + V) (n = 7).
Follow up	Not stated
Statistical tests	All statistical analyses were carried out using the SPSS medical package (SPSS, Chicago, IL, USA). Data are presented as the mean – standard error of the mean. Analysis of variance (ANOVA) was used to compare the control participants and patients with type 2 diabetes with or without DN graded by the Diabetic Neuropathy Study Group in Japan (DNSGJ) staging. Multivariate regression analysis was used to determine the independent relationship between the time to a complete colour change (CCC) in the Neuropad test or cross-sectional area of the sweat gland ducts, and clinical factors, neurological examinations or morphological parameters of corneal NFs. Receiver operating characteristic (ROC) curve analysis established cut-off levels of the time to CCC in the Neuropad test and cross-sectional area of the sweat gland ducts between the control participants and patients with type 2 diabetes. Sensitivity and specificity were equally weighted. A P-value of <0.05 was considered statistically significant.
Primary outcomes (including scoring	Neuropad test. For each participant, the investigators observed the time to CCC for each foot and confocal microscopy for defining corneal nerve fibre (CNF)

methods and timings of assessments)	changes: (i) CNF density/mm^2 (CNFD); (ii) corneal NF length mm/mm^2 (CNFL); (iii) corneal nerve branch density/mm^2 (CNBD); (iv) corneal nerve branch length mm/mm^2 (CNBL) emanating from the major nerve trunk; (v) tortuosity; and (vi) frequency/0.1 mm of beading. Confocal microscopy (CM) of sweat gland ducts. In patients with diabetic neuropathy, sudomotor function, as judged by the time required for CCC of a Neuropad, was impaired compared with that of controls ($P < 0.0001$), thereby showing deterioration was related to the severity of diabetic neuropathy ($P < 0.0001$). Multiple regression analysis showed that the time to CCC of the Neuropad prolonged and negatively correlated with CNFD, CNFL, CNBD and CNBL, and the cross-sectional area of the sweat gland ducts, and had a close direct relationship with the severity of DN.
Secondary outcomes (including scoring methods and timings of assessments)	Large Fibre Functions: Current perception threshold (CPT) and vibration perception threshold (VPT) values were measured as reported-using a neurometer (Neurotron, Baltimore, MD, USA) and a biothesiometer (Bio-Medical Instrument, Newbury, OH, USA), respectively. The lowest stimulus perceivable by the participant was defined as the CPT for that current frequency in each individual. To determine the VPT, eight readings were obtained and averaged. Nerve conduction studies were carried out by conventional procedures with an electromyography machine (Neuropak S1, NIHON KOHDEN, Tokyo, Japan). A motor nerve study was carried out on the median nerve, and a sensory nerve study was carried out on the ulnar nerve. Small Fibre Functions: Warm and cold perception thresholds (PTs) were determined using a thermal stimulator that was controlled by a Peltier element and a push-button switch (Intercross-200; Intercross Co., Tokyo, Japan). Warm and cold PTs were measured at the thenar eminence and cheek, respectively. The surface temperature of the stimulation probe was automatically set at the skin temperature of the target body region. The measurement was repeated five times and averaged. To assess the cardiovagal function of the autonomic nervous system, $CV_{R\text{-}R}$ was calculated from the R-R intervals of 200 samples on the electrocardiogram.

	The sensitivity and specificity of the time to CCC of the Neuropad and cross sectional area of the sweat gland ducts were assessed by ROC curve analysis. For the CCC of the Neuropad and the CSA of the sweat gland ducts, the sensitivity, specificity and tentative cut-off levels between the control participants and patients with type 2 diabetes were 83.1%, 84.0%, and 815 s, respectively, for the time to CCC of the Neuropad, and 73.3%, 74.0%, and $2282\mu m^2$, respectively, for the sweat gland duct cross sectional area.

Study title	**The Neuropad test: a visual indicator test for human diabetic neuropathy Quattrini C, Jeziorska M, Tavakoli M, Begum P, Boulton AJ, Malik RA. Diabetologia, Jun;51(6):1046-50 (2008)**
Objective	To compare the results of Neuropad assessment in the foot with established measures of somatic and autonomic neuropathy
Location	Manchester Diabetes Centre, Manchester Royal Infirmary, Manchester, UK
Design	Cross-sectional
Duration	N/A
Patient population	59 diabetic patients, 15 controls
Sample size	N=74
Inclusion criteria	Patients with type 1 and type 2 diabetes
Exclusion criteria	Chronic alcohol abuse, thyroid disease and lumbar spine disorders or any other causes of peripheral neuropathy
Intervention(s)	Neuropad test response change as normal (blue colour turned completely pink, score=0), patchy (patches of blue and pink, score=0.5), abnormal (remained blue, score=1.0). and NDS as follows. Patients underwent computer-aided sensory evaluator (CASE) IV quantitative sensory assessment including: heat-as-pain perception threshold visual analogue score (HP-VAS), cold detection threshold (CDT) and deep breathing heart rate variability (DB-HRV). Orthostatic hypotension as a measure of sympathetic dysfunction and was defined by a postural drop in BP of at least 20 mmHg Symptoms were assessed using the diabetic neuropathy symptom score and the short form of McGill's Pain Questionnaire. A 3 mm punch skin biopsy was taken from the dorsum of the foot.

Baseline differences	Neuropad test response pink: normal, Neuropad test response patchy: abnormal, Neuropad test blue: abnormal
Follow up	Not stated
Statistical tests	Statistical analysis was performed using SPSS 15.0 for Windows. Results are presented as means ± SEM. Spearman analysis was used to test for correlation of Neuropad ranks with all other measures of neuropathy. The Mann–Whitney test was used for comparison between two groups and the Kruskal–Wallis test was used to compare more than two groups. Post hoc multi-group comparison analysis was performed by a Tukey test (in the case of equal variances as assessed by Levene's test) or a Dunnet T3 test (in the case of unequal variances) tests. A χ^2 test was used to study associations between two dichotomous variables.
Primary outcomes (including scoring methods and timings of assessments)	Fifty-seven diabetic patients (20 type 1 and 37 type 2) aged 56 ± 1.4 years were classified in accordance with the Neuropad response as: normal (n = 16), patchy (n = 16) and abnormal (n = 21). Age, BMI and HbA_{1c} did not differ between patient groups with different Neuropad responses, whereas duration of diabetes ($p < 0.01$) and severity of neuropathy assessed via NDS ($p < 0.05$) and degree of postural hypotension did. According to the NDS, 12 patients had no neuropathy (NDS < 3); 18 mild neuropathy (NDS 3–5), 15 moderate neuropathy (NDS 6–8) and 12 severe neuropathy (NDS 9–10). The NDS was significantly higher in patients with an abnormal Neuropad response (6.5 ± 0.7) compared with patients with a normal response (3.3 ± 0.6), $p < 0.05$, and the Neuropad responses correlated with the severity of neuropathy defined by the NDS ($r_s = 0.450$, $p < 0.001$). Patients were further grouped into those with NDS < 5 (40%) and NDS ≥ 5 (60%). The sensitivity of an abnormal Neuropad response (either blue or patchy) in detecting neuropathy was 85% (negative predictive value 71%), while the specificity was 45% (positive predictive value 69%).
Secondary outcomes (including scoring methods and timings of assessments)	Skin biopsies The intra-epidermal nerve fibre density (IENFD) was significantly reduced in diabetic patients (5.69±0.51) compared with 15 age and sex matched non-diabetic control individuals (11.06±0.82, p<0.001). Diabetic patients with a normal Neuropad result had a non-significant reduction in IENFD (7.37±0.93). This was significantly reduced in patients with either a patchy (5.01±0.93) or absent (5.02±0.77) result (p=0.02). IENFD correlated with the Neuropad response (Spearman's rank coefficient r_s = -0.271, p = 0.04).

Study title	**Differences in skin microcirculation on the upper and lower extremities in patients with diabetes mellitus: relationship of diabetic neuropathy and skin microcirculation. Tomešová J, Gruberova J, Lacigova S, Cechurova D, Jankovec Z Rusavy Z. Diabetes Technology & Therapeutics Vol 15, Number 11 (2013)**
Objective	To determine differences in skin microcirculatory reactivity on the upper and lower extremities (UE and LE) in patients with type 2 diabetes. Additionally, to evaluate changes in skin microcirculation independently of the individual tests for peripheral diabetic neuropathy (DN), namely the Semmes–Weinstein monofilaments, the Bio-Thesiometer, and Neuropad.
Location	Diabetology Centre of the University Hospital Pilsen, Pilsen, Czech Republic
Design	Cross-sectional
Duration	N/A
Patient population	Patients with type 2 diabetes; 27 male, 25 female
Sample size	n = 52
Inclusion criteria	Type 2 diabetes
Exclusion criteria	Patients with a defect on an LE or with such defect in their history, as well as patients with Charcot's osteoarthropathy dermatitis, or history of an allergic reaction to the substances administered were excluded. Among other exclusion criteria were ischemic heart disease (diagnosed coronary insufficiency, arrhythmia, heart failure), peripheral vascular disease (impalpable peripheral pulse, claudications), severe renal disease (classified as glomerular filtration rate under 0.5mL/s), and the use of glucocorticoids, psychoactive substances, antineoplastic agents, or bronchodilators.
Interventions and comparators	Diabetic neuropathy present in 32 patients and absent in the remaining 20.

Baseline differences	Laser Doppler iontophoresis, Peripheral DN (monofilaments 10 g), the Bio-Thesiometer Vibration Perception Threshold (VPT) meter and Neuropad.
Follow up	N/A
Statistical tests	Wilcoxon paired and unpaired tests, Kruskal– Wallis test, Spearman correlation, and multiple regression analysis. The level of significance was set to $P < 0.05$.
Primary outcomes (including scoring methods and timings of assessments)	A statistically significant reduction in skin microvascular reactivity was found in LE compared with UE after acetylcholine administration. The same trend, although statistically insignificant, was observed in the reaction with sodium nitroprusside. Based on the tests for the presence of DN, the patients were divided in a group without DN and those with a DN present. Patients without DN had a statistically significantly shorter duration of diabetes, were younger, and had a considerably lower insulin daily dose in comparison with the patients with DN.
Secondary outcomes (including scoring methods and timings of assessments)	When comparing skin microvascular reactivity separately with individual tests for diagnosis of peripheral neuropathy (microfilament, VPT, and Neuropad), a statistically significant correlation was found for each test. Impaired skin microvascular reactivity to ACH (dominant on LE) in this study was demonstrated in all patients who had at least one of the tests for the presence of DN positive. In total, 11 patients were positive only with the Neuropad (VPT and monofilaments negative). Even in this group it was possible to demonstrate an already present mirocirculatory impairment. The study confirmed a close relationship of DN and impaired skin microcirculation. In order to reduce the number of patients with diabetic foot syndrome, it is necessary to identify the risk group with present incipient neuropathy and impaired microcirculation in a fast and inexpensive way. The Neuropad test fulfills the requirement.

Study title	**Evaluation of the self-administered indicator plaster Neuropad for the diagnosis of neuropathy in diabetes. Tentolouris N, Achtsidis V, Marinou K, Katsilambros N. Diabetes Care. Feb 31(2):236-7 (2008)**
Objective	To evaluate the relative reliability between patient and health care provider of the Neuropad test in the diagnosis of peripheral neuropathy and the ease of use of the test.
Location	Medical School, University of Athens, Athens, Greece
Design	Cross-sectional
Duration	Not stated
Patient population	Patients with type 1 and type 2 diabetes
Sample size	n = 156
Inclusion criteria	Adult patients with diabetes provided they were able to read and understand the written instructions for the use and evaluation of the Neuropad.
Exclusion criteria	Patients with dyschromasia, with severe visual loss, treated with medications affecting sweating, with known allergy to cobalt, and with critical limb ischemia.
Intervention(s)	Neuropad test in clinic by health care provider and subsequently at home by the patient
Baseline differences	N/A
Follow up	No patients lost to follow up.
Statistical tests	The k statistic was used to examine the agreement between patient and health care provider in the evaluation of the Neuropad as normal or abnormal.
Primary outcomes (including scoring methods and timings of assessments)	The agreement between patient and health care provider in the evaluation of Neuropad as normal (*n* = 92) or abnormal (*n* = 49) was 90.3%. The *k* statistic to measure overall agreement between patient and health care provider as normal or abnormal was very good (0.88 [95% CI 0.85–0.91]). The evaluation of the instructions and the test by the patients (median values, interquartile range) was as follows: easiness to understand the instructions for the use of the IPN 10.0 (9.0–10.0), easiness to use Neuropad 10.0 (9.0–10.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0–10.0).
Secondary outcomes (including scoring methods and timings of assessments)	Timing: 1 week after the first visit. The first and the second evaluator were blind to the results of the test. 1. Easiness to understand the instructions for the use of Neuropad (median score =10.0; interquartile range 9.0-10.0). Method: visual analogue scale 0–10, with 0 the most difficult and 10 the easiest. 2. Easiness to the use Neuropad (median score =10.0; interquartile range 9.0-10.0). Method: visual analogue scale 0–10, with 0 the most difficult and 10 the easiest. 3. Easiness to evaluate the result of Neuropad as normal or abnormal (median score =10.0; interquartile range 8.0-10.0). Method: visual analogue scale 0–10, with 0 the most difficult and 10 the easiest. Patients were asked to report whether they required any help for self-examination. A total of 32 patients (20.5%) reported that they requested help to perform self-testing. The evaluation of the instructions and the test by the patients (median values, interquartile range) was as follows: easiness to understand the instructions for the use of Neuropad 10.0 (9.0-10.0), easiness to use Neuropad 10.0 (9.010.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0-10.0).

Study title	**The diagnostic accuracy of Neuropad for assessing large and small fibre diabetic neuropathy. Ponirakis G, Petropoulos IN, Fadavi H, Alam U, Asghar O, Marshall A, Tavakoli M, Malik RA., Diabetic Med. 31(2): 1673 – 1680 (2014)**
Objective	To assess the diagnostic performance of Neuropad against established measures of both large and, more specifically, small fibre damage in patients with diabetes
Location	Institute of Human Development, Centre for Endocrinology and Diabetes, Faculty of Medical and Human Sciences, University of Manchester and NIHR/Wellcome Trust Clinical Research Facility, Manchester Diabetes Centre, Central Manchester University Hospitals, Department of Clinical Neurophysiology, Manchester Royal Infirmary, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
Design	Cross-sectional
Duration	>1 year
Patient population	127 people with diabetes mellitus (68 with Type 1 diabetes and 59 with Type 2 diabetes) with an average age of 57 ± 10 years
Sample size	n = 127
Inclusion criteria	Patients with Type 1 and Type 2 diabetes
Exclusion criteria	A history of neuropathy as a result of a non-diabetic cause and corneal trauma or surgery
Intervention(s)	Neuropathy assessments, assessment of sudomotor functions, corneal confocal microscopy

Baseline differences	89 patients without diabetic peripheral neuropathy and 38 with
Follow up	Not stated
Statistical tests	Statistical analysis was performed using StatsDirect statistical software, version 2.7.9. Investigators examined the distribution of the data by means of relevant histograms and the Shapiro-Wilk statistical test. All data were expressed as median (5th percentile, 95th percentile). The Mann–Whitney U-test was performed to analyse differences between the medians. A P-value < 0.05 was considered statistically significant. Receiver operating characteristic curve analysis was used to compare the diagnostic accuracy of Neuropad against measures of large and small nerve fibre damage and neuropathy symptoms. Receiver operating characteristic curve analysis established the area under the curve to determine the optimal sensitivity and specificity of the Neuropad test. Statistical difference between two receiver operating characteristic curves were expressed in P-values.
Primary outcomes (including scoring methods and timings of assessments)	In 127 people with diabetes aged 57.0 ± 9.7 years, 38 were diagnosed with peripheral neuropathy. The demographic and clinical characteristics of the participants with (n = 38) and without (n = 89) peripheral neuropathy are presented in Table 1. HbA1c, BMI, cholesterol and triglyceride levels did not differ between the two groups, but age (P = 0.01), duration of diabetes (P = 0.01) and blood pressure (systolic: P = 0.0004; diastolic: P = 0.05 were significantly greater in those with peripheral neuropathy. There were significant differences for the large fibre tests, comparing the group without diabetic peripheral neuropathy to the group with: Neuropathy Disability Score (NDS) (P < 0.0001), vibration perception threshold (VPT) (P < 0.0001), sensory nerve action potential (SNAP) (P < 0.0001), sensory nerve conduction velocity (SNCV) (P = 0.0004), peroneal motor nerve action potential (PMNAP) (P < 0.0001) and peroneal motor nerve conduction velocity (PMNCV) (P < 0.0001). Similarly, there were significant differences for the small fibre tests: warm perception threshold (WPT) (P < 0.0001), corneal nerve fibre density (CNFD) (P = 0.0002), corneal nerve fibre length (CNFL) (P < 0.0001) and Neuropad (P <

	0.0001). Neuropathic symptoms were also significantly different between the groups. Neuropad response was significantly lower in the group with diabetic peripheral neuropathy (50%, 0– 100) compared with the group without (90%, 8–100). The evaluation of Neuropad's percentage colour change was subjective, but the reproducibility was good. The coefficient of repeatability for intra- and inter-observer variability was 0.3 and 0.4, respectively.
Secondary outcomes (including scoring methods and timings of assessments)	The sensitivity and specificity of Neuropad for detecting large nerve fibre damage based on the Neuropathy Disability Score (NDS) was 70% and 50% respectively, for the vibration perception threshold (VPT) 83% and 53%, for sensory nerve action potential (SNAP) 70% and 64%, for sensory nerve conduction velocity (SNCV) 64% and 54%, for peroneal motor nerve action potential (PMNAP) 82% and 50% and for peroneal motor nerve conduction velocity (PMNCV) 81% and 54%, respectively. For small nerve fibre assessment using the warm perception threshold as a reference method, the sensitivity and specificity were 68% and 49%, respectively. However, sensitivity and specificity were significantly improved versus corneal nerve fibre length, with a sensitivity of 83% and specificity of 80%. Whilst the sensitivity of Neuropad in detecting diabetic peripheral neuropathy was high for measures of both large and small fibre damage, it showed high specificity only for small fibre neuropathy identified using corneal nerve fibre length as a reference method. The area under the curve for corneal nerve fibre length (85%) was significantly larger than for the Neuropathy Disability Score (NDS) (66%, P = 0.01), sensory nerve conduction velocity (SNCV) (63%, P = 0.006), peroneal motor nerve action potential (PMNAP) (69%, P = 0.04), peroneal motor nerve conduction velocity (PMNCV) (70%, P = 0.03) and was borderline significant against vibration perception threshold (73%, P = 0.06) and sensory nerve action potential (SNAP) (70%, P = 0.07). However, this high sensitivity and specificity could not be replicated against corneal nerve fibre density, which showed good sensitivity (74%) but relatively low specificity (60%). With neuropathic symptoms (DNS), the sensitivity was 78% and specificity 60%.

Study title	**Moisture status of the skin of the feet assessed by the visual test Neuropad correlates with foot ulceration in diabetes. Tentolouris N, Voulgari C, Liatis S, Kokkinos A, Eleftheriadou I, Makrilakis K, Marinou K, Katsilambros N. Diabetes Care 33:1112–1114 (2010)**
Objective	To examine the association between the moisture status of the skin of the feet with foot ulceration in subjects with diabetes
Location	Medical School, University of Athens, Athens, Greece
Design	Cross-sectional
Duration	14 months
Patient population	Patients with type 1 and type 2 diabetes
Sample size	n = 379
Inclusion criteria	Patients with diabetes
Exclusion criteria	Age >75 years, ankle- brachial pressure index <0.5, estimated creatinine clearance rate using the formula of Cockcroft-Gault <30 ml/min, amputation, significant foot swelling or infection, and causes of neuropathy other than diabetes
Intervention(s)	Assessment for peripheral neuropathy was based on symptoms (neuropathy symptom score [NSS]) and signs (neuropathy disability score [NDS]). Vibration perception threshold (VPT) was assessed using a biothesiometer (Biomedical Instruments, Newbury, OH) and the 10g Semmes-Weinstein monofilament (Bailey Instruments, Manchester, U.K.) perception. Monofilament was applied three times on three plantar sites (under the great toe and first and fifth metatarsal heads). Inability to perceive the monofilament at any site was considered abnormal. The Neuropad was applied for 10 min under the first metatarsal head in the sitting position at both feet and evaluated as normal (pink colour) or abnormal (blue colour or any other combination of colours). Peripheral artery disease was diagnosed in the presence of any of the following: history of intermittent claudication or revascularization procedure at the leg arteries, diminished or non-palpable pedal pulses, and ankle-brachial

	pressure index <0.9.
Baseline differences	Participants with foot ulcers (n = 121) as compared to those without foot ulcers (n = 258) were more often males (69.4% vs 50.4%, P=0.001), had longer diabetes duration (18 yrs vs 10 yrs, P<0.001), had higher HbA1c values (9.2 vs 7.4%, P<0.001), had worse indices on neurologic examination (NDS, VPT, monofilament testing, all P <0.001) and more commonly had abnormal Neuropad test results (95% vs 52.3%, P <0.001).
Follow up	No follow up
Statistical tests	Differences between the studied groups were tested using parametric or nonparametric methods according to the specific indications, whereas a chi square test was used to compare categorical data. Univariate and multivariate logistic regression analyses (stepwise backward method) were performed to look for associations between the studied parameters with foot ulceration. The area under the receiver operating characteristic (ROC) curve of various established risk factors for foot ulceration and of the Neuropad test was calculated. The area under the ROC curve indicates how informative a test for the prediction of foot ulceration is. P values < 0.05 were considered statistically significant.
Primary outcomes (including scoring methods and timings of assessments)	Multivariate logistic regression analysis after adjustment for age, sex, duration of diabetes, Hb A1C, NSS, and peripheral artery disease status demonstrated that the odds of foot ulceration increased with higher NDS [NDS≥6 vs. <6; OR 6.70, 95% confidence intervals (3.31-13.35)] , VPT (VPT ≥25 vs. <25 V; 11.91, 6.03-21.86) monofilament insensitivity vs. sensitivity (6.40, 3.09-13.28) as well as with an abnormal Neuropad result vs. a normal one (16.28 (6.27-38.24).
Secondary outcomes (including scoring methods and timings of assessments)	The area (±SE) under the ROC curve for the identification of patients with foot ulceration of VPT ≥25 vs. <25 V was 0.76 ± 0.02 (P <0.001; sensitivity 85.4%; specificity 67.6%), of NDS≥6 vs. <6 was 0.76 ± 0.02 (P < 0.001; sensitivity 75.7%; specificity 77.8%), of monofilament result (insensitivity vs. sensitivity) was 0.72 ± 0.03 (P <0.001; sensitivity 57.4%; specificity 86.3%), and of the Neuropad

	result (abnormal vs. normal) was 0.71± 0.03 (P <0.001; sensitivity 97.1%; specificity 49.3%). The area under the ROC curve of Neuropad testing did not differ significantly from that of VPT, NDS, and monofilament examination. No adverse events were observed from Neuropad use.

Study title	**A prospective study on the use of the indicator test Neuropad for the early diagnosis of peripheral neuropathy in type 2 diabetes. Papanas N, Papatheodorou K, Papazoglou D, Kotsiou S, Maltezos E. Exp Clin Endocrinol Diabetes. Feb 119(2) (2011)**
Objective	To evaluate the contribution of the indicator test Neuropad for sudomotor function to the early diagnosis of peripheral neuropathy in patients with type 2 diabetes mellitus.
Location	Outpatient Clinic of Obesity, Diabetes and Metabolism in the Second Department of Internal Medicine, Democritus University of Thrace, Greece
Design	Prospective cross-sectional
Duration	5 years
Patient population	109 type 2 diabetic patients (55 men, 54 women, mean age 56.15 ± 6.14 years and mean diabetes duration 3.51 ± 1.09 years)
Sample size	n = 109
Inclusion criteria	Patients with type 2 diabetes whose initial clinical examination (Neuropathy Disability Score, NDS) was negative for neuropathy.
Exclusion criteria	Age <17 years or >75 years, peripheral arterial occlusive disease, other potential causes of neuropathy (end-stage renal failure, alcohol abuse, Vitamin B12 depletion, malignancy, peripheral nerve lesions), thyroid disease, drugs (corticosteroids, antihistaminic and psychoactive drugs) which may affect sweating, as well as certain skin diseases (neurodermatitis, psoriasis, scleroderma, allergy to certain metals (chrome and cobalt), Raynaud syndrome, hyperhidrosia, acrocyanosis.
Intervention(s)	Neuropad assessments.

Baseline differences	70 patients had a normal Neuropad response on first examination; 39 patients had an abnormal Neuropad response on first examination.
Follow up	The first examination was performed between January and June 2004. Patients were re-examined 5 years later, between January and June 2009. On both occasions, patient evaluation comprised clinical examination for neuropathy by means of NDS, application of Neuropad and general physical examination.
Statistical tests	Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), Chicago, Illinois) version 13.0. Normally distributed quantitative variables were analysed by unpaired t-test. Qualitative variables were compared by Fisher's exact test (after Yates' correction where appropriate). The correlation between time until complete colour change of the test and NDS was evaluated by Spearman's rank coefficient. Agreement between NDS and Neuropad in the diagnosis of neuropathy was evaluated by the Kappa coefficient. Data were expressed as mean ±1 Standard Deviation ($\bar{X}$ ± 1SD). Significance was defined at a level of 5% ($p < 0.05$).
Primary outcomes (including scoring methods and timings of assessments)	Initially, 70 patients (64.22%) had normal and 39 (35.78%) patients had abnormal Neuropad results defined as groups A and B, respectively. On both examinations, there was 100% agreement between abnormal Neuropad response on the right and left foot. There was no change of Neuropad from abnormal to normal between the first and second examination. 2 patients from group A developed sudomotor dysfunction (abnormal Neuropad response) on re-examination, without developing neuropathy. NDS was significantly higher in group B vs. group A, on both first (4.23 ± 0.99 vs. 2.97 ± 0.72, $p < 0.001$) and second examination (4.63 ± 1.33 vs3.39 ± 0.91, $p < 0.001$).
Secondary outcomes (including scoring methods and timings of assessments)	At the second examination, 2/70 patients (2.86%) in group A and 10/39 patients (25.64%) in group B had developed neuropathy. Neuropathy was significantly ($p = 0.001$) more frequent in group B. On the second examination, Neuropad had 83.33% sensitivity and 68.04% specificity for neuropathy, as evaluated by NDS. There were 31 false positives and 2 false negatives. There
	was a modest but significant agreement (kappa = 0.259, $p < 0.001$) between Neuropad and NDS for the diagnosis of neuropathy.

7.5.1 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

N/A

7.5.2 Highlight any differences between patient populations and methodology in all included studies.

N/A

7.5.3 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

N/A

7.5.4 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

N/A

7.5.5

N/A

7.5.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

N/A

7.6 Critical appraisal of relevant studies

7.6.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7 Critical appraisal of randomised control trials

Study name		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?		
Was the concealment of		

treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

Study name		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort		

recruited in an acceptable way?		
Was the exposure accurately measured to minimise bias?		
Was the outcome accurately measured to minimise bias?		
Have the authors identified all important confounding factors?		
Have the authors taken account of the confounding factors in the design and/or analysis?		
Was the follow-up of patients complete?		
How precise (for example, in terms of confidence interval and p values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.7 Results of the relevant studies

7.7.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9 Outcomes from published and unpublished studies

Study name		
Size of study groups	**Treatment**	
	Control	
Study duration	**Time unit**	
Type of analysis	**Intention-to-treat/per protocol**	
Outcome	**Name**	
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Other outcome	**Name**	
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Comments		

7.7.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

N/A

7.8 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.8.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

No adverse events with Neuropad have been reported or disclosed as far as we are aware.

7.8.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

N/A

Table B10 Adverse events across patient groups

CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency						

7.8.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

N/A

7.8.4 Provide a brief overview of the safety of the technology in relation to the scope.

Neuropad is a low risk CE medical device Class I and is strictly for external use only. It should not be applied to any part of the body except the sole of the foot. If the skin

of the foot is badly cracked or if there obvious fissures or open wounds or the there are signs of local inflammation (red skin) the Neuropad should not be applied . Neuropads must not come into contact with the eyes or any mucus membranes and must not be inhaled or injected. People with a known intolerance to chromium, nickel or cobalt should not apply a Neuropad test pad.

The medically modified plaster substrate comprises a transparent polyolefin film and the adhesive used to stick the Neuropad on to a person's sole is a hypoallergenic medical grade polyacrylate glue. The indicator pad material is 100% viscose, binder reinforced.

7.9 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.9.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

An independent meta-analysis has been provided in this submission.

7.9.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A

7.10 Interpretation of clinical evidence

7.10.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Neuropad has been validated against both primary and secondary care diagnostic tests. The clinical efficacy of Neuropad has been determined in over 40 clinical studies, involving more than 1000 diabetic patients. The sensitivity of Neuropad is comparable with NCS and the neuropathy disability score (NDS), which significantly exceeds that seen with the monofilament and tuning fork tests. Furthermore, Neuropad has good sensitivity and specificity in the detection of patients with intermediate or high risk for foot ulceration determined by comparison with neurological deficits and vibration perception threshold (VPT)

Papanas et al., (2008). As Neuropad may detect neuropathic deficits before monofilament and vibration perception testing, it has potential as a screening test for early neuropathy and referral onward to specialist podiatry care. It may also be particularly useful in patients with communication or language difficulties who may not respond accurately to tests such as SWME monofilament.

Current primary-care tests for neuropathy are subjective and therefore prone to false negative and positive results. Neuropad is a non-subjective test with a sensitivity, specificity and reliability comparable to established secondary-care diagnostics. *Zick et al., (2003; Papanas et al., (2007); Papanas et al., (2008); Quattrini et al., (2008); Liatis et al., (2007);*

We propose that Neuropad could allow patients with neuropathy to be diagnosed earlier than is possible with current tests, allowing clinicians to target and triage those patients who should undergo more intense multifactorial intervention. *Gaede et al., (1999).*

7.10.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

All relevant identified studies have been conducted independently without either Sponsor or Manufacturer support or involvement other than in some cases the provision of free Neuropad tests. In addition, the Tsapas 2014 meta-analysis was entirely independently conducted. The weaknesses of published and unpublished studies may be the sample size and that there are no published prospective studies or randomized trials assessing the test's effectiveness. One of the principal advantages of implementing screening with Neuropad of patients with diabetes is the change of timeframe achieved in identification and potentially treatment of diabetic foot problems though earlier identification of at-risk patients.

7.10.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

7.10.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The published and unpublished clinical evidence provided is specifically related to sudomotor dysfunction in patients with diabetes and testing with the Neuropad in comparison with other established secondary care and primary care tests.

7.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Most studies, though principally European, were conducted outside the UK by investigators not working within the UK NHS.

7.10.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Patients with diabetes not having an existing diagnosis of DPN would all be eligible for testing with Neuropad either as part of the recommended annual diabetic foot examination, through screening, particularly of those patients failing to, unwilling, or unable to attend for an annual diabetic foot examination and also those patients,

particularly resident in care homes who due to cognitive, auditory or other impairment are unable to respond subjectively to testing with SWME or other sensory tests.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

Response

Health economics studies should include all types of economic evaluation and cost studies, including cost analyses and cost-effectiveness and budget-impact analyses. The methods used should be justified with reference to the decision problem.

Sufficient detail should be provided to enable the methods to be reproduced (the External Assessment Centre must be able to reproduce the search), and the rationale for any inclusion and exclusion criteria regarding search terms should be used.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria
Population
Interventions
Outcomes
Study design
Language restrictions
Search dates
Exclusion criteria
Population
Interventions
Outcomes
Study design
Language restrictions
Search dates

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Response

It is recommended that the number of published studies included and excluded at each stage is reported using the PRISMA statement flow diagram (available from *www.prisma-statement.org/statement.htm*)

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Outcome measures should be included if applicable. Patient outcomes could include gains in life expectancy, improved quality of life, longer time to recurrence, and comparative costs.

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Study 1 (20xx)						
Study 2 (20xx)						
Study 3 (20xx)						

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3 Quality assessment of health economic studies

Study name		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
8. Was/were the source(s) of effectiveness estimates used stated?		
9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		

13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		
25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives		

compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

A de novo cost analysis was developed to assess the impact on costs and outcomes of Neuropad as a test for diabetic neuropathy compared to the standard test with 10 g monofilament alone and together, from a UK NHS and personal social services perspective, as it has been outlined in the scope.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

As it has been outlined in the scope, the patient population included in the study refers to people who suffer from diabetes and are at risk of developing diabetic neuropathy, which could lead to foot ulcer and minor and major lower limbs amputations and even death in the long-run.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

Not applicable – there is no deviation from the scope.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

The cost-effectiveness of Neuropad was determined using a Markov model to simulate the health and economic outcomes of foot care in a hypothetical population of people with diabetes. Markov models are particularly useful in economic evaluations of progressive chronic conditions[1], as it is the case of diabetes and diabetic foot disease. Within Markov models, individuals are allocated into health states, with each state having specific costs and health outcomes, operating in cycles. People remain in each health state for one

cycle and can progress to a separate state at the end of the cycle or remain in the same state.

The current model contains six health states: no neuropathy, neuropathy, infected foot ulcer, minor amputation, major amputation and healed foot. Cycle length in this analysis will be of six months and the model covers a 3-year period.

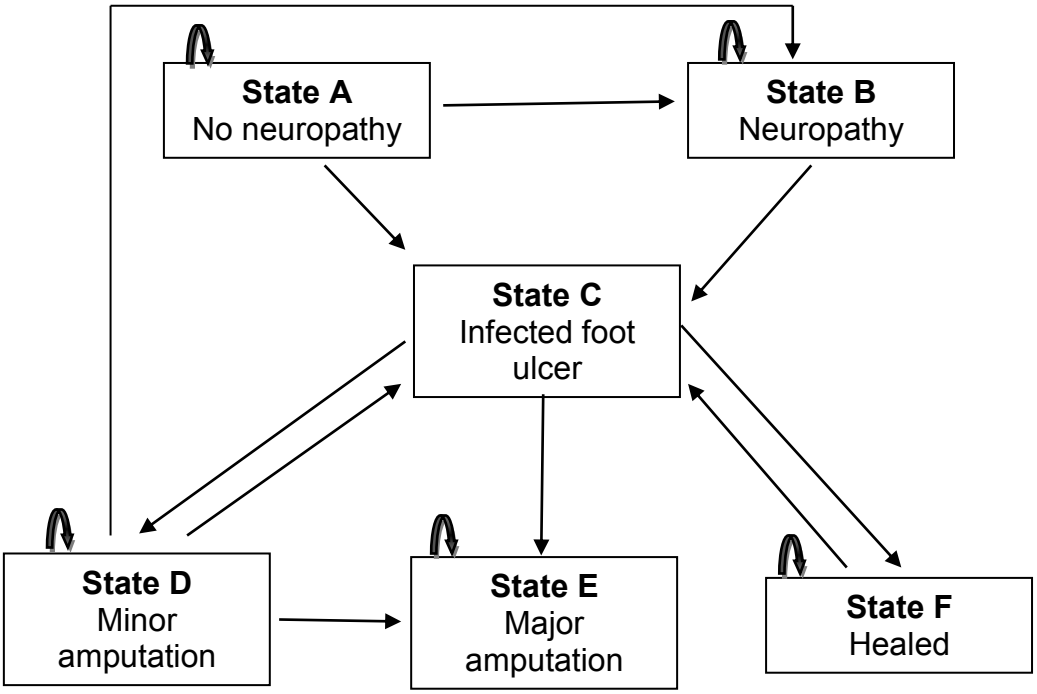


Figure 1: Model structure

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model is based on the clinical pathway previously described in section 3.3. The de novo economic model was developed using Microsoft Excel to estimate the cost-effectiveness derived from using Neuropad test as a diagnostic tool of diabetic neuropathy, alone and together with the 10-g Semmes-Weinstein Monofilament Examination (SWME), compared to using only the NHS standard care. The overall costs and outcomes will finally be compared between scenarios.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table C4: Cost model assumptions

Assumption	Justification
Individuals entering the model have to make a decision between the test to be taken: Neuropad or SWME. If Neuropad and an abnormal result is obtained, they would undergo the SWME test as well or not.	In line with the scope: compare the use of Neuropad + SWME vs SWME alone and Neuropad vs SWME
Patient survival is considered to be the same regardless of the test choice	There is no data to suggest otherwise; the aim is to promote early-detection and prevention of disease progression
Neuropad and SWME will be purchased only once (at the beginning, cycle 1)	
Time horizon of the model = 3 years	The Neuropad life span/shelf life is 3 years[2].
Within this 3-year period, mortality is not considered.	Previously neglected in another study analysing the cost-effectiveness of a tool to improve glycaemic control in people with diabetes at risk of developing neuropathic foot ulcers[3].
Neuropad sensitivity = 86% and specificity = 65%	Recent meta-analysis about the diagnostic accuracy of Neuropad[4].
SWME sensitivity = 98.5% and specificity = 55%	Study aiming to compare different diagnosis tests of neuropathy, being SWME one of them[5].
Purchase price Neuropad (to NHS, excluding VAT) = £7.28	Reference 2
Purchase price SWME (to NHS, excluding VAT) = £16.80	Reference 2
Associated costs (staff time/ training/ infrastructure) have not been included in the cost analysis	No costs associated with Neuropad, but SWME does require trained healthcare professional to perform the test, but not certained about how much staff time need to be to

	interpret an abnormal result of the test[2].
Cost per patient/use was neglected for both screening tools	It is uncertain how many times 1 monofilament can be used: some report they are reusable, some other state they should be replaced between patients to reduce infections[2]
Cost of stumps of amputations will be included in the cycle at which the amputation takes place, but also in the succeeding cycles as a cost of care for amputations	There is no data to suggest otherwise

9.1.7 Define what the model's health states are intended to capture.

State A represents the healthiest individuals, with no signs of diabetic neuropathy (so being healthy does not mean no disease, but no neuropathy), but still suffering from diabetes. State B refers to those who have been diagnosed of neuropathy, and State C includes patients who already have an infected foot ulcer. State D and E refer to patients who have progressed to minor and major, respectively, lower limb amputation. State F refers to ulcers that have been healed. The arrows in the model show how patients can progress through the model over the cycles.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C5 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Discount of 3.5% for costs	A discount rate of 3.5% is applied to all costs beyond 1 year	Recommended by NICE technology evaluation programme (NICE 2011)	NICE 2011
Discount of 3.5% for QALYs	A discount rate of 3.5% is applied to all QALYs beyond 1 year	QALYs should be discounted as costs are since health gains are also tradable	Claxton et al., 2011[6] Claxton et al., 2006[7]
Perspective (NHS/PSS)	UK NHS and PSS perspective	Recommended by NICE technology evaluation programme (NICE 2011)	NICE 2011
Threshold value	£30,000		NICE 2011
Cycle length	6 months	Consistent with the relevant clinical pathway	
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Outcomes from five different studies were used as utilities and probabilities in the de novo model.

1. Redekop, W. K.; Stolk, E. A.; Kok, E.; Lovas, K.; Kalo, Z.; Busschbach, J. J. V. “Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments” Diabetes Metab (2004) 30: 549-556

2. Ortegon, M. M.; Redekop, W. K.; Niessen, L. W. “Cost-effectiveness of prevention and treatment of the diabetic foot” Diabetes Care (2004) 27:901-907

3. Green, W. and Taylor. M. “Cost-effectiveness analysis of d-Nav for people with diabetes at high risk of neuropathic foot ulcers” Diabetes Ther (2016) 7: 511-525

4. Ragnarson Tennvall, G.; Apelqvist, J. “Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations” Diabetologia (2001) 44:2077-2087

5. Kostev, K.; Jockwig, A.; Hallwachs, A.; Rathmann, W. “Prevalence and risk factors of neuropathy in newly diagnosed type 2 diabetes in primary care practices: a retrospective database analysis in Germany and UK” Primary Care Diabetes (2014) 8(3): 250-255

Numbers 1 to 4 have been used for the utilities data, whereas the second, fourth and fifth papers have been of help for the estimation of transition probabilities between the different health states considered in the economic model.

The first four studies used in the current analysis aim to analyse the cost-effectiveness of different treatments or programmes for diabetic neuropathy and/or diabetic foot ulcers, using a Markov model approach, as it is done here.

It should be mentioned that utilities will be discounted at 3.5% after year 1, so no discount will be applied during cycle 1 (6 months) and 2 (12 months). In cycles 3 (18 months) and 4 (24 months), a 3.5% discount will be applied to the initial utility value, whereas in cycles 5 (30 months) and 6 (36 months), the discount will be applied to the utility values in cycles 3 and 4.

Table C6 Base Case Analysis utilities attached to health states

Health state	Utility value	95% CI	Reference
No active ulcer – no previous amputation	0.84	(0.81, 0.87)	Redekop et al., 2004[8]
No active ulcer – only 1 + toes amputated	0.74	(0.70, 0.78)	Redekop et al., 2004[8]
No active ulcer – one foot amputated	0.68	(0.63, 0.72)	Redekop et al., 2004[8]
No active ulcer – one leg amputated	0.62	(0.57, 0.67)	Redekop et al., 2004[8]
No active ulcer – both feet or legs amputated	0.51	(0.46, 0.55)	Redekop et al., 2004[8]
Active uninfected ulcer – no previous amputation	0.75	(0.71, 0.79)	Redekop et al., 2004[8]
Active uninfected ulcer – only 1 + toes amputated	0.68	(0.64, 0.73)	Redekop et al., 2004[8]
Active uninfected ulcer – one foot amputated	0.63	(0.59, 0.68)	Redekop et al., 2004[8]
Active uninfected ulcer – one leg amputated	0.57	(0.53, 0.62)	Redekop et al., 2004[8]
Active infected ulcer – no previous amputation	0.70	(0.66, 0.75)	Redekop et al., 2004[8]
Active infected ulcer – only 1 + toes amputated	0.65	(0.60, 0.69)	Redekop et al., 2004[8]
Active infected ulcer – one foot amputated	0.59	(0.54, 0.63)	Redekop et al., 2004[8]
Active infected ulcer – one leg amputated	0.55	(0.50, 0.59)	Redekop et al., 2004[8]
No neuropathy	0.84		Ortegon et al., 2004[9]
Neuropathy	0.74		Ortegon et al., 2004[9]
After healing with minor amputation	0.61		Ragnarson et al., 2001[10]

Table C7 Base Case Analysis transition probabilities

Health state	Value	Reference
Neuropathy prevalence (%)	2.4	Kostev et al., 2014[11]
No neuropathy – no neuropathy (%)	96.08	Ortegon et al., 2004[9]
No neuropathy – neuropathy (%)	2.37	Ortegon et al., 2004[9]
No neuropathy – infected foot ulcer (%)	1.54	Ragnarson et al., 2001[10]
Neuropathy – neuropathy (%)	94.90	Ortegon et al., 2004[9]
Neuropathy – infected foot ulcer (%)	5.10	Ortegon et al., 2004[9]
Infected foot ulcer – infected foot ulcer (%)	8.00	Ragnarson et al., 2001[10]
Infected foot ulcer – minor amputation (%)	35.00	Ragnarson et al., 2001[10]
Infected foot ulcer – major amputation (%)	17.00	Ragnarson et al., 2001[10]
Infected foot ulcer – healing (%)	40.00	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Minor amputation – neuropathy (%)	9.60	Ortegon et al., 2004[9]
Minor amputation – infected foot ulcer (%)	4.40	Ragnarson et al., 2001[10]
Minor amputation – minor amputation (%)	69.00	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Minor amputation – major amputation (%)	17.00	Ortegon et al., 2004[9]
Major amputation – major amputation (%)	100	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Healing – infected foot ulcer (%)	3.90	Ortegon et al., 2004[9]
Healing – healing (%)	96.10	Ortegon et al., 2004[9]

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Not applicable

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used and what other evidence is there to support it?

The patient pathway at each cycle and the following depends on the progression of the disease, as it is shown in Figure 1. The link between the outcome in a given specific cycle of the model and the final outcome will be determined by the transition probabilities, which refer to the likelihood of moving from one health state to another when a new cycle takes place.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Not applicable.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

In order to show the appropriate disease progression over time, we looked for guidance from medical doctors with expertise on diabetes and diabetes-related complications, particularly on diabetic neuropathy and diabetic foot ulcers, as prof. Alan Sinclair and prof. Mike Kirby. There were no conflicts of interest.

Professor Alan Sinclair FRCP

Professor Sinclair, an endocrinologist by speciality, is an internationally and nationally recognised researcher in the field of diabetes in older people. He is a World Health Organization (WHO)-recognised expert in diabetes and in 2014 was appointed to the WHO and International Association of Gerontology and Geriatrics (IAGG) Expert Group on Frailty reflecting his work in the area of diabetes and frailty.

The IDF (International Diabetes Federation) appointed Prof Sinclair to Co-Lead the Working party to produce Global Guidance on Managing Diabetes in Older People which is now published and available on the IDF website. Prof

Sinclair was the first to be appointed by the Department of Health to the position of National Clinical Lead for Diabetes in Older People. He is currently leading discussions for the Joint British Diabetes Societies (JBDS) with the Care Quality Commission (CQC) for developing quality diabetes standards in UK care homes: this follows on from his leadership of the first National Diabetes Audit in Care Homes (2013-4).

Professor M J Kirby FRCP

Professor Kirby has worked in the NHS for 36 years as a primary care physician. He also held two appointments in the cardiology department at Queen Elizabeth II Hospital and was responsible for the North Hertfordshire PCT echocardiography service. He was appointed Director of the Hertfordshire Primary Care Research Network in 1997 and more recently Consultant to Clinical Trials Coordinating Centre (CTCC). He is an Associate Member of The British Association of Urological Surgeons and Fellow of the Royal College of Physicians.

Professor Kirby is editor of the Primary Care Cardiovascular Journal and is on the Editorial Board of the British Journal of Diabetes and Vascular Disease, International Journal of Clinical Practice, The British Journal of Cardiology, Geriatric Medicine and the British Journal of Primary Care Nursing. Professor Kirby has written and lectured to a wide international audience on men's health, urology, erectile dysfunction, cardiovascular disease and diabetes. He has published more than 200 clinical papers and 23 books.

Criteria for selecting the experts

- Knowledge about diabetic foot care in England
- Awareness of current diabetic foot screening in England
- Medical background and specific knowledge on diabetic neuropathy so as to provide useful information on the economic model structure

Experts approached

We approached two experts, who have been mentioned previously: Professor. Alan Sinclair and Professor M J Kirby.

All information provided was internally consistent and consistent with the existing literature.

Information was gathered by in-person meetings, by email or by tele-conference communications.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C8 Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)	Source
Utility values assigned to specific health states*. 95%CI given, if available			
No active ulcer – no previous amputation	0.84	(0.81, 0.87)	Redekop et al., 2004[8]
No active ulcer – only 1 + toes amputated	0.74	(0.70, 0.78)	Redekop et al., 2004[8]
No active ulcer – one foot amputated	0.68	(0.63, 0.72)	Redekop et al., 2004[8]
No active ulcer – one leg amputated	0.62	(0.57, 0.67)	Redekop et al., 2004[8]
No active ulcer – both feet or legs amputated	0.51	(0.46, 0.55)	Redekop et al., 2004[8]
Active uninfected ulcer – no previous amputation	0.75	(0.71, 0.79)	Redekop et al., 2004[8]
Active uninfected ulcer – only 1 + toes amputated	0.68	(0.64, 0.73)	Redekop et al., 2004[8]
Active uninfected ulcer – one foot amputated	0.63	(0.59, 0.68)	Redekop et al., 2004[8]
Active uninfected ulcer – one leg amputated	0.57	(0.53, 0.62)	Redekop et al., 2004[8]
Active infected ulcer – no previous amputation	0.70	(0.66, 0.75)	Redekop et al., 2004[8]
Active infected ulcer – only 1 + toes amputated	0.65	(0.60, 0.69)	Redekop et al., 2004[8]
Active infected ulcer – one foot amputated	0.59	(0.54, 0.63)	Redekop et al., 2004[8]
Active infected ulcer – one leg amputated	0.55	(0.50, 0.59)	Redekop et al., 2004[8]
No neuropathy	0.84	NR	Ortegon et al., 2004[9]
Neuropathy	0.74	NR	Ortegon et al., 2004[9]
After healing with minor amputation	0.61	NR	Ragnarson et al., 2001[10]
Transition probabilities between health states			
Sensitivity Neuropad (%)	86	(79 – 91)	Tsapas et al., 2014[4]

Specificity Neuropad (%)	65	(51 – 76)	Tsapas et al., 2014[4]
Sensitivity SWME (%)	98.5	NR	Mythili et al., 2010[5]
Specificity SWME (%)	55	NR	Mythili et al., 2010[5]
Neuropathy prevalence (%)	2.4	NR	Kostev et al., 2014[11]
Minor amputations prevalence (%)	57.10	NR	Kerr, 2017[12]
Major amputations prevalence (%)	42.90	NR	Kerr, 2017[12]
No neuropathy – no neuropathy (%)	96.08	NR	Ortegon et al., 2004[9]
No neuropathy – neuropathy (%)	2.37	NR	Ortegon et al., 2004[9]
No neuropathy – infected foot ulcer (%)	1.54	NR	Ragnarson et al., 2001[10]
Neuropathy – neuropathy (%)	94.90	NR	Ortegon et al., 2004[9]
Neuropathy – infected foot ulcer (%)	5.10	NR	Ortegon et al., 2004[9]
Infected foot ulcer – infected foot ulcer (%)	8.00	NR	Ragnarson et al., 2001[10]
Infected foot ulcer – minor amputation (%)	35.00	NR	Ragnarson et al., 2001[10]
Infected foot ulcer – major amputation (%)	17.00	NR	Ragnarson et al., 2001[10]
Infected foot ulcer – healing (%)	40.00	NR	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Minor amputation – neuropathy (%)	9.60	NR	Ortegon et al., 2004[9]
Minor amputation – infected foot ulcer (%)	4.40	NR	Ragnarson et al., 2001[10]
Minor amputation – minor amputation (%)	69.00	NR	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Minor amputation – major amputation (%)	17.00	NR	Ortegon et al., 2004[9]
Major amputation – major amputation (%)	100	NR	Ortegon et al., 2004[9] Ragnarson et al., 2001[10]
Healing – infected foot ulcer (%)	3.90	NR	Ortegon et al., 2004[9]
Healing – healing (%)	96.10	NR	Ortegon et al., 2004[9]
Costs applied in the economic analysis*			
6 months cost per patient of primary and community care if neuropathy	£1,855.92	NR	Kerr, 2017[12]
6 months cost per	£8,620.8	NR	Kerr, 2017[12]

patient of primary and community care if infected foot ulcer			
6 months cost per patient of inpatient care for minor amputations	£2,105.89	NR	Kerr, 2017[12]
6 months cost per patient of inpatient care for major amputations	£4,106.85	NR	Kerr, 2017[12]
6 months cost per patient of inpatient care for procedures on stumps	£2,812.30	NR	Kerr, 2017[12]
6 months cost per patient of inpatient care for foot ulcers	£3,227.27	NR	Kerr, 2017[12]
6 months cost per patient of no neuropathy	£125,04		Green and Taylor, 2016[3]
Transition cost from infected foot ulcer to amputation **	£9,407	(£3,395 – 74,387)	Ragnarson et al., 2001[10]
Purchase price of Neuropad	£7.28	NR	Reference 2
Purchase price of 10-g SWME	£16.80	NR	Reference 2
Discount rate			
Discount rate (%) for any costs or QALYs beyond one year	3.5		NICE 2011 Claxton et al., 2011[6] Claxton et al., 2006[7]
NR: not reported *QALYs and costs discounted in cycles 3, 4, 5 and 6 ** Costs were originally Euros, so they have been convert to pounds and 2015 prices			

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The patients included in the scope are those who have diabetes and are at risk of developing neuropathy and it has to be tested, using Neuropad or 10-g

SWME. The following Health Resource Groups (HRGs) codes are currently used:

Table C9 HRGs codes for Neuropad and SWME

Tool	Price	HRG	Description
Neuropad	£7.28	KB03E	Diabetes with lower limb complications, with CC score 0-4
10-g SWME	£16.8	KB03E	Diabetes with lower limb complications, with CC score 0-4

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

In the cost analysis of Neuropad as a diagnostic test of neuropathy, the operations or procedures that take place are mainly amputations, whose OPCS codes are detailed in the below table:

Table C10 OPCS codes for operations and procedures considered in the model

Operation/procedure	OPCS code
Amputation of leg below knee	X095
Amputation through metatarsal bones	X104
Amputation of phalanx of toe	X112
Other specified amputation of toe	X118

Unspecified amputation of toe	X119
Reamputation ta higher level	X121
Revision of coverage of amputation stump	X124
Drainage of amputation stump	X125
Other specified operations on amputation stump	X128

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Targeted searches were performed to identify relevant and suitable point estimates (costs of care and utilities for specific health states) given the scope of the analysis. The literature has previously been mentioned and described for the different model inputs.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

Not applicable

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

Table C11 Price for the technology

Price of technology	Value	95% CI	Reference
Purchase price of Neuropad	£7.28	NR	Reference 2
Purchase price of 10-g SWME	£16.80	NR	Reference 2

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

Not applicable

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table C12 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£7.28	Reference 2
Consumables (if applicable)	0	Reference 2
Maintenance cost	N/A	Reference 2
Training cost	0	Reference 2
Other costs	N/A	Reference 2
Total cost per treatment/patient	£7.28	Reference 2

Table C13 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	£16.8	Reference 2
Consumables (if applicable)	£14.28 per 100 filaments*	Reference 2
Maintenance cost	N/A	Reference 2
Training cost	Requires trained healthcare professional time to perform test, but this is not known	Reference 2
Other costs	N/A	Reference 2
Total cost per treatment/patient	£16.8	Reference 2
* As in the analysis is considered as a single-use technology used in the first cycle of the model, these costs will not be considered		

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Table C14 List of health states and associated costs in the economic model if Neuropad is used as the diagnostic test

Health states	Items	Value	Reference
No neuropathy	**Technology cost**	£7.28	Reference 2
	Cost of care	£125.04	Green and Taylor, 2016[3]
	Total	£132.32	
Neuropathy	**Technology cost**	£7.28	Reference 2
	Cost of care	£1,855.92	Kerr, 2017[12]
	Total	£1,863.2	
Infected foot ulcer	**Technology cost**	£7.28	Reference 2
	Cost of care	£11,848.07	Kerr, 2017[12]
	Total	£11,855.35	
Minor amputation	**Technology cost**	£7.28	Reference 2
	Cost of care*	£2,105.89	Kerr, 2017[12]
	Cost of stumps care	£1,605.94	Kerr, 2017[12]
	Total	£3,718.22	
Major amputation	**Technology cost**	£7.28	Reference 2
	Cost of care*	£4,106.85	Kerr, 2017[12]
	Cost of stumps care	£1,206.36	Kerr, 2017[12]
	Total	£5,320.49	

Healing	**Technology cost**	£7.28	Reference 2
	Cost of care	£125,04	Green and Taylor, 2016[3]
	Total	£132.32	
***** An additional cost of £9,407 will be added if the patient moves from infected foot ulcer to amputation (Ragnarson et al., 2001)			

Table C15 List of health states and associated costs in the economic model if 10-g SWME is used as the diagnostic test

Health states	Items	Value	Reference
No neuropathy	**Technology cost**	£16.8	Reference 2
	Cost of care	£125.04	Green and Taylor, 2016[3]
	Total	£141.84	
Neuropathy	**Technology cost**	£16.8	Reference 2
	Cost of care	£1,855.92	Kerr, 2017[12]
	Total	£1,872.72	
Infected foot ulcer	**Technology cost**	£16.8	Reference 2
	Cost of care	£11,848.07	Kerr, 2017[12]
	Total	£11,864.87	
Minor amputation	**Technology cost**	£16.8	Reference 2
	Cost of care*	£2,105.89	Kerr, 2017[12]
	Cost of stumps care	£1,605.94	Kerr, 2017[12]
	Total	£3,728.63	
Major amputation	**Technology cost**	£16.8	Reference 2
	Cost of care*	£4,106.85	Kerr, 2017[12]
	Cost of stumps care	£1,206.36	Kerr, 2017[12]
	Total	£5,330.01	
Healing	**Technology cost**	£16.8	Reference 2
	Cost of care	£125,04	Green and Taylor, 2016[3]
	Total	£141.84	
***** An additional cost of £9,407 will be added if the patient moves from infected foot ulcer to amputation (Ragnarson et al., 2001)			

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Not applicable.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Not applicable

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

9.4 Approach to sensitivity analysis

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

We conducted sensitivity analysis on the following variables:

- Costs associated with the different health states
- Purchase price of Neuropad and SWME
- Discount rate
- Prevalence of neuropathy
- QALYs associated with the different health states
- Transition probabilities between health states

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic sensitivity analysis (DSA) was performed among the variables previously mentioned, both one-way and two-way sensitivity analysis. The major goal was testing which parameters were those with the greatest impact on the net benefit, whether the optimal strategy changes when the parameters are modified and, consequently, which value or values of that a specific variable lead to the change.

QALYs were assumed to increase or decrease in a 20% whereas the range of variation for costs was 33%. For the probabilities and prevalence of neuropathy in the value used for the UK population, the percentage of likely change was expected to be 20 too. Hence, the effects of an over or underestimation in any of the parameters included in the study would also be tested.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C17.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Cost of no neuropathy	£125.04	(83.778 – 164.2888)
Cost of neuropathy	£1,855.92	(1,243.664 – 2,468.3736)
Cost of infected foot ulcer	£11,848.07	(7,938.2069 - 15,757.9331)
Cost of minor amputation	£2,105.89	(1,410.9463 – 2,800.8337)
Cost of stumps minor amputation	£1,605.94	(1,075.9817 – 2,135.9040)
Cost of major amputation	£4,106.85	(2,751.5895 – 5,462.1105)
Cost of stumps minor amputation	£1,206.36	(808.2593 – 1,604.455)
Cost of healing	£125.04	(83.778 – 164.2888)
Transition cost from infected ulcer to amputation	£9,407	(6,302.69 – 12,511.31)
Purchase price of Neuropad	£7.28	(4.8776 – 9.6824)
Purchase price of 10-g SWME	£16.8	(11.256 – 22.344)
Discount rate (%)	3.5	(0.001 – 9.00)
Prevalence of neuropathy (%)	2.4	(1.896 – 2.844)
Utility No active ulcer – no previous amputation	0.84	(0.672 – 1.00)
Utility No active ulcer – only 1 + toes amputated	0.74	(0.592 – 0.888)
Utility No active ulcer – one foot amputated	0.68	(0.544 – 0.816)
Utility No active ulcer – one leg amputated	0.62	(0.496 – 0.744)
Utility No active ulcer – both feet or legs amputated	0.51	(0.408 – 0.612)
Utility Active uninfected ulcer – no previous amputation	0.75	(0.6 – 0.9)
Utility Active uninfected ulcer – only 1 + toes amputated	0.68	(0.544 – 0.816)
Utility Active uninfected ulcer – one foot amputated	0.63	(0.504 – 0.756)
Utility Active uninfected ulcer – one leg amputated	0.57	(0.456 – 0.684)
Utility Active infected ulcer – no previous amputation	0.70	(0.56 – 0.84)
Utility Active infected ulcer – only 1 + toes amputated	0.65	(0.52 – 0.78)
Utility Active infected ulcer – one foot amputated	0.59	(0.472 – 0.708)

Utility Active infected ulcer – one leg amputated	0.55	(0.44 – 0.66)
Utility No neuropathy	0.84	(0.672 – 1.00)
Utility Neuropathy	0.74	(0.592 – 0.888)
Utility After healing with minor amputation	0.61	(0.488 – 0.732)
Minor amputations prevalence (%)	57.10	(45.6 – 68.4)
Major amputations prevalence (%)	42.90	(34.4 – 51.6)
Probability No neuropathy – no neuropathy (%)	96.08	(76.864 – 100)
Probability No neuropathy – neuropathy (%)	2.37	(1.896 – 2.844)
Probability No neuropathy – infected foot ulcer (%)	1.54	(1.2344 – 1.8516)
Probability Neuropathy – neuropathy (%)	94.90	(75.92 – 100)
Probability Neuropathy – infected foot ulcer (%)	5.10	(4.08 – 6.12)
Probability Infected foot ulcer – infected foot ulcer (%)	8.00	(6.4 – 9.6)
Probability Infected foot ulcer – minor amputation (%)	35.00	(28.00 – 42.00)
Probability Infected foot ulcer – major amputation (%)	17.00	(13.6 – 20.4)
Probability Infected foot ulcer – healing (%)	40.00	(32.00 – 48.00)
Probability Minor amputation – neuropathy (%)	9.60	(7.68 – 11.52)
Probability Minor amputation – infected foot ulcer (%)	4.40	(3.52 – 5.28)
Probability Minor amputation – minor amputation (%)	69.00	(55.2 – 82.8)
Probability Minor amputation – major amputation (%)	17.00	(13.6 – 20.4)
Probability Major amputation – major amputation (%)	100	(80.00 – 100.00)
Probability Healing – infected foot ulcer (%)	3.90	(3.12 – 4.68)
Probability Healing – healing (%)	96.10	(76.88 – 100.00)
Sensitivity Neuropad (%)	86	(68.80 – 100.00)
Specificity Neuropad (%)	65	(52.0 – 78.00)
Sensitivity SWME (%)	98.5	(78.8 – 100.00)
Specificity SWME (%)	55	(44.00 – 66.00)

Table C17.2 Variables used in two-way scenario-based sensitivity analysis

Variable	Utility neuropathy	Utility no neuropathy
Base case	0.74	0.84
Minimum value	0.592	0.672
Maximum value	0.888	1.00

Variable	Specificity Neuropad	Specificity 10-g SWME
Base case	65	55
Minimum value	52.00	44.00
Maximum value	78.00	66.00

Variable	Price Neuropad	Price 10-g SWME
Base case	7.28	16.8
Minimum value	4.8776	11.256
Maximum value	9.6824	22.344

Variable	Cost neuropathy	Cost infected foot ulcer
Base case	1,855.92	11,848.07
Minimum value	1,243.664	7,938.2069
Maximum value	2,468.3736	15,757.9331

Variable	Cost infected foot ulcer	Cost minor amputation
Base case	11,848.07	2,105.89
Minimum value	7,938.2069	1,410.9463
Maximum value	15,757.9331	2,800.8337

Variable	Cost infected foot ulcer	Cost major amputation
Base case	11,848.07	4,106.85
Minimum value	7,938.2069	2,751.5895
Maximum value	15,757.9331	5,462.1105

Variable	Cost infected foot ulcer	Transition cost from infected foot ulcer to amputation
Base case	11,848.07	9,407
Minimum value	7,938.2069	6,302.69
Maximum value	15,757.9331	12,511.31

Variable	Cost minor amputation	Transition cost from infected foot ulcer to amputation
Base case	2,105.89	9,407
Minimum value	1,410.9463	6,302.69
Maximum value	2,800.8337	12,511.31

Variable	Cost major amputation	Transition cost from infected foot ulcer to amputation
Base case	4,106.85	9,407
Minimum value	2,751.5895	6,302.69
Maximum value	5,462.1105	12,511.31

Variable	Probability neuropathy - neuropathy	Cost neuropathy
Base case	94.90	1,855.92
Minimum value	75.92	1,243.664
Maximum value	100	2,468.3736

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Not applicable

9.5 Results of de novo cost analysis

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C18 Base-case results

	Total per patient cost (£)	Total QALYs per patient	Net Monetary Benefit per patient (£)*
Neuropad & SWME	6,943.88	2.2903	61,765.95
Neuropad only	5,585.21	2.3213	64,055,10
SWME only	6,953.63	2.2898	61,739,83

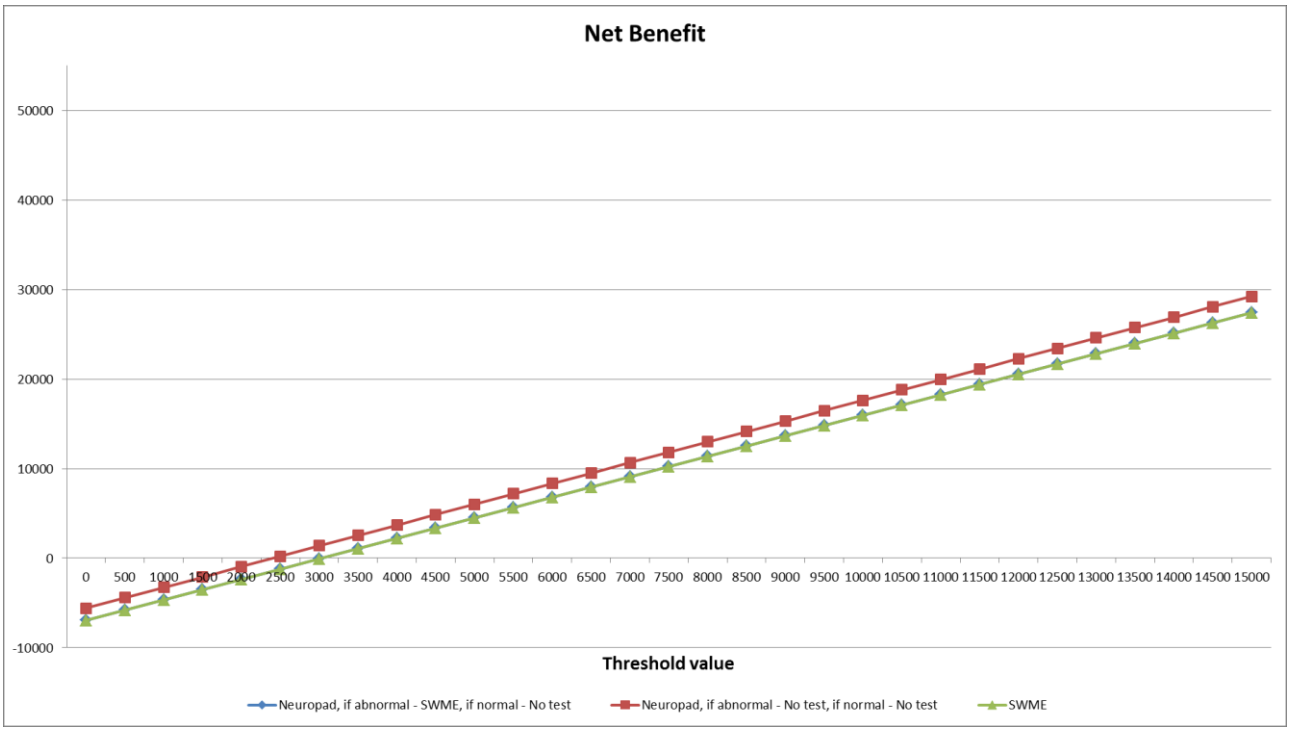
* Net Monetary Benefit = QALYs*Threshold - Cost

9.5.2 Report the total difference in costs between the technology and comparator(s).

Table C19 Incremental cost and outcomes results with respect to Standard care (10-g SWME)

	Incremental cost per patient (£)	Incremental QALYs per patient	Incremental Net Monetary Benefit per patient (£)
Neuropad & SWME	-9.7503	0.00055	26.1128
Neuropad only	-1,368,43	0.03156	2,315.27
SWME only	-	-	-

Figure 2 Net Monetary Benefit for the available strategies



9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Not applicable

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Table C20 provides costs data for each health pathway along the whole time horizon of the model (3 years) after a positive results in any of the diagnostic tests included. Each health pathway consists of six health states, each of them referring to one cycle. So, for example, the first pathway “Neuro – Neuro – Neuro – Neuro – Neuro - Neuro” denotes an individual that has always been in the diabetic neuropathy health state in every cycle, with no change. The table also shows the costs by diagnostic tool (Neuropad or 10-g SWME) or the combination of both.

“Neuro” refers to diabetic neuropathy; “IFU” is Infected foot ulcer; “MiAm” denotes Minor amputation; and “MaAm” is Major amputation

Table C20 Summary of costs by health state per patient

Possible health states along the model length	Cost If Neuropad + SWME	Cost If Neuropad only	Cost if SWME only
Neuro - Neuro - Neuro - Neuro - Neuro - Neuro	10,774.4038	10,757.6038	10,767.1238
Neuro - Neuro - Neuro - Neuro - Neuro - IFU	20,079.34369	20,062.54369	20,072.0637
Neuro - Neuro - Neuro - Neuro - IFU - IFU	29,384.28357	29,367.48357	29,377.0036
Neuro - Neuro - Neuro - Neuro - IFU - MiAm	30,567.64975	30,550.84975	30,560.3697
Neuro - Neuro - Neuro - Neuro - IFU - MaAm	32,058.88945	32,042.08945	32,051.6094
Neuro - Neuro - Neuro - Neuro - IFU - Healing	18,467.50496	18,450.70496	18,460.225
Neuro - Neuro - Neuro - IFU - IFU - IFU	39,026.70832	39,009.90832	39,019.4283
Neuro - Neuro - Neuro - IFU - IFU - MiAm	40,210.0745	40,193.2745	40,202.7945
Neuro - Neuro - Neuro - IFU - IFU - MaAm	41,701.3142	41,684.5142	41,694.0342
Neuro - Neuro - Neuro - IFU - IFU - Healing	28,109.92971	28,093.12971	28,102.6497
Neuro - Neuro - Neuro - IFU - MiAm - Neuro	32,400.62879	32,383.82879	32,393.3488
Neuro - Neuro - Neuro - IFU - MiAm - IFU	41,705.56867	41,688.76867	41,698.2887
Neuro - Neuro - Neuro - IFU - MiAm - MiAm	30,672.34969	30,655.54969	30,665.0697
Neuro - Neuro - Neuro - IFU - MiAm - MaAm	33,001.2569	32,984.4569	32,993.9769
Neuro - Neuro - Neuro - IFU - MaAm - MaAm	31,791.48511	31,774.68511	31,784.2051
Neuro - Neuro - Neuro - IFU - Healing - IFU	28,109.92971	28,093.12971	28,102.6497

Possible health states along the model length	Cost If Neuropad + SWME	Cost If Neuropad only	Cost if SWME only
Neuro - Neuro - Neuro - IFU - Healing - Healing	17,193,1511	17,176.3511	17,185.8711
Neuro - Neuro - IFU - IFU - IFU - IFU	48,669.13307	48,652.33307	48,661.8531
Neuro - Neuro - IFU - IFU - IFU - MiAm	49,852.49925	49,835.69925	49,845.2192
Neuro - Neuro - IFU - IFU - IFU - MaAm	51,343.73895	51,326.93895	51,336.4589
Neuro - Neuro - IFU - IFU - IFU - Healing	37,752.35446	37,735.55446	37,745.0745
Neuro - Neuro - IFU - IFU - MiAm - Neuro	42,043.05354	42,026.25354	42,035.7735
Neuro - Neuro - IFU - IFU - MiAm - IFU	51,347.99342	51,331.19342	51,340.7134
Neuro - Neuro - IFU - IFU - MiAm - MiAm	40,314.77444	40,297.97444	40,307.4944
Neuro - Neuro - IFU - IFU - MiAm - MaAm	43,767.07155	43,750.27155	43,759.7915
Neuro - Neuro - IFU - IFU - MaAm - MaAm	41,433.90986	41,417.10986	41,426.6299
Neuro - Neuro - IFU - IFU - Healing - IFU	37,752.35446	37,735.55446	37,745.0745
Neuro - Neuro - IFU - IFU - Healing - Healing	26,835.57585	26,818.77585	26,828.2958
Neuro - Neuro - IFU - MiAm - Neuro - Neuro	31,285.5395	31,268.7395	31,278.2595
Neuro - Neuro - IFU - MiAm - Neuro - IFU	43,581.46773	43,564.66773	43,574.1877
Neuro - Neuro - IFU - MiAm - IFU - IFU	52,886.40761	52,869.60761	52,879.1276
Neuro - Neuro - IFU - MiAm - IFU - MiAm	52,574.27962	52,557.47962	52,566.9996
Neuro - Neuro - IFU - MiAm - IFU - MaAm	52,574.27962	52,557.47962	52,566.9996
Neuro - Neuro - IFU - MiAm - IFU - Healing	41,969.629	41,952.829	41,962.349
Neuro - Neuro - IFU - MiAm - MiAm - Neuro	32,548.24874	32,531.44874	32,540.9687
Neuro - Neuro - IFU - MiAm - MiAm - IFU	41,853.18863	41,836.38863	41,845.9086
Neuro - Neuro - IFU - MiAm - MiAm - MiAm	30,819.96964	30,803.16964	30,812.6896
Neuro - Neuro - IFU - MiAm - MiAm - MaAm	34,272.26675	34,255.46675	34,264.9868
Neuro - Neuro - IFU - MiAm - MaAm - MaAm	33,900.16247	33,883.36247	33,892.8825
Neuro - Neuro - IFU - MaAm - MaAm - MaAm	31,621.08719	31,604.28719	31,613.8072
Neuro - Neuro - IFU - Healing - IFU - IFU	37,356.40912	37,339.60912	37,349.1291
Neuro - Neuro - IFU - Healing - IFU - MiAm	38,539.7753	38,522.9753	38,532.4953
Neuro - Neuro - IFU - Healing - IFU - MaAm	40,031.015	40,014.215	40,023.735
Neuro - Neuro - IFU - Healing - IFU - Healing	26,439.63051	26,422.83051	26,432.3505
Neuro - Neuro - IFU - Healing - Healing - IFU	26,439.63051	26,422.83051	26,432.3505
Neuro - Neuro - IFU - Healing - Healing - Healing	15,406.41152	15,389.61152	15,399.1315
Neuro - IFU - IFU - IFU - IFU - IFU	58,661.28307	58,644.48307	58,654.0031
Neuro - IFU - IFU - IFU - IFU -MiAm	59,844.64925	59,827.84925	59,837.3692
Neuro - IFU - IFU - IFU - IFU - MaAm	61,335.88895	61,319.08895	61,328.6089
Neuro - IFU - IFU - IFU - IFU - Healing	47,744.50446	47,727.70446	47,737.2245
Neuro - IFU - IFU - IFU - MiAm - Neuro	52,035.20354	52,018.40354	52,027.9235
Neuro - IFU - IFU - IFU - MiAm - IFU	61,340.14342	61,323.34342	61,332.8634
Neuro - IFU - IFU - IFU - MiAm - MiAm	50,306.92444	50,290.12444	50,299.6444
Neuro - IFU - IFU - IFU - MiAm - MaAm	53,759.22155	53,742.42155	53,751.9415
Neuro - IFU - IFU - IFU -MaAm - MaAm	51,426.05986	51,409.25986	51,418.7799
Neuro - IFU - IFU - IFU - Healing - IFU	47,744.50446	47,727.70446	47,737.2245
Neuro - IFU - IFU - IFU - Healing - Healing	36,827.72585	36,810.92585	36,820.4458
Neuro - IFU - IFU - MiAm - Neuro - Neuro	44,268.67784	44,251.87784	44,261.3978
Neuro - IFU - IFU - MiAm - Neuro - IFU	53,573.61773	53,556.81773	53,566.3377

Possible health states along the model length	Cost If Neuropad + SWME	Cost If Neuropad only	Cost if SWME only
Neuro - IFU - IFU - MiAm - IFU - IFU	59,887.56927	59,870.76927	59,880.2893
Neuro - IFU - IFU - MiAm - IFU - MiAm	62,566.42962	62,549.62962	62,559.1496
Neuro - IFU - IFU - MiAm - IFU - MaAm	64,057.66931	64,040.86931	64,050.3893
Neuro - IFU - IFU - MiAm - IFU - Healing	51,961.779	51,944.979	51,954.499
Neuro - IFU - IFU - MiAm - MiAm - Neuro	42,540.39874	42,523.59874	42,533.1187
Neuro - IFU - IFU - MiAm - MiAm - IFU	51,845.33863	51,828.53863	51,838.0586
Neuro - IFU - IFU - MiAm - MiAm - MiAm	40,812.11964	40,795.31964	40,804.8396
Neuro - IFU - IFU - MiAm - MiAm - MaAm	44,264.41675	44,247.61675	44,257.1368
Neuro - IFU - IFU - MiAm - MaAm - MaAm	43,892.31247	43,875.51247	43,885.0325
Neuro - IFU - IFU - MaAm - MaAm - MaAm	41,613.23719	41,596.43719	41,605.9572
Neuro - IFU - IFU - Healing - IFU - IFU	47,348.55912	47,331.75912	47,341.2791
Neuro - IFU - IFU - Healing - IFU - MiAm	48,531.9253	48,515.1253	48,524.6453
Neuro - IFU - IFU - Healing - IFU - MaAm	50,023.165	50,0006.365	50,015.885
Neuro - IFU - IFU - Healing - IFU -Healing	36,431.78051	36,414.98051	36,424.5005
Neuro - IFU - IFU - Healing -Healing - IFU	36,431.78051	36,414.98051	36,424.5005
Neuro - IFU - IFU - Healing - Healing - Healing	25,515.0019	25,498.2019	25,507.7219
Neuro - IFU - MiAm - Neuro - Neuro - Neuro	36,175.98799	36,159.18799	36,168.708
Neuro - IFU - MiAm - Neuro - Neuro - IFU	45,480.92787	45,464.12787	45,473.6479
Neuro - IFU - MiAm - Neuro - IFU - IFU	54,785.86776	54,769.06776	54,778.5878
Neuro - IFU - MiAm - Neuro - IFU - MiAm	54,473.73976	54,456.93976	54,466.4598
Neuro - IFU - MiAm - Neuro - IFU - MaAm	55,964.97946	55,948.17946	55,957.6995
Neuro - IFU - MiAm - Neuro - IFU - Healing	43,869.08914	43,852.28914	43,861.8091
Neuro - IFU - MiAm - IFU - IFU - IFU	63,298.48366	63,281.68366	63,291.2037
Neuro - IFU - MiAm - IFU - IFU - MiAm	63,358.45994	63,341.65994	63,351.1799
Neuro - IFU - MiAm - IFU - IFU - MaAm	65,607.40421	65,590.60421	65,600.1242
Neuro - IFU - MiAm - IFU - IFU - Healing	53,511.51389	53,494.71389	53,504.2339
Neuro - IFU - MiAm - IFU - MiAm - Neuro	54,811.22463	54,794.42463	54,803.9446
Neuro - IFU - MiAm - IFU - MiAm - IFU	64,116.16451	64,099.36451	64,108.8845
Neuro - IFU - MiAm - IFU - MiAm - MiAm	53,082.94553	53,066.14553	53,075.6655
Neuro - IFU - MiAm - IFU - MiAm - MaAm	56,535.24264	56,518.44264	56,527.9626
Neuro - IFU - MiAm - IFU - MaAm - MaAm	54,202.08094	54,185.28094	54,194.8009
Neuro - IFU - MiAm - IFU - Healing - IFU	53,511.51389	53,494.71389	53,504.2339
Neuro - IFU - MiAm - IFU - Healing - Healing	42,594.73528	42,577.93528	42,587.4553
Neuro - IFU - MiAm - MiAm - Neuro - Neuro	34,385.02519	34,368.22519	34,377.7452
Neuro - IFU - MiAm - MiAm - Neuro - IFU	43,689.96507	43,673.16507	43,682.6851
Neuro - IFU - MiAm - MiAm - IFU - IFU	52,994.90496	52,978.10496	52,987.625
Neuro - IFU - MiAm - MiAm - IFU - MiAm	52,682.77696	52,665.97696	52,675.497
Neuro - IFU - MiAm - MiAm - IFU - MaAm	54,174.01666	54,157.21666	54,166.7367
Neuro - IFU - MiAm - MiAm - IFU - Healing	42,078.12634	42,061.32634	42,070.8463
Neuro - IFU - MiAm - MiAm - MiAm - Neuro	32,656.74609	32,639.94609	32,649.4661
Neuro - IFU - MiAm - MiAm - MiAm - IFU	41,961.68597	41,944.88597	41,954.406
Neuro - IFU - MiAm - MiAm - MiAm - MiAm	30,928.46698	30,911.66698	30,921.187
Neuro - IFU - MiAm - MiAm - MiAm - MaAm	34,380.7641	34,363.9641	34,373.4841

Possible health states along the model length	Cost If Neuropad + SWME	Cost If Neuropad only	Cost if SWME only
Neuro - IFU - MiAm - MiAm - MaAm - MaAm	34,008.65982	33,991.85982	34,001.3798
Neuro - IFU - MiAm - MaAm - MaAm - MaAm	33,761.76839	33,744.96839	33,754.4884
Neuro - IFU - MaAm - MaAm - MaAm - MaAm	31,343.98425	31,327.18425	31,336.7043
Neuro - IFU - Healing - IFU - IFU - IFU	47,348,55912	47,331.75912	47,341.2791
Neuro - IFU - Healing - IFU - IFU - MiAm	48,531.9253	48,515.1253	48,524.6453
Neuro - IFU - Healing - IFU - IFU - MaAm	50,023.165	50,006.365	50,015.885
Neuro - IFU - Healing - IFU - IFU - Healing	36,431.78051	36,414.98051	36,424.5005
Neuro - IFU - Healing - IFU - MiAm - Neuro	40,722.47959	40,705.67959	40,715.1996
Neuro - IFU - Healing - IFU - MiAm - IFU	50,027.41947	50,010.61947	50,020.1395
Neuro - IFU - Healing - IFU - MiAm - MiAm	38,994.20049	38,977.40049	38,986.9205
Neuro - IFU - Healing - IFU - MiAm - MaAm	42,446.4976	42,429.6976	42,439.2176
Neuro - IFU - Healing - IFU - MaAm - MaAm	40,113.33591	40,096.53591	40,106.0559
Neuro - IFU - Healing - IFU - Healing - IFU	36,431.78051	36,414.98051	36,424.5005
Neuro - IFU - Healing - IFU - Healing - Healing	25,515.0019	25,498.2019	25,507.7219
Neuro - IFU - Healing - Healing - IFU - IFU	36,035.83517	36,019.03517	36,028.5552
Neuro - IFU - Healing - Healing - IFU - MiAm	37,219.20135	37,202.40135	37,211.9213
Neuro - IFU - Healing - Healing - IFU - MaAm	38,710.44105	38,693.64105	38,703.161
Neuro - IFU - Healing - Healing - IFU - Healing	25,119.05656	25,102.25656	25,111.7766
Neuro - IFU - Healing - Healing - Healing - IFU	25,119.05656	25,102.25656	25,111.7766
Neuro - IFU - Healing - Healing - Healing - Healing	14,202.27795	14,185.47795	14,194.9979

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Not applicable.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The results derived from the one-way sensitivity analysis are presented in Figures 2 (all parameters) and 3 (the top 10 variables affecting net benefit the most).

Figure 3: Base case DSA results

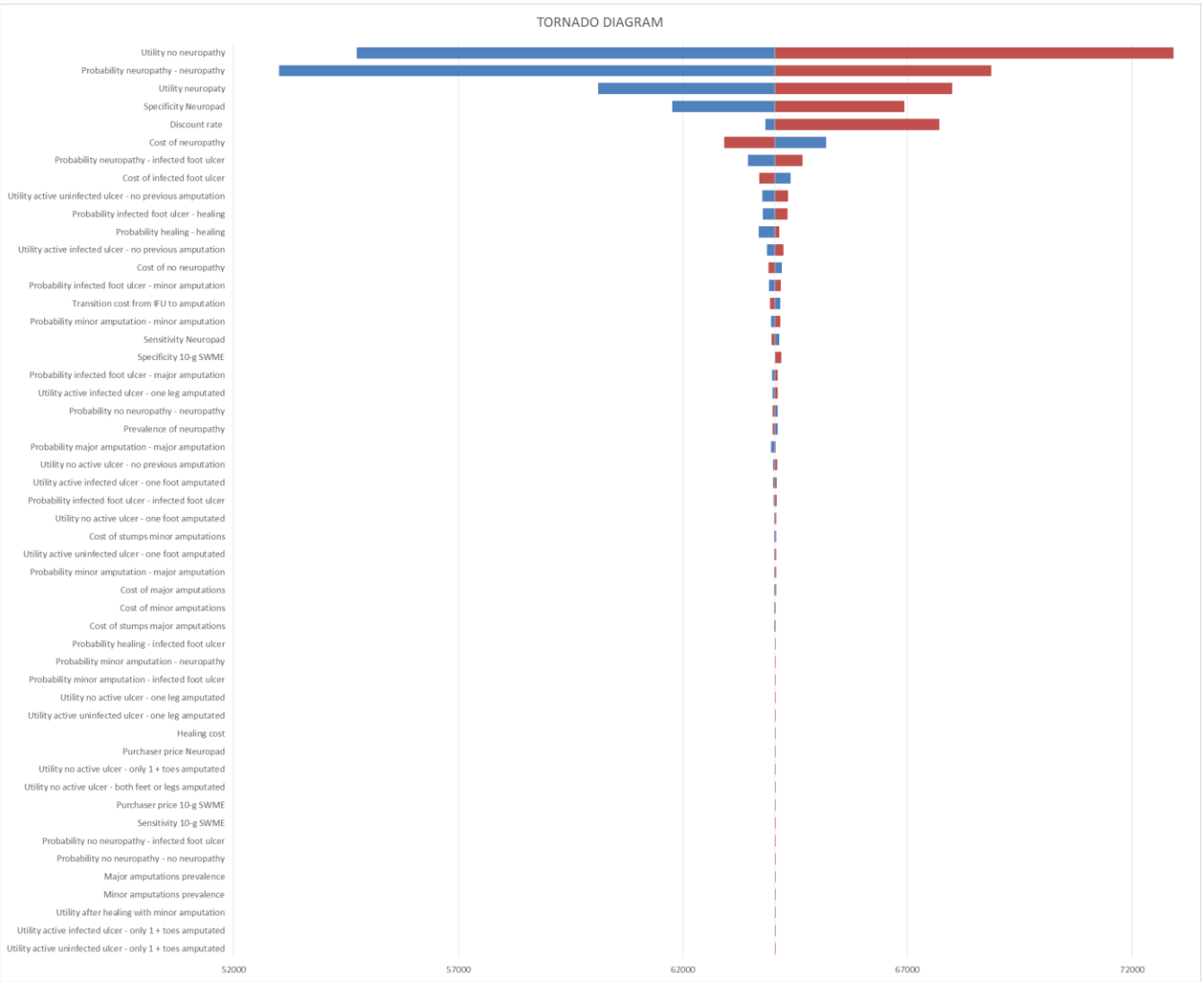
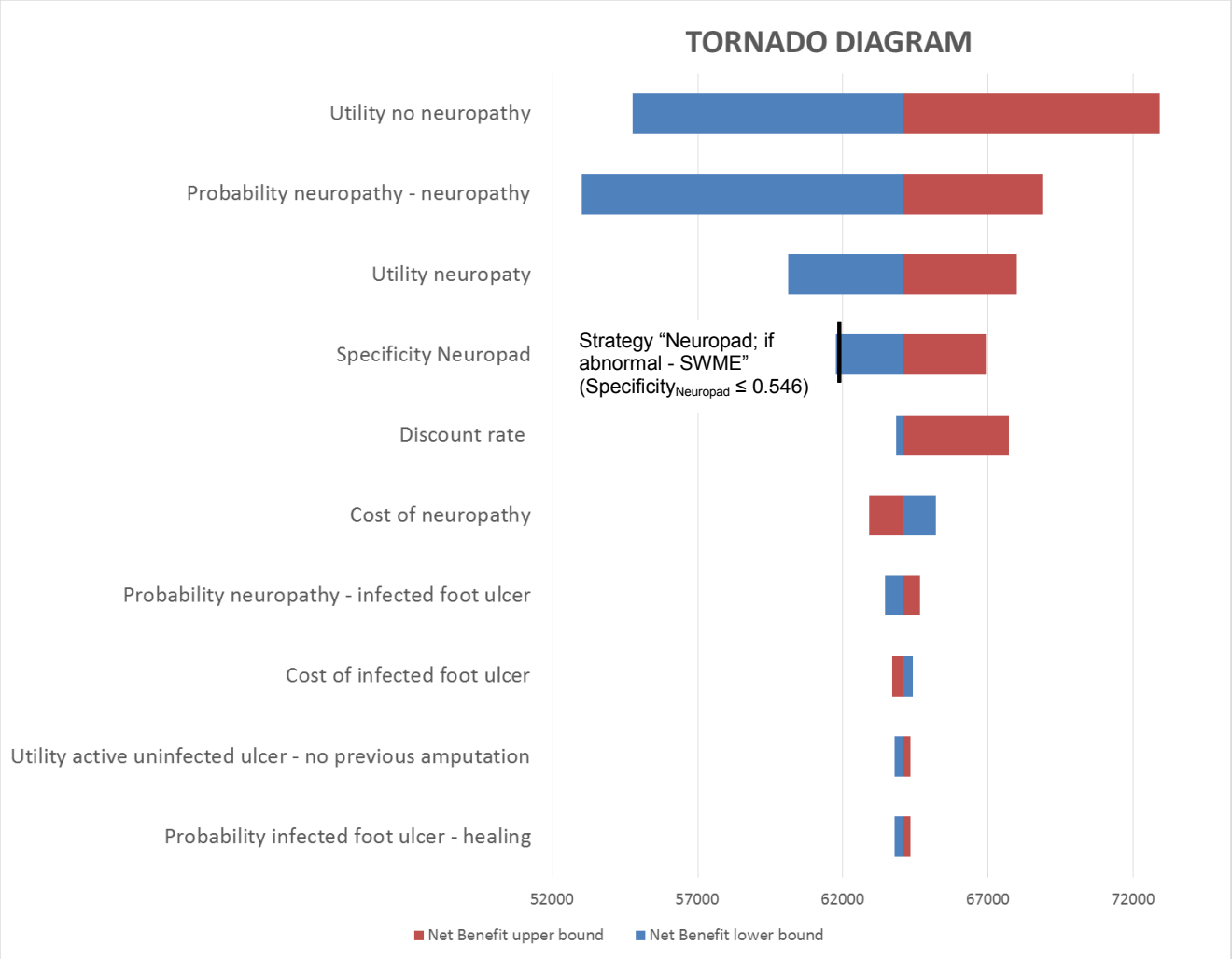


Figure 4: Base case DSA results for the top 10 variables



9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Figure 5 Two-way sensitivity analysis for the utility of neuropathy vs the utility of no neuropathy

		Utility no neuropathy																		
		0,672	0,6802	0,713	0,7212	0,7294	0,7622	0,7704	0,7786	0,8196	0,8278	0,836	0,877	0,8852	0,8934	0,9016	0,9426	0,9508	0,9918	1
Utility neuropathy	0,592	Neuropad, if abnormal - No test, if normal - No test																		
	0,666																			
	0,6734																			
	0,6808																			
	0,6882																			
	0,74																			
	0,7474																			
	0,7548																			
	0,7622																			
	0,7696																			
	0,777																			
	0,7844																			
	0,814																			
	0,8214																			
	0,8658																			
	0,8732																			
	0,8806																			
	0,888																			

Figure 6 Two-way sensitivity analysis for the specificity of Neuropad vs the specificity of 10-g SWME

		Specificity Neuropad																		
		0,52	0,533	0,5785	0,585	0,5915	0,611	0,6175	0,637	0,6435	0,65	0,676	0,6825	0,689	0,7085	0,715	0,7345	0,741	0,767	0,78
Specificity 10g-SWME	0,44																			
	0,4455																			
	0,451																			
	0,4895																			
	0,495																			
	0,5005																			
	0,506																			
	0,5115																			
	0,517																			
	0,5225																			
	0,528	Neuropad, if abnormal - No test, if normal - No test																		
	0,5335																			
	0,55																			
	0,5555																			
	0,561																			
	0,594																			
	0,5995																			
	0,605																			
	0,6105																			
	0,616																			
	0,6435																			
	0,649																			
	0,6545																			
	0,66																			

Figure 7 Two-way sensitivity analysis for the purchaser price of Neuropad vs the purchaser price of 10-g SWME

		Price Neuropad																		
		4,8776	5,11784	5,4782	5,83856	5,95868	6,31904	6,6794	6,79952	7,03976	7,15988	7,40012	7,8806	8,00072	8,12084	8,72144	8,96168	9,32204	9,44216	9,6824
Price 10g-SWME	11,256																			
	11,8104																			
	12,0876																			
	12,3648																			
	13,1964																			
	13,7508																			
	14,028																			
	14,8596																			
	15,1368																			
	15,6912																			
	16,5228																			
	16,8	Neuropad, if abnormal - No test, if normal - No test																		
	17,0772																			
	17,9088																			
	18,4632																			
	19,0176																			
	19,572																			
	20,1264																			
	20,6808																			
	21,2352																			
	21,7896																			
	22,344																			

Figure 8 Two-way sensitivity analysis for the cost of neuropathy vs the cost of infected foot ulcer

		Neuropathy cost																		
		1243,466	1365,95712	1427,202	1488,448	1549,693	1610,939	1672,184	1733,429	1794,675	1855,92	1917,165	1978,411	2009,033	2070,279	2131,524	2254,015	2315,26	2376,506	2468,374
Cost of infected foot ulce	7938,207																			
	8329,193																			
	8720,18																			
	9111,166																			
	9502,152																			
	9893,138																			
	10284,12																			
	10675,11																			
	11066,1																			
	11457,08																			
	11848,07	Neuropad, if abnormal - No test, if normal - No test																		
	12239,06																			
	12630,04																			
	13021,03																			
	13412,02																			
	13803																			
	14193,99																			
	14584,97																			
	14975,96																			
	15366,95																			
	15757,93																			

Figure 9 Two-way sensitivity analysis for the cost of infected foot ulcer vs the cost of minor amputations

		Cost of infected foot ulcer																		
		7938,207	8329,19321	8720,18	9111,166	9893,138	10284,12	10479,62	11066,1	11652,58	12043,56	12434,55	12825,54	13412,02	13803	13998,49	14780,47	14975,96	15171,45	15757,93
Cost of minor amputation	1410,946																			
	1480,441																			
	1549,935																			
	1619,429																			
	1688,924																			
	1758,418																			
	1827,913																			
	1897,407																			
	1966,901																			
	2001,648	Neuropad, if abnormal - No test, if normal - No test																		
	2071,143																			
	2105,89																			
	2175,384																			
	2244,879																			
	2279,626																			
	2349,12																			
	2418,615																			
	2488,109																			
	2557,603																			
	2592,351																			
	2661,845																			
	2731,339																			
	2800,834																			

Figure 10 Two-way sensitivity analysis for the cost of infected foot ulcer vs the cost of major amputations

		Cost of infected foot ulcer																		
		7938,207	8329,19321	8720,18	9111,166	9893,138	10088,63	10870,6	11066,1	11848,07	12239,06	12825,54	13021,03	13607,51	13803	14193,99	14389,48	14975,96	15171,45	15757,93
Cost of major amputation	2751,59																			
	2887,116																			
	3022,642																			
	3158,168																			
	3293,694																			
	3429,22																			
	3564,746																			
	3700,272																			
	3835,798																			
	3971,324																			
	4106,85	Neuropad, if abnormal - No test, if normal - No test																		
	4242,376																			
	4377,902																			
	4513,428																			
	4648,954																			
	4784,48																			
	4920,006																			
	5055,532																			
	5191,058																			
	5326,584																			
	5462,111																			

Figure 11 Two-way sensitivity analysis for the cost of infected foot ulcer vs the transition cost from infected foot ulcer to amputation

		Cost of infected foot ulcer																		
		7938,207	8133,70006	8915,673	9111,166	9893,138	10088,63	10870,6	11066,1	11848,07	12043,56	12434,55	12825,54	13021,03	13803	13998,49	14193,99	14780,47	15366,95	15757,93
Transition cost from IFU to amputations	6302,69																			
	6457,906																			
	6923,552																			
	7078,768																			
	7699,63																			
	7854,845																			
	8165,276																			
	8475,707																			
	8786,138																			
	9096,569																			
	9407	Neuropad, if abnormal - No test, if normal - No test																		
	9717,431																			
	10027,86																			
	10338,29																			
	10493,51																			
	10803,94																			
	11114,37																			
	11424,8																			
	11735,23																			
	12045,66																			
	12356,09																			
	12511,31																			

Figure 12 Two-way sensitivity analysis for the cost of cost of minor amputations vs the transition cost from infected foot ulcer to amputation

		Transition cost from IFU to amputations																		
		6302,69	6457,9055	6923,552	7078,768	7544,414	7854,845	8010,061	8630,923	8941,354	9096,569	9872,647	10027,86	10648,72	10959,16	11114,37	11735,23	11890,45	12356,09	12511,31
Cost of minor amputations	1410,946																			
	1480,441																			
	1549,935																			
	1619,429																			
	1688,924																			
	1758,418																			
	1827,913																			
	1897,407																			
	1966,901																			
	2036,396																			
	2105,89																			
	2175,384	Neuropad, if abnormal - No test, if normal - No test																		
	2244,879																			
	2314,373																			
	2383,867																			
	2453,362																			
	2522,856																			
	2592,351																			
	2661,845																			
	2731,339																			
	2800,834																			

Figure 13 Two-way sensitivity analysis for the cost of cost of major amputations vs the transition cost from infected foot ulcer to amputation

		Transition cost from IFU to amputations																	
		6302,69	6923,552	7078,768	7544,414	7854,845	8010,061	8475,707	8941,354	9096,569	9407	9872,647	10027,86	10648,72	10959,16	11114,37	11735,23	11890,45	12045,66	12511,31
Cost of major amputations	2751,59																			
	2887,116																			
	3022,642																			
	3158,168																			
	3293,694																			
	3429,22																			
	3564,746																			
	3700,272																			
	3835,798																			
	3971,324																			
	4106,85	Neuropad, if abnormal - No test, if normal - No test																		
	4242,376																			
	4377,902																			
	4513,428																			
	4648,954																			
	4784,48																			
	4920,006																			
	5055,532																			
	5191,058																			
	5326,584																			
	5462,111																			

Figure 14 Two-way sensitivity analysis for the transition probability of neuropathy - neuropathy vs the cost of neuropathy

		Cost of neuropathy																	
		1243,466	1304,71176	1396,58	1427,202	1488,448	1519,071	1580,316	1672,184	1702,807	1794,675	1825,297	1917,165	2039,656	2070,279	2162,147	2192,769	2315,26	2407,128	2468,374
Transition probability neuropathy - neuropathy	0,7592																			
	0,76522																			
	0,78328																			
	0,79532																			
	0,80736																			
	0,8194																			
	0,83144																			
	0,84348																			
	0,85552																			
	0,86756																			
	0,8796	Neuropad, if abnormal - No test, if normal - No test																		
	0,89164																			
	0,90368																			
	0,91572																			
	0,92776																			
	0,9398																			
	0,95184																			
	0,96388																			
	0,97592																			
	0,98796																			
	1																			

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

Not applicable.

9.5.9 What were the main findings of each of the sensitivity analyses?

One-way sensitivity analysis

The conclusions derived from the one-way sensitivity analysis is that performing Neuropad alone is always the optimal choice, compared to performing Neuropad and 10-g SWME together or 10-g SWME alone. There is only one exception: when the specificity of Neuropad drops below 0.546, the optimal strategy would be to use Neuropad as the first neuropathy diagnostic tool and, if an abnormal result is obtained, SWME should be performed too.

The three most sensitive Net Benefit drivers are:

- Utility of no neuropathy: when the value of the utility derived from not having neuropathy, but still being diabetic, varies by 20%, so between 0.672 and 1, the net benefit changes to £54,743.725 and £72,923.08, respectively

- The transition probability of being in the neuropathy health state in one cycle and remain in the same state in the following cycle period: if the probability varies by 20%, so between 0.7592 and 1, the net benefit changes to £53,006.062 and £68,873.22, respectively

- Utility of neuropathy: when the value of the utility derived from having neuropathy varies by 20%, so between 0.592 and 0.888, the net benefit changes to £60,114.844 and £67,995.36, respectively

However, some mention should be made to the only parameter of the model on which a change in its value would change the optimal strategy:

- The specificity of Neuropad: when its value changes by 20%, so between 0.52 and 0.78, the net benefit changes to £61,762.647 and £66,928.53, respectively. Moreover, as mentioned before, in case the Neuropad´s specificity lies below 0.546, the optimal strategy would be performing the 10-

g SWME to detect diabetic neuropathy once an abnormal results has been obtained with Neuropad, when the net benefit drops to £61,762.647

Two-way sensitivity analysis

Similar findings are obtained from the two-way sensitivity analysis, compared to the one-way sensitivity analysis. The aim was to test whether changes in more than one parameter at the same time would lead to a change in the optimal strategy (testing neuropathy only with Neuropad). Looking at the figures 5-14, performing the Neuropad test alone is always the optimal choice, compared to performing Neuropad and 10-g SWME together or 10-g SWME alone.

One could expect that, since when the specificity of Neuropad was modified in the one-way analysis, the strategy changed, the same would happen when doing the two-way analysis of this same variable together with another. However, as Figure 6 shows, there is no change in the optimal strategy in this case.

9.5.10 What are the key drivers of the cost results?

Both the one-way and two-way sensitivity analyses show that the results are quite robust, irrespective of the change of the parameters. One exception should be made when changing solely the specificity of Neuropad below 54.6%.

Moreover, as Figure 4 shows, utility of no neuropathy, the transition probability from neuropathy to neuropathy state and neuropathy utility are the most sensitive variables modifying the net benefit.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

Additional results that have been considered in the analysis, but not asked in the template, refer to the potential health gains that could be derived from the use of Neuropad:

1. As it is reported in Table C19, testing neuropathy only with Neuropad would lead to an incremental Quality-Adjusted Life Years (QALYs) of

0.03156. Moreover, the incremental Net Monetary Benefit per patient with Neuropad would be £2,315.27, taking into account both costs and health gains.

2. Table C19 also shows that additional performing Neuropad together with SWME is not increasing the costs. Actually, compared to using SWME only as the diagnostic test, performing both test would lead to £9.7503 savings per patient and 0.00055 health gains, QALYs.

9.6 Subgroup analysis

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

As it has been previously stated elsewhere in the document, care home residents are at greater risk of developing diabetic neuropathy and no appropriate care and foot screening is provided, so this will be the only subgroup considered in the de novo economic model.

9.6.2 Define the characteristics of patients in the subgroup(s).

According to a report published by the British Diabetic Association (2010)[13], "there is a lack of state registered podiatrists for (care home) residents with diabetes of all ages, especially those at highest risk of diabetic vascular and neuropathic damage". Hence, it seems reasonable to take such group of the population into consideration when evaluating Neuropad as a diagnostic tool of diabetic neuropathy.

However, it should be mentioned that, due to lack of data about the diabetic neuropathy prevalence within UK care home residents, no actual prevalence of diabetic neuropathy could be used in the analysis. Nevertheless, It has been found in the literature that for a subsample of 497 Dutch care home residents, the prevalence of actual neuropathy pain was 10.9% (95% CI 8.4 – 13.8%) and 7.7% for the residents suffering from diabetes[14]. Hence, diabetic neuropathy prevalence

will be modified in the current analysis from its value for the overall sample (2.4%) up to 15%, which is a above the upper bound of the 95% CI provided in the Dutch paper.

9.6.3 Describe how the subgroups were included in the cost analysis.

Sensitivity analysis for diabetic neuropathy prevalence (2.4 – 15%) will be run given the lack of data for the specific UK population, and results for costs, QALYs and Net Benefit will be reported.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

When the prevalence of diabetic neuropathy is modified from its original value (2.4%), costs, QALYs and the Net Monetary Benefit change.

- The baseline value of costs is £5,585.21 when the prevalence of diabetic neuropathy is 2.4%. When the prevalence is modified, testing diabetic neuropathy only with Neuropad stands always as the optimal strategy. Costs increase from £5,585.21 to £6,448.3950. More detailed information is given in Table C21.

- The baseline value of QALYs is 2,3213 when the prevalence of diabetic neuropathy is 2.4%. When the prevalence is modified, testing diabetic neuropathy only with Neuropad is always the optimal strategy. QALYs decrease from 2,3213 to 2,3015. More detailed information is given in Table C22.

- The baseline value of the Net Monetary Benefit is £64,055.10 when the prevalence of diabetic neuropathy is 2.4%. When the prevalence is modified, testing diabetic neuropathy only with Neuropad remains as the optimal strategy. The Net Monetary Benefit decrease from £64,055.10 to £62597,1007. More detailed information is given in Table C23.

Table C21 Change in costs

	0.024	0.02715	0.0303	0.03345	0.0366	0.03975
Optimal value	5585.21	5608.584429	5630.118034	5651.65164	5673.185245	5694.718851
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0429	0.04605	0.0492	0.05235	0.0555	0.05865
Optimal value	5716.252456	5737.786061	5759.319667	5780.853272	5802.386878	5823.920483
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0618	0.06495	0.0681	0.07125	0.0744	0.07755
Optimal value	5845.454089	5866.987694	5888.5213	5910.054905	5931.588511	5953.122116
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0807	0.08385	0.087	0.09015	0.0933	0.09645
Optimal value	5974.655721	5996.189327	6017.722932	6039.256538	6060.790143	6082.323749
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0996	0.10275	0.1059	0.10905	0.1122	0.11535
Optimal value	6103.857354	6125.39096	6146.924565	6168.458171	6189.991776	6211.525381
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1185	0.12165	0.1248	0.12795	0.1311	0.13425
Optimal value	6233.058987	6254.592592	6276.126198	6297.659803	6319.193409	6340.727014
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1374	0.14055	0.1437	0.14685	0.15
Optimal value	6362.26062	6383.794225	6405.327831	6426.861436	6448.395041
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

Table C22 Change in QALYs

	0.024	0.02715	0.0303	0.03345	0.0366	0.03975
Optimal value	2.321301143	2.320806528	2.320311912	2.319817297	2.319322681	2.318828066
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0429	0.04605	0.0492	0.05235	0.0555	0.05865
Optimal value	2.31833345	2.317838835	2.31734422	2.316849604	2.316354989	2.315860373
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0618	0.06495	0.0681	0.07125	0.0744	0.07755
Optimal value	2.315365758	2.314871142	2.314376527	2.313881911	2.313387296	2.31289268
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0807	0.08385	0.087	0.09015	0.0933	0.09645
Optimal value	2.312398065	2.31190345	2.311408834	2.310914219	2.310419603	2.309924988
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0996	0.10275	0.1059	0.10905	0.1122	0.11535
Optimal value	2.309430372	2.308935757	2.308441141	2.307946526	2.30745191	2.306957295
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1185	0.12165	0.1248	0.12795	0.1311	0.13425
Optimal value	2.30646268	2.305968064	2.305473449	2.304978833	2.304484218	2.303989602
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1374	0.14055	0.1437	0.14685	0.15
Optimal value	2.303494987	2.303000371	2.302505756	2.30201114	2.301516525
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

Table C23 Change in Net Monetary Benefit

	0.024	0.02715	0.0303	0.03345	0.0366	0.03975
Optimal value	64055.10	64015.6114	63979.23933	63942.86727	63906.4952	63870.12313
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0429	0.04605	0.0492	0.05235	0.0555	0.05865
Optimal value	63833.75106	63797.37899	63761.00692	63724.63485	63688.26278	63651.89071
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0618	0.06495	0.0681	0.07125	0.0744	0.07755
Optimal value	63615.51864	63579.14657	63542.77451	63506.40244	63470.03037	63433.6583
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0807	0.08385	0.087	0.09015	0.0933	0.09645
Optimal value	63397.28623	63360.91416	63324.54209	63288.17002	63251.79795	63215.42588
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.0996	0.10275	0.1059	0.10905	0.1122	0.11535
Optimal value	63179.05381	63142.68175	63106.30968	63069.93761	63033.56554	62997.19347
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1185	0.12165	0.1248	0.12795	0.1311	0.13425
Optimal value	62960.8214	62924.44933	62888.07726	62851.70519	62815.33312	62778.96106
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

	0.1374	0.14055	0.1437	0.14685	0.15
Optimal value	62742.58899	62706.21692	62669.84485	62633.47278	62597.10071
Optimal strategy	Neuropad only	Neuropad only	Neuropad only	Neuropad only	Neuropad only

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide

references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model structure was designed using Microsoft Excel to emulate the different clinical pathways that can be developed once a person with diabetes has been diagnosed with neuropathy. Expert clinical advisers were consulted for their approval on the disease progression model.

Moreover, a literature search was performed in order to apply the available evidence to the transition probabilities between disease health states included in the model and the utilities derived from these health states, as well as official reports about the sensitivity and specificity of the diagnostic tools compared in the analysis. Finally, data on costs was obtained from both the literature and a recent report which assesses the economic burden of diabetic foot care in the particular case of the United Kingdom.

Robust internal quality assurance with multiple rounds of review was performed to ensure that the model performs as intended.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previous analysis comparing the use of Neuropad as a neuropathy diagnostic tool in people with diabetes, compared with the standard care (10-g SWME) has been made before. Hence, the findings obtained in the current economic analysis cannot be compared to the existing literature. Moreover, the present cost-effectiveness analysis can lead to two main conclusions, which can be of great interest:

1. If we aim to compare two different technologies that are intended to diagnose or measure the same thing, neuropathy, then this should only be done with Neuropad, according to our findings, as it saves around

£1,368.43 per patient and has also incremental gains in terms of QALYs with respect to the standard of care (10-g SWME).

2. But, if what we want to ask ourselves is whether testing different components of neuropathy with different technologies (sudomotor function with Neuropad and sensitivity/sensation in the feet with 10-g SWME) is going to increase the costs, we would also be able to answer the question. And the answer would be no; actually, we would be saving money (9.75 pounds per patient).

Hence, following these two main conclusions, it would make perfect sense for the NHS to deploy Neuropad first by mailing a test to people with diabetes or asking them to pick the test up from a community pharmacy, for example. Those that test positive could then be tested using SWME, if convenient, or even referred to secondary care for a firm diagnosis.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The costs analysis is relevant to all groups of patients and NHS settings in England, who have already been identified in the scope: “People with diabetes undergoing routine foot-care checks by health care workers in primary and secondary care settings and/or undertaking a DPN self-test in the home”. Moreover, due to the fact that Neuropad is very flexible in terms of use (in-clinic, with SWME, without SWME, at home, no need for clinic visits and with near 100% reproducibility), it would also be beneficial for those approximately 400,000 people with diabetes in England who never have an annual foot test and the opportunity to screening this population using Neuropad.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strength of the analysis relies on the fact that reliable data has been used to assess the implementation of Neuropad as a diagnostic tool of neuropathy. Moreover, the “memoryless” problem is avoided by using a Markov model[1]. This has been particularly relevant for the estimation of the utilities and transition

probabilities from each health state since the value of a given health state will depend on the previous health state. If another model had been used, such as a decision tree model, our results could be biased as the progression of the disease would not have been taken into account. Another strength that should be mentioned is the recent data that has been used to impute the cost derived from diabetic foot care for the particular case of England[12].

The conclusion derived from the analysis seem to be robust, as it has already been shown in the one-way and two-way sensitivity analysis. Nevertheless, a number of limitations should also be mentioned, which are listed below:

1. Other complications that were derived from diabetes and could increase the care costs were not included in the model. However, costs were varied in the sensitivity analysis by 33% percent and the results were quite robust to changes (both decrease or increase) in costs.

2. One of the assumptions of the model was that SWME cost only referred to the cost per patient, but did not include consumable costs or required trained staff, which is needed but it is not known ascertained how much. However, SWME cost was also modified in the sensitivity analysis and no change was noticed.

3. Lack of data on previous comparison between Neuropad and other diabetic neuropathy tests limit the comparison of our results, which are particularly significant in terms of savings when Neuropad is compared to SWME, both used in isolation.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Additional analysis that could be undertaken to enhance the robustness or completeness of the results would mainly refer to the limitations named before (more detailed data on SWME costs) or a local evaluation of costs in an NHS hospital and community care home, to make comparisons, where people with diabetes are screened using Neuropad and more precise data on their particular

health status (other diabetes-related diagnoses) and costs of care could be available.

References

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

10.1.2 The date on which the search was conducted.

Response

10.1.3 The date span of the search.

Response

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Response

10.1.6 The inclusion and exclusion criteria.

Response

10.1.7 The data abstraction strategy.

Response

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

10.2.2 The date on which the search was conducted.

Response

10.2.3 The date span of the search.

Response

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.2.6 The inclusion and exclusion criteria.

Response

10.2.7 The data abstraction strategy.

Response

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Response

10.3.2 The date on which the search was conducted.

Response

10.3.3 The date span of the search.

Response

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for

example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Response

10.4.2 The date on which the search was conducted.

Response

10.4.3 The date span of the search.

Response

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.4.6 The inclusion and exclusion criteria.

Response

10.4.7 The data abstraction strategy.

Response

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

12 an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined

13 a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted

14 an executable electronic copy of the cost model has been submitted

- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

14.1 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided,

NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company

representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

14.2 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NICE National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT 318 - The Neuropad test for inadequate sweat gland function in the early detection of diabetic foot neuropathy

Expert Adviser Questionnaire Responses

Name of Expert Advisers	Job Title	Professional Organisation/ Specialist Society	Nominated by	Ratified
Professor Michael Kirby	Visiting Professor to the Faculty of Health & Human Sciences	Royal College of Physicians	Sponsor	Yes
Dr Umesh Dashora	Consultant Physician	Association of British Clinical Diabetologists	NICE	Yes
Ms Catherine Gooday	Principal Podiatrist, Diabetic Foot Clinic	Diabetes UK	NICE	Yes
Dr Andrew Holton	Consultant Clinical Neurophysiologist	British Peripheral Nerve Society	Specialist Society	-
Professor Solomon Tesfaye	Consultant Diabetologist	Royal College of Physicians	Sponsor	Yes
Dr James Holt	Consultant Neurologist	British Peripheral Nerve Society	Specialist Society	-
Dr Jonathan Roddick	GP with a special interest in Diabetes	Royal College of General Practitioners	NICE	Yes
Dr Antonin Gechev	Consultant Neurophysiologist	British Peripheral Nerve Society	Specialist Society	-

YOUR PERSONAL EXPERIENCE (IF ANY) WITH THIS TECHNOLOGY

Question 2: Please indicate your experience with this technology?

Expert Advisers	I have had direct involvement with this	I have referred patients for its use	I manage patients on whom it is used in another part of their care pathway	I would like to use this technology but it is not currently available to me
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Yes**	Blank	Blank	Blank
Dr Umesh Dashora **Consultant Physician**	No	No	No	**Yes**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	No	No	No
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	Blank	Blank	**Yes**	No
Professor Solomon Tesfaye **Consultant Diabetologist**	**Yes**	No	No	**Yes**
Dr James Holt **Consultant Neurologist**	No	No	No	**Yes**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	No	No	**Yes**
Dr Antonin Gechev **Consultant Neurophysiologist**	No	No	No	**Yes**

Any Comments?	
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**I have found it useful to detect neuropathy**
Dr Umesh Dashora **Consultant Physician**	**Blank**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I am aware of this technology but do not think it is superior and therefore continue to use the monofilament. It costs considerably more than the monofilament**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Blank**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Blank**
Dr James Holt **Consultant Neurologist**	**I would be interested in using this product as a simple way of assessing for small fibre neuropathy in non-diabetic patients attending the neurology clinic.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Blank**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Blank**

Question 3: Have you been involved in any kind of research on this technology? If Yes, please describe?

Expert Advisers	Yes/No	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	No	Blank
Dr Umesh Dashora **Consultant Physician**	No	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	Blank
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	No	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	**Yes**	**We have just started to use it in our combined diabetes screening clinic to see how it relateds to neuropathy assessment using the Toronto Clinical Scoring System**
Dr James Holt **Consultant Neurologist**	No	Blank
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	No	Blank

THIS PRODUCT (TECHNOLOGY) AND ITS USE

Question 4: How would you best describe this technology?

Expert Advisers	It is a minor variation on existing technologies with little potential for different outcomes and impact	It is a significant modification of an existing technology with real potential for different outcomes and impact	It is thoroughly novel - different in concept and/ or design to any existing
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	Blank	Blank	**Yes**
Dr Umesh Dashora **Consultant Physician**	**Yes**	No	No
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	No	**Yes**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Yes**	No	No
Professor Solomon Tesfaye **Consultant Diabetologist**	No	**Yes**	**Yes**
Dr James Holt **Consultant Neurologist**	No	**Yes**	No
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	No	**Yes**
Dr Antonin Gechev **Consultant Neurophysiologist**	Blank	**Yes**	Blank
Any Comments?			

Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**It is novel and entirely different from the current methods of testing**
Dr Umesh Dashora **Consultant Physician**	**Blank**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**This technology does identify a different type of neuropathy to the existing tools (autonomic neuropathy) used. The monofilament (current tool) does not actually identify neuropathy as such, but instead idenitifies patients at increased risk of developing foot ulceration .** **In the diabetic foot it is the prevention of foot ulceration that is of key importance.** **If the earlier detection of neuropathy reduces the number of people who develop** **Page 3 of 9** **foot ulceration then the test would be of interest, however this would need to be proved in a clinical trial.** **I think the outcome of any review on this technology would conclude similar findings as to those reported by NICE for the vibratip. We need more evidence before we can justify its use.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Blank**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Blank**
Dr James Holt **Consultant Neurologist**	**It is similar to concept though not in design to a sudomotor test (known as the 'sympathetic skin response' test or SSR test) performed by neurophysiologists on request, often to examine the possibility of small fibre neuropathy in non-diabetic patients, which can affect sudomotor function. In the SSR test, the sudomotor electrical response to a small electric shock can be measured by recording electrodes on the palms of the hands and soles of the feet; the Neuropad appears to be far simpler and probably cheaper way of assessing sudomotor function.**

Dr Jonathan Roddick **GP with a special interest in Diabetes**	**I am not aware of anything similar**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Blank**

Question 5: What is the most appropriate use (e.g. clinical indication) for the technology?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**As an adjuct to other methods of testing for neuropathy in the clinic currently in use**
Dr Umesh Dashora **Consultant Physician**	**Where the diagnosis is in doubt and the feet are at risk**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I feel that the only place for this technology would be in patients who lack the cognitive ability for the monofilament test. This would make health care workers aware of the fact that these people are at increased risk of developing foot ulceration**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**I am currently uncertain. As portrayed, it is suggested to help the patient with diabetes, and his Physcian, after clinical care to his advantages with respect to future, impairment (eg avoiding/postponing peripheral vascular disease leading to lower-limb amputation) or premature death.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Diabetic Neuropathy/The Diabetic Foot**

Dr James Holt **Consultant Neurologist**	**The typical senario would be a way for diabetologists to provide evidence for diabetic polyneuropathy, which typically affects small and large fibres, including autonomic (sympathetic and parasympathetic) fibres. Diabetic polyneuropathy can usually be diagnosed on clinical grounds (history and examination) and I am not convinced of the value of the Neuropad in this instance, which could lead to error if considered 'essential' for diagnosis, which it wouldn't be. However, I do see this test as being of potential value in a subset of early diabetic polyneuropathy patients, where symptoms are ambiguous. Although this test is aimed at diabetic patients, I would be interested in this technology for use in a small number of patients who attend my neuromuscular clinic, to provide evidence of isolated small fibre neuropathy (and replace a more complex neurophysiological test, described above in my response to Q4). If available, I would be interested in seeing whether the test could be validated by my colleague Dr Gosal in Manchester (by correlating with results of skin biopsy, a definitive test), who runs a small fibre neuropathy clinic.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Blank**
Dr Antonin Gechev **Consultant Neurophysiologist**	**The most appropriate use of this technology would be for screening of patients' symptoms in the early stage of any case of suspected small fibre peripheral neuropathy, i.e. diabetes related; idiopathic; painful neuropathies etc.**

COMPARATORS (including both products in current routine use and also "competing products")

Question 6: Given what you stated is the appropriate indication (clinical scenario) for its use, what are the most appropriate "comparators" for this technology which are in routine current use in the NHS?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Filament test. Sensitivity to touch may be tested using a soft nylon fiber called a monofilament.** **Nerve conduction studies. This test measures how quickly the nerves in arms and legs conduct electrical signals.** **Electromyography (EMG). Often performed along with nerve conduction studies, electromyography measures the electrical discharges produced in muscles.** **Quantitative sensory testing. This noninvasive test is used to assess how nerves respond to vibration and changes in temperature.**

Dr Umesh Dashora **Consultant Physician**	**Monofilament testing, neurothesiomenter**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Monofilament, neurothesiometer, calibrated tuning fork. However these tests do not measure autonomic neuropathy.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Sympathetic skin response, tests (various) for cardiovascular autonomic neuropathy, Quantitative Thermal Threshold (Qsens) etc.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**SUDOSCAN**
Dr James Holt **Consultant Neurologist**	**The SSR test is a comparative test, but is (rightly) not in use for diabetic patients, which can be diagnosed clinically without the need for specialist tests. These comments would also apply to Neuropad, though this is a simpler test and there may well be patients with ambiguous symptoms where this test may prove useful. Neuropad is likely to be more reliable than SSR test, which can appear falsely negative if the patient is stressed or in pain.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**10g monofilament neuropathy testing**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Sympathetic skin response or Quantitative Sensory Testing (QST) – types of Neurophysiological assessments**

Question 7: "Competing products": Are you aware of any other products which have been introduced with the same purpose as this one?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Autonomic testing. blood pressure in erect and supine positions and assessment of ability to sweat.** **10-g Semmes-Weinstein monofilament examination [SWME] using a 5.07/10-g monofilament applied to a noncallused site on the dorsum of the first toe just proximal to the nail bed. The SWME threshold is defined as the total number of times the application of the 10-g monofilament is not perceived** **Vibration testing a 128-Hz tuning fork applied to the bony prominence bilaterally situated at the dorsum of the first toe just proximal to the nail bed. . The vibration testing threshold is defined as the total number of times the application of the vibrating tuning fork and the dampening of vibration is not felt** **Superficial pain sensation can be conducted using a sterile Neurotip (Owen Mumford, Oxford, U.K.) applied four times in an arrhythmic manner to the two sites described for the SWME. The superficial pain threshold was defined as the total number of times the application of the pain sensation was not perceived**
Dr Umesh Dashora **Consultant Physician**	**No**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**As above**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**There are many, some not new**
Professor Solomon Tesfaye **Consultant Diabetologist**	**No**
Dr James Holt **Consultant Neurologist**	**I am not aware of any**

Dr Jonathan Roddick **GP with a special interest in Diabetes**	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	**Induces skin wrinkling; however it is not widely introduced amongst the Neurologists at NHS**

POSSIBLE BENEFITS FOR PATIENTS

Question 8: What are the likely additional benefits for patients of using this technology, compared with current practice/ comparators?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**tests sweating, early diagnosis of foot problems**
Dr Umesh Dashora **Consultant Physician**	**If there is evidence that it is more objective than monofilament or neuroptip testing that it should be used.**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Identifying neuropathy in patients in which the monofilament is inappropriate**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Doubtful, but I am open-minded, prepared to learn.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**It is simple, visual and has educational potential for diabetic foot patients. Also it may be used for screening for neuropathy objectively. A negative result rules out neuropathy.**
Dr James Holt **Consultant Neurologist**	**I am not convinced of value in all but a subset of diabetic polyneuropathy patients, but see my comments in my response to Q5 about potential value in some diabetic patients and in the far rarer condition of suspected small fibre neuropathy.**

Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Much more likely to pick up early evidence of neuropathy**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Accessible at patients' home and useful for follow up**

Question 8.1: Is each additional benefit likely to be realised in practice? What are the likely obstacles?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**time it takes to do the test in a busy clinic**
Dr Umesh Dashora **Consultant Physician**	**The patients identified as neuropathic may have more checks and treatment. Inconclusive evidence may reduce uptake**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Cost and time**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Realised in practice: No Likely obstacles: Various, numerous.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Yes. Obstacle: its niche will need to be clearly defined. It takes at least 10min and may not be easy to perform in a busy clincal practice.**
Dr James Holt **Consultant Neurologist**	**i think benefits could be realised, mainly in providing a timely diagnosis than to any different treament, and only in a subset of patients, bus see risks mentioned in my response to Q8.2.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**would be need to be available in every GP, hospital diabetes clinic and podiatry clinic practice to be really effective.**

Dr Antonin Gechev **Consultant Neurophysiologist**	**1. Yes. 2.Co-morbidities affecting the feet would potentially affect the results**

Question 8.2: How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for patients are being realised?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Reduction in foot damage**
Dr Umesh Dashora **Consultant Physician**	**Rate of amputaitons after startining the use of this technology**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**It is diffcult to measure the benefit, this tool identifies neuropathy. The benefit would be a reduction in the number of patients with diabetes developing foot ulceration, but there are so many other factors that will influence whether a patient develops a foot ulcer**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Cohorts of patients with Diabetes to be seperated by result of the test and followed up.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Cost benefit analysis**
Dr James Holt **Consultant Neurologist**	**Difficult, and posslble benefits of early diagnosis (which may not lead to treatment, as diabetic polyneuropathy has no specific treatment available, aside perhaps attempting better control of blood sugars) would need to be balanced with risks (of overuse in those where a diagnosis can be made clinically without tests, and of overdiagnosis -**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**confirmed cases of neuropathy.** **reduction in neuropathic foot ulcers**

Dr Antonin Gechev **Consultant Neurophysiologist**	**The benefits could be measured with pain analogue scale scores changes or compared to the neurophysiology tests mentioned above**

Question 8.3: How good is this evidence for each of these additional benefits?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**moderate, more studies need to be done in a clinic setting**
Dr Umesh Dashora **Consultant Physician**	**Not seen much**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**The development of foot ulceration is multifactoral**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**I have consulted on this with our Professor of Diabetology (Dr Adrian Walker).**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Reasonable**
Dr James Holt **Consultant Neurologist**	**Not good, plus there are concerns if the Neuropad has not been validated in patients with early diabetic polyneuropathy (ideally by a study using skin biopsy, the 'gold standard' test for small fibre neuropathy, which is typically an early feature of diabetic polyneuropathy (which ultimately affects small and large fibres).**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**reduction in foot ulcers should be easily measured.** **confirmed cases of neuropathy more difficult**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Give confidence and motivation to the patients with treatment compliance**

Question 8.4: Please add any further comment on the claimed benefits of the technology to patients, as you see applicable

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Early diagnisis of neuropathic changes**
Dr Umesh Dashora **Consultant Physician**	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	Blank
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	**Will do if I am invited to revew the full application.**
Dr James Holt **Consultant Neurologist**	**Has the Neuropad been validated, and will real benefits trump potential risks? See comments above.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	**It is cost effective**

POSSIBLE BENEFITS FOR THE HEALTHCARE SYSTEM

Question 9: What are the likely additional benefits for the healthcare system of using this technology, compared with current practice/ comparators?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Saving cost**
Dr Umesh Dashora **Consultant Physician**	**More objectivity has been claimed**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I am not sure there are many additional benefits to the general population. As stated the benefits will be to a small group of people in which the monofilament is not suitable.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**None. At present, I see this as a futile distraction**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Ease of use. Can be performed at home.**
Dr James Holt **Consultant Neurologist**	**It would be a cheaper and simpler test compared with the SSR test, for use in non-diabetic patients with suspected isolated small fibre neuropathy. For diabetic patients, I am sure some could benefit, but there are risks, including unnecessary expenditure or misuse of the test (see above).**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Much more cerainty in diagnosis.** **much more objective output rather than a subjective test**
Dr Antonin Gechev **Consultant Neurophysiologist**	**It is an objective although qualitative measurement requiring limited training and is not time consuming**

Question 9.1: Is each additional benefit likely to be realised in practice? What are the likely obstacles?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Incorrect use, & time issues**
Dr Umesh Dashora **Consultant Physician**	**There is some improvement expected if the calims are substantiated by research**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**The main obstacle will be the cost of purchase. This test takes 15 mins to complete most appointments for a diabetes annual review are not this long. If this new method is more sensitive than the monofilament it would increase the number of referrals to foot protection services.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Biggest bottleneck is quality clinical research in Diabetes.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Yes potentially. However, the context of its use will need to be clearly defined.**
Dr James Holt **Consultant Neurologist**	**See above comments for Q8**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Probably**
Dr Antonin Gechev **Consultant Neurophysiologist**	**1. Yes. 2. Challenging to standardise consecutive measurements**

Question 9.2: How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for the healthcare system are being realised?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Reduction in foot ulcers for example**
Dr Umesh Dashora **Consultant Physician**	**Amputation rates**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**It is diffcult to compare this technology to current methods as the monofilament detects people at risk of developing a foot ulceration, where as the neuropad identifies autonomic neuropathy. They are the same but different.The benefit would be a reduction in the number of patients with diabetes developing foot ulceration, but there are so many other factors that will influence whether a patient develops a foot ulcer**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Compared with controls, age-specific mortality and lower-limb amputation.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Ultimately by reduction in hard endpoints such as hospital visit/addmission rates with foot problems; amputation rates etc.**
Dr James Holt **Consultant Neurologist**	**See above comments for Q8**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**See 8.2**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Difficult to tell**

Question 9.3: How good is this evidence for each of these additional benefits?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Moderate**
Dr Umesh Dashora **Consultant Physician**	**Reamins to be seen and evaluated**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Blank**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**To my knowledge, there is none**
Professor Solomon Tesfaye **Consultant Diabetologist**	**There is some evidence but I suspect it is not very not robust**
Dr James Holt **Consultant Neurologist**	**See above comments for Q8**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**See 8.3**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Difficult to tell**

Question 9.4: Please add any further comment on the claimed benefits of the technology to the healthcare system, as you see applicable

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**would depend on good training and careful use**
Dr Umesh Dashora **Consultant Physician**	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	Blank
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	Blank
Dr James Holt **Consultant Neurologist**	**See above comments for Q8**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	**Difficult to tell**

FACILITIES, TRAINING AND FUNCTIONING

Question 10: ***Are there any particular facilities or infrastructure which needs to be in place for the safe and effective use of this technology?***

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**No**
Dr Umesh Dashora **Consultant Physician**	**Minimal training**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**No**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**RCT in patients suffering diabetes**
Professor Solomon Tesfaye **Consultant Diabetologist**	**No**
Dr James Holt **Consultant Neurologist**	**Blank**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Needs equipment provision for the test across priimary and secondary care**
Dr Antonin Gechev **Consultant Neurophysiologist**	**I don't think so**

Question 11: Is special training required to use this technology safely and effectively?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Yes**
Dr Umesh Dashora **Consultant Physician**	**No**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**No**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**No**
Professor Solomon Tesfaye **Consultant Diabetologistno**	**No**
Dr James Holt **Consultant Neurologist**	**Yes, medical training: use by diabetic nurses might lead to misuse and unnecessary expense, however if Neuropad turns out to be very cheap, these risks may be considered minimal.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Yes**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Basic trading is required**

Question 12: Please comment on any issues relating to the functioning, reliability and maintenance of this technology which may be important to consider if it is introduced

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Disposable pads**
Dr Umesh Dashora **Consultant Physician**	**None**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I am not able to answer this question**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Trivial, or none**
Professor Solomon Tesfaye **Consultant Diabetologist**	**The electrodes will have a "use by" date and this will need to be adhered to.**
Dr James Holt **Consultant Neurologist**	**It should be validated as outlined above in Q8.3**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Not sure**
Dr Antonin Gechev **Consultant Neurophysiologist**	**I am not aware of those**

COSTS

Question 13: Please provide any comments on the likely cost consequences of introducing this technology. In particular, please comment on the implications of this technology replacing the comparator/s you have described above

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Cost of the disposable**
Dr Umesh Dashora **Consultant Physician**	**Unlikely to be costly**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Considerably more expensive than current tools, will require more time to complete**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Inappropriate, misleading and a diversion**
Professor Solomon Tesfaye **Consultant Diabetologist**	**There will be a significant cost implication as current methods are less expensive (10g monofilament and Tunning fork). However, if this technology reduces hospital visits and amputations (around £40K per amputation - hospital cost alone) the benefits may be substancial**
Dr James Holt **Consultant Neurologist**	**The SSR test I have mentioned above is infrequently performed, so financial gains minimal. The Neuropad being easier to use would be far easier to validate however, through correlation with skin biopsy results (not widely available, except in some research and clinical settings, such as in Manchester).**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**Could be very expensive to introduce**
Dr Antonin Gechev **Consultant Neurophysiologist**	**I am not aware of any**

GENERAL ADVICE BASED ON YOUR SPECIALIST KNOWLEDGE

Question 14: Is there controversy about any aspect of this technology or about the care pathway?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**No**
Dr Umesh Dashora **Consultant Physician**	**Not known**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**Cost/benefit**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Apart from lack of evidence (I am prepared to learn) , none.**
Professor Solomon Tesfaye **Consultant Diabetologist**	**No**
Dr James Holt **Consultant Neurologist**	**Possibly, see above**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**No**
Dr Antonin Gechev **Consultant Neurophysiologist**	**Not to my knowledge**

Question 15: If NICE were to develop guidance on this technology, how useful would this be to you and your colleagues?

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Useful in routine foot clinics**
Dr Umesh Dashora **Consultant Physician**	**It will have some use in difficult times**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**No not really**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**Very useful**
Professor Solomon Tesfaye **Consultant Diabetologist**	**Very**
Dr James Holt **Consultant Neurologist**	**Not hugely useful, unless based on comprehensive evaluation of validity and wider potential uses.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**helpful if the equipment was widely availble**
Dr Antonin Gechev **Consultant Neurophysiologist**	**That would be preferable and also very useful**

Question 16: Do any subgroups of patients need special consideration in relation to the technology (for example, because they have higher levels of ill health, poorer outcomes, problems accessing or using treatments or procedures)? Please explain why

Expert Advisers	Comment
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	**Long standing diabetes**
Dr Umesh Dashora **Consultant Physician**	**None**
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**As discusses earlier this technology may benefit patients who are unsuitable for the monofilament test.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	**No**
Professor Solomon Tesfaye **Consultant Diabetologist**	**It might have a special use in educating foot patients.**
Dr James Holt **Consultant Neurologist**	**Patients with isolated small fibre neuropathy are very difficult to confidently diagnose, with no good tests except the invasive and expensive skin biopsy (requiring great pathological expertise to interpret), which is only available in some specialist centres and often only for research purposes. If validated against skin biopsy, this could be a really valuable and relatively cheap clinical tool.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	**May be more difficult for housebound patients**
Dr Antonin Gechev **Consultant Neurophysiologist**	**I think this technology would be useful for screening in relatively early stages of patients symptoms.**

CONFLICTS OF INTEREST

Question 18.1: Do you or a member of your family have a personal financial interest? The main examples are as follows:

Expert Advisers	Consultancies or directorships	Clinicians receiving payment for a procedure	Fee-paid work	Shareholdings	Financial interest in a company's product	Expenses and hospitality	Funds	Personal non-pecuniary interest
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	No	No	No	No	No	No	No	No
Dr Umesh Dashora **Consultant Physician**	No	No	No	No	No	No	No	No
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	No	No	No	No	No	No	**Yes**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	No	No	No	No	No	No	No	No
Professor Solomon Tesfaye **Consultant Diabetologist**	**Yes**	No	No	No	No	No	No	No
Dr James Holt **Consultant Neurologist**	No	No	**Yes**	No	No	No	No	No
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	No	No	No	No	No	No	No

Dr Antonin Gechev **Consultant Neurophysiologist**	No	No	No	No	No	No	No	No
If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.								

Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	Blank
Dr Umesh Dashora **Consultant Physician**	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I was an author on this paper which might be relevant** **Rayman G, Vas PR, Baker N, Taylor CG, Gooday C, Alder AI, Donohoe M. The Ipswich Touch Test - A simple method for detecting 'at risk feet' in inpatients with diabetes. Diabetes Care. 2011; 34:1517-1518**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	**I have received honoraria (be it less than £1000/ year) for attending advispory board meetings for the Company**
Dr James Holt **Consultant Neurologist**	**I was on a drug company advisory panel for a treatment of inflammatory neuropathy and was paid a fee, but this is of no relevance to the Neuropad or the group of patients where Neuropad might be used. I should declare that most diabetic polyneuropathy patients are managed by diabetologists, not neurologists, and thus I am more interested in the potential value of Neuropad in those patients I do see, namely suspected isolated small fibre neuropathy patients.**
Dr Jonathan Roddick **GP with a special interest in Diabetes**	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	Blank

Question 18.2: Do you have a non-personal interest? The main examples are as follows:

Expert Advisers	Grant for the running of a unit	Grant or fellowship for a post or member of staff	Commissioning of research	Contracts with or grants from NICE
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	No	No	No	No
Dr Umesh Dashora **Consultant Physician**	No	No	No	No
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	**Yes**	**Yes**	No
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	No	No	No	No
Professor Solomon Tesfaye **Consultant Diabetologist**	No	No	No	No
Dr James Holt **Consultant Neurologist**	No	No	No	No
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	No	No	No
Dr Antonin Gechev **Consultant Neurophysiologist**	No	No	No	No

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.	
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	Blank
Dr Umesh Dashora **Consultant Physician**	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	**I have received an NIHR Clinical doctoral fellowship grant which has been paid to my employer to allow me to study for a PhD.** **The team I manage are currently working on several CRN adopted research trials on the management of the diabetic foot for which my employer receives payment.** **Leucopatch® in the management of hard-to-heal Diabetic Foot Ulcers. Commercially funded. Foot Ulcer Microbiome in Diabetes exploratory study (FUMID). Sponsor Nottingham University.** **A randomised, double blind, placebo controlled multicentre trial, examining the effect of Natrox™ on the rates of healing for chronic diabetic foot ulcers (TODFU). Commercially funded.** **A phase 1b, blinded, randomised, multicentre, multiple-ascending dose study of the safety, tolerability pharmacokinetic of UTTR1147A administered by subcutaneous injection in patients with non-healing neuropathic diabetic foot ulcers. Commercially funded.**
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	Blank
Dr James Holt **Consultant Neurologist**	Blank
Dr Jonathan Roddick **GP with a special interest in Diabetes**	Blank

Dr Antonin Gechev **Consultant Neurophysiologist**	Blank

Question 18.3: Do you or your organisation or department have any links with, or funding from the tobacco industry?

Expert Advisers	Yes or No?	*If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.*
Professor Michael Kirby **Visiting Professor to the Faculty of Health & Human Sciences**	No	Blank
Dr Umesh Dashora **Consultant Physician**	No	Blank
Ms Catherine Gooday **Principal Podiatrist, Diabetic Foot Clinic**	No	Blank
Dr Andrew Holton **Consultant Clinical Neurophysiologist**	No	Blank
Professor Solomon Tesfaye **Consultant Diabetologist**	No	Blank
Dr James Holt **Consultant Neurologist**	No	Blank
Dr Jonathan Roddick **GP with a special interest in Diabetes**	No	Blank
Dr Antonin Gechev **Consultant Neurophysiologist**	No	Blank