Title: Neuropad test for the early detection of diabetic foot neuropathy

Produced by:	King's Technology Evaluation Centre
Authors:	Catey Bunce, Reader in Medical Statistics, KiTEC Anastasia Chalkidou, Senior Health Technology Assessor, KiTEC Kate Goddard, Health Technology Assessor, KiTEC Naomi Herz, Health Technology Assessor, KiTEC Murali Kartha, Senior Health Economist, KiTEC Stephen Keevil, Director, KiTEC Tom Langford, Health Technology Assessor, KiTEC Tom Macmillan, Information Specialist, KiTEC Mark Pennington, Senior Lecturer in Health Economics, KiTEC Jennifer Summers, Post-Doctoral Research Fellow in Medical Statistics, KiTEC
Correspondence to:	Joanne Moffitt Joanne.moffitt@kcl.ac.uk
Date completed:	10/07/2017

Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

None.

Acknowledgements

The authors would like to thank the following expert advisers who were appointed by NICE:

- Dr Antonin Gechev, Consultant Neurologist, West Hertfordshire Hospitals NHS Trust
- Dr James Holt, Consultant Neurologist, The Walton Centre NHS Foundation Trust
- Prof Solomon Tesfaye, Consultant Physician and Honorary Professor of Diabetic Medicine, Sheffield Teaching Hospitals NHS Foundation Trust

Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
CCM	Corneal confocal microscopy
CI	Confidence interval
DH	Department of Health
DNS	Diabetic neuropathy symptoms
DPN	Diabetic peripheral neuropathy
EAC	External Assessment Centre
GP	General practitioner
Hz	Hertz
IENFD	Intraepidermal nerve fibre density
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MNSIE	Michigan neuropathy screening instrument examination
MNSIQ	Michigan neuropathy screening instrument questionnaire
MTEP	Medical Technologies Evaluation Programme
NCS	Nerve conduction study
NDS	Neuropathy disability score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE NG	NICE guideline
NICE QS	NICE quality standard
NMB	Net monetary benefit
NPV	Negative predictive value
NSS	Neuropathy symptoms score
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QSART	Quantitative sudomotor axon reflex test
QUADAS 2	Revised Quality Assessment of Diagnostic Accuracy Studies
QALY	Quality adjusted life years
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SD	Standard deviation

UK	United Kingdom
VPT	Vibration perception test
Vs	Versus

1 Executive Summary

The clinical evidence submitted by the sponsor consisted of 7 original published studies, 2 unpublished studies and 1 meta-analysis. The sponsor did not carry out a quality appraisal or meta-analysis of the primary studies (they instead submitting a pre-existing meta-analysis). The EAC included 3 published studies (Quattrini et al. 2008, Ponirakis et al. 2014, Tentolouris et al. 2008 and 2 unpublished studies (Sanz et al. 2016, Tentolouris et al. 2017) from the sponsor submission and excluded 4 published studies (Ishibashi et al. 2014, Papanas et al. 2011, Tomesova et al. 2013, Tentolouris et al. 2010). The EAC carried out an independent systematic review. Thirteen additional studies were identified (9 full texts and 4 abstracts). After exclusions, 18 studies were included. All studies investigated the diagnostic accuracy of the Neuropad against a reference standard (most commonly the Neuropathy Disability Score [NDS], a standard neuropathy scoring system). Two published studies assessed the Neuropad against a comparative screening test (10g monofilament). Results 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). No evidence was found for the accuracy of combining the Neuropad and 10g monofilament test. One published and 2 unpublished longitunial studies found that an abnormal Neuropad result was associated with an increased risk of foot ulceration. One study assessed reliability of the test in a home setting (the primary intended use of the Neuropad) indicating that the test results had significant agreement between the healthcare provider and the patient. The remaining studies were carried out in a secondary or tertiary care setting. The sponsor included a pre-existing meta-analysis (Tsapas et al. 2014). This was excluded because many studies had overlapping populations and/or did not match the assessment scope. Eighteen studies were included in Tsapas et al. (2014). The EAC included 8 of these studies (Aubert et al. 2013, Didangelos et al. 2006, Forth et al. 2010, Freitas et al. 2009, Quattrini et al. 2008, Spallone et al,. 2009, Ziegler et al. 20011, Ziegler et al. 2012). Others were excluded on the basis of

overlapping populations (for example the Papanas studies had significantly overlapping populations), populations which did not match the assessment scope, unclear reference standards (both in terms of test and thresholds used). The EAC carried out a meta-analysis on 5 diagnostic accuracy studies (Liatis et al. 2007, Kamenov et al. 2010, Freitas et al. 2009, Manes et al. 2014, Tentolouris et al. 2008), resulting in a pooled sensitivity and specificity of 89.4% and 60.3%, respectively, against NDS (NDS≥5) as a reference standard (noting that there was high heterogeneity in the outcomes). The EAC considers the 5 studies included in the meta-analysis to be pivotal. Also of importance are the 2 UK studies with fulltext publications (Quattrini et al. 2008, Ponirakis et al. 2014), and the study providing evidence for home use (Tentolouris et al. 2008).

The sponsor submitted an economic model for the Neuropad. The sponsor did not provide any search strategy or complete the economic evidence section in the submission. Their search retrieved no economic evidence for the technology. After carrying out an independent systematic review, the EAC confirmed that no economic evidence was found. The sponsor submitted a *de novo* Markov model using sensitivity and specificity values from the literature to model neuropathy detection, followed by disease progression over a time horizon of 3 years for patients who tested positive for neuropathy. The EAC considers the sponsor's model to be flawed, undermining the analysis and inference drawn from the model results. Robust conclusions require a revision of the model structure and parameters. The EAC produced a revised model with a new structure and parameters to rectify the issues identified with the sponsor's model: ignoring patients testing negative for neuropathy (regardless of true neuropathy status) and combining all true and false positive cases. The base case analysis and all sensitivity analyses revealed that the use of Neuropad is not cost saving compared to 10 g monofilament. If the neuropad is combined with monofilament, there are cost-savings. However, the key parameters (sensitivity and specificity) applied in this strategy are based on theoretical calculation assuming complete independence of the 2 tests and not clinically evidenced.

In conclusion, the usefulness of the Neuropad within current clinical guidelines is unclear. The Neuropad is intended as an adjunctive screening test and the sponsor has also stated that the Neuropad can be used as a standalone test. Current UK guidance requires annual foot checks which include the use of a monofilament (and/or a tuning fork). The 10g monofilament is the most commonly used screening test which tests for loss of protective sensation in the feet (associated with large fibre neuropathy and moderate to advanced foot risk). While the evidence indicates that Neuropad may be non-inferior to the monofilament and may in fact be more sensitive (though less specific), there is not enough robust head-to-head evidence to support superiority. Neuropad tests for an earlier stage of diabetic peripheral neuropathy (DPN) than the monofilament, which is associated with lower risk of foot problems. People with diabetes would only be referred to the foot protection service if diagnosed loss of protective sensation, which is associated with moderate or advanced foot risk (detected, for example, by the monofilament, as outlined in NICE NG19). The EAC is unaware of UK guidance for management of early stage DPN (which is less likely to be accompanied by loss of protective sensation and therefore more likely to lead to a low foot risk classification). It is unclear how Neuropad will impact 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. Benefits may be found in populations where other standard screening tests are not possible (such as people with communication difficulaties), however no studies were submitted or retrieved in these populations. More evidence would be helpful on the reliability of the test to adequately conclude that the test is objective enough to be used by carers or patients at home.

2 Background

2.1 Overview and critique of company's description of clinical context

Overall, the sponsor's description of the clinical context is appropriate and incorporates most of the relevant guidelines for the NHS, however guidance is broadly about management of diabetes and the diabetic foot, rather than diagnosis, and not specific to small fibre neuropathy and diabetic peripheral neuropathy (DPN).

The sponsor provided a brief overview of diabetes and DPN in the UK (including the prevalence and economic cost of diabetes and description of DPN).

Relevant guidance

At the moment, there are no detailed guidelines for the systematic assessment and diagnosis of DPN in the UK (in particular for early stage DPN). The sponsor listed guidance from the 3 following sources to describe the clinical pathway of care:

- NICE NG19 Diabetic foot problems: prevention and management. NICE NG19 recommends the assessment of DPN using a monofilament test, which will identify people with loss of protective sensation, associated with moderate to advanced DPN and a higher risk of foot ulceration. The monofilament assessment will help identify people at risk of foot problems rather than seek out all those with DPN.

- NICE NG28 Type 2 diabetes in adults: management.

- Local guidance from Northern Devon Healthcare NHS Trust on how to use the 10g monofilament to screen the diabetic foot. The EAC notes that there are other UK examples of local guidance for using the monofilament, such as NHS Highland, and Royal Devon and Exeter NHS Foundation Trust. The EAC notes that local guidance differs, for example, in the number of sites to be tested.

The sponsor suggests the current pathway by listing the guidance above, but does not provide an explicit description or suggestion specifically about pathways for how DPN is assessed currently in primary or secondary care. The EAC understands that there is no current method for patient self-testing.

Only the 10g monofilament test is referred to as a test for screening the diabetic foot. Despite the large number of comparators in the scope (which include standard screening tests), no further guidance is given on testing for DPN or loss of protective sensation using different standard methods including the 128 Hz tuning fork, or standard neuropathy scoring systems such as the Neuropathy Disability Score (NDS).

For example, Diabetes UK describes the following process at annual foot checks: After removing shoes and socks, feet are examined (including looking for corns, calluses and changes in shape. Feet should be tested for numbness or changes in sensation using a tuning fork or monofilament. Questions are asked about the feet and general diabetes management. The patient is then told about results and level of risk for foot problems. If the patient's feet are at increased or high risk they should be referred to the foot protection service.

Therefore in addition to the monofilament test for loss of protective sensation, the 128 Hz tuning fork may also be used to test for vibration perception. More rarely a neurothesiometer or the Vibratip may also be used for vibration perception. Clinical examination for reflexes is may also be used but is not standard practice.

The EAC notes that other guidance includes the British Society for Clinical Neurophysiology Guidelines: Generalised Peripheral Neuropathy, which are widely accepted in Neurophysiology Departments in the UK. The American Diabetes Association has provided definitions and assessment strategies in their recent position statement (Pop-Busui et al. 2017).

The EAC also notes that composite clinical scoring systems, such as the NDS can be used to objectively measure DPN severity (Vas et al. 2015). For

example, the NDS score uses a threshold score of 0-2 to rule out DPN, 3-5 to indicate mild neuropathy and 6 and over to indicate moderate or severe neuropathy. The NDS is commonly used as reference standard for Neuropad in the clinical evidence section of the submission (see section 3). Early identification and foot risk stratification will allow an increased window of opportunity to ensure at-risk patients are enrolled in an appropriate foot protection programme. Though DPN is monotonic, Bus et al (2016) estimates that upto 75% of foot ulcers are preventable with the appropriate intervention (including home monitoring of foot temperature, pressure-relieving therapeutic footwear, and certain surgical interventions).

Issues relating to current practice

The sponsor describes the overall issue with current clinical practice, specifically the importance of early detection of DPN for helping patients make behavioural changes to reduce the risk of unperceived trauma and identify those patients who should undergo more intense interventions. The EAC agrees that some publications indicate that early detection of potential risk factors for ulceration can decrease the frequency of wound development. (Clayton and Elasy 2009, Zhang et al. 2014), but is unaware of any current guidance for management of early DPN specifically.

The sponsor notes that the challenge is that not all people with diabetes receive an annual foot test. Approximately 15% of people who should be receiving annual foot tests, do not (NHS England, 2011-2012). Reasons why people may not attend foot tests were not given by the sponsor, but may include inability to attend appointments due to transport and mobility issues (Martin et al. 2012).

The sponsor also notes that there is variation in the testing process specifically for the use of the 10g monofilament, suggesting that at least 3 site tests involving the plantar aspects of the great toe, the third metatarsal, and the fifth metatarsals should be used to maximise diagnostic value (Feng et al., 2009). The sponsor could expand on this by noting that in the UK there is no standardised method of assessing DPN with any standard diagnostic test, however it is typically assessed by a touch test using simpler methods such

as 10g monofilament, or a vibration test using a 128 Hz tuning fork (NICE MTG 22, Diabetes UK).

The sponsor describes a key benefit of the test being that it is "categorical and objective". An abnormal result indicates that the test can be reported to the GP who will advise an annual review and repeat of the test. The sponsor notes that if there is patchy or no colour change (indicative of sudomotor dysfunction), the GP may administer monofilament testing and/or send a referral for further testing. The EAC notes that these processes would ordinarily be carried out irrespective of Neuropad test result as per current guidance. The EAC suggests that to validate the claim of the test's objectivity and impact on the decision to use a monofilament test, evidence is required to a) describe the reproducability and repeatability of the Neuropad test in order to test its objectivity (particularly for use in self-testing by an untrained patient or carer) and b) compare the accuracy of the Neuropad with the monofilament. NICE NG19 recommends the use of the 10g monofilament assessment to identify people at foot risk (primarily assessing large fibre neuropathy that is associated with loss of protective sensation rather than identify all people with DPN). The Neuropad assesses sudomotor dysfunction, and sudomotor dysfunction may be the earliest manifestation of small fibre neuropathy (Low et al. 2006), which tends to precede large fiber neuropathy (Breiner et al. 2014). Theoretically, this indicates that the Neuropad may be able to detect neuropathy at an earlier stage than the monofilament. However, treatment may not ensue at the earlier stages of neuropathy, and entry into a foot protection programme is more likely if there is evidence of further progression of the disease. 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 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.

Potential changes to current services

The Neuropad test is indicated for use as an adjunctive test with sensation tests, in particular the monofilament, in primary care or home settings as part of the diagnostic process. The sponsor also states that it can be used as a standalone test. The sponsor notes that the test was designed principally for home use and that it is the only self-testing device for sudomotor dysfunction in these settings. The sponsor describes a potential new pathway pertaining to the home setting with Neuropad being used to carry out testing by the patient or carer at home. The implication is that the Neuropad would provide an opportunity for more people to undergo testing for DPN by doing so themselves at home. The sponsor notes that test packs could be acquired by the patient directly contacting the GP practice to request a pack or from a local pharmacist (with an official letter, presumably from the GP). The sponsor claims that the triggers for Neuropad use would be (a) as part of the annual diabetes foot test as specified in NICE NG19, as a routine adjunct to monofilament with the Neuropad test being provided to all diabetes patients *before* they attend an annual foot test bringing their results with them and (b) speculatively in newly diagnosed patients or those patients with diabetes that a healthcare professional may have specific concerns such as overall poor glycaemic control. The sponsor states that there is no 'trigger' for the patient to self–selectively contact the GP practice and notes that this would be a reactive and less effective way of identifying patients with DPN.

The EAC notes that the benefit of this current pathway is unclear. In the case that the test is adjunctive to other standard screening tests (such as the monofilament), the patient would be expected to attend the clinic whether the test result was normal or abnormal. In the case of standalone use, there is a lack of evidence and guidance into how to manage early DPN. More evidence for this and also the clinical outcomes and cost effectiveness of Neuropad may support assessment of the pathways for this diagnosis (for example, in home setting and in people with communication difficulties).

Currently, it is recommended that patients attend an annual foot check with their GP (see Diabetes UK). One expert noted that the Neuropad could be useful if used in the home setting with people who are unable to attend a clinic visit – if the results were normal, then no further tests would be required that year. However, there is a lack of evidence and guidance into how to assess and manage early DPN therefore the clinical pathway for a standalone Neuropad response is unclear on this basis. In addition, NICE NG19 recommends that the person should be referred to a foot protection service if their feet are deemed to be at moderate or high risk (rather than low risk, associated either healthy feet or with earlier stage DPN). Leese et al. (2006) found that that there was a low (99.6%) risk of patients classified as low risk of ulceration developing a foot ulcer (using similar criteria to those in NICE NG19). This was 83 times more likely in the high risk group, and 6 times more likely in medium risk group.

Potential additional tests required

The sponsor indicates that tests carried out in secondary care settings are required for a definitive diagnosis of DPN. The tests suggested include nerve conduction studies (NCS), vibration perception thresholds (VPT), intraepidermal nerve fibre density (IENFD), quantitative sudomotor axon reflex test (QSART), and corneal confocal microscopy (CCM). The expert advisors for the assessment noted that nerve conduction studies and/or electromyography tend to be used as confirmatory tests.

However, these are not tests or requirements for “selecting or monitoring” patients. As the test can be administered as part of annual routine foot checks, the EAC does not expect that additional tests, investigations or administration requirements will be needed for selecting or monitoring patients.

Potential additional facilities required

The sponsor stated that no additional resources would be required for claimed benefits to be realised.

The EAC concurs that if the test is carried out in a home setting, no additional healthcare resources are likely to be required. In secondary care, a potential clinical limitation of Neuropad (noted in Quattrini et al. 2008) may be the 10 minutes needed for screening in a busy diabetic clinic. If the Neuropad increases the number of people identified as being at risk of foot problems, this may increase the number of people who are referred to a foot protection service (NICE NG19).

Potential tests which may no longer be needed if Neuropad is introduced

The sponsor suggests that the 128 Hz tuning fork and other vibration tests may not be required as these help "identify patients with sensory deficits which may be carried out using the standard 10g monofilament test". The sponsor states that "Neuropad test plus the 10g monofilament test and a foot examination by a suitably qualified healthcare professional combined would assess for [DPN] comprising motor, sensory and autonomic neuropathy in clinic".

Sensory tests for vibration and touch sensations involve different nerve pathways (NICE MTG22). Therefore it may not be accurate to claim that the 10g monofilament would identify the same patients as vibration tests. No rationale is provided for replacing vibration tests with Neuropad. Though it is not standardised, both tests may be used in clinical practice to provide the clinician with a characterisation of the loss of sensation on the feet.

Potential ways the NHS can disinvest from tests, investigations, interventions, facilities or technologies with the intervention of Neuropad

The sponsor suggests that 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 a foot examination and free up more time in the clinic or GP surgery". The EAC does not believe that this would be the case. As an adjunctive test, the Neuropad is intended to complement other standard diagnostic tests which are administered by an appropriate healthcare professional. Therefore, routine testing (for example, using the monofilament) would still be carried out and the Neuropad test is an

addition to the clinical pathway, rather than a replacement of any component. As a standalone test, there is a lack of evidence and guidance into how to assess and manage early DPN, therefore the potential consequences of the Neuropad test results on patient management are not clear.

The EAC believes that potential benefits may primarily stem from earlier DPN detection rather than a decrease in attendance for foot examination at a diabetic foot clinic or GP surgery. The EAC notes this benefit is caveated, as they are unaware of current UK guidance for management of early DPN. The use of Neuropad will not free up clinic time if patients still need to attend their annual appointment. Another benefit may arise if patients for some reason cannot attend a clinic and have to be tested in the home setting (this is dependent on the usefulness of the Neuropad in isolation and potential future changes to guidance with regard to actions stemming from early DPN detection). There may be a resource utilisation benefit if these patients no longer require NHS-funded transportation. Another issue relating to current practice is that current screening tests require a patient to communicate whether they can feel a sensation (touch or vibration). In practice, people with cognitive impairments may have associative factors that make them fulfil the high risk criteria for foot problems. The Neuropad may provide benefits in people with cognitive impairment or communication difficulties as it is not dependent on an individual's verbal response, unlike sensation-based tests. However, as with home testing, the benefit may depend on the use of Neuropad in place of (rather than as an adjunct to) monofilament or other standard screening tests carried out by a healthcare professional. There is a lack of evidence and guidance into how to assess and manage early DPN, therefore the effect of the Neuropad result on patient management is currently unclear.

2.2 Critique of company's definition of the decision problem

Table 1 Critique of decision problem

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	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." Submission: All submitted evidence involved patients with diabetes. Evidence was submitted from 2 UK studies (Quattrini et al., 2008; Ponirakis et al., 2014).	Yes	The evidence submitted meets the final scope for the population. All populations in submitted evidence were patients with type 1 or 2 diabetes. All sponsor submitted studies were from secondary care settings. None involved primary care settings, and one study was carried out in the home setting (Tentolouris et al. 2008). Papanas et al. (2011) was excluded as it was discovered through correspondence with the author that there was significant population overlap with Manes et al. (2014). The EAC retrieved an additional UK study (Forth et al. 2010) to bring the total to 3 UK studies (2 fulltext and 1 abstract).
Intervention	Scope: Neuropad Submission: Neuropad test for identification of sudomotor dysfunction and diabetic autonomic neuropathy	Yes	The term "diabetic autonomic neuropathy" was used as opposed to DPN. The sponsor clarified that "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". Sudomotor dysfunction is being used as a proxy for DPN. No description of training requirements were given (although these are understood by the EAC to be minimal). Regulatory requirements are complied with.
Comparator(s)	Scope: "- 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),	Partially	The list of comparators within the scope is broad; including tests from both primary and secondary care. Apart from the 10g monofilament, no further contextual information was given about most other tests within the scope, including "standard neuropathy scoring systems" which were commonly used as the reference standard in the evidence. Section 3.5 of the sponsor submission lists some secondary care tests that could be used to confirm diagnosis. Very few studies presented compared screening tests against each other (against a reference standard). Most studies compared Neuropad against one or more reference standards (which are also with in the scope for comparators). The EAC retrieved 2 full text studies (Aubert et al., 2013; Freitas et al., 2009) that compared monofilament against Neuropad using a reference standard.

	Sudoscan, corneal confocal microscopy, NC-stat DPN check)" Submission: The sponsor discusses the 10g monofilament comparator (in section 3.2). In section 3.7, the sponsor indicates that the use of Neuropad may negate the need to use tests of vibration perception, such as the tuning fork. In section 3.5, the sponsor lists secondary care tests that may be carried out to confirm the diagnosis: • Nerve conduction studies (NCS) • Vibration perception threshold (VPT) • Intraepidermal nerve fibre density (IENFD) • Quantitative sudomotor axon reflex test (QSART) • Corneal confocal microscopy (CCM)		The scope includes both single tests (such as monofilament) and composite tests (such as the NDS). No other sources for comparators were presented. The following were the most commonly found comparators / reference standards in the evidence (see section 3.3): - 10g monofilament: This is the most common test used in primary care for screening for DPN. It uses a nylon filament that is pressed onto the foot until it buckles (with 10g of force to buckle). Patients are asked whether they can feel the touch of the device. - The Neuropathy Disability Score (NDS): The NDS is a simple composite score (out of 10) for neuropathy assessment. This is widely used in diabetes neuropathy research as it allows for quantification of clinical assessment. The NDS takes into account vibration perception (evaluated with a 128 Hz tuning fork), temperature perception at the dorsum of the foot (evaluated with the cold/hot tip of the same tuning fork), ability to discriminate sharp

	In terms of the evidence presented (7 studies, 1 meta-analysis) – Neuropad was compared with a reference standard rather than standard screening tests in most cases. Reference standards were mostly based on standard neuropathy scoring systems (either NDS on its own or in combination with other tests). One study (Tentolouris et al. 2010) compared monofilament against Neuropad using a reference standard to identify people with foot ulcerations.		from dull after a pinprick or ability to detect a 10g force exerted with a monofilament, and Achilles reflex (reported as normal or reduced). - VPT: This tests the levels of vibration perception using devices such as a biothesiometer or neurothesiometer. Contrary to the sponsot submission, this is a screening test (rather than a confirmation test for DPN). - Michigan neuropathy screening instrument questionnaire and examination (MNSIQ, MNSIE): This test comprises a 15-item self-administered questionnaire and a lower extremity examination that includes inspection and assessment of vibratory sensation and ankle reflexes. - Neuropathy Symptoms Score (NSS): The NSS consists of symptoms of muscle weakness, sensory disturbances, autonomic symptoms and can be further divided into 17 items (Dyck, 1980). An NSS score of ≥ 1 could be considered abnormal. - Diabetic Neuropathy Symptoms (DNS) score: This assesses pain, numbness, tingling and ataxia. The maximum score of

			DNS is 4 points, 1 point or more indicates neurological abnormalities.
Outcomes	Scope: “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	Partially	Outcomes presented as the selection criteria in the submission are not clear e.g. “Positive or negative test result” (table B1) or “Neuropad test result” (table B3). It is unclear which of the outcomes in the scope this refers to. In the sponsor submission outcomes are tablulated by study (table B6). One meta-analysis and 7 original studies are presented. Most outcomes in the evidence submitted relates to sensitivity and specificity of Neuropad compared with NDS on its own or in combination with other tests. Four sponsor-submitted published studies (Ishibashi et al., 2014; Papanas et al. 2011; Tentolouris et al., 2010; Tomesova et al., 2013) were excluded from the EAC submission due to overlapping populations or outcomes that did not clearly match the scope.

	- Device-related adverse events." The outcome given in table B1 for selection criteria was "positive or negative test result". Presumably, this refers to whether the Neuropad has given a normal or abnormal result (it does not necessary describe the accuracy of the test). Details on outcomes are given by study submitted in tables B6. Outcomes in studies submitted primarily refer to sensitivity and specificity of the Neuropad (against a reference standard).		
Cost analysis	Scope: 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.	Partially	The cost analysis includes strategies relevant to the primary care setting, though the scope listed all specialist tests. The EAC agrees with the sponsor's approach of limiting the analysis to primary care strategies, to the lack of available data and ensure relevance to practice.

	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	No evidence for subgroup analysis was submitted.	No	No clinical evidence for patient subgroups outlined in the scope was submitted. In the economic submission, a higher prevalence of DPN was assumed for people in care homes and results were provided as a sub group analysis. The EAC systematic review did not find published evidence appropriate for subgroup analysis. The scope referred to people in community settings and people with communication difficulties or cognitive impairment as subgroups of interest.

Special considerations, including issues related to equality
No equality issues were identified in the sponsor submission (see section 6).

The EAC notes that a number of population groups are identified by the scope as having potential special considerations for equality. The scope identifies the following groups: "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."

The EAC has not identified equality issues other than those highlighted in the scope.

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The sponsor provided details of their search strategy separately from the original submission following a request for information from the EAC. The sponsor ran 2 searches: firstly, a search of PubMed with the term 'Neuropad', and secondly a search of Derwent Drug File, Embase and Medline via the Proquest tool using the same term. The first search elicited 41 results as did the second, following the removal of duplicates and irrelevant studies. The sponsor provided a simple PRISMA flow diagram (see Appendix A).

Although the sponsor's search strategy was clear and reproducible the EAC decided a more sensitive search was required and therefore developed a new

search strategy. This contained a broader set of free-text terms and keywords and was run in Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Global Health, HMIC, Cochrane, PubMed and Web of Science. The EAC also searched for grey literature using a simpler set of search terms (see Appendix A for search strategies and PRISMA flow diagram).

3.2 Critique of the company's study selection

Table 2 Sponsor's inclusion criteria

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

Of the 41 studies retrieved by their search strategy the sponsor initially included 27 ("18 from a meta-analysis, 6 studies concerning sudomotoric dysfunction, 1 prospective study and 2 studies of diabetic foot examination and self-testing"). They then excluded all of the studies which contributed to the meta-analysis and 2 studies which had no English translation; this left 8 studies.

The EAC considered these exclusion criteria to be inappropriate and subsequently included a larger number of studies (18 for qualitative analysis,

5 of which were meta-analysed). The EAC excluded the meta-analysis (Tsapas, et al. 2014) because it was secondary research and some studies had overlapping populations and/or did not match the assessment scope.

3.3 Included and excluded studies

The sponsor's submission included 7 original full text studies (Ishibashi et al. 2014, Quattrini et al. 2008, Papanas et al. 2011, Ponirakis et al. 2014, Tentolouris et al. 2008, Tentolouris et al. 2010, Tomesova et al. 2013) and 1 meta-analysis (Tsapas et al. 2014), see table 3. The sponsor also submitted 2 unpublished studies (Sanz et al. 2016 (submitted)), Tentolouris et al. (2017 submitted)).

Table 3 List of sponsor submitted published studies

Primary study reference	Study name	Population	Intervention	Comparator
Ishibashi et al (2014) Excluded by the EAC	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) Included by the EAC	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) Excluded by the EAC	Differences in Skin microcirculation on the upper and lower extremities in Patients with diabetes mellitus: Relationship of diabetic neuropathy and	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.

	skin microcirculation			
Ponirakis et al (2014) Included by the EAC	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) Included by the EAC	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) Excluded by the EAC	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 (2011) Excluded by the EAC	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	NDS
Tsapas et al (2014) Excluded by the EAC	A simple plaster for screening for diabetic neuropathy: a diagnostic test accuracy systematic review and meta-analysis.	3470 diabetic patients	Neuropad test result	Full analysis to meta analysis chapter

Table 4 List of sponsor submitted unpublished studies

Primary study reference	Study name	Population	Intervention	Comparator
Tentolouris et al. 2017 (submitted) Included by the EAC	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 submitted) Included by the EAC	Utility of sudomotor function test (Neuropad) as a clinical tool in risk stratification system of diabetic patient.	263 patients with diabetes	Neuropad test result	Prospective results For incidence of foot ulceration NDS.

The EAC reviewed all primary studies identified by the sponsor. All studies that did not fit the EAC's inclusion criteria were excluded from further review. The EAC included 3 of the 7 original published studies submitted by the sponsor. The EAC included both unpublished studies. For a summary of the EAC's included studies, including those also accepted and excluded by the sponsor, see tables 5 and 6 (below).

Included studies

The EAC included the following 18 studies (13 fulltexts, and 5 abstracts [1 fulltext and 1 abstract are unpublished]):

Aubert et al. (2013)

Aubert et al. (2013) compared Neuropad and the monofilament against the NDS (threshold ≥6) for peripheral neuropathy screening accuracy in people attending the Diabetes and Cardiology departments of a French hospital (n=200). People were asked to spend 10 minutes with socks and shoes off. The colour change for the Neuropad was assessed at 10 and 20 minutes. The Neuropad had significantly lower sensitivity of 93.8% compared with the monofilament specificity of 23.2%, whereas the monofilament had a sensitivity

of 68.8% and a specificity of 94.1% (not significantly different). The Neuropad was more sensitive but less specific than the monofilament test at 10 minutes.

Critical appraisal

The authors noted that the Neuropad test was performed last and therefore may have been influenced by previous peripheral neuropathy clinical assessment. Furthermore, skin temperature, which may modify Neuropad results, was not measured. A relatively low disease prevalence was reported in the study population (15.8%). The study was partially funded by sponsor.

Didangelos et al. (2006) (abstract only)

Didangelos et al. (2006) evaluated the accuracy of Neuropad against MNSIQ, MNSIE, VPT with biothesiometer as reference standards (n=174). This resulted in the following sensitivities for Neuropad: 78%, 73%, 73%, 95% and the following specificities: 92%, 90%, 81%, 69% respectively. The authors concluded that Neuropad had a high sensitivity and specificity in detecting DPN compared with MNSIQ, MNSIE and biothesiometer and a high sensitivity but moderate specificity compared with the monofilament.

Critical appraisal

The scope comparators (for example the monofilament) are used as the reference standard in this study. The study is an abstract and does not provide details on the methodology (for example Neuropad application time and the process for monofilament use was unstated and setting was unclear).

Forth et al. (2010) (abstract only)

Forth et al. (2010) assessed the accuracy of the Neuropad against the NDS (n=66). Using a cut-off NDS value ≥ 3 the results were as follows: sensitivity: 79.3%; specificity: 63.2%; PPV: 69.4%; and NPV: 84.3%. The performance of the Neuropad for the diagnosis of DPN using a cut-off NDS value ≥ 6 was as follows: sensitivity: 91.3%; specificity 66.7%; PPV: 58.3%; and NPV: 93.7%.

Critical appraisal

The study is an abstract and does not provide details on the methodology. The sample size is relatively small. According the the information in Tsapas et al. (2014), this was a UK based study but the setting was unclear.

Freitas et al. (2009)

Freitas et al. (2009) compared the accuracy of the Neuropad and monofilament against NDS (≥6) with people recruited from the Endocrinology and Orthopaedics service in Portuguese hospital (n=40). Testing with the Neuropad resulted in a specificity of 44%, but a sensitivity of 100%. The monofilament resulted in a sensitivity and specificity of 82% and 94%, respectively. The authors suggested that the Neuropad was a simple, sensitive test for DPN, and that based on the false positive results they considered it to be useful in detecting neuropathy in an earlier phase than the monofilament.

Critical appraisal

The study was translated from Portuguese to English. The study had a relatively small sample size. People with foot ulcerations were mentioned in the results section (as they had not been excluded a priori). The monofilament assessment was not adequately described.

Kamenov et al. (2010)

Kamenov et al. (2010) assessed the accuracy of Neuropad against NDS thresholds of ≥3 and ≥6 in people recruited from the Endocrinology clinical at a Bulgarian hospital (n=264). Using NDS ≥3, the sensitivity and specificity of Neuropad was 76.3% and 56.1% respectively. Using NDS ≥6, the sensitivity and specificity of Neuropad was 79.3%and 42.9% respectively. The authors concluded that Neuropad was a sensitive test for detecting sudomotor neuropathy (and as a surrogate/proxy for DPN) and identification of patients at higher risk for chronic diabetes complications.

Critical appraisal

The study had a relatively large sample size. The population was inpatients recruited from the Endocrinology clinic of a hospital; Neuropad is more likely to be used in outpatient populations.

Liatis et al. (2007)

Liatis et al. (2007) assessed the performance of the Neuropad against NDS (with a threshold of ≥5) in a population recruited from the Diabetes outpatient clinic of a Greek hospital (n=117). The authors reported a "high" sensitivity and "relatively low" specificity of 86% and 67.2% respectively. The PPV and the NPV of the Neuropad were 66.2% and 86.5%, respectively. The authors concluded that Neuropad has good sensitivity and NPV for the diagnosis of neuropathy.

Critical appraisal

The authors describe a limitation of their study is that that a more precise estimate of Neuropad's performance in detecting neuropathy could be obtained by comparing its results with those of the QSART or of the sympathetic skin response test. However, the comparator used does fall within the scope of this report.

Manes et al. (2014)

Manes et al. (2014) compared Neuropad against NDS ≥ 6 in a multicentre study across 5 diabetes clinics in Greece (n = 1010). The sensitivity and specificity of the Neuropad were 94.9% and 70.2% respectively. The PPV and NPV were 46.3% and 98.1% respectively. The authors concluded that the high sensitivity of the Neuropad would render it an "excellent" screening tool for excluding neuropathy in people with type 2 diabetes.

Critical appraisal

This was the largest study retrieved in the systematic review. All study participants had type 2 diabetes. Two authors served as advisory board members for the sponsor which may have introduced bias.

Marinou (2005) (abstract only)

Marinou et al. (2005) (n=116) assessed the diagnostic accuracy of Neuropad for the detection of DPN. The sensitivity, specificity, PPV and NPV for Neuropad against NDS was: 86%, 68.2%, 67.2% and 86.5%. The authors concluded that Neuropad has a high sensitivity and a low specificity for the detection of DPN, suggesting that it may be a useful screening tool for patients with diabetes.

Critical appraisal

The study is an abstract and does not provide details on the methodology, and did not include the cut-off thresholds in reference tests. The application of Neuropad timing is unclear.

Mendivil et al. (2016)

Mendivil et al. (2016) assessed the diagnostic accuracy of Neuropad against NDS≥3. Patients were recruitefrom the diabetes clinic in Colombia where the study was performed (n=154). The study found a sensitivity of 74.6%, specificity of 36.1%, PPV of 48.5% and NPV of 63.8% for Neuropad.

Critical appraisal

The study primarily investigated cardiovascular autonomic neuropathy but included analysis on DPN. The study was partially funded by sponsor. The authors suggest that Neuropad has potential for the everyday detection of multiple types of DN in primary care.

Ponirakis et al. (2014)

Ponirakis et al. (2014) (n=127) assessed the diagnostic accuracy of Neuropad against large fibre tests (NDS, VPT, peroneal motor nerve conduction velocity) and small nerve fibre assessments (neuropathy symptoms, corneal nerve fibre length, and warm perception threshold). Participants were recruited from a diabetes clinic. Against NDS (> 2) Neuropad had 70% sensitivity and 50% specificity, against vibration perception threshold (> 14 V)

Neuropad had 83% sensitivity and 53% specificity, and peroneal motor nerve conduction velocity (< 42 m/s) had 81% sensitivity and 54% specificity. The diagnostic accuracy was highest against corneal nerve fibre length (sensitivity 83% and specificity of 80%). The authors concluded that Neuropad had a high sensitivity and moderate specificity against the large fibre neuropathy assessments.

Critical appraisal

This study was performed in the UK at a diabetes clinic. The NDS cut-off threshold is lower in this study when compared with other included studies. The study appropriately examined a wide range of comparators with reference standards.

Quattrini et al. (2008)

Quattrini et al. (2008) assessed the diagnostic accuracy of Neuropad against NDS≥5. The population (n=57) included 20 Type 1 and 37 Type 2 diabetes patients, aged an average of 56±1.4 years. Patients were classified as normal (n=16), patchy (n=16) and abnormal (n=21). The sensitivity of Neuropad against NDS at 10 minutes was 85%, specificity was 45%, PPV was 69% and NPV was 71%. The authors concluded that the Neuropad test may be a simple indicator for screening patients with diabetic neuropathy.

Critical appraisal

The sample size was relatively small. This was a UK based study. The publication provided well-described methodology. Neuropad was applied to plantar surface of the big toe. In accordance with manufacturer recommendations, Neuropad should ideally be applied beneath the big or little toe on the plantar surface of the foot.

Sanz et al. (unpublished but submitted, 2016) (abstract only)

Sanz et al. (2016) compared Neuropad with monofilament in combination with biothesiometer (VPT) for predicting foot ulceration in people with diabetes

(n=263). People were recruited from the Diabetic Foot Unit of a Spanish public research university. Sixty (22.8%) patients developed foot ulcers during a mean follow-up of 41.55 ± 3.5 [35-48] months. The Neuropad test had a sensitivity of 100% and a specificity of 31.53%. The combination of monofilament/Biothesiometer resulted in 83.33% of sensitivity and 50.74% of specificity. The authors indicate that the addition of the Neuropad to diabetes foot care would help prevent under-diagnosis of DPN.

Critical appraisal

This is an unpublished abstract (communication with the author indicates that the full paper is submitted and under review). Though the study is as yet unpublished, the EAC considered the study design (longitudinal) and outcome (association between Neuropad result and observed foot ulceration) relevant for inclusion. The monofilament and biothesiometer results are presented in combination, therefore a direct comparison of the Neuropad with the monofilament cannot be carried out.

Spallone et al. (2009)

Spallone et al. (2009) (n=51) aimed to determine the diagnostic accuracy of the Neuropad against the MNSI-Q and the MDNS. VPT was measured with a biothesiometer and the definition of DPN required the presence of at least 2 abnormalities. Patients were consecutively recruited among outpatients attending a diabetic clinic in Italy. At 10 minutes, the sensitivity, specificity, PPV and NPV were 85%, 32%, 45%, and 77%, respectively; at 15 minutes, the measurements were 80%, 61%, 57% and 83%, respectively; at 18 minutes they were 60%, 74%, 67% and 76%, respectively. The authors concluded that Neuropad is a reliable diagnostic tool of moderate accuracy and extending the observation period to 15 minutes provides improved diagnostic usefulness.

Critical appraisal

The sample size was relatively small. One author served as an advisory board member for the sponsor which may introduce bias.

Tentolouris et al. (2008)

Tentolouris et al. (2008) evaluated the diagnostic accuracy of Neuropad using NDS ≥5 and NSS ≥3 in people recruited from the outpatient diabetes clinic at a Greek hospital (n = 156). The study also assessed reliability and reproducibility between patient and healthcare provider. Mean follow up was 5.5 +/- 2.5 years. The sensitivity, specificity, PPV and NPV of Neuropad were 87%, 66%, 94%, 79%, respectively. The k statistic to measure overall agreement between patient and health care provider of the Neuropad found 90.3% agreement. The study noted that 20% of the patients, particularly those who are older or had kinetic and/or visual impairment reported that they requested help for self-testing. The authors concluded that the high degree of reliability and easiness of Neuropad suggests that it can be used for self-testing to identify peripheral neuropathy.

Critical appraisal

The findings from this study with high sensitivity but lower specificity is in line with other studies (Liatis et al. 2007), however the authors note that false negative results of a screening test are a limiting factor. The authors also stated that when administering Neuropad, it should be considered that a majority of people who requested help for self-testing were older and had kinetic and/or visual impairment.

Tentolouris et al. (2014) (abstract only)

Tentolouris et al. (2014) (n=308) examined the association between Neuropad or NDS testing and foot ulceration in people with diabetes. Patients were recruited from 2005 to 2012. An abnormal result for Neuropad testing at baseline was associated with increased odds for foot ulceration (OR 4.2, CI 1.8-9.8). Similarly, the adjusted OR of NDS>6 versus NDS<6 for foot ulceration was 8.5 (CI 3.3-21.7). The OR for foot ulceration was not increased significantly (p=0.09) in those having mild neuropathy (NDS 3-5) vs. those having no neuropathy. The authors concluded that abnormal Neuropad testing is associated with a 4-fold higher risk for foot ulceration.

Critical appraisal

The study is an abstract and does not provide details on the methodology. The setting is unclear. The diagnostic accuracy was expressed as an odds ratio.

Tentolouris et al. (unpublished but submitted, 2017)

Tentolouris et al. (2017) compared Neuropad with NDS ≥6 for predicting foot ulceration in people with diabetes (n=221). The median follow-up period was 5 years (interquartile range 4.0-8.0) years and the mean follow-up period was 5.5 ± 2.6 years. People were recruited from European diabetes centres. The accuracy of NDS for predicting foot ulceration was as follows: sensitivity was 67% (48-81), specificity 83% (77-88), PPV 41% (28-55) and NPV 93% (88-96). Neuropad had sensitivity of 85% (67-94), specificity 51% (44-58), PPV 23% (16-32) and NPV 95% (88-98). People with abnormal NDS had 9.7 times greater chance of developing foot ulceration at some time of the disease, compared to subjects with normal result ($p<0.001$), while the odds ratio (OR) for those with abnormal Neuropad results compared to normal was 5.8 ($p<0.001$).

Critical appraisal

The study is an unpublished fulltext and the EAC. The outcome measures are similar to Sanz et al. (2016, submitted). Though the study is as yet unpublished, the EAC would consider the study design (longitudinal) and outcome (association between Neuropad result and observed foot ulceration) relevant if more information about the study status is obtained at a later date. The study indicated that approximately 30% of the study population overlapped with populations in Tentolouris et al. (2014) and Papanas et al. (study or studies unspecified).

Ziegler et al. (2011)

Ziegler et al. (2011) assessed the diagnostic accuracy of Neuropad at 3 cut-off points (10, 15, and 320 minutes). The study recruited consecutive

participants of the German Diabetes Study (n=151), a prospective study evaluating the long-term course of diabetes in people with recently diagnosed with diabetes. Sensitivity of Neuropad for diagnosis of overall DPN and small-fibre dysfunction was 87.5% and 80.0%, respectively, in type 1 diabetes (n=52) for the 10-minute threshold. The sensitivity for the same measurement was 65.1% and 67.7% for type 2 diabetes (n=99). Specificity ranged from 44.7-48.2% in both diabetes types. The authors concluded that the 10-minute cut-off for Neuropad provides a relatively high sensitivity and modest specificity for both overall DPN and small-fibre dysfunction.

Critical appraisal

The individual tests listed as the reference standards are the same battery of tests used in NDS. The study was restricted to people newly diagnosed with diabetes, and there are notable age differences between the diabetic types. Two authors have served as advisory board members for the sponsor.

Ziegler et al. (2012)

Ziegler et al. (2012) compared the diagnostic accuracy of Neuropad using MNSI, monofilament, or a combination of the 2 as the reference standard. Eligible subjects were aged 61-82 (n=940) were from the KORA (Cooperative Health Research in the Region of Augsburg) F4 study (2006-2008), a German population based survey. The sensitivity and specificity of Neuropad using (reading time: 10 min) for the diagnosis of polyneuropathy (using MNSI score >3) in people with diabetes were 76.7% and 35.5%, respectively. Sensitivity and specificity were similar for MNSI>2, MNSI-MF>2, MNSI-MF>3 and MF alone.

Critical appraisal

Two authors have served as advisory board members for the sponsor which may have introduced bias.

Excluded studies

The following sponsor submitted studies were excluded:

Ishibashi et al. (2013)

Ishibashi et al. (2013) determined the correlation between sudomotor dysfunction quantified by Neuropad test, corneal C fiber pathology and the cross-sectional area of sweat gland ducts in patients with type 2 diabetes (n=78). The reproducibility of the Neuropad test was evaluated in 6 healthy volunteers by repeating the test 5 times. Intra-individual variatipon was 10.6%. People were recruited from a diabetes outpatient clinic in Japan. The study reported that abnormal Neuropad test results correlated with sudomotor dysfunction and diabetic neuropathy.

Critical appraisal

The study outcomes do not appear relevant to scope. The outcomes of the study correlate sudomotor dysfunction (as assessed by Neuropad) with corneal nerve fibre neuropathy. The performance of the Neuropad itself is not assessed. The reproducibility of the Neuropad was assessed in healthy volunteers rather than in people with diabetes and was in a small sample (n=6).

Papanas et al. (2011)

Papanas et al. (2011) assessed Neuropad performance against NDS ≥6 as reference standard in peple with type 2 diabetes recruited from a diabetes outpatient clinic of a hospital in Greece (n=109). The sensitivity and specificity of the Neuropad were 94.9% and 70.2% respectively. The authors concluded that the results suggested a potential utility of Neuropad for the earlier diagnosis of neuropathy in type 2 diabetes.

Critical appraisal

The study is within scope, however the study overlaps significantly with Manes et al. (2014) which is a larger multi-centre study (information from

direct correspondence with the study author). Therefore the study was excluded.

Tentolouris et al. (2010)

Tentoulouris et al. (2010) investigated the association between Neuropad response and foot ulceration in people with diabetes (n=379). The sensitivity and specificity of the Neuropad were 97.1% and 49.3% respectively. The authors concluded that dryness of the skin of the feet assessed by the Neuropad test correlates with foot ulceration and suggested that Neuropad may be included in the screening tests for the prediction of foot ulceration in people with diabetes.

Critical appraisal

There was a significant number of people with foot ulceration included in the sample. The outcomes of interest (sensitivity and specificity) are not split by people with or without ulceration. People with ulceration would not ordinarily be screened for DPN, as the likelihood that they already have it is very high, and they would already be put under a more intense management care pathway.

Tomesova et al. (2013)

Tomesova et al. (2013) assessed the relationship of diabetic neuropathy (as tested by the Neuropad) and skin microcirculation (as tested by laser Doppler iontophoresis) in people with type 2 diabetes (n=52). The study confirmed a close relationship of diabetic neuropathy and impaired skin microcirculation. The authors noted that it appeared that autonomous neuropathy (assessed using the Neuropad) precedes the manifestation of somatosensory neuropathy (assessed with VPT or monofilament).

Critical appraisal

The outcomes do not assess the performance or impact of the Neuropad. The study does indicate that sudomotor dysfunction may precede loss of protective sensation (and therefore that Neuropad may detect an earlier stage of DPN than monofilament or biothesiometer (for VPT).

Table 5 Table of included studies

For each of the ‘design’, ‘participants’ and ‘outcomes’ entries green, amber or red colour coding indicates whether the study matches the scope fully, partially, or not at all: 

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC Comments

Aubert (2013) Fulltext	Prospective, cross-sectional, observational cohort comparing the Neuropad and the monofilament for patients with and without peripheral arterial occlusive disease. Neuropad 10 minutes with socks and shoes off, and colour change at 10 and 20 minutes. Patchy/no colour change = abnormal Reference standard: NDS (≥6) Partially funded by company Intervention Comparator Reference standard	200 (196 with type 2 diabetes; 160 male, 40 female; mean age 66, 63 years; diabetes duration 16, 12 years) Patients from the Diabetes and Cardiology departments of a French hospital DPN prevalence: 15.8% (31 of 200)	Sensitivity, specificity, PPV, NPV	Against NDS =>6: Sensitivity: Overall 10 mins: 93.8%, 20 mins: 68.8%. With peripheral arterial occlusive disease after 10 mins: 91.3%, 20 mins: 73.9%. Without disease 10 mins: 100%, 20 mins: 55.6% Specificity: Overall 10 mins: 23.2, 20 mins: 57.7%. With peripheral arterial occlusive disease after 10 mins: 20%, 20 mins: 61.5%. Without disease 10 mins: 25.2%, 20 mins: 55.3% PPV: Overall 10 mins: 18.9%, 20 mins: 23.7%. With peripheral arterial occlusive disease after 10 mins: 28.8%, 20 mins: 40.5%. Without disease 10 mins: 10.5%, 20 mins: 9.8% NPV: Overall 10 mins: 95.1%, 20 mins:90.7%. With peripheral arterial occlusive disease	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. All patients had coronary artery disease and/or diabetes with peripheral arterial occlusive disease. Study partially funded by sponsor.

				after 10 mins: 86.7%, 20 mins: 87%. Without disease 10 mins: 100%, 20 mins: 93.4% Against Monofilament: Sensitivity: Overall 68.8%. With peripheral arterial occlusive disease 65.2% Without disease 77.8% Specificity: Overall 94.1% With peripheral arterial occlusive disease 92.3% Without disease 95.2%	

Didangelos (2006) Abstract	Prospective, cross-sectional, observational cohort assessing Neuropad performance Neuropad Application times unstated Patchy/no colour change = abnormal Reference standards: Michigan neuropathy screening instrument questionnaire and examination (MNSIQ, MNSIE), application of 10g monofilament and VPT with biothesiometer. Funding unclear. Intervention ● Comparator N/A Ref standard ●	174 (95 with type 2 diabetes; 86 male, 88 female; mean age 49.8 ± 16.1 years; diabetes duration 17.3 ± 7.7 years). Setting unclear DPN prevalence: MNSIQ: 63.8% (111 of 174) MNSIE: 68.4% (119 of 174) Biothesiometer: 62.6% (109 of 174) Monofilament: 33.9% (59 of 174) ●	Sensitivity, specificity ●	Against MNSIQ: Sensitivity = 78% Specificity = 92% Against MNSIE: Sensitivity = 73% Specificity = 90% Against biothesiometer: Sensitivity = 73% Specificity = 81% Against monofilament Sensitivity = 95% Specificity = 69%	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. The scope comparators are used as the reference standard in this study. The study is an abstract and does not provide details on the methodology.

Forth (2010) Abstract	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad 10 minutes with Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: NDS (≥3 and ≥6). Funding unclear. Intervention 🟢 Comparator N/A Ref standard 🟢	66 (non-diabetic controls: n=18, age: 53.5 ±11.6 years; diabetic subjects without neuropathy: n=19, age: 59.4±9.2; diabetic subjects with painless DPN: n=18, age: 62.2±8.9; and diabetic patients with painful DPN; n=11, age: 61.7 ±10.2 years) Setting unclear DPN prevalence: 43.9% (29 of 66) 🟡	Sensitivity, specificity, PPV, NPV 🟢	Using NDS ≥3: Sensitivity = 79.3% Specificity = 63.2% PPV = 69.4% NPV = 84.3% Using NDS ≥6: Sensitivity = 91.3% Specificity = 66.7% PPV = 58.3% NPV = 93.7%	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. The study is an abstract and does not provide details on the methodology. Tsapas et al. (2014) mention that this is a UK study.

Freitas (2009) Fulltext	Prospective, cross-sectional, observational cohort comparing Neuropad and the monofilament. Neuropad 5 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: NDS (≥6) No external funding sources. Intervention ● Comparator ● Ref standard ●	40 (22 NDS confirmed neuropathy: 15 men, mean age 57.9, diabetes duration 15.4 years. 18 no neuropathy confirmed: 10 men, mean age 63.6 and diabetes duration 11.8 yrs) Endocrinology and Orthopaedics service in Portuguese hospital DPN prevalence: 55% (22 out of 40) ●	Sensitivity, specificity ●	For Neuropad Sensitivity = 100% Specificity = 44% PPV = 69% NPV = 100% For Monofilament: Sensitivity = 100% Specificity = 38% PPV = 59.38% NPV = 100%	Included in the Tsapas et al. meta-analysis paper but not individually by sponsor. Relatively small sample size. People with foot ulcerations were mentioned in the results section (as they had not been excluded a priori). No conflicts of interest declared, and no external sources of funding.

Kamenov (2010) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Reference standard: NDS (≥3 and ≥6). Funding unclear. Neuropad tests provided by distributor. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Intervention Comparator N/A Ref standard	264 (203 with type 2 diabetes; 126 male, 138 female; mean age 55.4+/-12.0; DM duration of 9.3+/-7.1 years) DPN prevalence: 78.4% (207 out of 264) One Bulgarian hospital	Sensitivity and specificity, PPV, NPV	Using NDS ≥3: Sensitivity = 76.3% Specificity = 56.1% PPV = 86.3% NPV = 39.5% Using NDS ≥6: Sensitivity = 79.3% Specificity = 42.9% PPV = 62.8% NPV = 63.0%	Not included by sponsor No conflict of interest declared.

Liatis (2007) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: NDS (≥5), NSS (≥3), VPT (DPN diagnosed when at least 2 tests indicate an abnormal result) Funding unclear. Intervention Comparator N/A Ref standard	117 (108 type 2 diabetes; mean age 61.4; mean diabetes duration 10.9 years) Diabetes outpatient Clinic of 1 Greek hospital DPN prevalence: 42.7% (50 of 117)	Sensitivity and specificity, PPV, NPV	Against NDS ≥5 Sensitivity = 86% (95% CI 80.0-92.0) Specificity = 67.2% (95% CI 59.0-75.0) PPV = 66.2% (95% CI 58.0-74.0) NPV = 86.5% (95% CI 80.0-92.0)	Not included by sponsor No conflict of interest declared.

Manes (2014) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad: 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: NDS (≥6) Funding unclear. Intervention Comparator N/A Ref standard	1010 (all with type 2 diabetes; 608 male, 402 female; mean age 63.90±10.26; diabetes duration 12.24±7.75 years) Five diabetes clinics in Greece DPN prevalence: Overall peripheral neuropathy: 21.3% Small fibre neuropathy: 26.1%	Sensitivity and specificity, PPV, NPV	Overall peripheral neuropathy: Sensitivity = 94.9% Specificity = 70.2% PPV = 46.3% NPV = 98.1% Small fibre neuropathy: Sensitivity = 85.6% Specificity = 71.2% PPV = 52.2% NPV = 93.3%	Not included by sponsor The paper details results for overall nerve fibre dysfunction and small nerve fibre dysfunction. Results for small nerve fibre dysfunction have been included in this table. Sudomotor dysfunction is a result of small nerve fibre damage and this was assessed by NDS1, which is described by the authors as a component of the NDS specially dedicated small fibre dysfunction. Two authors have served as advisory board members for the sponsor.

Marinou (2005) Abstract	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad: Application of Neuropad timing is unclear. Criteria for colour change for abnormal result unclear. Reference standard: NDS, NSS, VPT (criteria for diagnosis unclear) Funding unclear. Intervention 🟢 Comparator N/A Ref standard 🟡	116 (9 with type 1, 107 with type 2 diabetes; 64 male, 52 female; mean age 61.6) DPN prevalence: 43.1% (50 of 116) 🟢	Sensitivity and specificity, PPV, NPV 🟢	Against NDS (no clear threshold) Sensitivity = 86% Specificity = 68.2% PPV = 67.2% NPV = 86.5%	Not included by sponsor The study is an abstract and does not provide details on the methodology. Cut off thresholds in reference tests not given. Criteria for disease duration was 5 years, but mean duration was not stated.

Mendivil (2016) Fulltext	Prospective, cross-sectional, observational cohort evaluation assessing cardiovascular autonomic neuropathy, in addition to distal symmetric neuropathy. Neuropad performance. Neuropad 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: NDS (≥3) Study partially funded by distributor. Intervention  Comparator N/A Ref standard 	154 (74 male, 80 female; mean age 61.4; diabetes duration 12.2 years) One Colombian hospital DPN prevalence: 45% 	Sensitivity and specificity, PPV, NPV 	Sensitivity = 74.6% Specificity = 36.1% PPV = 48.5% NPV = 63.8%	Not included by sponsor Primarily investigating cardiovascular autonomic neuropathy, but also separately investigates DPN. Partially funded by sponsor.

Ponirakis (2014) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: Multiple Funding from NIH and Juvenile Diabetes Research Council Intervention Comparator N/A Ref standard	127 (68 with type 1 diabetes and 59 with type 2 diabetes; 90 male, 37 female; mean age 57± 9.7 years) Diabetes clinic in UK hospital DPN prevalence: 30.0% (38 of 127)	Sensitivity and specificity, PPV, NPV	Against large fibre tests: NDS (=>3) Sensitivity: 70% Specificity: 50% PPV, NPV (%): 63, 57 VPT (>14 volts) Sensitivity: 83% Specificity: 53% PPV, NPV (%): 45, 39 Sural nerve action potential (<3 µV) Sensitivity: 70% Specificity: 64% PPV, NPV (%): 26, 92 Sural nerve conduction velocity (<43 m/s) Sensitivity: 64% Specificity: 54% PPV, NPV (%): 45, 72 Peroneal motor nerve action potential (<2 mV) Sensitivity: 82% Specificity: 50% PPV, NPV (%): 31, 91 Peroneal motor nerve conduction velocity (<42 m/s)	Included by the sponsor UK study with a large number of comparisons with reference standards. The NDS cut-off threshold is lower than in other selected studies. Neuropad applied after callus removal. No conflict of interest declared.

				Sensitivity: 81% Specificity: 54% PPV, NPV (%): 59, 78 Against small fibre tests: Warm perception threshold (>43°C) Sensitivity: 68% Specificity: 49% PPV, NPV (%): 26, 44 Corneal nerve fibre density (<24 *n*/mm^2) Sensitivity: 74% Specificity: 60% PPV, NPV (%): 54, 78 Corneal nerve fibre length (<14 mm/mm2) Sensitivity: 83% Specificity: 80% PPV, NPV (%): 49, 95 Neuropathy symptoms: DNS score =>2 Sensitivity: 78% Specificity: 60% PPV, NPV (%): 34, 91	

Quattrini (2008) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: NDS (≥5) Funding from NIH and Diabetes UK. Neuropad tests were provided by the distributor. Intervention ● Comparator N/A Ref standard ●	57 (20 with type 1, and 37 with type 2 diabetes; mean age 56±1.4 years Diabetes clinic in UK hospital DPN prevalence: 78.9% (45 out of 57) 18 mild neuropathy (NDS 3–5), 15 moderate neuropathy (NDS 6–8) 12 severe neuropathy (NDS 9–10) ●	Sensitivity and specificity, PPV, NPV ●	Against NDS ≥5 Sensitivity = 85% Specificity = 45% PPV = 69% NPV = 71%	Included by the sponsor UK study with well described methodology. Relatively small sample size. NDS score mismatch: NDS cut-off for neuropathy/no neuropathy was 5 out of 10. However in the prevalence, it was stated that above 3 was classified as mild neuropathy. Results are missing n=4 patients. Neuropad was applied to plantar surface of the big toe. In accordance with the manufacturer recommendations, neuropad should *ideally* be applied beneath the big or little toe on the plantar surface of the foot. No conflict of interest declared.

Sanz (2016) [Unpublished abstract]	Longitudinal prospective cohort study. Sudomotor function test (Neuropad not specified) compared with monofilament /Biothesiometer for predicting ulcers. Reference standard: Foot ulceration Mean follow up: 41.55 ± 3.5 [35-48] months Funding not stated. Intervention Comparator Ref standard (not in scope, but is relevant)	263 patients with diabetes enrolled consecutively at a outpatients clinic (Diabetic Foot Unit at a public research university), Spain. No age, sex or type of diabetes information.	Sensitivity and specificity in predicting the development of diabetic foot ulcers in follow up period of 35-48 months.	60 (22.8%) patients developed foot ulcer during a mean follow-up of 41.55 ± 3.5 [35-48] months. The Neuropad test had a sensitivity of 100% and a specificity of 31.53%. Monofilament/Biothesiometer (83.33% of sensitivity and 50.74% of specificity)	*Included by sponsor, included by EAC.* This is an unpublished study. The authors were contacted for further information and clarified that the study has been submitted for publication. Though the study is as yet unpublished, the EAC considered the study design (longitudinal) and outcome (association between Neuropad result and observed foot ulceration) relevant for inclusion.

Spallone (2009) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q), MDNS. VPT with biothesiometer . Cold and warm thermal perception. Definition of DPN required the presence of at least 2 abnormalities. Intervention Comparator N/A Ref standard	51 (29 male, 22 female; 24 with type 1, 27 with type 2 diabetes; mean age 44.9 ± 13.7 years; mean diabetes duration 14.7 ± 10.7 years). Diabetes clinic in Italian hospital DPN prevalence: 39% (20 of 51)	Sensitivity and specificity, PPV, NPV	2+ abnormalities amongst symptoms, deficits, VPT and cold/warm perception - 10 mins): Sensitivity = 85% Specificity = 32% PPV = 45% NPV = 77% 2+ abnormalities amongst symptoms, deficits, VPT and cold/warm perception - 15 mins) Sensitivity = 80% Specificity = 61% PPV = 57% NPV = 83% 2+ abnormalities amongst symptoms, deficits, VPT and cold/warm perception - 18 mins: Sensitivity = 60% Specificity = 74% PPV = 67% NPV = 76%	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. The study investigated Neuropad accuracy with different times of test pad application (10, 15 and 20 minutes). Only the 10 minute results have been included (as per manufacturer instructions for use. Relatively small sample size. One author has served as an advisory board member for the sponsor.

Tentolouris (2008) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: NDS (≥5) and NSS (≥3). Mean follow up: 5.5 +/- 2.5 years. Intervention Comparator N/A Ref standard	156 participants (82 male, 7 type 1, age 59.6 ± 15.5 years) Outpatient clinic in Greece DPN prevalence: 56.9%	Sensitivity and specificity, PPV, NPV Reliability and reproducibility	Unclear comparator for NDS (no threshold described): sensitivity = 87% specificity = 66% PPV = 94% NPV = 79% The k statistic to measure overall agreement between patient and health care provider of the Neuropad was “very good”: 90.3% agreement, k = 0.88 (95% CI 0.85–0.91). 20.5% people reported that they requested help to perform self-testing.	Included by the sponsor The paper indicates it had similar results to Liatis, S., et al. (2007). Evaluation of self testing at home: 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 Neuropad 10.0 (9.0-10.0), easiness to use the Neuropad 10.0 (9.010.0), and easiness to evaluate the test as normal or abnormal 10.0 (8.0-10.0).

Tentolour is (2014) Abstract	Prospective, longitudinal, observational cohort to examine the association between Neuropad or NDS testing and foot ulceration. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: Foot ulceration Intervention Comparator N/A Ref standard	308 participants with diabetes (153 males; 280 with type 2 diabetes; mean age 62.8 +/- 11.3 years; mean diabetes duration 12.4 +/- 9.7 years) Setting unclear DPN prevalence: 51.9% (160 out of 308) The mean follow-up was 5.5 +/- 2.5 years.	Probability of developing foot ulceration	An abnormal result for Neuropad testing at baseline was associated with increased odds (OR, 95% confidence intervals) for foot ulceration [4.2 (1.8-9.8)]. Similarly, the adjusted OR of NDS>6 vs. NDS<6 for foot ulceration was 8.5 (3.3-21.7). The OR for foot ulceration was not increased significantly (p=0.09) in those having mild neuropathy (NDS 3-5) vs. those having no neuropathy.	Not included by sponsor 5 year follow up The study population included people with prediabetes and diabetes. Only the results for people with diabetes were extracted for this report. Monofilament identified abnormality defined as inability to perceive monofilament at any site during 3 applications.

Tentolouris (2017) [Unpublished fulltext]	Prospective longitudinal cohort study comparing Neuropad with NDS≥6 for prediction of foot ulceration Neuropad 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Reference standard: foot ulceration Mean follow up: the median follow-up period was 5 years (interquartile range 4.0-8.0) years and the mean follow-up period was 5.5 ± 2.6 years. (added after final submission of report) Funding unclear. Neuropad tests provided by sponsor. Intervention Comparator Ref standard	221 participants. 115 (52%) were females, mean age was 66.1 years (23 - 93) and the median of disease duration was 9.0±8.8 years. Six outpatient diabetes clinics in Europe	Sensitivity, specificity, PPV, NPV	NDS for prediction of foot ulceration: Sensitivity = 67% (48-81) Specificity 83% (77-88) PPV 41% (28-55) NPV 93% (88-96). Neuropad for prediction of foot ulceration: Sensitivity of 85% (67-94) Specificity 51% (44-58) PPV 23% (16-32) and NPV 95% (88- 98). People with abnormal NDS had NDS 9.7 times greater chance of developing foot ulceration compared to subjects with normal result (p<0.001), while the odds ratio (OR) for those with abnormal Neuropad compared to normal was 5.8 (p<0.001).	*Included by sponsor, excluded by EAC.* The outcomes are similar to Sanz et al. (2016, submitted). Though the study is as yet unpublished, the EAC would consider the study design (longitudinal) and outcome (association between Neuropad result and observed foot ulceration) relevant if more information about the study status is obtained at a later date. It is unclear if there is overlap with other published studies with the same author (Tentolouris). The follow up times are unclear. The author contacted the EAC after the final report was submitted to note that around 30% of the study population overlaps with the populatioins in Tentolouris et al. (2014) and Papanas (study or studies unspecified).

Ziegler (2011) Fulltext	Prospective, cross-sectional, observational cohort study assessing Neuropad performance. Part of wider German Diabetes study. Neuropad Colour change at 10, 15 and 20 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standard: For distal symmetric polyneuropathy (also known as DPN); ≥1 abnormal nerve conduction velocity measurement plus NDS ≥ 2 or ≥1 abnormal quantitive sensory testing parameter For small fibre dysfunction: ≥1 abnormal thermal perception threshold (warm or cold) Intervention Comparator N/A Ref standard	52 participants with Type 1 diabetes [35 men; age 33.5±12.0 years] and 99 participants with Type 2 diabetes [63 men;age52.9±10.3 years] Diabetic Foot Clinic in Germany DPN prevalence: 15.4% in Type 1 diabetes (8 participants) and 43.4% in Type 2 diabetes (43 participants), Total: 33.8% (51 out of 151)	Sensitivity and specificity, PPV, NPV	At 10 minutes. For distal symmetric polyneuropathy; Type 1 diabetes; Sensitivity = 87.5% Specificity = 47.7 % PPV = 23.3% NPV = 95.4% Type 2 diabetes; Sensitivity = 65.1% Specificity = 48.2% PPV = 49.1% NPV = 64.3% For small fibre dysfunction: Type 1 diabetes; Sensitivity = 80.0% Specificity = 44.7% PPV = 13.3 % NPV = 95.4% Type 2 diabetes; Sensitivity = 67.7% Specificity = 47.1% PPV = 36.8% NPV = 76.2%	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. The individual tests listed as the reference standards are the same battery of tests used in NDS. Resticted to those newly diagnosed with diabetes. Notable age differences between diabetic types. Two authors have served as advisory board members for the sponsor. The sponsor was involved neither in study design nor in data collection.

Ziegler (2012) Fulltext	Prospective, cross-sectional, observational cohort study assessing Neuropad performance. Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standards: MNSI, monofilament or a combination. Intervention Comparator N/A Ref standard	201 participants with diabetes (58.2% male, age 71.8±5.5 years) Recruited from German population-based health survey. DPN prevalence: 29.9% (60 of 201)	Sensitivity and specificity, PPV, NPV	Using MNSI>2 Sensitivity = 75.7% (lower 95% CI 66.1) Specificity = 36.3% (lower 95% CI 29.1) PPV = 40.9% (lower 95% CI 33.8) NPV = 71.9% (lower 95% CI 61.2) Using MNSI-MF>2 Sensitivity = 74.4% (lower 95% CI 65.5) Specificity = 36.5% (lower 95% CI 29.0) PPV = 46.7% (lower 95%CI39.4) NPV = 65.6% (lower 95%54.7) Using MNSI>3 Sensitivity = 76.7% (lower 95%ci 66)	Included in the Tsapas et al. (2014) meta-analysis paper but not individually by sponsor. Prediabetes data not included in this table as it is out of scope. Monofilament identified abnormality used 10 applications and ≤8 defined as abnormal. Two authors have served as advisory board members for the sponsor.

				Specificity = 35.5 (lower95%CI 28.8) PPV = 33.6 (lower 95%CI 26.9) NPV = 78.1 (lower 95%CI 67.9) Using MNSI-MF>3 Sensitivity = 75.4 (lower 95%CI 65.4) Specificity = 35.6 (lower95%CI 28.7) PPV = 38.0 (lower 95%CI 31) NPV = 73.4 (lower 95% 62.9) Using MF Sensitivity = 75% (lower 95%CI 54.4) Specificity = 32.6% (lower 95%CI 26.8%) PPV =	

				10.9 (lower 95%CI 6.9) NPV = 92.2% (lower 95% CI 84.3)	
Excluded studies	**Design and intervention(s)**	**Participants**	**Outcomes**	**Results**	**Comments (including EAC view of exclusion)**
Ishibashi (2013)	Observational study Neuropad (no comparator) Corneal Microscopy as reference standard. No financial support. Intervention 🟢 Comparator 🔴 Ref standard 🟢	78 participants with type 2 diabetes and 28 age-matched controls recruited from an outpatient clinic, Japan. All participants aged between 30-65. No sex information. 🟢	Correlations between sudomotor function, sweat gland duct size and corneal nerve fiber pathology. Time to complete colour change of neuropad indicator test. 🔴	In patients with diabetic neuropathy, sudomotor function, as judged by the time required for complete colour change of a Neuropad, was impaired compared with that of controls ($p < 0.0001$). Sudomotor function was negatively associated with corneal nerve fibers ($p < 0.002$) and branches ($p < 0.01$), and influenced by the severity of diabetic neuropathy ($p < 0.0001$)	*Included by sponsor, excluded by EAC.* The outcomes of the study correlate sudomotor dysfunction (as assessed by Neuropad) with corneal nerve fibre neuropathy. The performance of the Neuropad itself is not assessed. The study provides results of reproducibility of Neuropad results as assessed in 6 healthy volunteers. The population does not clearly fit the scope and it is a small sample.

Papanas (2011) Fulltext	Prospective, cross-sectional, observational cohort assessing Neuropad performance. Reference standard: NDS (≥6) Neuropad 10 minutes with socks and shoes off, and colour change at 10 minutes. Patchy/no colour change = abnormal Funding unclear. Intervention ● Comparator N/A Ref standard ●	109 (all with type 2 diabetes; 55 male, 54 female; mean age 64.3 ± 7.3; mean diabetes duration 12.8 ± 4.3) Outpatient clinic in 1 Greek hospital. DPN prevalence: 11% (12 of 109) ●	Sensitivity and specificity ●	Sensitivity = 83.33% Specificity = 68.04%	*Included by sponsor, excluded by EAC.* The study was excluded after correspondence with the author revealed that the population significantly overlapped with Manes et al. (2014).

Tentolour is (2010)	Prospective observational cohort study into Neuropad performance. Funding not stated Neuropad Colour change at 10 minutes. Unclear how long socks and shoes were left off. Patchy/no colour change = abnormal Reference standards: NSS, monofilament, NDS≥ 6, and VPT≥25 Intervention Comparator N/A Ref standard	379 participants - 258 participants without foot ulceration (130 males, 15 Type 1, 60.0 ± 11.7years) and 121 participants with foot ulceration (84 males, 8 Type 1, 63.2 ± 10.2years) Diabetes clinic in Greece DPN prevalence: Without foot ulceration: 44.2% (114 out of 258) with foot ulceration: 94.2% (114 of 121) Total: 60.2% (228 out of 379)	Sensitivity and Specificity of Neuropad for identifying people with foot ulcerations.	Sensitivity = 97.1% Specificity = 49.3%	*Included by sponsor, excluded by EAC.* There was a significant number of people with foot ulceration included in the sample. The outcomes of interest (sensitivity and specificity) are not split by people with or without ulceration. People with ulceration would not ordinarily be screened for DPN, as the likelihood that they already have it is very high, and they would already be put under a more intense management care pathway.

Tomesova (2013)	Prospective cohort study. Neuropad Method of application unclear Intervention Comparator Ref standard N/A	52 people with type 2 diabetes. 27 males, 25 female. Mean age 60 (42-68) years. Duration of diabetes; 13 (9-19) years	Relationship of diabetic neuropathy and skin microcirculation	The study confirmed a close relationship of diabetic neuropathy and impaired skin microcirculation.	*Included by sponsor, excluded by EAC.* The outcomes do not assess the performance or impact of the Neuropad.
Tsapas (2014)	Intervention comparator Ref standard	3470 participants	Sensitivity and Specificity	Mean sensitivity and specificity were 86% (95% CI 79 to 91) and 65% (95% CI 51 to 76) respectively.	This is a meta analysis and not a primary study. Many included studies had overlapping populatons and/or did not match the scope. The results presented in this table are based on the aggregate results in this meta analysis.

3.4 Overview of methodologies of all included studies

- All original studies submitted by the sponsor had prospective, cross-sectional, observational cohort designs. All but 3 studies included by the EAC had prospective, cross-sectional, observational cohort studies. Three studies (Sanz et al. 2016 [unpublished], Tentolouris et al. 2014, Tentolouris et al. 2017 [unpublished]) were prospective, longitudinal, observational cohort studies. No RCTs were found. All studies evaluated the intervention specified in the scope.

- All studies (18) investigated the diagnostic accuracy of the Neuropad test (17 investigated the sensitivity, specificity against a reference standard, and 1 study (Tentolouris et al. 2014) reported the odds ratio against foot ulceration). One study (Tentolouris 2008) also investigated reproducibility of results, and 3 studies (Sanz et al. 2016 [unpublished] Tentolouris et al. 2014, Tentolouris et al. 2017 [unpublished]) assessed the association between Neuropad testing and the development of foot ulcers.

- Two studies assessed Neuropad versus another comparative screening test (the 10g monofilament) against a reference standard – Aubert et al. (2013), Freitas et al. (2009). All diagnostic accuracy studies assessed Neuropad against a reference standard. Most studies (10) assessed the Neuropad against the NDS reference test. Four stated that they used ≥3 (Forth et al. 2010, Kamenov et al. 2010, Mendivil et al. 2016, Ponirakis et al. 2014), 2 used ≥5 (Liatis et al. 2007, Quattrini et al. 2008) and 5 used ≥6 (Aubert et al. 2013, Forth et al. 2010, Freitas et al. 2009, Kamenov et al. 2010, Manes et al. 2014) as 1 or multiple cut off thresholds. The threshold cut-off for NDS was unclear in 1 study (Marinou et al. 2005). Six studies used a combination of reference standards (Didangelos et al. 2006, Liatis et al. 2007, Marinou et al. 2005, Spallone et al. 2009, Ziegler et al. 2011, Ziegler et al 2012). The unpublished studies (Sanz et al. 2016, Tentolouris et al. 2017) and published study (Tentolouris et al. 2014) assessed the predictive value of Neuropad against the development of

foot ulceration. The 5 remaining diagnostic accuracy studies that did not assess Neuropad against NDS or foot ulceration used a combination of tests including VPT, MNSIQ/MNSIE and NSS).

- Most studies were carried out in adult outpatient populations. One study assessed the Neuropad in an adult inpatient population (Kamenov et al. 2010). The setting was secondary or tertiary care in most studies but Tentolouris (2008) included results from patient self-assessment testing at home.

- Mean ages ranged from 44.9 (Spallone et al. 2009) to 71.8 years (Ziegler et al. 2012). Mean diabetes duration ranged from 9.3 (Kamenov et al. 2010) to 17.3 years (Didangelos et al. 2006). Disease prevalence ranged from 15.8% (Aubert et al. 2013) to 78.9% Quattrini et al. 2008).

- Adequate baseline characteristics (where age, gender, duration of diabetes were all reported) were provided in 9 studies.

- All studies were from European countries. Three UK studies (Forth et al. 2010, Quattrini et al. 2008, Ponirakis et al. 2014) were included. All other studies were from either Greece, Germany, Italy, France, Bulgaria, Spain or Portugal.

- Procedure for using the Neuropad. Eight studies assessed the Neuropad test with 5/10 minutes socks off and 10 minutes with the plaster applied. Seven studies described application time of 10 mins but not how long shoes/socks were removed for. In 4 studies the application timing was unclear.

- Clear follow up times were recorded in 2 studies (both longitudinal): Sanz et al. (2016), Tentolouris et al. (2014). The follow up time in Tentolouris et al. (2017) was unclear but 4 and 7 year time intervals were implied.

- Environmental characteristics were detailed in 9 papers (temperature).

- Two studies reported sample size calculations (Mendivil et al. 2016, Ponirakis et al. 2014).

3.5 Overview and critique of the company's critical appraisal

The sponsor did not provide a critical appraisal of the studies included with their submission. The sponsor stated they did not have the resources or expertise to complete a full critical appraisal of the relevant studies.Therefore, the EAC carried out a quality appraisal of the final 18 studies selected for inclusion in the systematic review.

Eighteen studies were presented in the form of a meta-analysis (Tsapas et al. 2014) included in the submission. This meta-analysis contained additional results which were not made publicly available in the original publications. This additional information is not available online and the EAC could not verify the validity of the results. The EAC chose to exclude all information only available from secondary sources (such as a meta-analysis).

The QUADAS-2 (revised Quality Assessment of Diagnostic Accuracy Studies) tool (Whiting et al., 2011) was used to structure the critical appraisal and reduce variability in assessment of risk of bias and applicability. This tool is available online (www.quadas.org) and is recommended for use in critical appraisal of diagnostic accuracy studies. The tool assesses the risk of study bias (internal validity) in four domains (patient selection, index test, reference standard, flow and timing), and the applicability of the study to the decision problem (external validity or generalisability) in three domains (patient selection, index test, and reference standard). All domains are categorised as low (risk of bias or applicability), high, or unclear, and no attempt is made to formally grade the strength of evidence the study provides.

The standard QUADAS-2 checklist was adapted in accordance with a previous published QUADAS-2 assessment of screening tests for diabetic peripheral neuropathy (Yang et al., 2014). This involved the addition of a question to the 'index tests' domain for if there was more than one index standard used in the study. Secondly, in the 'flow and timing' domain, the first

question was reworded to specify the maximum time interval between the index test and applying Neuropad.

Details of the QUADAS-2 tool signalling questions are available in Appendix D. The results of the assessment are illustrated in figures 1 – 4 below.

Full text (13)

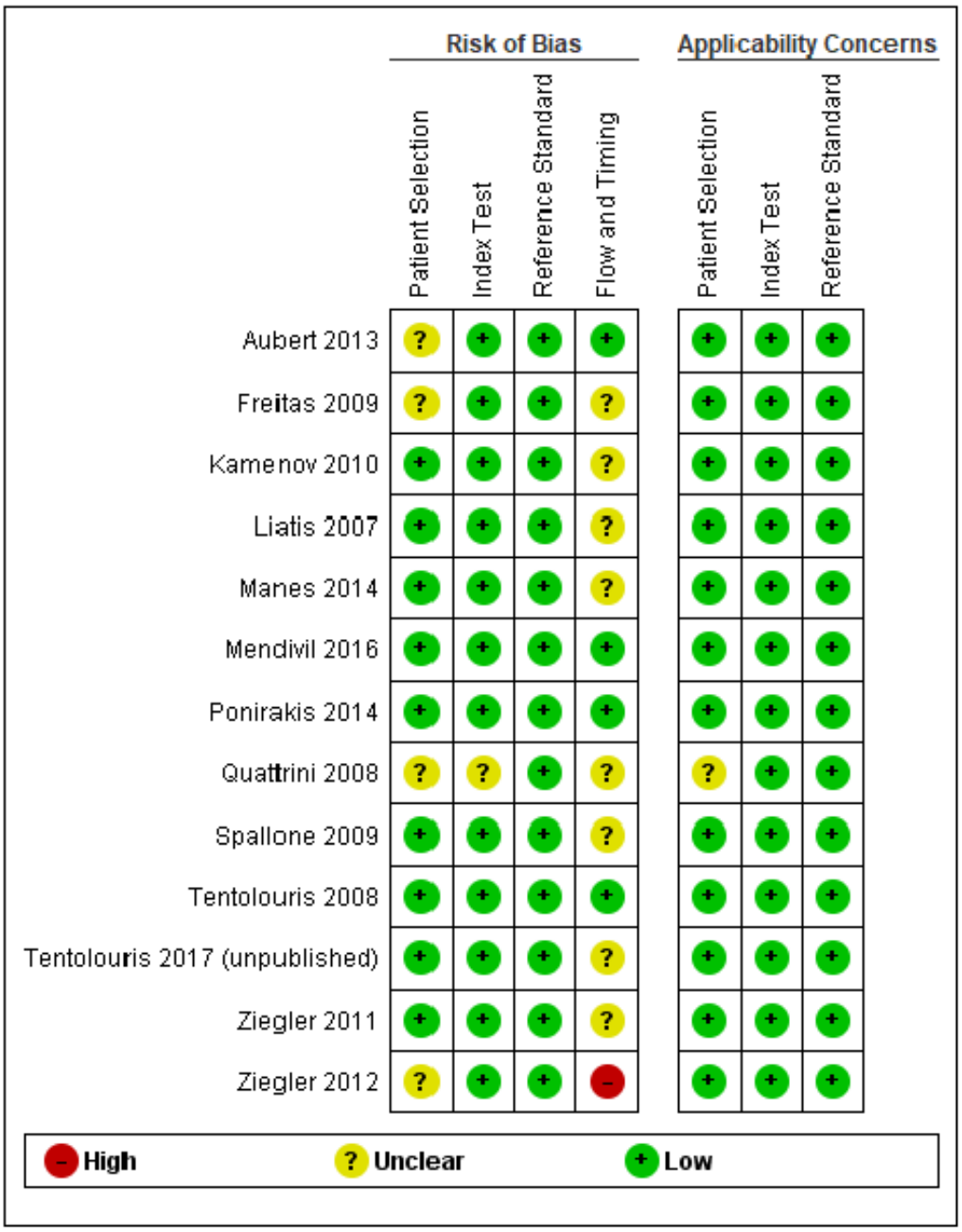


Figure 1 - Risk of bias and applicability concerns summary for full-text studies.

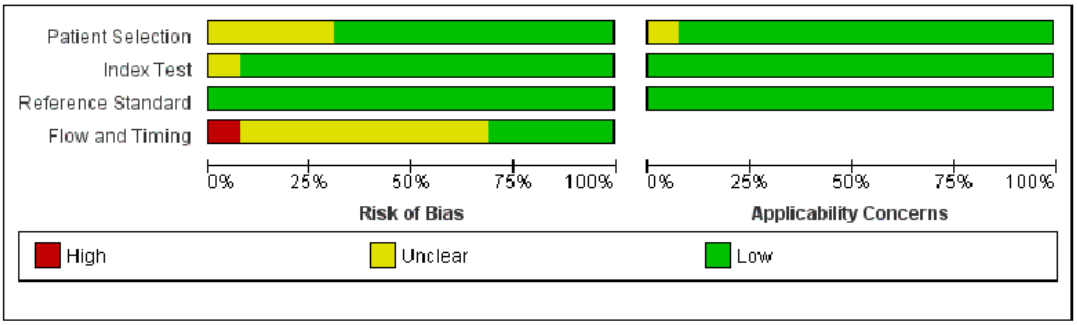


Figure 2 - Risk of bias and applicability concerns graph for full-text studies.

Abstract only (5)

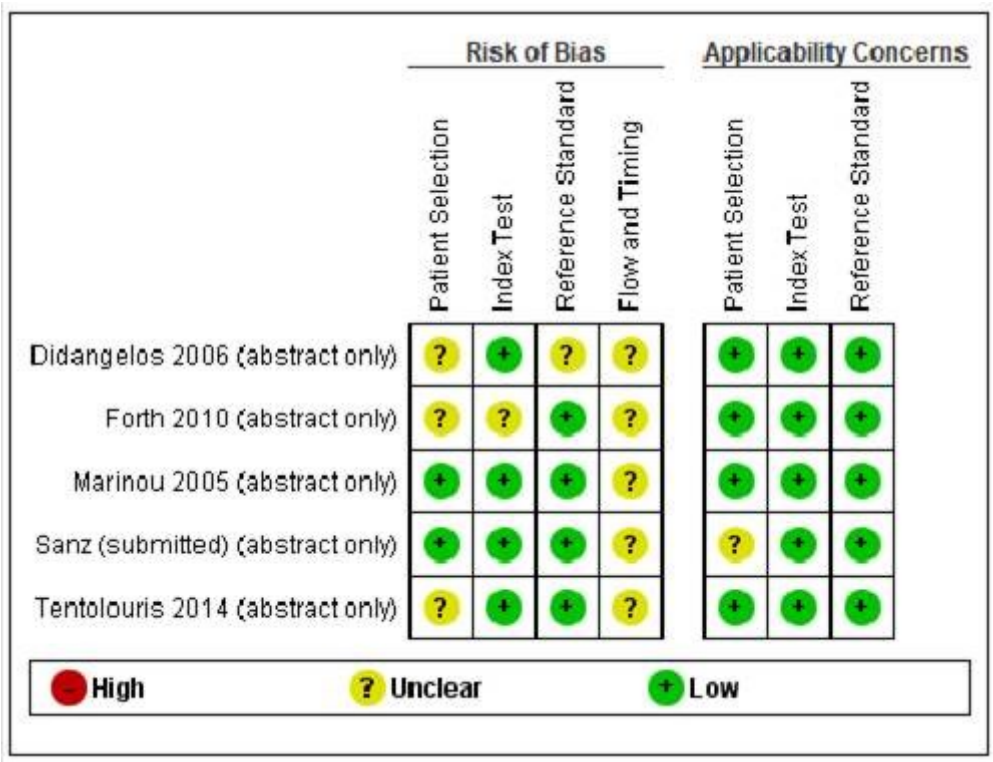


Figure 3 - Risk of bias and applicability concerns summary for abstract-only studies.

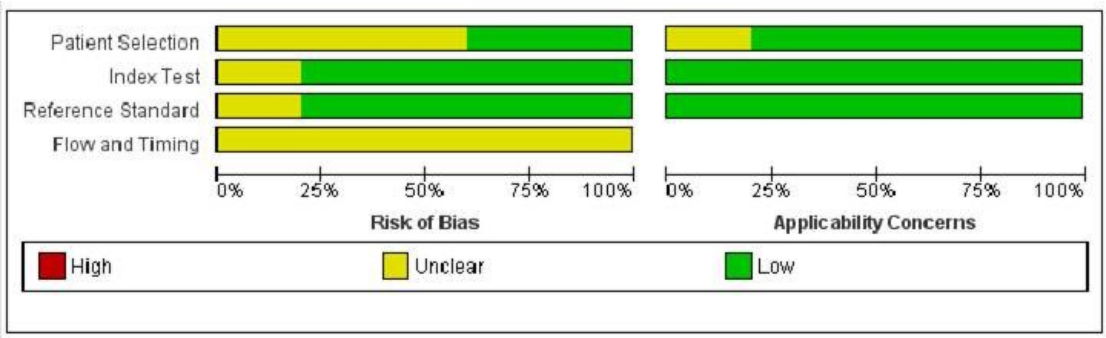


Figure 4 - Risk of bias and applicability concerns graph for abstract-only studies

Full-text and abstract-only studies were visualised separately due to the lack of information available on the methodology in the abstract-only papers. As a result, the risk of bias for abstract-only papers has considerably more uncertainty. These unpublished conference abstracts were not later developed into full-text publications, potentially reflecting poor methodological quality but also raising the possibility of publication bias.

The only indication of high risk of bias in the QUADAS-2 assessment was for the 'flow and timing' of Ziegler et al., 2012. This was due to inclusion of

participants diagnosed with prediabetes and 8 participants with diabetes being excluded from the final results. As prediabetes is out of the scope of this assessment, results on participants with prediabetes were excluded and it was possible to extract the information on participants with diabetes only. The 8 participants with diabetes were excluded by the authors due to incomplete data on neuropathy. The EAC decided these were not significant reasons for exclusion.

3.6 Results

The sponsor presented results from 7 published and 2 unpublished original studies. After excluding Ishibashi et al. (2014), Papanas et al. (2014), Tentolouris et al. (2010) and Tomesova et al. (2013), the EAC accepted 5 of the studies as eligible for the assessment report (3 published, 2 unpublished). The 5 studies are included in table 5 in section 3.3 along with 9 full texts and 4 abstracts not identified by the sponsor.

Only 2 studies (Aubert et al. 2013, Freitas et al. 2009) included a direct comparison of a standard screening test (the 10g monofilament) with the Neuropad test against a reference standard. The remaining diagnostic accuracy studies assessed Neuropad performance against standard neuropathy scoring (as described in the scope under comparators), or longitudinally against foot ulceration.

3.7 Description of the adverse events

The manufacturer reported that there were no adverse events recorded relating to Neuropad since its launch in 2006. The EAC searched the MHRA and FDA-MAUDE databases and found no evidence of adverse events. The nature of the technology means that adverse events are extremely unlikely.

3.8 Description and critique of evidence synthesis and meta-analysis

The sponsor did not carry out an independent meta-analysis. They submitted a pre-existing meta-analysis (Tsapas et al. 2014). The EAC excluded the meta-analysis from the clinical evidence primarily because it was secondary evidence and also because there was significant heterogeneity in the papers

that were included. The papers included by the authors used a variety of reference standards. The sensitivity/specificity results were pooled regardless of the reference standard used. This may lower the confidence in the results.

Although the outcomes in Tsapas et al. (2014) (86% sensitivity and 65% specificity) are broadly representative of the papers included in this assessment, the EAC has performed their own meta-analysis with more stringent criteria (for example, better defined reference standards). The EAC also note that several of the studies included in Tsapas have overlapping patient populations. Whilst the paper describes using meta-regression to explore the reference standard the power of this would have been very low, and therefore important differences might not be detected. A valid sub-group analysis requires a minimum of n=10 studies (using NDS of various thresholds), and this study only had 10 studies in total before meta-regression.

The included studies were reviewed and population outcome data were extracted. Results presented included values for sensitivity, specificity, PPV and NPV. The EAC back-calculated the true positive, true negative, false positives and false negatives based on the information provided within each study. This was done as a quality control measure before finalising study inclusion for the meta-analysis.

Pooled values were calculated for each peripheral neuropathy comparator (and the differing thresholds were applicable) to Neuropad. Sensitivity and specificity for every study is depicted in forest plots were fitted using metandi and midas in Stata 14, to assess diagnostic test accuracy and heterogeneity in results where ≥ 4 studies were available. The EAC performed the meta-analyses using a bivariate random-effects model.

After careful review of papers, several studies were considered by the EAC as suitable for a meta-analysis (table 6). There was only 1 paper currently suitable for comparison of Neuropad with monofilament.

Table 6 Studies included in meta-analysis

References	Study population (diabetic type)	Comparator(s)	Comparator thresholds	Total Population
Freitas et al. (2009)	Unclear which type(s)	NDS	NDS≥6	N=40
		Monofilament	Undefined threshold	
Kamenov et al. (2010)	Types 1 & 2 (diabetic inpatients)	NDS	NDS≥3	N=264
			NDS≥6	
Liatis et al. (2007)	Types 1 & 2	NDS	NDS≥5	N=117
Manes (2014)	Type 2 only	NDS	NDS ≥ 6	N = 1010
Tentolouris et al. (2008)	Types 1 & 2	NDS	Undefined threshold	N=156

The EAC notes the following:

- Freitas et al. (2009): Study included patients with ulceration and text needed to be translated from Portuguese to English using Google Translate. Furthermore, the monofilament assessment was not adequately described. Please see notes below concerning a meta-analysis using monofilament as the comparator.

  The EAC also notes that the cross-tabs in table 1 and 3 of Freitas et al. (2009) were used to calculate the sensitivity, specificity, PPV and NPV values in the meta-analysis.

- Kamenov et al. (2010): The EAC notes that all study patients were described as ‘inpatients’.

- Liatis et al. (2007): The EAC notes that one of the study authors is ‘Tentolouris’ whom also led another relevant study (Tentoulouris et al. 2008) considered for inclusion in the EAC meta-analysis. The EAC has attempted contact with both authors to clarify if there is any study patient overlap. At the time of running this analysis, no response has been received. Therefore, the EAC assumes no study patient overlap at the time of running the meta-analysis.

- Tentolouris et al. (2008): The EAC notes that no thresholds are given in the paper for NDS scores. Tentolouris references a paper by Young et al. (1993) which states that using the NDS, ‘a score of 3-5 was regarded as evidence of mild neuropathic signs, 6-8 as moderate and a score of 9 or 10 as severe signs of neuropathy’. Therefore, for the purposes of the present meta-analysis, the EAC considered the NDS threshold to be ≥6. The EAC reconstructed the 2x2 table which yielded a different PPV to that reported in the paper, as indicated in the table 7.

- Back-calculation: The following studies at the time of doing the EAC meta-analysis did not provide accurate and/or lacked the necessary information to perform the required back-calculation as described above table 6: Aubert et al. (2013), Quattrini et al. (2008), Ponirakis et al. (2014) and Ziegler et al. (2012). The analysis was conducted using the 2x2 tables which cross tabulate the new test against the reference standard. In some instances it was not possible to do this using the data reported in the studies – this is most likely due to missing data for one or both tests not being explicitly reported

- Quattrini et al. (2008): The EAC notes that the Quattrini et al. study, was also excluded from the meta-analysis due to 2 further issues (aside from back calculation issues): firstly, the Neuropad was applied to the ‘great toe’ which does not fit with the manufacturer guidelines and secondly, the data presented in the study did not add up to the

study population total. The text reports Neuropad results for n=53 patients, but n=58 are presented in a table. The results reported for sensitivity, specificity, PPV and NPV values are therefore not consistent with each other.

Other issues to note:

- Monofilament comparator: Only one paper, Freitas et al. (2009), provided the necessary information to back calculate the necessary data for the monofilament as a comparator to Neuropad. It may be possible to compare these results to Aubert et al. (2013) in the future if the missing/incorrect information was made available. This comparison would need to ignore the differing definitions (or absence of definition) of abnormal results using monofilament between the 2 studies. Aubert used different threshold for defining abnormal response, whilst Freitas provides no definition.

- Diabetic types: The EAC note that no studies included in the EAC meta-analysis provided study results broken down by diabetic types (1 and 2). Therefore, the EAC was unable to assess sub-group variations.

The following table documents the data extracted from the considered studies broken down into comparators and thresholds (table 7).

Table 7 EAC meta-analysis considered studies with results (unless stated, values are direct from studies).

Reference	Sensitivity	Specificity	PPV	NPV	Prevalence
Neuropad vs NDS≥3					
Kamenov et al (2010)	76.3%	56.1%	86.3%	39.5%	Not provided* EAC calculated: 78.4%
Mendivil et al (2016)	74.6%	36.1%	48.5%	63.8%	45 % EAC revised*:

					44.7%
Neuropad vs NDS≥6					
Freitas et al (2009)	Not provided* EAC calculated: 100%	Not provided* EAC calculated: 44%	Not provided* EAC calculated: 69%	Not provided* EAC calculated: 100%	Not provided* EAC calculated: 55.0%
Kamenov et al (2010)	79.3%	42.9%	62.8%	63%	Not provided* EAC calculated: 54.9%
Manes et al (2014)	94.9%	70.2%	46.3%	98.1%	21.3%
Neuropad vs NDS≥5					
Liatis et al (2007)*	86.0%	67.2%	66.2%	86.5%	Not provided* EAC calculated: 42.7%
Neuropad vs NDS: not defined					
Tentolouris et al (2008)	87%	66%	94 % EAC revised*: 79.41%	79 % EAC revised*: 77.78%	56.9 % EAC revised*: 59.62%
Neuropad vs Monofilament					
Freitas et al (2009)	82% EAC revised: 100%	94 % EAC revised: 38%	Not reported EAC revised: 59.38%	Not reported EAC revised: 100%	Not reported EAC revised: 47.5%

*EAC back calculated these values for entry into the meta-analysis.

Three studies had a NDS threshold of ≥6, one used a threshold of ≥5, 1 had no clear threshold (but EAC assume NDS≥6) and three used a threshold of ≥3. In total, n=5 studies considered for the mate-analysis to compare Neuropad vs NDS (NDS≥5). The EAC's initial meta-analysis followed the lines

of that undertaken by Tsapas et al. (2014), in that it ignored variation in NDS thresholds. In the case of Kamenov et al. (2010) which has 2 thresholds reported, the EAC used the higher threshold of ≥6.

The EAC note that although there are n=3 studies with a NDS threshold of ≥3, it is not recommended to perform a meta-analysis in STATA using a bivariate model, as it requires a minimum of n=4 studies (Takwoingi et al. 2016).

Using ≥5 threshhold of NDS (and only the higher Kamenov et al. threshold of ≥6) and comparing to Neuropad (n=5 studies), the EAC meta-analysis found:

- Sensitivity: 89.4 % (83.2% to 93.5 %)
- Specificity: 60.3 % (50.9 % to 69 %)

Figure 5 displays the forest plot of this meta-analysis comparing Neuropad vs NDS (≥5).

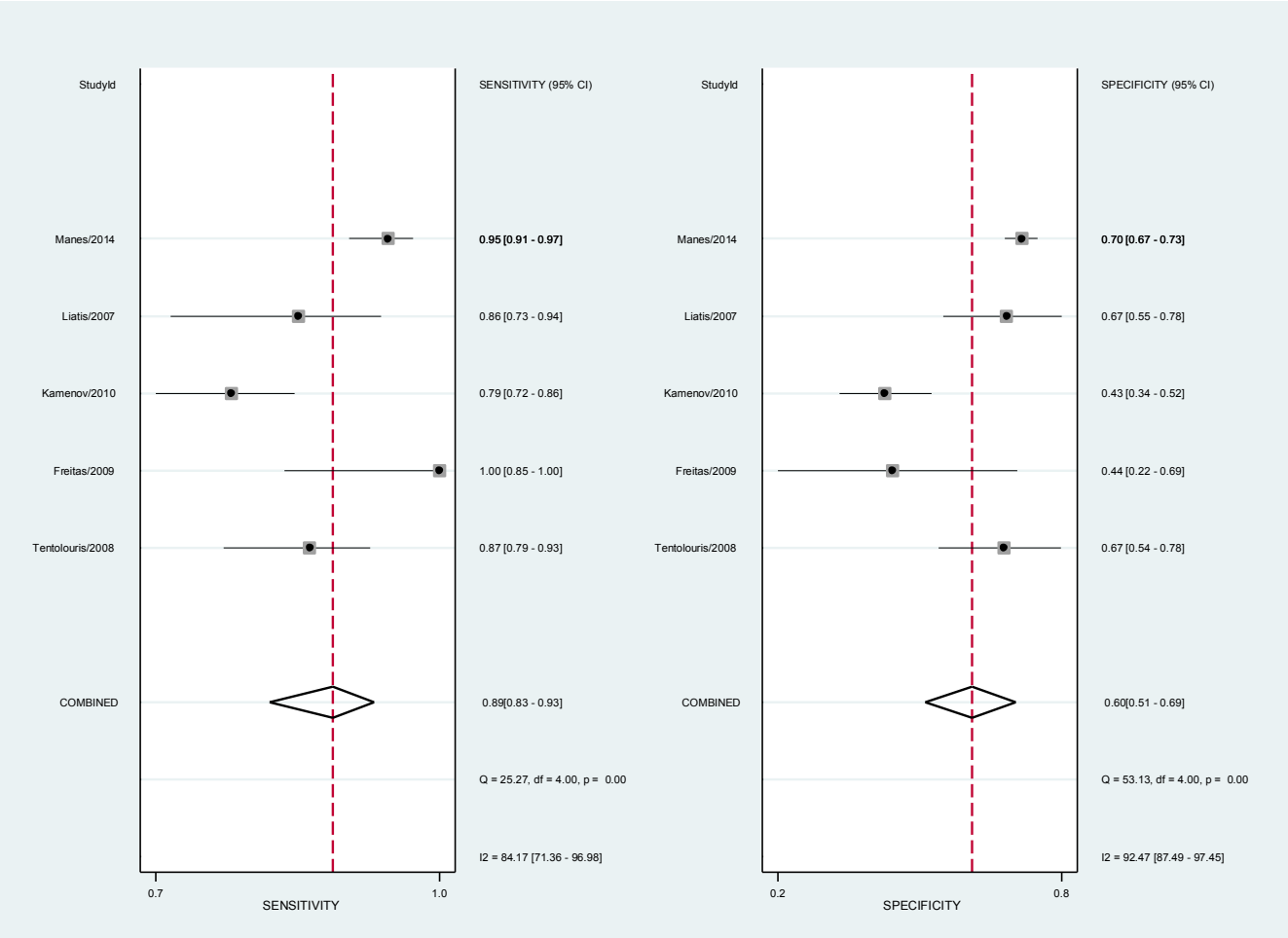


Figure 5 Forest plot of Neuropad against NDS ≥ 5

The I^2 value in figure 5 is 84.2 % (95%CI 71.4 to 97.0) for sensitivity and 92.5% (87.5% to 97.4%) for specificity.

The following table (8) provides the summary results of the EAC meta-analysis of Neuropad vs NDS (NDS≥5 [using highest threshold for Kamenov et al. 2010]). The EAC notes the high heterogenity in the meta-analysis.

Table 8 Results of the EAC meta-analysis of Neuropad vs NDS (≥5)

Meta-analysis	Studies	Pooled pop.	Sensitivity	Specificity
Neuropad vs NDS ≥ 5	N = 5	N = 1587	89.4 % (83.2% to 93.5 %) I^2: 84.2 % (95%CI 71.4 to 97.0)	60.3 % (50.9 % to 69 %) I^2:92.5 % (87.5 % to 97.4 %)

3.9 Ongoing studies

The manufacturer included 2 unpublished studies which were not found by either their literature search or the EAC's. The EAC searched for ongoing trials (ClinicalTrials.gov, ISRCTN and ICTRP [WHO]) and found 1 unpublished study which has been completed but the results are not available (NCT00895440).

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The sponsor did not provide any search strategy or complete the economic evidence section in the submission. The sponsor confirmed that a search was undertaken of EconLit, Medline and Google Scholar using the keywords "Neuropad", "costs", "costs analysis", "economic analysis", "economic consequences" and "cost-effectiveness analysis". The search did not yield any economic evidence on the technology. To confirm this, the EAC conducted its own search for economic evidence.

The EAC had decided a more sensitive search was required for the clinical evidence and therefore a new search strategy was developed. This contained a broader set of free-text terms and keywords and was run from 2003 in Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Global Health, HMIC, Cochrane, PubMed and Web of Science. The EAC also searched for grey literature using simpler search terms (see Appendix A for search strategies and PRISMA flow diagram). Following application of cost and economic filters, the searches retrieved 382 abstracts related to economic evidence. After reviewing these abstracts, the EAC confirmed that no economic evidence was available for the technology.

Critique of the company's study selection

NA

Included and excluded studies

NA

Overview of methodologies of all included economic studies

NA

Overview and critique of the company's critical appraisal for each study

NA

Does the company's review of economic evidence draw conclusions from the data available?

NA

4.2 Company de novo cost analysis

As no economic evidence was retrieved for the technology, the sponsor submitted a de novo Markov model using sensitivity and specificity values from the literature to model neuropathy detection, followed by disease progression over a time horizon of 3 years for patients who tested positive for neuropathy. (Note: the sponsors model did not distinguish true and false positive tests.)

Patients

The patient population included in the model are people who suffer from diabetes. Patients with diabetes are at risk of developing diabetic neuropathy, which increases the risk of foot ulcer and subsequent minor/major lower limb amputation and death. The sponsor has modelled disease progression for 3 years after an initial test and has not included death, citing as justification, an assumption made by Green and Taylor (2016) that there is no discernible impact of neuropathy on the risk of death. Whilst this is debateable, the EAC is of the opinion that a longer time horizon in line with literature (Ortegon et al 2004; Ragnarson et al 2001) and inclusion of death would have been appropriate.

Technology & Comparator(s)

The technology used as the intervention is Neuropad and is aligned with the scope.The sponsor has compared Neuropad with 2 alternative testing strategies: 10-g monofilament; and a combined strategy of using both 10-g monofilament and Neuropad. Given that Neuropad has a higher relevance in a primary care setting than a secondary care setting, the comparators included are appropriate. NICE clinical experts also suggested that Neuropad, monofilament or tuning forks are not used widely in a secondary care setting. Further, as revealed by the EAC's clinical review, there is limited evidence on

specialist tests compared with Neuropad. The Neuropathy Disability Score is widely reported as a research tool, but rarely used in routine practice. Consequently, the EAC is of the opinion that, the sponsor's comparison of Neuropad with 10-g monofilament is more relevant and reflects actual practice in the NHS. The use of Neuropad as a self testing device for patients is plausible (Tentolouris et al 2008), but there are practical aspects to be considered before adoption by NHS (such as how will Neuropad be delivered to patients for testing? How will the results be reported back to primary care? Are there test result recall issues?). There may be additional administration costs for home testing.

Model structure

The sponsor has submitted a Markov model which applies an NHS and personal social services perspective, for estimating the cost-effectiveness of the techonology against 2 comparators: 10-g monofilament test only; and a Neuropad test followed by a 10-g monofilament test if positive. A newly diagnosed cohort of patients with diabetes entering the model are tested for Neuropathy. All those testing positive are then modelled in 6-month time cycles for a period of 3 years to simulate the progression of their diabetic foot disease. The different health states and their transitions (indicated by arrows) are shown in figure 6. Note:whilst transitions from State A to State B or State C are depicted in figure 6, the actual model submitted by the sponsor did not

include these transitions.

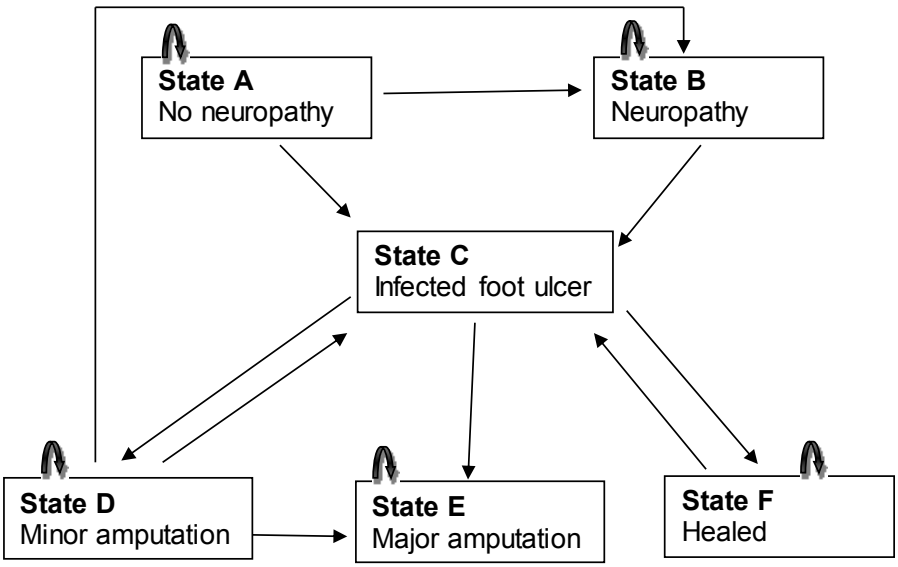


Figure 6 Sponsor's model structure.

Markov models are relevant to model disease progression in chronic conditions, and the EAC thinks that the sponsor's use of Markov model structure is appropriate. However there are many issues with the sponsor's model structure and their modelling approach which are detailed below.

- To estimate the cost-effectiveness of the technology against the comparators, the sponsor has taken a net-benefit approach which uses both utilities and costs for the different health states to estimate the net monetary benefit (NMB) by valuing a gain of one quality adjusted life year at £30,000. A positive NMB is taken to indicate the technology is cost-effective. Whilst this is the approach for most technology appraisals, NICE adopts a cost-consequences approach for evaluating medical technology programmes(NICE 2011). For these methods, only the cost and resource consequences need to be modelled. Utilities need not be included to estimate the net benefit. For this report, the EAC has considered only the cost of the technology and comparators and the resulting cost-savings from the sponsor's submission.

- The sponsor has used a recursive decision tree structure to model the Markov transitions. This has resulted in a rather bushy tree structure making readability difficult and placing a practical limitation on the time horizon. The EAC recommends a simple and commonly used Excel Markov model structure.

- The sponsor's model has included only those testing positive for neuropathy. All patients testing negative (both true and false negatives) are not modelled further i.e. they are treated as healthy individuals. The EAC thinks this is a flaw in the model because false negatives are at elevated risk of infected ulcers and likely to receive no preventive care. In the sponsor's model all positive cases (false or true) have been combined as 'positive cases' and modelled for the progression of diabetic foot disease without distinguishing those patients who actually have neuropathy. This is not agreeable to the EAC, since patients with a false positive result are at a much lower risk of foot ulceration.

- The 6 health states included by the sponsor are relevant and appropriately capture the long term progression of Neuropathy. A cycle length of 6 month is consistent with other Markov models (Ortegon et al 2004; Ragnarson et al 2001). The cycle length in these studies was determined from previously reported wound healing times between 3 to 7 months (Ragnarson et al 2001).

- Mortality is increased in patients with infected foot ulcer and is particularly elevated following amputation. The sponsor has not included death citing the reason that the time horizon of the model is short and there is no discernible increased mortality risk associated with neuropathy. The test will impact on mortality through the likelihood of correct diagnosis and the subsequent implementation of ulceration risk reduction programmes. The EAC thinks it would be appropriate to include death.

- The NICE scope requested 2 subgroups to be considered (people in community setting and people with communication difficulties or

cognitive impairment). Instead, due to the lack of data, the sponsor considered 1 additional subgroup: people in care homes who are at greater risk of developing diabetic neuropathy. This setting was modelled by assuming a higher prevalence of neuropathy. No UK specific prevalence rate for neuropathy in care home residents was available; a prevalence of 10.9% (van Kollenburg et al 2012) was used in the model. The EAC confirmed with its own systematic review no reasonable data was available for any meaningful sub group analysis. Further, the EAC thinks that there might be a possible role for Neuropad in populations with communication difficulties where the 10g monofilament test is not applicable.

Given the above issues with the model structure, the EAC thinks that the de novo model submitted by the sponsor needs considerable revision. The major changes to the revised model should have:

- Simple Markov structure with only cost consequences modelled.
- Negative cases included.
- True and false positive cases modelled separately
- Death state included

Summary of the base case

The sponsor's model reports the net monetary benefit after valuing utilities accrued at £30,000 per QALY and combining with costs. As pointed out earlier in the report, since MTEP uses a cost-consequences approach, the EAC considered only the estimated costs for the technology and comparators, and estimated the cost savings (table 9).

Table 9 Company's base case results

	Expected cost (£)	Cost saving(£) per patient [+]
Neuropad (Technology)	**5,585**	**-**
10g Monofilament (Comparator)	**6,954**	**1,369**
Neuropad + 10g Monofilament* (Comparator)	**6,944**	**1,359**

***Monofilament test is conditional on an abnormal result on Neuropad test.

[+] Range of cost-savings could not be estimated as the sponsor's model reports net-benefit results.

Clinical parameters and variables

There are a number of assumptions around the clinical parameters and variables used in the model, which are described and critiqued below. The sponsor consulted two clinical advisers for their approval on the disease progression model.

- The Markov model uses sensitivity and specificity values of Neuropad and 10-g Monofilament to segregate positive and negative neuropathy cases. The positives then enter the disease progression states (figure 6) transitioning between states during 6 month cylces for a time horizon of 3 years. As discussed under the model structure section, the EAC has concerns regarding the sponsor's assumption that once a negative result is obtained, the individual will remain healthy (no ulceration) for the remainder of the three year time horizon of the model. Neuropathy may develop at a later stage in healthy patients.Patients with neuropathy and falsely diagnosed (false negatives) are at increased risk of ulceration compared to patients correctly diagnosed and entering a foot care programme (assuming the programme is effective). A transition probability from 'no neuropathy to infected foot ulcer' is listed but is not applied in the model. These limitations has been accounted for in the Markov model revised by the EAC.

- The model assumes 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 (figure 6). The EAC is of the opinion that it is unreasonable to combine true and false results. In its revised model, the EAC has included false negative and positive as separate health states to overcome this limitation.

- Mortality is not incorporated in the sponsor's model.This is following the assumption made by Green and Taylor (2016), that there is no discernible difference between patients with or without neuropathy with regards to risk of death. On table C4 of the sponsor's submission, the shelf life (3 years) of Neuropad is also cited as a justification for the time-horizon. The EAC did not consider this a relevant consideration as the shelf life of the technology does not influence disease progression. The EAC is of the opinion that the 3 years time horizon is limited and a longer time horizon consistent with literature (Ortegon et al 2004; Ragnarson et al 2001) would yield a more robust analysis. The EAC considered a 10 year time horizon as sufficient to capture the longer term cost impact of neuropathy. The EAC used a 10 year time horizon and also included mortality.

- A prevalence rate of 2.4%(Kostev et al 2014) neuropathy has been used in the model taken from a longitudinal study of newly diagnosed diabetics from general practices in UK. The EAC considers this an appropriate source. The parameter is appropriate if it is assumed that the model commences when newly diagnosed diabetics are tested for DPN.

- Sensitivity (86%) and specificity (65%) values for Neuropad have been taken from the metanalysis results provided by Tsapas et al (2014). In the clinical review undertaken by the EAC, the Tsapas meta-analysis has been excluded primarily due to significant heterogeneity in the studies included in the meta-analysis and overlap in study populations. Specifically , the included studies used a variety of reference

standards. The EAC has performed its own meta-analysis and the results have been used to revise the model.

- Sensitivity (98.5%) and specificity (55%) values for 10-g monofilament test have been sourced from literature (Mythili et al 2010). The EAC would like to highlight that this study was undertaken in a diabetic population in India and more relevant UK based estimates are available. In particular, there are reasonable sensitivity (84%) and specificity (83%) estimates for a UK population available from the MTEP VibraTip evaluation (Willits et al 2015). Since the EAC meta-analysis could not estimate any reliable sensitivity and specificity estimates for monofilament, the EAC used the estimates from the VibraTip evaluation (Willits et al 2015) in its revised model.

- Transition probabilities (Sponsor's submission table C7) between the different health states have been estimated from 2 studies (Ortegon et al 2004; Ragnarson et al 2001). The sponsor indicated that the 2 studies reported the most appropriate models available in the literature upon which to base the sponsor's Markov model. The literature search was conducted on Medline, EconLit and Google Scholar for 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".The EAC also undertook two new searches for transition probabilities separately for diabetic foot and diabetic peripheral neuropathy (Appendix C). Review of the search results confirmed that the 2 studies included by the sponsor represented the most appropriate economic models for Neuropathy. Other studies examined from the searches primarily dealt with outcomes of diabetic foot ulcers. However, the EAC noted some discrepancies between parameters reported in the studies and the sponsor's model.

- It is unclear how the sponsor estimated the probability for remaining in the ‘no-neuropathy’ state as 96.08%. The original study (Ortegon et al 2004) reports a different value.

- A transition probability for ‘no-neuropathy’ to ‘neuropathy’of 2.37% is applied in the sponsor’s model. The derivation of this parameter is unclear as the cited source (Ortegon et al (2004)) reports a different value.

- The 6 month probability of transition from ‘no-neuropathy’ to ‘infected foot ulcer’ is parameterised as 1.54% but the cited source reports a value of 0.15% (Ragnarson et al 2001).

- The sponsor has sourced the transition probability for neuropathy patients to remain in the same state from Ortegon et al (2004). This is estimated as 94.9% but the paper reports this to be only 90%.

- It is unclear to the EAC how the transition probability of 5.10% for neuropathy patients transitioning from neuropathy into an infected foot ulcer state was estimated.

- The six month transition probabilities from ‘infected foot ulcer’ to ‘minor amputation’ (35%) and ‘healing’ (40%) is taken from Ragnarson et al (2001). However, the transition from ‘infected foot ulcer’ to ‘major amputation’ (17%) is different from the value cited in the source (9%).

- The sponsor’s model included a transition of 8% for unhealed ulcers.The source of this parameter is unclear; the cited source ; Ragnarson et al (2001) does not provide estimates of unhealed ulcers. The National Diabetes Foot Care Audit Report for England and Wales reports 26.4% of patients remain in an ulcerated state at 6 months (HQIP 2017). The EAC based its estimate of patients with unresolved foot ulcers on the data from HQIP in its revised model. Data from the EURODIALE Study (Promphers et al 2008), a prospective cohort study of 1,088 diabetic foot ulcer patients across 14 centres in Europe

provides more recent data for other transitions; infected foot ulcers to minor/major amputation and death. The EAC used these estimates in its revised model.

- A transition probability of 9.6% from the 'minor amputation' state into 'neuropathy' state is applied by the sponsor and Ortegon et al (2004) cited as the source. However, the EAC could not find the data supporting this estimate in the paper.

- The transition probability of 4.4% from 'minor amputation' to 'infected foot ulcer' is taken from Ragnarson et al (2001) and the transition probability of 17% from 'minor amputation' to 'major amputation' is taken from Ortegon et al (2004). The sponsor estimates a probability of 69% for transitions from 'minor amputation' to 'major amputation'. However, Ortegon et al (2004) estimates this probability as 76% and Ragnarson et al (2001) estimates it as 80%.

- Ortegon et al (2004) estimates 85% of patients with a healed ulcer will remain in that state; an estimate of 80% for the same parameter is provided in Ragnarson et al (2001). Given this, the EAC is unable to reconcile the sponsor's estimate of 96.1%. Further, estimates for the probability of further ulceration from the healed state of 4.4% (Raganarson et al 2001) and 2.85% (Ortegon et al 2004) do not match with the sponsor's estimate of 3.90%.

Given the above issues, the EAC thinks that the model has to be revised with appropriate clinical parameters, which the EAC has done (see section 4.4).

Resource identification, measurement and valuation

A number of assumptions on resource identification, measurement and valuation have been applied to estimate costs used in the model, which are described and critiqued below:

- Costs for each health state in the Markov model have been sourced from published literature (Kerr 2017). Kerr (2017) used Hospital

Epsisode Statistics for England, national tariffs and NHS reference costs to estimate NHS spending on diabetes –related foot problems in England. Whilst the cited source is useful, there are a few issues in how the sponsor has used these costs which are described below.

- The 6 month cost of community & primary care for patients with neuropathy is estimated at £1,855. This estimate 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 a 6 month cost of £1,855 as used by the sponsor, is on the high side, since many patients with neuropathy will not have ulcers.The only other estimate of the cost of a foot care programme the EAC found is McCabe et al (1998). They reported a 2 year cost of £757 per patient (in 1991 prices) to provide a protection programme in a diabetic foot clinic in the UK. After adjusting for current prices, it is £1300 over two years or £325 over 6 months, which the EAC thinks is more reasonable to be used in the model.

- The cost of treating an infected ulcer is estimated at £11,848 for a six month cycle and the EAC felt that these estimates were high. The sponsor confirmed that the cost included primary and community care (£8,620 for 6 months) and hospitalisation costs of £3,227 over 6 months. The primary and community care cost is based on a weekly cost of £359 (£8,616 for 6 months)per patient reported in Kerr (2017), which is agreeable to the EAC. The hospitalisation cost estimates are taken from Kerr (2017), and derived from analysis of Hospital Episode Statistics (HES).The weighted average of all foot ulcers grouped to ulcer-specific HRGs and other HRGs reported in Kerr (2017) is £4,376 which is inconsistent with the value of £3,277 used by the sponsor. It is unclear how the sponsor estimated this cost. Futhermore, the EAC does not agree with the sponsor's assumption that all infected ulcers will require hospitalisation. The NHS costing report on implementing

the NICE guideline on diabetic foot problems estimates that only 40% of the infected ulcers require hospitalisation (NICE 2015).

If it is assumed that only 40% would require hospitalisation, the 6 month cost would include the primary and community care cost plus the cost of 40% of the patients requiring hospitalisation. As there is considerable uncertainity surrounding these estimates, a sensitivity analysis is recommended.

- A 6 month cost of minor amputation of £2,105 and major amputation of £4,106 has been estimated by the sponsor from Kerr (2017). The cost is derived by dividing total annual costs reported in Kerr by the total number of admissions. In addition to this, a surgery cost (£9,407) has been added, along with stump procedure costs. Though it is reasonable to use the estimates from Kerr (2017), a more recent estimate is available from NHS reference costs(DOH 2016). For the minor amputation episode, the EAC regards the NHS reference cost of £5,937 (weighted average for HRG codes YQ24A -YQ26C inclusive) as appropriate. In case of major amputation episode, the cost would be £11,755 (weighted average for HRG codes YQ21A - YQ22B inclusive). Further, a cost for hospital based rehabilitation after surgery of £392 (HRG code VC14Z: Rehabilitation for Amputation of Limb) needs to be added to the treatment costs. To reflect post amputation costs, the sponsor has included a cost for stump procedures as an ongoing cost. The cost of £2,812 (apportioned between major and minor amputations admissions) is reported by the sponsor to be sourced from Kerr (2017). The EAC is of the opinion that procedures on stumps are not appropriate to be used as post discharge costs. Kerr (2017) provides some good life time estimates for post discharge care for minor amputation (£1,038) and major amputation (£5,519). These include the cost of prosthesis, physiotherapy, transport and wheelchair costs and are lifetime costs. Since the EAC plans to model the disease progression for only 10 years, a monthly post discharge cost would be more appropriate. As a part of the economic analysis for NICE

guidance (NG19) for Diabetic foot problems: prevention and management, monthly post amputation care for minor amputation (£64) and major amputation (£418) have been estimated (NICE 2016). In its revised model, the EAC used these estimates of the post amputation care cost.

- The sponsor reports a 6 month cost per patient with 'no neuropathy' of £125 (weekly cost of £5.21), drawn from the literature (Green & Taylor 2016). The estimate reported by Green and Taylor (2016) comes from a 2006 Health Technology Assessment report (Nelson et al 2006), for patients who are at a risk of developing ulcers. Hence, it may not be applicable for patients with no neuropathy. The sponsor's model applied this estimate to patients in the healed state, which the EAC thinks is reasonable. For patients with no neuropathy, the care provided for diabetic patients in NHS primary care is a usually a 20 minute consultation with a diabetic nurse (£14) and 10 minute consulation with a GP (£33) during the annual check up (unit costs from Curtis & Burns 2016). This gives an annual cost of £47 for patients with diabetes.

- A discount rate of 3.5% applied to costs beyond 1 year is as per the NICE reference case.

Technology and comparators' costs

The sponsor has used the list price of £7.28 as the cost of Neuropad per patient, which is agreeable to the EAC. The sponsor has used a price of £16.80 per patient for 10g monofilament test. This estimate is taken from the NICE briefing note for Neuropad. This is not appropriate because the £16.80 price used by the sponsor refers to the reusable holder of the monofilament. There is a cost of £14.28 per 100 filaments.Whilst the sponsor has performed a sensitivity analysis on test costs, the EAC does not agree with the base case estimate for the 10g monofilament and regards the sensitivity analysis as insufficient. In a previous MTEP assessment of VibraTip, Willits et al (2015) estimate a monofilament would have a useful life of 200 patients before

requiring replacement. Willits et al (2015) estimated a cost per examination of 7.6 pence (Range 3.04 – 19p). The EAC believes this estimate to be more realistic and has used it in its revised model. Further, the sponsor claims that they are not certain about the staff costs associated with Neuropad. Though it is difficult to estimate the precise time required, some staff time will be required if used in a primary care setting to administer the test. In case of monofilament too, some staff time will be required to administer and interpret an abnormal result. Based on expert advice, it is assumed that it will take a minute of staff time (diabetic nurse cost in a GP practice) for monofilament test. For Neuropad, the test requires an application contact time of 10 minutes (Quattrini et al 2008). However, staff time will be minimal (a minute) for application and interpretation, assuming the nurse undertakes other tasks in the interevening period. After inclusion of a minute of diabetic nurse cost (unit costs from Curtis & Burns 2016) to the costs for both tests, the estimated monofilament examination cost per patient is 80 pence and the estimated cost is £8 for Neuropad.

Sensitivity analysis

Deterministic sensitivity analysis was performed by the sponsor on a number of variables (health state costs, purchasing price of Neuropad and monofilament, Transition probabilities and discount rate). The main finding of the sensitivity analysis is that performing Neuropad test alone is always the optimal choice, except when the specificity of Neuropad drops below 55%, where the combined test strategy (monofilament conditional on an abnormal result of Neuropad) becomes optimal. Sub group analysis of care home residents was achieved by varying the prevalence rate of neuropathy in the sensitivity analysis, which showed that neuropad was always the optimal strategy, although it increased the cost. As the sensitivity analysis shows impact on net-benefit and not on cost-savings, and is implemented using a flawed model structure as previously noted, the sponsor's sensitivity analysis is not particularly useful for this assessment. However, the EAC agrees with the variables included in the sensitivity analysis.

4.3 Interpretation of economic evidence

The sponsor interprets the results of the economic model as the first of its kind, as there has been no previous analysis reported. The main conclusions reached by the sponsor are;

- If 2 different technologies that are intended to diagnose neuropathy are considered, then this should be done with Neuropad alone as it saves a cost of £1,369 per patient when compared to 10-g monofilament.
- Even if neuropad is used along with monofilament, it still gives a cost-saving of £9.75

Based on these conclusions, the sponsor recommends the NHS deploy Neuropad by mailing the test to people with diabetes or asking them to pick up the test from a community pharamacy. Those that test positive could be referred for further tests. Recommending Neuropad as a home testing device is plausible but there may also be additional administration costs. The EAC considers the sponsor's model to be flawed and erroneous, undermining the analysis and inference drawn from the model results. Robust conclusions require a revision of the model structure and parameters.

4.4 Results of EAC analysis

Due to the issues with the sponsor's model structure, clinical and cost parameters previously outlined, the EAC revised it accordingly with a changed structure and parameter estimates. The assumptions used in the EAC analysis are detailed below.

Model Structure & Assumptions

- A Markov model with a time horizon of 10 years and 6 month cycles has been constructed. The model supports a NICE medical technology recommended cost-consequences analysis and captures only costs and the resultant cost savings. Utilities have not been included in the model. Costs are discounted at 3.5%.

- The EAC model simulates a cohort of 1000 patients newly diagnosed with diabetes with a prevalence of DPN of 2.4% (Kostev et al 2014). The model is shown in figure 7. Health states and transitions included in the EAC model but not the original sponsor's model are shown in green. These additional health states address limitations identified in the sponsor's model, particularly the failure to distinguish between true positive and false positive diagnoses.

- Reflecting the greater relevance of Neuropad in a primary care setting, 3 main strategies were assessed:1) using Neuropad alone; 2) using monofilament alone; and 3) using monofilament on neuropathy positive cases after Neuropad testing (a positive diagnosis is inferred from a positive result on both tests). The model assumes that the testing happens in a primary care setting during the annual diabetic check. The NICE scope requested 2 subgroups to considered (people in community setting and people with communication difficulties or cognitive impairment). The clinical evidence review did not find any data specific to these 2 groups. The EAC considers their analysis to be representative of scenarios in which testing is undertaken during the annual diabetes check-up and where testing with Neuropad is undertaken by the patient at home on two assumptions: that testing at home has the same sensitivity and specificity as testing in a primary care setting; and that the costs associated with home testing or testing in the clinic are the same. Currently, foot risk assessment cannot be easily undertaken when there is cognitive impairment, since the monofilament test requires a verbal response. In such cases, no testing is routinely undertaken. To address this subgroup, the EAC considered an additional strategy of 'No-testing' in its analysis. The results of this strategy is not included in the main analysis, as monofilament testing is current practice and clinically superior to no testing.

- In order to keep the model tractable a number of assumptions are made. All patients are tested prior to entry into the model and placed in 1 of 4 health states: No DPN (true negative), DPN (true positive), DPN

(false negative); false positive. Patients not yet diagnosed with DPN are assumed to be tested annually. Multiple tests undertaken on the same patient are highly unlikely to be conditionally independent. We assumed complete dependence.That is to say we assumed that where a patient without DPN tested negative in the first test, all subsequent tests would give the same result conditional on the patient remaining free of DPN. In the model patients accrue test costs annually but the possibility of a false or true diagnosis of DPN is only calculated for the portion of the population who develop DPN. This assumption was tested in sensitivity analysis.

- The EAC assumed that the only confirmatory test of neuropathy undertaken after referral to a foot care programme is monofilament. Experts confirmed that specialist tests such as nerve conduction studies are only undertaken in specialist neurology centres. The EAC model does not include any further referral to specialist centres, since most of the neuropathy patients will be primarily treated at diabetic foot clinics.

- In evaluating the strategy of testing with both Neuropad and monofilament ,the EAC assumed the tests were completely independent and calculated sensitivity and specificity for the combined tests accordingly. It should be noted that there is an absence of clinical evidence on the sensitivity and specificity of both tests combined.

- Further assumptions include: population mortality is independent of age; all patients enter the foot care programme after ulceration occurs; patients testing positive for DPN join the foot care programme and no further tests for DPN are undertaken; and once a major amputation has occurred ulceration of the ipsilateral foot does not occur.For the scenario in which patients are tested at home we make two further assumptions: that the sensitivity and specificity of Neuropad in the home environment is the same as in the clinic; and that positive tests will be followed by a clinic referral including a monofilament test for

which the only additional cost is that of undertaking the monofilament test.

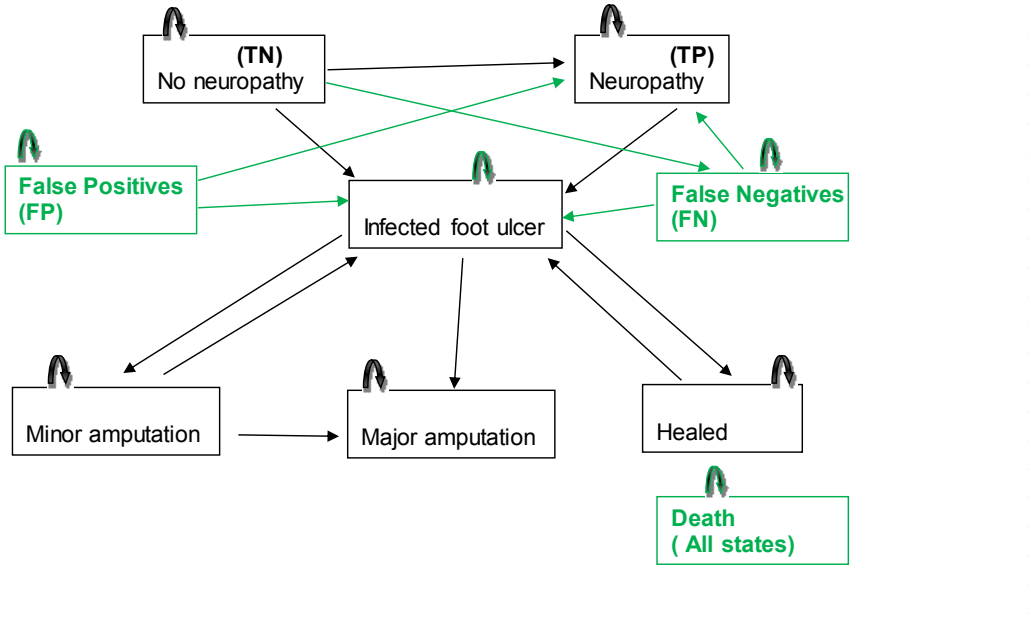


Figure 7 EAC's model structure

Clinical Parameters

The EAC revised the parameters used by the sponsor and also added new parameters for the added health states. Most of the parameters were sourced from Ortegon et al (2004) and Ragnarson et al (2001), who reported previous economic evaluations using a Markov model of the diabetic foot. Table 10 provides the clinical parameters (base case) and assumptions used to estimate the transition probabilitiesfor the revised model.

Table 10 Clinical parameters and assumptions in the EAC model

	Sponsor's Estimate	Source	EAC Estimate	Source & Assumptions
Clinical Parameters				
DPN Prevalence	0.024	Kostev et al (2014)	0.024	Kostev et al (2014)
Test Sensitivity (Neuropad)	0.86	Tsapas et al (2014)	0.89	EAC Meta-analysis
Test Specificity (Neuropad)	0.65	Tsapas et al (2014)	0.60	EAC Meta-analysis

Test Sensitivity (10g Monofilament)	0.985	Mythili et al (2010)	0.84	Willits et al(2015)
Test Specificity (10g Monofilament)	0.55	Mythili et al (2010)	0.83	Willits et al(2015)
Test Sensitivity (Neuropad + 10g Monofilament)	-	Applied sequentially if abnormal on Neuropad	0.75	Calculated : $Sensitivity_{Neuropad}$ * $Sensitivity_{Monofilament}$
Test Specificity (Neuropad + 10g Monofilament)	-	Applied sequentially if abnormal on Neuropad	0.93	Calculated : $Specificity_{Neuropad}$ +(1- $Specificity_{Neuropad}$)* $Specificity_{Monofilament}$
Incidence of Neuropathy	0.0237	Unclear, though cited Ortegon et al (2004)	0.0199	Ortegon et al (2004)
No Neuropathy infected foot ulcer rate	0.015	Unclear, though cited Ragnarson et al(2001)	0.0026	Ortegon et al (2004)
No Neuropathy death rate	-		0.02	Ortegon et al (2004)
False positive infected foot ucler rate*	-		0.00195	Estimated by applying effectiveness(diabetic foot programme)
False positive death rate	-		0.02	Assumed same as No neuropathy
Neuropathy infected foot ulcer rate	0.051	Unclear, though cited Ortegon et al (2004)	0.014	Ragnarson et al(2001)
DPN Death rate	-		0.02	Assumed same as No neuropathy
False negative infected foot ulcer rate^	-		0.0187	Estimated by applying

				effectiveness(diabetic foot programme)
Persistent infected foot ulcer	-		0.264	HQIP (2017)
Infected foot minor amputation rate	0.35	Ragnarson et al(2001)	0.13	Promphers et al (2008)
Infected foot major amputation rate	0.17	Unclear, though cited Ragnarson et al(2001)	0.05	Promphers et al (2008)
Infected foot ulcer to healed	0.40	Ragnarson et al(2001)	0.496	Derived probability
Infected foot death rate	-		0.06	Promphers et al (2008)
Minor amputation infected foot rate	0.044	Ragnarson et al(2001), but not included ulcers with critical ischaemia	0.073	Ragnarson et al (2001), including ulcers with critical ischaemia
Minor amputation major amputation rate	0.17	Ortegon et al (2004)	0.17	Ortegon et al (2004)
Minor amputation death rate	-		0.027	Ragnarson et al (2001)
Major amputation death rate	-		0.12	Ragnarson et al (2001)
Healed to infected foot rate	0.039	Unclear, though cited Ortegon et al (2004)	0.073	Ragnarson et al (2001), including ulcers with critical ischaemia
Healed death rate	-		0.027	Ragnarson et al (2001)
Effectiveness of diabetic foot programme	-		0.25	Ragnarson et al (2001)
Infected foot ulcer (hospitalization proportion)	-		0.40	NICE(2015)

*Lower rate estimated by EAC because they enter into a foot programme

^Higher rate estimated by EAC because they do not enter into a foot programme

Transition Probabilities

Using the clinical parameters listed in table 10, the EAC estimated the transition probabilities to be applied in the model. The transition probabilities for the different health state applied to the 4 strategies are presented in table 11.

Table 11 Transition probabilities in the EAC model

	Sponsor Estimate	Source	EAC Estimate				Source
			Neuro-pad	Monofilament	Neuropad + Monofilament	No Testing	
Transition Probabilities (6 months)							
No testing cycle- No Neuropathy to No Neuropathy			0.958	0.958	0.958	0.958	Estimated
No testing cycle- No Neuropathy to False negative (undiagnosed neuropathy)			0.0199	0.0199	0.0199	0.0199	Ortegon et al (2004)
No testing cycle - No Neuropathy to Infected foot ulcer			0.0026	0.0026	0.0026	0.0026	Ortegon et al (2004)
No testing cycle - No Neuropathy to Death			0.02	0.02	0.02	0.02	Ortegon et al (2004)
No testing cycle - False positive to False Positive			0.958	0.958	0.958	0.958	Estimated
No testing cycle-False positive to Neuropathy			0.0199	0.0199	0.0199	0.0199	Ortegon et al (2004)
No testing cycle-False positive to			0.002	0.002	0.00195	0.00195	Estimated by applying effectiveness (diabetic

Infected foot ulcer							foot programme)
No testing cycle-False positive to Death			0.02	0.02	0.02	0.02	Assumed same as No neuropathy
No testing cycle - False Negative to False Negative			0.961	0.961	0.961	0.961	Estimated
No testing cycle - False Negative to Infected foot ulcer			0.0187	0.0187	0.0187	0.0187	Estimated by applying effectiveness (diabetic foot programme)
No testing cycle - False Negative to Death			0.02	0.02	0.02	0.02	Assumed same as Neuropathy
No Neuropathy to No Neuropathy	0.9608	Unclear, though cited Ortegon et al (2004)	0.958	0.958	0.958	0.958	Estimated
No Neuropathy to Neuropathy	0.0237	Unclear, though cited Ortegon et al (2004)	0.017	0.016	0.015	0.000	Estimated
No Neuropathy to False negative			0.002	0.003	0.005	0.019	Estimated
No Neuropathy to Infected foot ulcer	0.0154	Unclear, though cited Ragnarson et al (2001)	0.0026	0.0026	0.0026	0.0026	Ortegon et al (2004)

No Neuropathy to Death			0.02	0.02	0.02	0.02	Ortegon et al (2004)
False positive to False Positive			0.958	0.958	0.958	0.958	Estimated
False positive to Neuropathy			0.0199	0.0199	0.0199	0.0199	Ortegon et al (2004)
False positive to Infected foot ulcer			0.002	0.002	0.00195	0.00195	Estimated by applying effectiveness (diabetic foot programme)
False positive to Death			0.02	0.02	0.02	0.02	Assumed same as No neuropathy
Neuropathy to Neuropathy	0.949	Unclear, though cited Ortegon et al (2004)	0.966	0.966	0.966	0.966	Estimated
Neuropathy to Infected foot ulcer	0.051	Unclear, though cited Ortegon et al (2004)	0.014	0.014	0.014	0.014	Ragnarson et al(2001)
Neuropathy to Death			0.02	0.02	0.02	0.02	Assumed same as No neuropathy
False Negative to Neuropathy			0.858	0.808	0.721	0.000	Test sensitivity
False Negative to False Negative			0.10	0.15	0.24	0.96	Estimated
False Negative to Infected foot ulcer			0.0187	0.0187	0.0187	0.0187	Estimated by applying effectiveness (diabetic foot programme)

False Negative to Death			0.02	0.02	0.02	0.02	Assumed same as Neuropathy
Infected foot ulcer to infected foot ulcer	0.08	Unclear, and not reported in the cited Ragnarson et al (2001)	0.264	0.264	0.264	0.264	HQIP (2017)
Infected foot ulcer to minor amputation	0.35	Ragnarson et al (2001)	0.13	0.13	0.13	0.13	Promphers et al (2008)
Infected foot ulcer to major amputation	0.17	Unclear, though cited Ragnarson et al (2001)	0.05	0.05	0.05	0.05	Promphers et al (2008)
Infected foot ulcer to healed	0.4	Ragnarson et al (2001)	0.496	0.496	0.496	0.496	Promphers et al (2008)
Infected foot ucler to Death			0.06	0.06	0.06	0.06	Promphers et al (2008)
Minor amputation to infected foot ulcer	0.044	Ragnarson et al (2001)	0.073	0.073	0.073	0.073	Ragnarson et al (2001)
Minor amputation to Minor amputation	0.69	Unclear, though cited Ortegon et al (2004) & Ragana rson et al(2001)	0.73	0.73	0.73	0.73	Estimated
Minor amputation	0.17	Ortegon et al (2004)	0.17	0.17	0.17	0.17	Ortegon et al (2004)

to Major amputation							
Minor amputation to Death			0.027	0.027	0.027	0.027	Ragnarson et al (2001)
Major amputation to major amputation	1	Ortegon et al (2004) & Raganarson et al(2001)	0.88	0.88	0.88	0.88	Ragnarson et al (2001)
Major amputation to Death			0.12	0.12	0.12	0.12	Ragnarson et al (2001)
Healed to healed	0.961	Unclear, though cited Ortegon et al (2004)	0.90	0.90	0.90	0.90	Estimated
Healed to infected foot ulcer	0.39	Unclear, though cited Ortegon et al (2004)	0.073	0.073	0.073	0.073	Ragnarson et al (2001)
Healed to death			0.027	0.027	0.027	0.027	Ragnarson et al (2001)

Cost Parameters

Due to the issues regarding cost parameters discussed in the earlier section, the EAC revised the cost parameters and used them in the revised model. Table 12 provides the cost parameters (base case) and assumptions used .

Table 12 Cost parameters in the EAC model

	Sponsor's Estimate	Source	EAC Estimate	Source & Assumptions
Cost				
Neuropad	£7.28	Sponsor list price	£8	Sponsor, Curtis & Burns (2016) for staff cost

Monofilament /examination	£16.80	NICE briefing note, includes only the cost of the reusable holder	£0.80	Willits et al (2015) , Curtis & Burns(2016) for staff cost
Health state (6 month)				
No neuropathy (only annual diabetic check)	£125	Green & Taylor (2016), not used in the model	£23.50	Cutin & Burns(2016), staff cost for 30 minute consultation
Neuropathy (foot clinic)	£1,855	Kerr(2017), these are cost of treating ulcers with no or mild infection	£325	McCabe et al (1998), Estimated foot clinic cost
Infected foot ulcer (primary & community care)	£8,620	Kerr(2017), rounded from £8,616	£8,616	Kerr(2017), weekly cost of £359
Infected foot ulcer (hospitalization)	£3,277	Kerr (2017), inconsistent estimates	£4,376	Kerr (2017),weighted average of all foot ulcers grouped to ulcer-specific HRGs and other HRGs
Minor amputation + hospital rehabilitation	£11,512	Kerr (2017) (£2,105). Also a transition cost of £ 9,407 (Ragnarson et al 2001) and a stump procedure cost has been added.	£6,329	DOH (2016), weighted average for HRG codes YQ24A - YQ26C inclusive + HRG code VC14Z: Rehabilitation for Amputation of Limb
Minor amputation (post care)	£1,605	Kerr (2017), stump procedure cost used as a post care	£384	NICE (2016), monthly cost of £64
Major amputation + hospital rehabilitation	£13,513	Kerr (2017) (£4,106). Also a transition cost of £ 9,407 (Ragnarson et al 2001) and a stump procedure cost has been added.	£12,147	DOH (2016), weighted average for HRG codes YQ21A - YQ22B inclusive + HRG code VC14Z: Rehabilitation for Amputation of Limb
Major amputation (post care)	£1,206	Kerr (2017), stump procedure cost used as a post care	£2,508	NICE (2016), monthly cost of £418

Sensitivity Analysis

To deal with uncertainty surrounding the clinical and cost parameters, a deterministic sensitivity analysis was performed on the parameters. The range used in the sensitivity analysis depended on whether estimates were available in literature. If there were no literature estimates, appropriate ranges were estimated. The parameters and range used is presented in table 13. Further, a sensitivity analysis was also performed after making a structural change in

which the EAC assumed multiple tests on the same patients are conditionally independent at every retest.

Table 13 Range used in the Sensitivity analysis

	Base Case	Range (Low)	Range (High)	Justification
Clinical Parameters				
DPN Prevalence	0.024	0.019	0.03	Kostev et al (2014)
Test Sensitivity (Neuropad)	0.89	0.83	0.93	EAC Meta analysis
Test Specificity (Neuropad)	0.60	0.51	0.69	EAC Meta analysis
Test Sensitivity (10g Monofilament)	0.84	0.75	0.94	Willits et al(2015)
Test Specificity (10g Monofilament)	0.83	0.75	0.91	Willits et al(2015)
Test Sensitivity (Neuropad + 10g Monofilament)	0.75			Varied according to sensitivity of component tests
Test Specificity (Neuropad + 10g Monofilament)	0.93			Varied according to specificity of component tests
Test Sensitivity (No testing)	0.00			NA
Test Specificity (No testing)	1.00			NA
Incidence of Neuropathy	0.0199	0.01	0.04	Estimated
No Neuropathy infected foot ulcer rate	0.0026	0.002	0.0045	Estimated
No Neuropathy death rate	0.02	0.01	0.04	Estimated
False positive infected foot ucler rate	0.00195			Varied alongside 'No neuropathy infected foot ulcer' rate
False positive death rate	0.02	0.01	0.04	Same as No neuropathy death rate
Neuropathy infected foot ulcer rate	0.014			Varied alongside 'False negative infected to foot ulcer' rate
Neuropathy death rate	0.02	0.01	0.04	Same as No neuropathy death rate
False negative infected foot ulcer rate	0.0187	0.01	0.05	Estimated
False negative death rate	0.02	0.01	0.04	Same as No neuropathy death rate
Persistent infected foot ulcer	0.264	0.2	0.3	Estimated

Infected foot minor amputation rate	0.13	0.1	0.35	Estimated, high range based on Ragnarson et at (2001)
Infected foot major amputation rate	0.05	0.03	0.17	Estimated, high range based on Sponsor's estimate
Infected foot ulcer to healed	0.496			Will change when other proportions are varied
Infected foot death rate	0.06	0.04	0.08	Estimated
Minor amputation infected foot rate	0.073	0.044	0.1	Estimated, low range based on Ragnarson et al (2001)
Minor amputation major amputation rate	0.17	0.1	0.25	Estimated
Minor amputation death rate	0.027	0.02	0.04	Estimated
Major amputation death rate	0.12	0.08	0.16	Estimated
Healed to infected foot rate	0.073	0.044	0.1	Same as Minor amputation infected foot rate
Healed death rate	0.027	0.02	0.04	Same as Minor amputation death rate
Effectiveness of diabetic foot programme	0.25	0.1	0.5	Estimated
Cost				
Neuropad	£8	£7.28	£10	Estimated, Low range based on list price without staff cost
Monofilament/examination	£0.80	£0.75	£0.90	Willits et al (2015)
Health state(6 month)				
No neuropathy(only annual diabetic check)	£23.50	£12	£35	Low range 15 minutes(consultation), High 45 minutes
False positive(same as Neuropathy)	£325	£150	£600	Same as Neuropathy state
Neuropathy(foot clinic)	£325	£150	£600	Estimated
False Negative(only annual diabetic check)	£23.50	£12	£35	Same as No neuropathy state
Infected foot ulcer(primary & community care)	£8,616	£1,800	£12,000	Estimated, Low range based on Kerr(2017)
Infected foot ulcer(hospitalization)	£4,376	£1,300	£7,500	Estimated, Low range based on HRG KB03E
Minor amputation + hospital rehabilitation	£6,329	£3,000	£16,000	Low range based on HRGYQ26C, High HRG YQ24A
Minor amputation(post care)	£384	£200	£600	Estimated
Major amputation + hospital rehabilitation	£12,147	£8,000	£20,000	Low range based on HRG YQ22B, High HRG YQ21A

Major amputation(post care)	£2,508	£1,200	£4,000	Estimated
Healed (same as Neuropathy)	£325	£150	£600	Same as Neuropathy state

Base-case analysis results

Table 14 provides the results of the base case analysis. Using Neuropad is not cost saving compared to any other strategies. The no testing strategy has the least cost followed by Monofilament tested on all positive case reported by Neuropad. However, these two strategies have to be interpreted with extreme caution. The no-testing strategy, whilst cheaper than the alternative tests, is likely to deliver inferior outcomes. The Neuropad + Monofilament strategy has applied sensitivity and specificity values assuming the two tests are completely independent. There is insufficient clinical evidence to confirm such an assumption. It should also be noted that the Neuropad and monofilament test saves money by increasing specificity at the cost of sensitivity. As such it may deliver poorer health outcomes than either the Neuropad or monofilament test alone.

Table 14 Base case analysis

	Expected cost/patient (£)	Cost saving/patient* (£)
Neuropad	£3,893	
10g Monofilament	£3,118	£775
Neuropad + 10g Monofilament	£2,818	£1,075
No Testing	£2,101	£1,792

* Compared against Neuropad

Sensitivity analysis results

Sensitivity analysis (deterministic) performed on variables listed in Table 13 showed that none of the parameters changed the ranking of test strategies according to cost. Neuropad was not cost saving in any of the scenarios.

Varying most of the parameters had little impact the results. Exceptions were test specificity (Neuropad & Monofilament), DPN incidence, mortality and effectiveness of the diabetic foot programme. Of the cost parameters, only the annual diabetic check for those with no neuropathy, diabetic foot clinic cost for those with neuropathy and the primary and community care cost for infected foot ulcers had a significant impact on the cost savings results when varied in sensitivity analysis. The results of the sensitivity analysis thus confirms the robustness of the base case results; neuropad is not cost saving compared to other strategies. Results of the sensitivity analysis are presented in Appendix E.

Structural Sensitivity Analysis

The base model assumed that patients with no neuropathy who tested negative would continue to test negative unless they developed Neuropathy. The EAC tested this assumption by applying a structural change in the model and assuming conditional independence; i.e at every retest the patient may receive a different result. The results of this analysis (table 15) show that whilst costs rise (due to an increase in false positives over multiple testing cycles), the ranking of Neuropad is not changed; neuropad is not cost saving compared to other strategies.

Table 15 Structural sensitivity analysis

	Expected cost/patient (£)	Cost saving/patient* (£)
Neuropad	£5,297	
10g Monofilament	£4,384	£913
Neuropad + 10g Monofilament	£3,518	£1,779
No Testing	£2,101	£3,196

* Compared against Neuropad

Subgroup analysis

As discussed in the earlier sections, no specific data could be found for people living in community settings. The EAC examined the impact of an

increase in prevalence of DPN (expected to be higher for people in community setting) in the sensitivity analysis (Appendix E). At a prevalence of 3%, Neuropad was not cost saving compared to other strategies.

For people with communication difficulties, a monofilament test cannot be used as verbal responses cannot be elicited. In such circumstances patients are not routinely tested. In its revised model, the EAC added a no testing strategy which turned out to be the least costly option (Table 13). This would suggest the diabetic foot programme does not reduce costs although it may well improve health related quality of life. The MTEP uses a cost consequences approach which does not evaluate quality of life. Consequently, the EAC is of the opinion that Neuropad may be a useful testing strategy for people on whom other tests like monofilament cannot be applied.

Model validation

A stage wise validation was applied to the EAC model. The model structure and parameters were validated by the EAC's clinical advisers. The model was checked independently by the designer and by a second health economist .

4.5 EAC Interpretation of economic evidence

In order to rectify the issues of the sponsor's model, the EAC rebuilt the model using newer parameters and structure. A de novo model was required since the sponsor and the EAC did not find any published evidence related to the technology. The EAC had included 4 strategies, 1) Neuropad 2) Monofilament 3) Neuropad and monofilament and 4) No testing. As strategy 3 was built on a theoretical calculation of the joint sensitivity and specificity of Neuropad and Monofilament, caution should be exercised while using the results as there is no clinical evidence to inform the joint sensitivity and specificity. It should also be noted that the combined testing strategy achieves cost savings by ensuring fewer patients (both true positive and false positive) enter the foot care programme. As such it would be expected to deliver poorer health outcomes than either of the single testing strategies alone. In comparions between

Neuropad and Monofilament alone, the monofilament strategy is the most cost saving strategy to be used in a primary care setting. The base case and sensitivity analysis confirms this. However, where the monofilament test cannot be used, Neuropad may have a role (people with communication difficulties and cognitive impairment).

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC's base case cost is lower than estimated by the sponsor (table 16), despite the shorter time horizon of 3 years in the sponsor's model compared to the 10 years used by the EAC. The sponsor assumed all patients testing positive were at increased risk of ulceration whether or not they actually had neuropathy. In fact the positive predictive value of the tests are low at a prevalence of 2-3%. The sponsor also assumed a higher cost of £1,855 for patient who entered the diabetic foot programme, whereas the EAC considered a lower cost of £325. Further, the sponsor assumed that all the patients who had an infected foot ulcer required hospitalization, the EAC assumed only 40% required hospitalization. In the case of monofilament, the sponsor assumed a cost of £16.80 for every tested patient, which was significantly reduced by the EAC to £0.80. These differences in assumptions and parameters used have resulted in a much lower cost with the EAC's model when compared to the sponsor's model.

Table 16 Base case cost difference

	EAC's Cost* (£)	Sponsor's cost* (£)
Neuropad	£3,893	£5,585
10g Monofilament	£3,118	£6,954
Neuropad + 10g Monofilament	£2,818	£6,944
No Testing	£2,101	-

* Compared against Neuropad

5 Conclusions

5.1 Conclusions on the clinical evidence

The included evidence does not strongly support the sponsor's claims that Neuropad has been validated against primary tests (section 7.10 of the sponsor submission). Only 2 studies were found that validated the Neuropad against the monofilament. The 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). While the evidence indicates that Neuropad may be non-inferior to the monofilament and may in fact be more sensitive (though less specific), there is not enough robust head-to-head evidence to support superiority. The claim that the sensitivity of Neuropad is "comparable with "NCS" (nerve conduction studies) and the NDS, which significantly exceeds that seen with the monofilament and tuning fork tests" was not supported by the evidence. In the meta-analysis, the Neuropad had a sensitivity of 89.4% and a specificity of 60.3% compared with the NDS (at a threshold of ≥5). The sponsor also claims that 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)". Insufficient evidence was found for the performance of Neuropad against VPT. However unpublished longitudinal studies (Sanz et al. 2016 and Tentolouris et al 2017) indicated that the Neuropad may have a higher sensitivity but lower specificity than the NDS or a combination of VPT and monofilament for predicting future foot ulceration. 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", this in theory is a benefit of the Neuropad, however, no studies were found to provide evidence for benefits in this subgroup. The sponsor 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 healthcare professional. Though evidence is limited, the study appears to support the sponsor’s claims.

The performance of the Neuropad in the included studies was relevant to the population and intervention outlined in the scope. According to the EAC quality appraisal, included studies were low in bias, however there was high heterogeneity in methods used .The sponsor did not carry out its own meta-analysis, but did submit an independently published meta-analysis (Tsapas et al. 2014). Although the outcomes (86% sensitivity and 65% specificity) were broadly representative of the papers included in this assessment, the EAC performed their own meta-analysis. Five studies were included in the overall meta-analysis, yielding a pooled sensitivity and specificity of 89.4% and 60.3%, respectively, which are comparable to Tsapas et al. (2014). The meta-analysis suggested there was a substantial level of heterogeneity in study outcomes. Additionally, the evidence was subject to a number of other uncertainties. Only 1 study (Tentolouris et al. 2008) was carried out in the most relevant setting (home testing). All other studies were carried out in secondary or tertiary care settings. The majority of papers assessed Neuropad against a reference standard (typically the NDS), but reference standards and thresholds varied substantially.

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. It is 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.

5.2 Conclusions on the economic evidence

The sponsor modelled the disease progression after testing, for 3 different strategies; Neuropad alone, Monofilament alone and Monofilament used on positive cases reported by Neuropad. The results showed that using Neuropad alone was an optimal strategy. The EAC reviewed the sponsor's economic submission and found that there were inherent flaws that needed to be rectified. The EAC revised the model structure to separate patients with a true and false positive result. Clinical parameters were primarily sourced from literature and the EAC validated estimates with clinical advisers familiar with a UK setting. The EAC included all the three strategies considered by the sponsor in their revised model. Additionally, a no testing strategy as a possible representation of people with communication difficulties or cognitive impairment was also included. In the base case, the EAC found that Neuropad was not cost saving compared to the monofilament test. The least costly option was the no testing strategy followed by the strategy where Neuropad and Monofilament were jointly used.

The EAC model has limitations. Firstly, the EAC assumed that the initial test results will not change when patients are retested every year unless the patient develops neuropathy. The EAC assumed so, because the retest is applied on the same patient, and the results of a new test are unlikely to be completely independent of the previous test. In reality there is a risk of a false positive result when the test is applied to a patient in a subsequent year who has not developed neuropathy. The cost of £325 for a diabetic foot programme was taken from a 1998 study (inflated to present value) as the EAC did not find more recent estimates relevant to a UK setting. The uncertainity surrounding this estimate was checked in the sensitivity analysis and this did not alter the conclusions. The EAC used a 6 month probability of 1.4% of infected foot ulcer in patients with neuropathy (Ragnarson et al 2001). The EAC could not find any national data on foot ulcer incidence and prevalence in diabetes in England but note that Kerr (2017) reports an annual incidence of 2%. The EAC tested this parameter in sensitivity analysis which did not impact the cost saving conclusions.

6 Summary of the combined clinical and economic sections

The clinical review found a paucity of evidence for Neuropad in the primary or home care settings or for its comparative effectiveness against the 10g monofilament. The EAC meta-analysis of 5 studies indicated that Neuropad has a sensitivity of 89.4% and a lower specificity of 60.3% compared with NDS (with a threshold of ≥5). Two unpublished longitudinal studies (Sanz et al. 2016 and Tentolouris et al 2017) indicated that the Neuropad may have a higher sensitivity but lower specificity than the NDS or a combination of VPT and monofilament for predicting future foot ulceration. 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.

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 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.

7 Implications for research

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). There was a paucity of evidence for Neuropad in the primary care and home setting. Further investigation would be required in these settings which are the primary intended use of the Neuropad.

There is insufficient evidence investigating how Neuropad compares with sensation tests used in primary care (primarily the 10g monofilament). This is necessary to better understand the diagnostic value of the Neuropad compared with pre-existing tests that would currently be carried out as routine.

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. 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.

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. Therefore 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. This change in the pathway would, however, require evidence for Neuropad's effectiveness on patient-important outcomes and cost-effectiveness of implementation in the diagnostic pathway.

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 testing during early stage DPN may be.

The evaluation has highlighted a lack of evidence on the effectiveness and cost-effectiveness of foot care programmes. An intuition that such preventative care will reduce costs does not appear to be borne out by the modelling undertaken by the EAC. Given the scale of DPN an evaluation of the effectiveness and cost-effectiveness of foot care programmes is overdue.

The value of testing for neuropathy is entirely dependent on the effectiveness of ulcer prevention programmes.

References

Aubert, C. E., J. Le Doeuff, J. Lajou, et al. (2013) "Influence of peripheral arterial occlusive disease on the Neuropad® test performance in patients with diabetes." Diabetic Medicine 30(5): 178-174

Breiner A., Lovblom LE., Perkins BA et al. (2014) “Does the prevailing hypothesis that small-fiber dysfunction precedes large-fiber dysfunction apply to type 1 diabetic patients?” Diabetes Care 37(5):1418-24

Bus SA., van Netten JJ. (2016) A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metabolison Research and Reviews 32(S1): 195-200

Clayton, W. and T. A. Elasy (2009) "A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients." Clinical Diabetes 27(2): 52-58

Curtis L. & Burns, A. (2016) Unit Costs of Health and Social Care 2016, Personal Social Services Research Unit, University of Kent, Canterbury. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php [Accessed on 12 June 2017]

Department of Health (2016). NHS reference Cost 2015-2016 available at https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [Accessed 10 June 2017]

Didangelos, T., I. Zografou, A. Papageorgiou, et al. (2006) "Validation of a new diabetic autonomic neuropathy bedside test (Plaster) vs. the MNSI, monofilament of 10 gr test and biothesiometer: P186." Diabetic Medicine 23 Suppl.(4): 78-78

Dyck, P. J., W. R. Sherman, L. M. Hallcher, et al. (1980) "Human diabetic endoneural sorbitol, fructose, and myo-inositol related to sural nerve morphometry." Annals of Neurology 8(6): 590-596

Feng, Y., F. J. Schlösser and B. E. Sumpio (2009) "The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy." Journal of Vascular Surgery 50(3): 675-682.e671

Forth, R., V. Joanne and N. Tentolouris (2010) "Use of Neuropad in the diagnosis of diabetic peripheral neuropathy." Diabetic Foot Study Group

Freitas, C., A. Carvalho, G. Melo-Rocha, et al. (2009) "O teste com NEUROPAD: Na deteccao precoce da neuropatia periferica do doente diabetico (THE NEUROPAD TEST In the Screening of Peripheral Neuropathy in Diabetic Patients)." Acta Medica Portuguesa 22(6): 729-734

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

Healthcare Quality Improvement Partnership(2017). National Diabetes Foot Care Audit Report 2014-2016. Available at http://www.hqip.org.uk/public/cms/253/625/19/731/NDFA_2017_Report_PPT_Format_Final%20to%20HQIP.pdf?realName=vbKPm8.pdf&v=0 [Accessed on 14 June 2017]

Ishibashi, F., R. Kojima, A. Kawasaki, et al. (2014) "Correlation between sudomotor function, sweat gland duct size and corneal nerve fiber pathology in patients with type 2 diabetes mellitus." Journal of Diabetes Investigation 5(5): 588-596

Kamenov, Z. A., J. J. Petrova and V. G. Christov (2010) "Diagnosis of diabetic neuropathy using simple somatic and a new autonomic (Neuropad®) tests in the clinical practice." Experimental and Clinical Endocrinology and Diabetes 118(4): 226-233

Kerr, M (2017). “Diabetic foot care in England: an economic study” Insight Health Economics (January 2017), For Diabetes UK available at https://www.diabetes.org.uk/Upload/Shared%20practice/Diabetic%20footcare%20in%20England,%20An%20economic%20case%20study%20(January%202017).pdf [Accessed 09 June2017]

Kostev, K.; Jockwig, A.; Hallwachs, A.; Rathmann, W(2014). “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 8(3): 250-255

Leese, GP., Reid F., Green V., et al. (2006) “Stratification of foot ulcer risk in patients with diabetes: a population-based study.” The International Journal of Clinical Practice 60(5): 541-545

Liatis, S., K. Marinou, N. Tentolouris, et al. (2007) "Usefulness of a new indicator test for the diagnosis of peripheral and autonomic neuropathy in

patients with diabetes mellitus." Diabetic Medicine 24(0742-3071 (Print)): 1375-1380

Low VA., Sandroni P., Fealey RD et al. “Detection of small-fiber neuropathy by sudomotor testing.” Muscle Nerve 34(1):57-61

Manes, C., N. Papanas, T. Exiara, et al. (2014) "The indicator test Neuropad in the assessment of small and overall nerve fibre dysfunction in patients with type 2 diabetes: a large multicentre study." Experimental & Clinical Endocrinology & Diabetes 122(3): 195-199

Marinou, K., S. Maggana, S. Liatis, et al. (2005) "Usefullness of the indicator plaster neuropad for the diagnosis of peripheral and autonomic neuropathy in patients with diabetes mellitus." Diabetologia 48(A360-A360

Martin, S. J., S. Bassi and R. Dunbar-Rees (2012) "Commitments, norms and custard creams - a social influence approach to reducing did not attends (DNAs)." Journal of the Royal Society of Medicine 105(3): 101-104

McCabe CJ, Stevenson RC, Dolan AM (1998). “Evaluation of a diabetic foot screening and protection programme”. Diabet Med.;15(1):80-4.

Mendivil, C. O., W. Kattah, A. Orduz, et al. (2016) "Neuropad for the detection of cardiovascular autonomic neuropathy in patients with type 2 diabetes." Journal of Diabetes and its Complications 30(1): 93-98

Mythili, A.; Kumar, K. D.; Subrahmanyam, K. A. V.; Venkateswarlu, K.; and Butchi, R. G(2010). “A comparative study of examination scores and quantitative sensory testing in diagnosis of diabetic polyneuropathy” Int J Diabetes Dev Ctries 30(1): 43-48

Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, Claxton K, Bell-Syer SE, Jude E, Dowson C, Gadsby R, O'Hare P, Powell J (2006). A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers. Health Technol Assess.10(12):iii-iv, ix-x, 1-221.

NICE (2011). Medical Technologies Evaluation Programme:Methods guide available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-medical-technologies/Medical-technologies-evaluation-programme-methods-guide.pdf [Accessed on 12 June 2017]

NICE (2015) . Costing report : Implementing the NICE guideline on diabetic foot problems(NG 19) available at https://www.nice.org.uk/guidance/ng19/resources/costing-report-pdf-544624525 [Accessed on 12 June 2017]

NICE (2016). Appendix J Health Economics : Diabetic foot problems: prevention and management NICE guideline [NG19] available at https://www.nice.org.uk/guidance/ng19/evidence/appendix-j-health-economics-pdf-15672915541 [Accessed on 13 June 2017]

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

Papanas, N., K. Papatheodorou, D. Papazoglou, et al. (2011) "A Prospective Study on the use of the Indicator Test Neuropad ® for the Early Diagnosis of Peripheral Neuropathy in type 2 Diabetes." Experimental and Clinical Endocrinology & Diabetes 119(02): 122-125

Ponirakis, G., I. N. Petropoulos, H. Fadavi, et al. (2014) "The diagnostic accuracy of Neuropad® for assessing large and small fibre diabetic neuropathy." Diabetic Medicine 31(12): 1673-1680

Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. “Diabetic Neuropathy: A Position Statement by the American Diabetes Association.” Diabetes Care. 2017;40(1):136-54).

Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, Jirkovska A, Piaggesi A, Ragnarson-Tennvall G, Reike H, Spraul M, Van Acker K, Van Baal J, Van Merode F, Ferreira I, Huijberts M(2008). “Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study”. Diabetologia. 51(5):747-55

Quattrini, C., M. Jeziorska, M. Tavakoli, et al. (2008) "The Neuropad test: A visual indicator test for human diabetic neuropathy." Diabetologia 51(6): 1046-1050

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

Sanz, I., Lazaro JL., Garcia AT et al. (2016) “Utility of sudomotor function test as a clinical tool in risk stratification system of diabetic patient” [unpublished transcript provided by author]

Spallone, V., R. Morganti, M. Siampli, et al. (2009) "Neuropad as a diagnostic tool for diabetic autonomic and sensorimotor neuropathy." Diabetic Medicine 26(7): 686-692

Sun, P. C., H. D. Lin, S. H. Jao, et al. (2008) "Thermoregulatory sudomotor dysfunction and diabetic neuropathy develop in parallel in at-risk feet." Diabetic Medicine 25(4): 413-418

Takwoingi Y (2016). “Meta-anlysis of test accuracy studies in Stata: a bivariate model approach.” Version 1.1 April 2016. Available from: http://methods.cochrane.org/sdt/.

Tavakoli, M., C. Quattrini, P. Begum, et al. (2010) "Neuropad and corneal confocal microscopy: New indicators for human diabetic neuropathy." Diabetologia 53(S443-S444

Tentolouris, N., V. Achtsidis, K. Marinou, et al. (2008) "Evaluation of the self-administered indicator plaster neuropad for the diagnosis of neuropathy in diabetes." Diabetes Care 31(2): 236-237

Tentolouris, N., N. Papanas, G. Panagoulias, et al. (2014) "The association between Neuropad testing with foot ulceration in diabetes." Diabetologia 1)(S471-S471)

Tentolouris, N., G. Panagoulias, N. Papanas et al. (2017) “The Neuropathy Disability Score and the Indicator Plaster Test Neuropad predict foot ulceration in diabetes” [unpublished transcript provided by author]

Tentolouris, N., C. Voulgari, S. Liatis, et al. (2010) "Moisture status of the skin of the feet assessed by the visual test neuropad correlates with foot ulceration in diabetes." Diabetes Care 33(5): 1112-1114

Tomešová, J., J. Gruberova, S. Lacigova, 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." Diabetes Technology & Therapeutics 15(11): 968-975

Tsapas, A., A. Liakos, P. Paschos, et al. (2014) "A simple plaster for screening for diabetic neuropathy: A diagnostic test accuracy systematic review and meta-analysis." Metabolism: Clinical and Experimental 63(4): 584-592

Whiting, P. F., A. W. S. Rutjes, M. E. Westwood, et al. (2011) "QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies." Ann Intern Med 155(8): 529-536

Yang, Z., Y. Zhang, R. Chen, et al. (2014) "Simple tests to screen for diabetic peripheral neuropathy." Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.:CD010975. DOI: 10.1002/14651858.CD010975.

Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH (1993). “A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population.” Diabetologia 36:150-154.

van Kollenburg, E.G.; Lavrijsen, J.C.; Verhagen, S.C.; Zuidema, S.U.; Schalkwijk, A; Vissers, K.C (2012). “Prevalence, causes and treatment of neuropathic pain in Dutch nursing home residents: a retrospective chart review” J Am Geriatr Soc 60(8): 1418-1425

Vas P., Sharma S “Distal Sensorimotor Neuropathy: Improvements in Diagnosis.” The Review of Diabetic Studies 12(1-2): 29–47

Willits, I., et al. (2015). "VibraTipTM for Testing Vibration Perception to Detect Diabetic Peripheral Neuropathy: A NICE Medical Technology Guidance." Applied Health Economics and Health Policy 13(4): 315-324

Zhang Y., Li J., Wang T et al. (2014) “Amplitude of sensory nerve action potential in early stage diabetic peripheral neuropathy: an analysis of 500 cases”. Neural Regeneration Research 9(14):1389-94

Ziegler, D., N. Papanas, W. Rathmann, et al. (2012) "Evaluation of the Neuropad sudomotor function test as a screening tool for polyneuropathy in the elderly population with diabetes and pre-diabetes: The KORA F4 survey." Diabetes/Metabolism Research and Reviews 28(8): 692-697

Ziegler, D., N. Papanas and M. Roden (2011) "Neuropad: Evaluation of three cut-off points of sudomotor dysfunction for early detection of polyneuropathy in recently diagnosed diabetes." Diabetic Medicine 28(11): 1412-1415

Appendices

- Appendix A: EAC clinical and economic evidence search strategies
- Appendix B: Data table
- Appendix C: EAC economic data evidence search strategy
- Appendix D: QUADAS-2 tool signalling questions
- Appendix E – Results of sensitivity analysis

Appendix A: EAC clinical and economic evidence search strategies

EAC Search strategies

Search date: 26-April-2017

- Embase 1974 to 2017 Week 17

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Global Health 1973 to 2017 Week 15
- HMIC Health Management Information Consortium 1979 to January 2017

1	exp Diabetes Mellitus/	759565
2	(diabet* or pre-diabet*).tw,hw,kw,ot.	897336
3	1 or 2	901684
4	exp Peripheral Nervous System Diseases/	59406
5	(peripheral nerv* adj5 (diseas* or disorder*)).tw,hw,kw,ot.	5776
6	exp Polyneuropathies/	33433
7	polyneuropath*.tw,hw,kw,ot.	25534
8	or/4-7	95884
9	3 and 8	27020
10	exp Diabetic Neuropathies/	20268
11	(diabet* and (neuropath* or nervous system disease* or polyneuropath* or lesion* or ulcer* or patholog* or ((fibre or fiber or sudomotor) adj (dysfunction or disfuntion))) and (foot or feet or extremit* or peripher*)).tw,hw,kw,ot.	32482
12	10 or 11	43814
13	9 or 12	45452
14	(quantitative sensory test* or tactile circumferential discriminator).tw,hw,kw,ot.	2386
15	(biothesiometer or neurothesiometer or maxivibrometer or vibrameter or vibratron or Case IV system).tw,hw,kw,ot.	299
16	((light touch or vibration) adj3 perception*).tw,hw,kw,ot.	995
17	(nerve conduction adj3 (test* or examination* or stud*)).tw,hw,kw,ot.	8451
18	tuning fork*.tw,hw,kw,ot.	640
19	(quantitative sensory adj5 test*).tw,hw,kw,ot.	2421
20	((vibration* or perception*) adj3 threshold*).tw,hw,kw,ot.	3530

21	((objective or simple) adj test*).tw,hw,kw,ot.	6643
22	(monofilament* or vibration perception* or ankle reflex*).tw,hw,kw,ot.	4885
23	nerve conduction velocit*.tw,hw,kw,ot.	6843
24	(vibration adj3 test*).tw,hw,kw,ot.	589
25	(SWMT or VPT or QST or TCD).tw,hw,kw,ot.	8455
26	((latency or velocity or amplitude) adj3 diagnos*).tw,hw,kw,ot.	605
27	((large fiber or large fibre) adj6 (function* or disfunction* or dysfunction* or impairment*)).tw,hw,kw,ot.	112
28	((Semmes-Weinstein monofilament or steel ball-bearing or two-point discriminator) adj6 test*).tw,hw,kw,ot.	253
29	((steel adj3 (ball-bearing or ball bearing)) and test*).tw,hw,kw,ot.	7
30	((sensor* or neuro*) adj3 (test* or devic*)).tw,hw,kw,ot.	88619
31	(vibrat* adj3 (perception* or measure* or sensation*)).tw,hw,kw,ot.	3396
32	vibratometry.tw,hw,kw,ot.	6
33	(vibrotactile adj3 measurement*).tw,hw,kw,ot.	30
34	(nylon adj3 filament*).tw,hw,kw,ot.	120
35	(Frey* or neuropen or ipswich touch test* or IpTT).tw,hw,kw,ot.	5562
36	(tactile adj3 (perception or threshold* or sensation*)).tw,hw,kw,ot.	2338
37	(pressure adj3 (sensation* or perception*)).tw,hw,kw,ot.	1258
38	(tendon adj3 reflex*).tw,hw,kw,ot.	7471
39	(ankle jerk or Achilles tendon reflex*).tw,hw,kw,ot.	571
40	(exp ankle/ or exp achilles tendon/) and exp reflex/	1503
41	sudomotor function.tw,hw,kw,ot.	370
42	sweat gland.tw,hw,kw,ot.	10016
43	sweat produc*.tw,hw,kw,ot.	370

44	sweat respon*.tw,hw,kw,ot.	176
45	(colo?r and plaster).tw,hw,kw,ot.	73
46	(nerv* adj3 (funtion* or disfunction* or dysfunction* or impairment* or integrity or assess*)).tw,hw,kw,ot.	13798
47	Vibratip.tw,hw,kw,ot.	12
48	Neurotip.tw,hw,kw,ot.	10
49	NeuroPen.tw,hw,kw,ot.	15
50	Neuropathy Disability Score.tw,hw,kw,ot.	275
51	(early adj3 (identi* or detect*)).tw,hw,kw,ot.	127073
52	(nerv* adj3 dens* adj3 biops*).tw,hw,kw,ot.	103
53	(sudomotor axon adj3 test*).tw,hw,kw,ot.	255
54	QSART.tw,hw,kw,ot.	212
55	corneal confocal microscopy.tw,hw,kw,ot.	363
56	(nc-stat or DPNcheck* or DPN-check*).tw,hw,kw,ot.	41
57	sudoscan.tw,hw,kw,ot.	100
58	or/14-57	288419
59	13 and 58	5751
60	(neuropad or neuropadtm).mp.	75
61	TRIGOcare.af.	6
62	60 or 61	75
63	59 or 62	5767
64	limit 63 to yr="2003 -Current"	4047
	Re-run in Medline	2179
	Re-run in Global Health	235
	Re-run in HMIC	2

Search date: 26-April-2017

- Cochrane Libraries

ID	Search	Hits
#1	[mh "Diabetes Mellitus"]	20233
#2	diabet* or pre-diabet*	55085
#3	#1 or #2	55154
#4	[mh "Peripheral Nervous System Diseases"]	3626
#5	peripheral nerv* near/5 (diseas* or disorder*)	1062
#6	[mh Polyneuropathies]	310
#7	polyneuropath*	764
#8	{or #4-#7}	4550
#9	#3 and #8	1303
#10	[mh "Diabetic Neuropathies"]	1345
#11	diabet* and (neuropath* or nervous system disease* or polyneuropath* or lesion* or ulcer* or patholog* or ((fibre or fiber or sudomotor) next (dysfunction or disfuntion))) and (foot or feet or extremit* or peripher*)	3751
#12	#10 or #11	4197
#13	#9 or #12	4324
#14	quantitative sensory test* or tactile circumferential discriminator	666
#15	biothesiometer or neurothesiometer or maxivibrometer or vibrameter or vibratron or Case IV system	3570
#16	(light touch or vibration) near/3 perception*	141
#17	nerve conduction near/3 (test* or examination* or stud*)	440
#18	tuning fork*	45
#19	quantitative sensory near/5 test*	343
#20	(vibration* or perception*) near/3 threshold*	624
#21	(objective or simple) next test*	559
#22	monofilament* or vibration perception* or ankle reflex*	852
#23	nerve conduction velocit*	517
#24	vibration near/3 test*	71
#25	SWMT or VPT or QST or TCD	711
#26	(latency or velocity or amplitude) near/3 diagnos*	68
#27	(large fiber or large fibre) near/6 (function* or disfunction* or dysfunction* or impairment*)	13
#28	(Semmes-Weinstein monofilament or steel ball-bearing or two-point discriminator) near/6 test*	40
#29	(steel near/3 (ball-bearing or ball bearing)) and test*	1
#30	(sensor* or neuro*) near/3 (test* or devic*)	9183
#31	vibrat* near/3 (perception* or measure* or sensation*)	259
#32	vibratometry	1
#33	vibrotactile near/3 measurement*	1

#34	nylon near/3 filament*	14
#35	Frey* or neuropen or ipswich touch test* or IpTT	1340
#36	tactile near/3 (perception or threshold* or sensation*)	138
#37	pressure near/3 (sensation* or perception*)	265
#38	tendon near/3 reflex*	187
#39	ankle jerk or Achilles tendon reflex*	67
#40	([mh Ankle] or [mh "Achilles Tendon"]) and [mh Reflex]	37
#41	sudomotor function	37
#42	sweat gland	154
#43	sweat produc*	304
#44	sweat respon*	486
#45	colour and plaster	22
#46	nerv* near/3 (funtion* or disfunction* or dysfunction* or impairment* or integrity or assess*)	1205
#47	Vibratip	3
#48	Neurotip	6
#49	NeuroPen	5
#50	Neuropathy Disability Score	368
#51	early near/3 (identi* or detect*)	4344
#52	nerv* near/3 dens* near/3 biops*	3
#53	sudomotor axon	14
#54	QSART	8
#55	corneal confocal microscopy	162
#56	nc-stat or DPNcheck* or DPN-check*	4
#57	sudoscan	2
#58	{or #14-#57}	23030
#59	#13 and #58	1201
#60	neuropad or neuropadtm or TRIGOcare	1
#61	#59 or #60 Publication Year from 2003	1032

Search date: 27-April-2017

- PubMed

Search	Query	Items found
#65	Search ((#13 and #61)) OR #62 Filters: Publication date from 2003/01/01	2492
#64	Search ((#13 and #61)) OR #62	4575
#62	Search ((neuropad or neuropadtm)) OR TRIGOcare	41
#61	Search (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #27 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60)	134073

#60	Search sudoscan*	34
#59	Search ("nc-stat" or DPNcheck* or DPN-check*)	24
#58	Search "corneal confocal microscopy"	236
#57	Search "QSART"	89
#56	Search "sudomotor axon"	150
#55	Search nerve fiber density biopsy	3114
#54	Search ("early identification") OR "early detection"	72546
#53	Search ("Vibratip" or "Neurotip" or "Neuropen" or "Neuropathy Disability Score")	167
#52	Search ("nerve dysfunction") OR "nerve assessment"	2073
#50	Search (color) AND plaster	51
#49	Search "sweat response"	97
#48	Search "sweat production"	264
#47	Search "sudomotor function"	215
#46	Search ((Ankle[Mesh Terms]) OR Achilles Tendon[Mesh Terms]) AND Reflex[Mesh Terms]	1119
#45	Search "ankle jerk"	122
#44	Search "tendon reflex"	620
#43	Search (("pressure sensation") or ("pressure threshold"))	924
#42	Search (("tactile threshold") OR ("tactile perception") OR ("tactile measure") OR "tactile sensation")	1946
#41	Search ((neuropen) or ("ipswich touch test") or (IpTT))	31
#38	Search nylon filament*	84
#37	Search "vibrotactile measurement"	99
#36	Search vibratometry	4
#35	Search (("vibration perception") OR "vibration measure") OR "vibration sensation"	2645
#34	Search ("sensory test") OR "neurop* test*"	18297
#33	Search "two-point discriminator test"	5
#32	Search "steel ball-bearing"	13
#31	Search "Semmes-Weinstein monofilament"	313
#30	Search large fibre dysfunction	364
#27	Search ("SWMT" or "VPT" or "QST" or "TCD")	8357
#25	Search vibration test*	162
#24	Search nerve conduction velocit*	4826
#23	Search (monofilament* or vibration perception* or ankle reflex*)	3504
#22	Search ("objective test*" or "simple test*")	2844
#21	Search ("vibration threshold" or "perception threshold")	1250
#20	Search "quantitative sensory test*"	47
#19	Search "sweat gland*"	5646
#18	Search "tuning fork*"	548
#17	Search (("nerve conduction test") OR "nerve conduction exam*") OR "nerve conduction study"	8637
#16	Search ("light touch perception") OR "vibration perception"	609

#15	Search ("biothesiometer" or "neurothesiometer" or "maxivibrometer" or "vibrameter" or "vibratron" or "Case IV system")	177
#14	Search ("quantitative sensory test") OR "tactile circumferential discriminator"	53
#13	Search (#9 or #12)	21947
#12	Search (#10 or #11)	19498
#11	Search (diabetic neuropathies) AND feet	8466
#10	Search Diabetic Neuropathies[Mesh Terms]	19462
#9	Search (#3 and #8)	15786
#8	Search (#4 or #5 or #6 or #7)	145240
#7	Search peripheral nerve disorders	141520
#6	Search polyneuropath*	14984
#5	Search Polyneuropathies[Mesh Terms]	24412
#4	Search Peripheral Nervous System Diseases[Mesh Terms]	131114
#3	Search (#1 or #2)	583663
#2	Search diabetes	583663
#1	Search Diabetes Mellitus[Mesh Terms]	360812

Search date: 27-April-2017

- Web of Science

Set	**Results**	
# 40	1,814	#39 OR #38 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2003-2017
# 39	57	TS=((neuropad or neuropadtm) OR TRIGOcare) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 38	2,639	#37 AND #7 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 37	117,490	#36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017

# 36	59,678	TS=("sudomotor axon" or "QSART" or "corneal confocal microscopy" or "nc-stat" or DPNcheck* or DPN-check* or sudoscan) OR TS=(nerve fiber density biopsy) OR TS=(("early identification") OR "early detection") OR TS=("Vibratip" or "Neurotip" or "Neuropen" or "Neuropathy Disability Score") OR TS=(("nerve dysfunction") OR "nerve assessment") OR TS=((color OR colour) AND plaster*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 35	571	TS=("sudomotor function" or "sweat production" or "sweat response") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 34	2,326	TS=(((ankle) OR (achilles tendon)) AND (reflex)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 33	513	TS=("tendon reflex" or "ankle jerk") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 32	1,030	TS=(("pressure sensation") or ("pressure threshold")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 31	1,915	TS=(("tactile threshold") OR ("tactile perception") OR ("tactile measure") OR "tactile sensation") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 30	47	TS=((neuropen) or ("ipswich touch test") or (IpTT)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 29	450	TS=(nylon filament*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 28	2	TS=("vibrotactile measurement") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 27	10	TS=(vibratometry)

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 26	753	TS=((("vibration perception") OR "vibration measure") OR "vibration sensation") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 25	16,264	TS=(("sensory test") OR "neurop* test*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 24	5	TS=(two-point discriminator test) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 23	49	TS=("steel ball-bearing") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 22	306	TS=("Semmes-Weinstein monofilament") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 21	22	TS=("large fibre dysfunction" OR "large fiber dysfunction") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 20	6,103	TS=("SWMT" or "VPT" or "QST" or "TCD") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 19	4,143	TS=("vibration test*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 18	3,874	TS=("nerve conduction velocit*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 17	4,234	TS=(monofilament* or"ankle reflex*")

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 16	7,755	TS=("objective test*" or "simple test*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 15	1,325	TS=("vibration threshold" or "perception threshold") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 14	1,602	TS=("quantitative sensory test*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 13	4,611	TS=("sweat gland*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 12	1,920	TS=("tuning fork") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 11	994	TS=(("nerve conduction test") OR ("nerve conduction exam*") OR ("nerve conduction study")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 10	614	TS=(("light touch perception*") or ("vibration perception*")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 9	159	TS=(biothesiometer or neurothesiometer or maxivibrometer or vibrameter or vibratron or "Case IV system") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 8	2,970	TS=(quantitative sensory test* or tactile circumferential discriminator) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 7	20,341	#6 OR #5

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 6	18,943	TS=((diabet*) AND (neuropath* OR nervous system disease* OR polyneuropath* OR lesion* OR ulcer* OR patholog*) AND (feet or foot or peripher* or extremit*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 5	4,403	#1 AND (#2 or #3 or #4) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 4	4,993	TS=(peripheral nerve disorder*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 3	15,830	TS=(polyneuropath*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 2	12,122	TS=(Peripheral Nervous System Diseas*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 1	598,081	TS=(diabet*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017

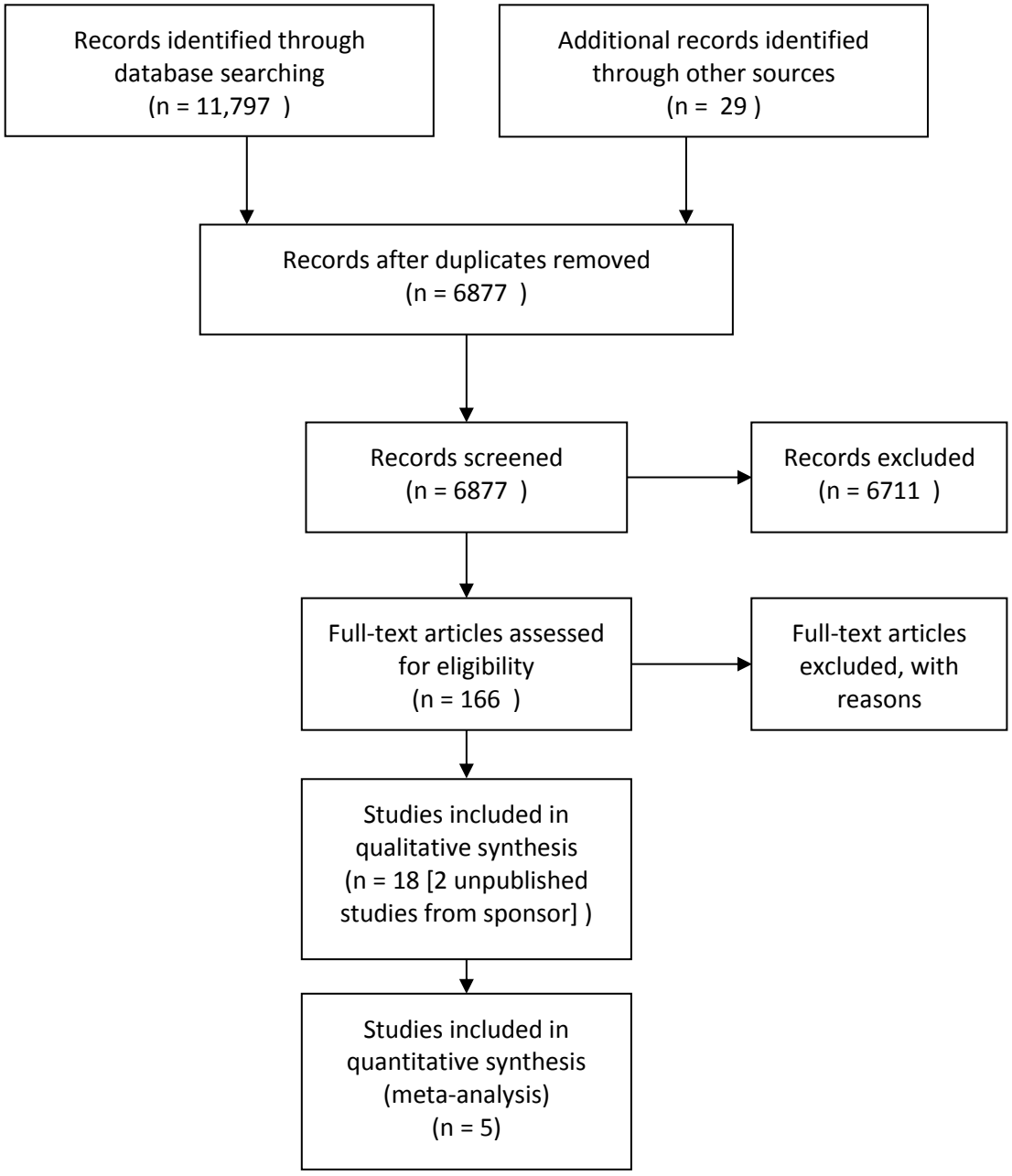
Search date: 27-April-2017

- Grey literature – all searched (“neuropad” OR “neuropadtm”)

American Diabetes Association (http://professional.diabetes.org/CONTENT/PREVIOUS-SCIENTIFIC-SESSIONS-ABSTRACTS-POSTERS-AND-WEBCASTS)	6
Diabetic Foot Study Group (http://dfsg.org/) Google search string: neuropad site:dfsg.org	15
www.greylit.org/	0
www.opengrey.eu/	0

http://oaister.worldcat.org/	6
ntrl.ntis.gov/NTRL/	1
http://webarchive.nationalarchives.gov.uk/adv_search/	1

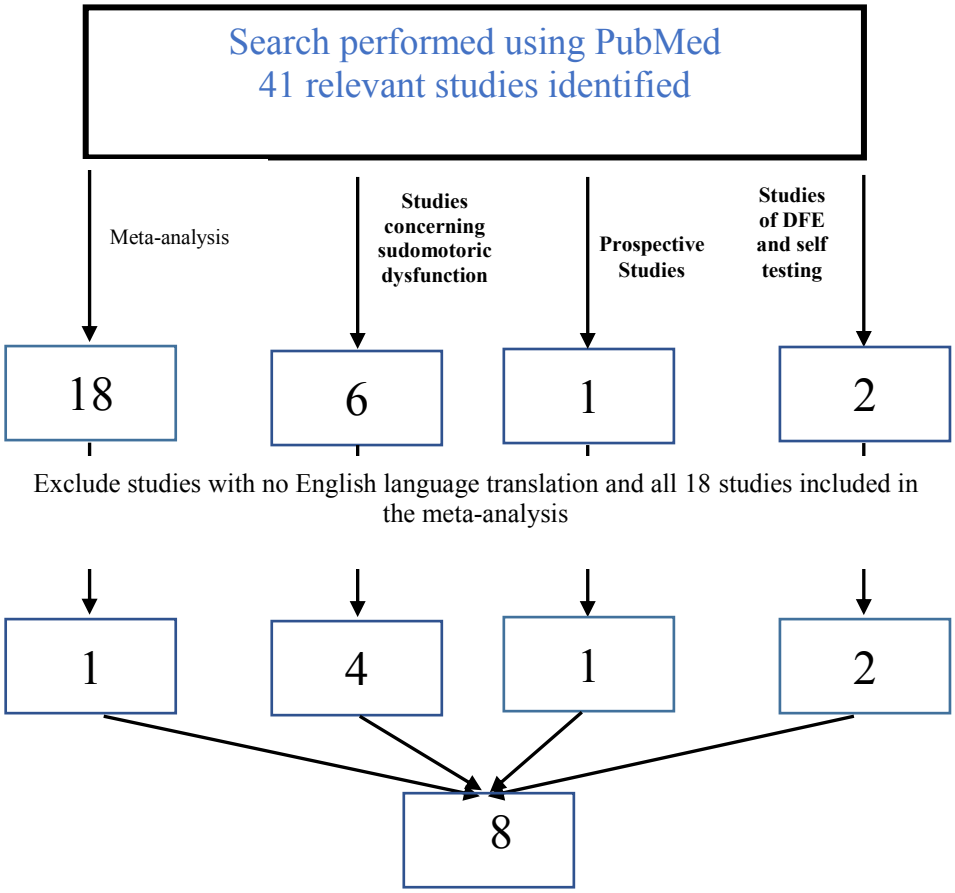
EAC PRISMA 2009 Flow Diagram



Sponsor search strategy

Set#	Searched for	Results
S1	neuropad	193°

Sponsor PRISMA flow diagram



Appendix B: Data table

Study	Abstract or fulltext	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Results	Usefulness to decision problem

Aubert et al. 2013	**Fulltext**	Single-centre prospective, France	200 people with DM (160 male, mean 66/63 yrs (with/without peripheral arterial occlusive disease), diabetes duration 16/12 yrs	Neuropad (10 minutes socks off, measured at room temp after 10 & 20 minutes) vs. monofilament. NDS =>6 (reference test)	Sensitivity and Specificity	Neuropad 10 min, sensitivity and NPV 93.8 and 95.1%; specificity and PPV 23.2 and 18.9%. Monofilament sensitivity and NPV 68.8 and 94.1%; specificity and PPV 94.1 and 68.8%.	High. Neuropad significantly better sensitivity ($p<0.04$) and significantly worse specificity ($p<0.0001$) compared to monofilament.

Didangelos 2006	**Abstract**	Unclear	174 patients (79 type 1 DM, 88 women), mean age 49.8 and mean duration of DM = 17.3 yrs	Neuropad vs. MNSIQ (michigan neuropathy screenin instrument), MNSIE, Biothesiometer, monofilament (reference tests, separately)	Sensitivity and Specificity	Against MNSIQ: Sensitivity = 78% Specificity = 92% Against MNSIE: Sensitivity = 73% Specificity = 90% Against biothesiometer: Sensitivity = 73% Specificity = 81% Against Monofilament Sensitivity = 95% Specificity = 69%	Medium. Abstract only.

Forth (2010) [Abstract] Not included by sponsor	**Abstract**	Prospective cohort, UK study, site unclear	66 subjects (non-diabetic controls: n=18, age: 53.5 ±11.6 years; diabetic subjects without neuropathy: n=19, age: 59.4±9.2; diabetic subjects with painless DPN: n=18, age: 62.2±8.9; and diabetic patients with painful DPN; n=11, age: 61.7 ±10.2 years)	Neuropad measured after 10 minutes. NDS =>3 or =>6 (reference test)	Sensitivity and specificity, PPV, NPV	Using a cut-off NDS value =>3 was as follows: sensitivity: 79.3%; specificity: 63.2%; positive predictive value: 69.4%; and negative predictive value: 84.3%. The performance of the test Neuropad for the diagnosis of DPN using a cut-off NDS value =>6 was as follows: sensitivity: 91.3%; specificity 66.7%; positive predictive value: 58.3%; and negative predictive value: 93.7%.	Medium. Abstract only.

Freitas et al. 2009	**Fulltext**	Single Centre Prospective, Portugal	40 people with diabetes (22 NDS confirmed: 15 men, mean age 57.9, diabetes duration 15.4 yrs. 18 not-NDS confirmed: 10 men, mean age 63.6 and DD 11.8 yrs)	Neuropad (socks off 5 minutes, measured after 10 minutes) vs. monofilament. NDS =>6 (reference test)	Sensitivity and Specificity	Under Semmes-Weinstein monofilament test, sensitivity and specificity was 100% and 38%, respectively, and with the Neuropad® test, a specificity of 44%, but a sensitivity of 100%.	High
Kamenov (2010) Not included by sponsor	**Fulltext**	Prospective cohort One hospital Bulgaria	264 inpatients (M/F=126/138) with DM type 1/2 (61/203), mean age 55.4+/-12.0 and DM duration of 9.3+/-7.1 years	Neuropad measured after 10 minutes. NDS=>3/NDS=>6 (reference test)	Sensitivity and specificity, PPV, NPV	Neuropad against NDS=>3/NDS=>6: sensitivity=76.3/79.3, specificity=56.1/42.9, PPV=86.3/62.8 and NPV=39.5/63.0 predictive values, and diagnostic accuracy 72.2/62.9%	Medium, no comparator.

Liatis (2007) Fulltext Not included by sponsor	**Fulltext**	Prospective cohort One hospital in Greece	117 consecutive diabetic individuals recruited from the diabetes outpatient clinic. Mean age 61.4, (9 type 1, 108 type2), mean diabetes duration 10.9 yrs	Neuropad (socks off 10 minutes, measured at room temp after 10 minutes). NSS, NDS, VPT (reference tests)	Sensitivity and specificity, PPV, NPV	Of the 50 patients with PSN, 43 had a positive NIT (sensitivity 86%) and, out of the 67 patients without PSN, a negative NIT was obtained in 45 patients (specificity 67%). The positive and the negative predictive value of the NIT in detecting PSN were 66.2 and 86.5%, respectively	High Relevant outcome, well described methdology. Overall gender split not mentioned.
Manes (2014) [Fulltext] Not included by sponsor	**Abstract**	Prospective cohort (Unclear) Five diabetes centres in Greece	The study included 1010 type 2 diabetic patients randomly recuited 608 males (60.19%). Mean age and diabetes duration were	Clinical examination and symptoms - not specified	Sensitivity and specificity, NPV of Neuropad for overall nerve fibre dysfunction and for small fibre nerve dysfunction	For overall nerve fibre dysfunction, abnormal Neuropad defined as patchy/blue had 94.9% sensitivity, 70.2% specificity and 98.1% negative predictive value (NPV), while for small fibre dysfunction the	Medium Discusses the accuracy of Neuropad against a reference standard. However, this was only an abstract.

			63.90±10.26 and 12.24±7.75 (yrs)			corresponding values were 85.6%, 71.2% and 93.3%. For overall nerve fibre dysfunction, abnormal Neuropad defined as blue had 64% sensitivity, 96% specificity and 91% NPV, while for small fibre dysfunction the corresponding values were 52%, 96% and 85%. The odds ratios (ORs) of Neuropad patchy/blue for overall and for small fibre dysfunction were 43.7 and 14.7, respectively. The ORs of Neuropad blue for overall and for small fibre dysfunction were 45.7 and 24.9, respectively.	

Marinou (2005) [Abstract only] Not included by sponsor	**Abstract**	Prospective cohort? One hospital in Greece	116 patients (64 men and 52 women, mean age 61.6 years) with DM (9 with type 1 and 107 with type 2 diabetes) of at least 5 years duration. Randomly recruited	Neuropathy symptoms score (NSS), the neuropathy disability score (NDS) and the vibration sensitivity threshold (presumably combined)	Sensitivity and specificity, PPV, NPV	PN was documented in 50 out of 116 patients (43.1%). The sensitivity of Neuropad in diagnosing PN was found 86% (43/50 patients) while itsspecificity was 68.2% (45/66 patients). Positive predictive value was 67.2% (43/64 patients) and negative predictive value was 86.5% (45/52 patients).	Medium Discusses the accuracy of Neuropad against a reference standard. However, this was only an abstract. How the reference standard was applied is unclear.

Mendivil (2016) Fulltext Not included by sponsor	**Fulltext**	Prospective cohort One hospital Colombia	The study sample comprised 154 participants, with a good balance between sexes (51.9% women). Mean age was 61.4 years and mean diabetes duration 12.2 years. P	PSN was diagnosed when at least 2 of 3 tests were abnormal (NDS > or = 3, NSS and VPT)	Sensitivity and specificity, NPV of Neuropad	Sensitivity = 74.6% Specificity = 36.1% PPV = 48.5% NPV = 63.8%	Medium The aim was to test for the presence of Cardiac Autonomic Neuropathy (CAN). Study procedures described in detail.
Papanas et al. 2011	**Fulltext**	Single Centre Prospective, Greece	109 T2DM (55 men)	Neuropad, NDS ≥ 6	Sensitivity and Specificity	Neuropad had 83.33% sensitivity and 68.04% specificity for neuropathy	Medium

Ponirakis et al .2014	**Fulltext**	Single-centre Prospective cohort, UK	127 adults (68 with Type 1 diabetes and 59 with Type 2 diabetes) with an average age of 57 +/- 10 years.	Neuropad Large nerve fibre assessments: Neuropathy Disability Score, vibration perception threshold, peroneal motor nerve conduction velocity; Small nerve fibre assessments: neuropathy symptoms (Diabetic Neuropathy Symptoms score) corneal nerve fibre length and warm perception threshold.	Sensitivity and Specificity	Against large fibre tests: NDS (>2) Sensitivity: 70% Specificity: 50% PPV, NPV (%): 63, 57 VPT (>2) Sensitivity: 83% Specificity: 53% PPV, NPV (%): 45, 39 Sural nerve action potential (<3 uV) Sensitivity: 70% Specificity: 64% PPV, NPV (%): 26, 92 Sural nerve conduction velocity (<43 m/s) Sensitivity: 64% Specificity: 54% PPV, NPV (%): 45, 72 Peroneal motor nerve action potential (<2 mV) Sensitivity: 82% Specificity: 50%	High, prospective UK study evaluating Neuropad against a number of reference standards (large and small fibre tests). Relevant outcomes.

						PPV, NPV (%): 31, 91 Peroneal motor nerve conduction velocity (<42 m/s) Sensitivity: 81% Specificity: 54% PPV, NPV (%): 59, 78 Against small fibre tests: Warm perception threshold (>43°C) Sensitivity: 68% Specificity: 49% PPV, NPV (%): 26, 44 Corneal nerve fibre density (<24 n/mm2) Sensitivity: 74% Specificity: 60% PPV, NPV (%): 54, 78 Corneal nerve fibre length (<14 mm/mm2) Sensitivity: 83% Specificity: 80% PPV, NPV (%): 49, 95	

						Neuropathy symptoms: DNS score Sensitivity: 78% Specificity: 60% PPV, NPV (%): 34, 91	

Quattrini (2008) Fulltext Included by sponsor	**Fulltext**	Prospective cohort UK study, site unclear	Fifty-seven diabetic patients (20 type 1 and 37 type 2) aged 56±1.4	NDS (>5/10) quantitative sensory assessment - HP-VAS, CDT,DB-HRV symptoms scored by DNS and McGIll's pain questionnaire	Sensitivity and specificity compared to NDS. Correlation with comparators.	The sensitivity of an abnormal Neuropad response in detecting clinical neuropathy (neuropathy disability score ≥5) was 85% (negative predictive value 71%) and the specificity was 45% (positive predictive value 69%).	High No breakdown of population given. Uk study.
Spallone (2009) Not included by sponsor	**Fulltext**	Prospective cohort Rome, one diabetic clinic, Italy	51 diabetic patients (29 males) Age was 44.9 ± 13.7 years (mean ± sd), diabetes duration 14.7 ± 10.7 years	Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q) and the Diabetic Neuropathy Score (DNS). Vibration perception threshold (VPT) was measured using the Biothesiometer . Cold (CTT) and warm thermal perception (WTT) DNI (> 2) - Definition	Time until the complete colour change(CCCtime) Sensitivity, specitivity, PPV, NPV per time group (10, 15 and 20 mins)	For 10 mins Sensitivity = 85% Specificity = 32% PPV = 45% NPV = 77%	Medium/High Questionable CCC outcome measure (however, does provide accuracy for 10 mins), but interesting conclusion. Comparator is not clear.

				of DPN required the presence of at least two abnormalities among symptoms, deficits, VPT and CTT and⁄or WTT.			
Tavakoli et al. 2010 (abstract only)	**Abstract**	Unclear	100 diabetics (Type I/II: 61/39)	Neuropad, CCM, NDS, VPT (no detail on thresholds)	correlation of results of tests	The Neuropad response correlated with NDS (rs=0.456, p= 0.000), VPT (rs= 0.330, p=0.000), NFD (rs=- 0.365, p=0.000), NBD (rs=-0.377, p=0.000), and NFL (rs=-0.395, p=0.000). Conclusion: Neuropad therefore detects mild neuropathy whilst CCM detects nerve damage at the very earliest stage. As	Low

						both tests are non-invasive they offer considerable potential as screening tools.	
Tentolouris 2008	**Fulltext**	Single centre prospective	156 diabetic adults	neuropa-thy symptom score and the neuropathy disability score (no detail on thresholds)	Sensitivity and specificity Reliability and reproducibility	Sensitivity 0.87 (95% CI 0.81– 0.92), specificity 0.66 (0.58–0.73), positive predictive value 0.94 (0.90–0.97), and negative predictive value 0.79 (0.72–0.85). The k statistic to measure overall agreement between patient and health care provider of the Neuropad was very good: 0.88 (95% CI 0.85–0.91).	High

Tentolouris et al. 2010	**Fulltext**	Prospective, Greece	379 diabetics	Neuropad, VPT, monofilament, NDS (=>6 - severe NP), NSS (Assessment for peripheral neuropathy was based on symptoms (neuropathysymptom score [NSS]) and signs (neuropathy disability score [NDS])	Sensitivity and Specificity	Neuropad result (abnormal vs. normal) was 0.71 +/- 0.03 (P > 0.001; sensitivity 97.1%; specificity 49.3%) monofilament result (insensation vs. sensation) was 0.72 +/- 0.03 (P > 0.001; sensitivity 57.4%; specificity 86.3%)	Medium
Tentolouris et al. 2014 (abstract only)	**Abstract**	Multicentre Prospective, Greece	308 diabetics (155 females and 153 males; 280 with type 2 diabetes; mean age 62.8 +/- 11.3 years; mean diabetes duration 12.4 +/- 9.7 years)	Neuropad, NDS NDS 0-2 were considered as having no neuropathy, those with NDS 3-5 as having mild neuropathy and those with NDS >6 as having severe neuropathy	probability of abnormal neuropad and symptoms	Neuropad testing at baseline was associated with increased odds (OR, 95% confidence intervals) for foot ulceration [4.2 (1.8-9.8)]. Similarly, the adjusted OR of NDS>6 vs. NDS<6 for foot ulceration was 8.5 (3.3-21.7). The OR for foot ulceration was not increased	Medium

						significantly (p=0.09) in those having mild neuropathy (NDS 3-5) vs. those having no neuropathy.	
Ziegler et al. 2011	**Fulltext**	Single Centre Prospective, Germany	52 T1DM and 99 T2DM	Neuropad, NDS,(>2) or (1<) abnormal quantitative sensory testing parameter	Time, Sensitivity and Specificity	Sensitivity of Neuropad for the diagnosis of distal symmetric polyneuropathy and small-fibre dysfunction was highest in Type 1 diabetes for the 10-min threshold reaching 87.5 and 80.0%, respectively, while it was modestly high in Type 2 diabetes at 65.1 and 67.7%, respectively. Specificity in both diabetes types was modest for the 10-min threshold (44.7-	Low

						48.2%). It was highest for the 20-min threshold (83.8-89.3%) at the cost of poor sensitivity at 12.5-34.9%. Negative predictive values were relatively high for all three cut-off points in both types of diabetes (64.1-97.1%) at the cost of poor positive predictive values at 12.5-71.4%.	
Ziegler et al. 2012	**Fulltext**	Single Centre Prospective, Germany, follow up on the KORA S4 study	201 diabetes, 231 prediabetes, 486 healthy controls	Neuropad, MNSI (>3), monofilament (MNSI-MF)	Sensitivity and Specificity	Against MF: Sensitivity = 75.0% Specificity = 32.6% Against MNSI (>3) Sensitivity = 76.7% Specificity = 35.5%	Medium, Might not be relevant if prediabetes is not in the scope

Appendix C: EAC economic data evidence search strategy

Diabetic Foot (Medline, Embase and Cochrane Libraries)

1	"Prevention of diabetes-related foot ulcers and amputations: a cost-utility analysis based on Markov model simulations".ti.	1
2	*diabetic foot/	6318
3	markov chains/	12151
4	transition prob*.tw.	2443
5	Cost-Benefit Analysis/	71407
6	or/3-5	82539
7	2 and 6	99
8	1 or 7	99

Peripheral Neuropathy (Medline, Embase and Cochrane Libraries)

1	exp Diabetes Mellitus/	376357
2	(diabet* or pre-diabet*).tw,hw,kw,ot.	592590
3	1 or 2	594308
4	exp Peripheral Nervous System Diseases/	134626
5	(peripheral nerv* adj5 (diseas* or disorder*)).tw,hw,kw,ot.	24166
6	exp Polyneuropathies/	25076
7	polyneuropath*.tw,hw,kw,ot.	15278
8	or/4-7	140161
9	3 and 8	16439
10	exp Diabetic Neuropathies/	20209
11	(diabet* and (neuropath* or nervous system disease* or polyneuropath* or lesion* or ulcer* or patholog* or ((fibre or fiber or sudomotor) adj (dysfunction or disfuntion))) and (foot or feet or extremit* or peripher*)).tw,hw,kw,ot.	18758
12	10 or 11	29032
13	9 or 12	30419
14	markov chains/	12198
15	transition prob*.tw.	2450
16	Cost-Benefit Analysis/	71614
17	or/14-16	82780

18	13 and 17	178

Appendix D: QUADAS-2 tool signalling questions

Domain 1 - Patient Selection	
Describe the patient sampling:	
1. Was a consecutive or random sample enrolled?	Yes/No/No Information
2. Was a case-control design avoided?	Y/N/NI
3. Did the study avoid inappropriate exclusions?	Y/N/NI
Risk of bias: Could the selection of patients have introduced bias?	Low/High/Unclear
Applicability: Are there concerns that the included patients and setting do not match the review question?	Low/High/Unclear
Domain 2 – Index Test	
List the index tests:	
1. Were the index test results interpreted without knowledge of the results of the reference standard?	Y/N/NI
2. If a threshold was used, was it pre-specified?	Y/N/NI

3. (If multiple index tests are being compared), were the results of the index test interpreted without knowledge of other index test results?	Y/N/NI
Risk of bias: Could the conduct or interpretation of the index test have introduced bias?	Low/High/Unclear
Applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low/High/Unclear
Domain 3 – Reference standard	
Target condition and reference standard(s):	
1. Is the reference standards likely to correctly classify the target condition?	Y/N/NI
2. Were the reference standard results interpreted without knowledge of the results of the index tests?	Y/N/NI
Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias?	Low/High/Unclear
Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question?	Low/High/Unclear
Domain 4 – Flow and Timing	
Detail the flow and timing of the study:	
1. Did all patients receive the same reference standard?	Y/N/NI

2. Were all patients included in the analysis?	Y/N/NI
3. Was there an appropriate interval between index test and reference standard? (6 months or less)	Y/N/NI
Risk of bias: Could the patient flow have introduced bias?	Low/High/Unclear

Appendix E – Results of sensitivity analysis

Sensitivity Analysis DPN Prevalence

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	0.019	0.03	0.019	0.03
Neuropad	£3,867	£3,924		
10g Monofilament	£3,089	£3,153	£779	£770
Neuropad + 10g Monofilament	£2,787	£2,855	£1,080	£1,068
No Testing	£2,078	£2,128	£1,789	£1,795

Sensitivity Analysis Sensitivity Neuropad

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	0.83	0.93	0.83	0.93
Neuropad	£3,889	£3,895		
10g Monofilament	£3,118	£3,118	£770	£777
Neuropad + 10g Monofilament	£2,810	£2,822	£1,078	£1,073
No Testing	£2,101	£2,101	£1,787	£1,794

Sensitivity Analysis Specificity Neuropad

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	0.51	0.69	0.51	0.69
Neuropad	£4,192	£3,613		
10g Monofilament	£3,118	£3,118	£1,074	£495
Neuropad + 10g Monofilament	£2,870	£2,770	£1,322	£843
No Testing	£2,101	£2,101	£2,091	£1,512

Sensitivity Analysis Sensitivity Monofilament

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	0.75	0.94	0.75	0.94
Neuropad	£3,893	£3,893		
10g Monofilament	£3,108	£3,127	£785	£766
Neuropad + 10g Monofilament	£2,806	£2,829	£1,087	£1,064
No Testing	£2,101	£2,101	£1,792	£1,792

Sensitivity Analysis Specificity Monofilament

	Expected cost		Cost saving	
	Low	High	Low	High
	0.75	0.91	0.75	0.91
Neuropad	£3,893	£3,893		
10g Monofilament	£3,379	£2,857	£514	£1,036
Neuropad + 10g Monofilament	£2,921	£2,716	£972	£1,178
No Testing	£2,101	£2,101	£1,792	£1,792

Sensitivity Analysis Incidence of Neuropathy

	Expected cost		Cost saving	
	Low	High	Low	High
	0.01	0.04	0.01	0.04
Neuropad	£3,499	£4,577		
10g Monofilament	£2,660	£3,913	£839	£664
Neuropad + 10g Monofilament	£2,339	£3,648	£1,159	£929
No Testing	£1,782	£2,660	£1,717	£1,917

Sensitivity Analysis Infected foot ulcer without Neuropathy

	Expected cost		Cost saving	
	Low	High	Low	High
	0.002	0.0045	0.002	0.0045
Neuropad	£3,733	£4,391		
10g Monofilament	£2,945	£3,658	£788	£733
Neuropad + 10g Monofilament	£2,639	£3,376	£1,094	£1,015
No Testing	£1,916	£2,677	£1,817	£1,715

Sensitivity Analysis Death rate with or without Neuropathy and without ulceration/amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.01	0.04	0.01	0.04
Neuropad	£4,271	£3,257		
10g Monofilament	£3,423	£2,605	£848	£652
Neuropad + 10g Monofilament	£3,095	£2,354	£1,177	£903
No Testing	£2,289	£1,782	£1,982	£1,475

^Also applies for false positive, false negative and neuropathy death rate

Sensitivity Analysis Infected foot ulcer risk with Neuropathy

	Expected cost		Cost saving	
	Low	High	Low	High
	0.01	0.05	0.01	0.05
Neuropad	£3,594	£4,811		
10g Monofilament	£2,817	£4,042	£777	£769
Neuropad + 10g Monofilament	£2,514	£3,751	£1,080	£1,060
No Testing	£1,686	£3,317	£1,908	£1,494

Sensitivity Analysis Persistent infected foot ulcer¬

	Expected cost		Cost saving	
	Low	High	Low	High
	0.02	0.03	0.02	0.03
Neuropad	£3,809	£3,946		
10g Monofilament	£3,031	£3,173	£778	£773
Neuropad + 10g Monofilament	£2,729	£2,874	£1,079	£1,072
No Testing	£2,000	£2,164	£1,808	£1,782

¬Foot remains ulcerated at 6 months

Sensitivity Analysis Infected foot ulcer minor amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.1	0.35	0.1	0.35
Neuropad	£3,853	£4,172		
10g Monofilament	£3,077	£3,407	£776	£765
Neuropad + 10g Monofilament	£2,776	£3,112	£1,077	£1,060
No Testing	£2,054	£2,433	£1,799	£1,739

Sensitivity Analysis Infected foot ulcer major amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.03	0.17	0.03	0.17
Neuropad	£3,864	£4,057		
10g Monofilament	£3,088	£3,288	£776	£769
Neuropad + 10g Monofilament	£2,787	£2,991	£1,076	£1,066
No Testing	£2,066	£2,297	£1,798	£1,760

Sensitivity Analysis Infected foot death rate¬

	Expected cost		Cost saving	
	Low	High	Low	High
	0.04	0.08	0.04	0.08
Neuropad	£3,911	£3,876		
10g Monofilament	£3,136	£3,100	£774	£776
Neuropad + 10g Monofilament	£2,837	£2,800	£1,074	£1,076
No Testing	£2,122	£2,081	£1,789	£1,795

¬Also changes infected foot healed proportions

Sensitivity Analysis Ulceration rate after previous ulcer/amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.044	0.1	0.044	0.1
Neuropad	£3,787	£3,984		
10g Monofilament	£3,008	£3,212	£779	£771
Neuropad + 10g Monofilament	£2,706	£2,914	£1,081	£1,069
No Testing	£1,976	£2,208	£1,811	£1,775

* Also applies to healed to infected foot rate

Sensitivity Analysis Minor amputation to major amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.1	0.25	0.1	0.25
Neuropad	£3,868	£3,912		
10g Monofilament	£3,092	£3,137	£776	£774
Neuropad + 10g Monofilament	£2,792	£2,838	£1,076	£1,074
No Testing	£2,071	£2,123	£1,797	£1,788

Sensitivity Analysis Death rate after previous ulcer or minor amputation

	Expected cost		Cost saving	
	Low	High	Low	High
	0.02	0.04	0.02	0.04
Neuropad	£3,897	£3,887		
10g Monofilament	£3,122	£3,111	£775	£775
Neuropad + 10g Monofilament	£2,822	£2,811	£1,075	£1,075
No Testing	£2,105	£2,094	£1,791	£1,793

Sensitivity Analysis Major amputation death rate

	Expected cost		Cost saving	
	Low	High	Low	High
	0.08	0.16	0.08	0.16
Neuropad	£3,913	£3,877		
10g Monofilament	£3,139	£3,102	£774	£776
Neuropad + 10g Monofilament	£2,840	£2,801	£1,074	£1,076
No Testing	£2,125	£2,083	£1,788	£1,795

Sensitivity Analysis Diabetic foot programme effectiveness (reduction of ulceration risk)

	Expected cost		Cost saving	
	Low	High	Low	High
	0.1	0.5	0.1	0.5
Neuropad	£4,049	£3,624		
10g Monofilament	£3,246	£2,897	£803	£727
Neuropad + 10g Monofilament	£2,930	£2,624	£1,119	£1,000
No Testing	£2,101	£2,101	£1,948	£1,522

Sensitivity Analysis Neuropad test cost

	Expected cost		Cost saving	
	Low	High	Low	High
	£7.28	£10	£7.28	£10
Neuropad	£3,890	£3,902		
10g Monofilament	£3,118	£3,118	£772	£783
Neuropad + 10g Monofilament	£2,814	£2,830	£1,076	£1,071
No Testing	£2,101	£2,101	£1,789	£1,800

Sensitivity Analysis Monofilament test cost

	Expected cost		Cost saving	
	Low	High	Low	High
	£0.75	£0.90	£0.75	£0.90
Neuropad	£3,893	£3,893		
10g Monofilament	£3,118	£3,119	£775	£774
Neuropad + 10g Monofilament	£2,818	£2,818	£1,075	£1,075
No Testing	£2,101	£2,101	£1,792	£1,792

Sensitivity Analysis Cost for patients without neuropathy

	Expected cost		Cost saving	
	Low	High	Low	High
	£12	£35	£12	£35
Neuropad	£3,814	£3,972		
10g Monofilament	£3,009	£3,228	£805	£744
Neuropad + 10g Monofilament	£2,695	£2,942	£1,119	£1,030
No Testing	£1,945	£2,257	£1,869	£1,715

^ Also applies to costs in false negative state

Sensitivity Analysis Cost of foot care programme

	Expected cost		Cost saving	
	Low	High	Low	High
	£150	£600	£150	£600
Neuropad	£2,664	£5,824		
10g Monofilament	£2,351	£4,325	£314	£1,499
Neuropad + 10g Monofilament	£2,267	£3,685	£397	£2,139
No Testing	£2,050	£2,182	£615	£3,642

Sensitivity Analysis Infected foot community cost

	Expected cost		Cost saving	
	Low	High	Low	High
	£1,800	£12,000	£1,800	£12,000
Neuropad	£3,189	£4,243		
10g Monofilament	£2,390	£3,479	£799	£763
Neuropad + 10g Monofilament	£2,077	£3,186	£1,112	£1,056
No Testing	£1,261	£2,518	£1,928	£1,724

Sensitivity Analysis Infected foot hospital cost

	Expected cost		Cost saving	
	Low	High	Low	High
	£1,300	£7,500	£1,300	£7,500
Neuropad	£3,766	£4,022		
10g Monofilament	£2,987	£3,252	£779	£771

Neuropad + 10g Monofilament	£2,684	£2,954	£1,082	£1,068
No Testing	£1,949	£2,255	£1,817	£1,767

Sensitivity Analysis Minor amputation cost

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	£3,000	£16,000	£3,000	£16,000
Neuropad	£3,852	£4,013		
10g Monofilament	£3,075	£3,243	£776	£771
Neuropad + 10g Monofilament	£2,775	£2,945	£1,077	£1,068
No Testing	£2,052	£2,244	£1,800	£1,769

Sensitivity Analysis Support costs following minor amputation

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	£200	£600	£200	£600
Neuropad	£3,886	£3,901		
10g Monofilament	£3,111	£3,126	£775	£775
Neuropad + 10g Monofilament	£2,811	£2,827	£1,075	£1,074
No Testing	£2,093	£2,111	£1,793	£1,790

Sensitivity Analysis Major amputation cost

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	£8,000	£20,000	£8,000	£20,000
Neuropad	£3,849	£3,976		
10g Monofilament	£3,073	£3,204	£777	£772
Neuropad + 10g Monofilament	£2,772	£2,906	£1,077	£1,070
No Testing	£2,049	£2,200	£1,800	£1,776

Sensitivity Analysis Support costs following Major amputation

	Expected cost		Cost saving	
	Low	**High**	**Low**	**High**
	£1,200	£4,000	£1,200	£4,000
Neuropad	£3,829	£3,966		
10g Monofilament	£3,052	£3,194	£777	£772

Neuropad + 10g Monofilament	£2,750	£2,896	£1,079	£1,070
No Testing	£2,025	£2,187	£1,804	£1,779