NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

VibraTip for testing vibration perception in the detection of diabetic peripheral neuropathy

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

The VibraTip (McCallan Medical) is a device resembling a small key ring fob that provides a near-silent vibration of consistent amplitude at a frequency similar to that of a calibrated tuning fork. It is intended for use when testing a person's vibration perception during routine checks for diabetic peripheral neuropathy (DPN) in people who have type 1 or type 2 diabetes.

The VibraTip probe is applied to the patient's foot twice: once while non-vibrating and once while vibrating. The patient is asked to indicate when they feel the vibration. If the vibration is not detected this may suggest the development of DPN and the clinician may investigate further. The VibraTip is intended as an alternative to or replacement for the devices that are currently used in NHS clinical practice for testing foot sensory function, such as the 10 g monofilament (light touch/pressure sensation) and the calibrated tuning fork or biothesiometer (vibratory sensation). The device is designed to provide a consistent application compared with the variable vibration and cold touch of the tuning fork, and to offer continuous operation over its battery life (compared with the 10 g monofilament, which needs resting after every 10 full patient foot examinations).

The VibraTip received a CE mark in March 2010 and is indicated to test for vibration perception in the foot during routine checks for DPN.

2 Proposed use of the technology

2.1 Disease or condition

Diabetic peripheral neuropathy (DPN) is thought to result from high blood sugar levels causing nerve damage. Symptoms depend on the specific system affected, but include numbness, tingling and pain in the feet and hands, muscle weakness and foot ulcers. Early diagnosis lowers the chance of developing serious complications, with studies showing a reduction or delay in nerve damage through meticulous blood sugar control.

2.2 Patient group

Diabetes affects an estimated 3.75 million people in the UK, around 850,000 of which are thought to be unaware that they have the condition. Around 60% of people with diabetes are susceptible to DPN and diabetes is the most common cause of peripheral neuropathy in the UK. Diabetes is also on the rise: the current prevalence rate of 7.4% (diagnosed and undiagnosed) is likely to increase to 8.5% in 2020 and to 9.5% by 2030, driven by demographic changes and increasing obesity.

2.3 Current management

Type 2 diabetes foot problems: prevention and management of foot problems (NICE clinical guideline 10) and Type 1 diabetes: diagnosis and management of type 1 diabetes (NICE clinical guideline 15) both recommend a structured programme of regular (annual) foot surveillance, risk assessment and education by trained personnel to raise awareness of the condition. The annual foot examination should include a visual check, palpation of pulses and assessment of foot sensory nerve function. The sensory nerve function component may include assessment of touch/pressure using a 10 g monofilament or a test of vibration perception using either a biothesiometer or calibrated tuning fork. In clinical practice, biothesiometers are reported to have been replaced by neurothesiometers which work in the same way but have a self-contained battery, allowing for greater portability. The 10 g monofilament should not be used to test more than 10 people in one session and should be rested for 24 hours thereafter. Both guidelines are currently being updated with anticipated publication in 2015.

Classification of risk (low, increased, high, ulcer present) in the annual check is on the basis of sensation, pulses, deformity, skin changes or previous ulcers. This may result in referral to a specialist foot protection team comprising podiatrists, orthotists and footcare specialists (nurses with training in dressing of diabetic foot wounds and diabetologists with expertise in lower limb complications). The assessment will typically result in increased foot checks every 3–6 months with a vascular assessment and an assessment of

footwear. For people at particularly high risk of ulcer formation, foot examinations may be undertaken every 1–3 months, incorporating an intensive footcare education programme and the use of specialist footwear insoles and skin and nail care. Self-monitoring and self-inspection is both taught and encouraged.

There is currently no agreed standard on the number or location of the sites on each foot which should be examined when testing for touch sensation or vibration perception.

2.4 Proposed management with new technology

The VibraTip provides a near-silent vibration to test vibration perception in the foot during routine (at least annual) checks for DPN.

It is intended as an alternative to or replacement for current methods used for screening for vibration perception, such as the calibrated tuning fork.

NICE type 2 diabetes footcare guidance states that examination of patients' feet should include testing of foot sensation using a 10 g monofilament or vibration (using biothesiometer or calibrated tuning fork).

NICE guidance also states that people with diabetes should be encouraged to monitor and inspect their own feet. The sponsor states that some patients may be given a VibraTip device by their foot protection team to assist in this. It should be noted, however, that current guidelines do not make recommendations on self-monitoring using the 10 g monofilament or a tuning fork.

2.5 Equality issues

No equality issues were identified.

3 Sponsor's claimed benefits

The benefits to patients claimed by the sponsor are:

- The ease and speed of the test together with the device's reliability mean earlier diagnosis of neuropathy, leading to improved footcare and the prevention of ulcers and amputations.

The benefits to the health system claimed by the sponsor are:

- Less user variability, making the VibraTip test for DPN more consistent than a tuning fork test.
- The ease and speed of testing means that little user training is required.
- The VibraTip's smaller size makes it more portable and accessible than comparators.
- The device is tolerant to regular cleaning and can be cleaned easily, aiding compliance with infection control guidelines.

4 Decision problem

Table 1 Summary of the decision problem

Population	People (adults and children) with type 1 or 2 diabetes undergoing routine footcare checks by healthcare workers in primary and secondary care settings
Intervention	VibraTip
Comparator(s)	The comparators are • a 10 g monofilament • a calibrated tuning fork • biothesiometer
Outcomes	The outcome measures to consider include: • sensitivity and specificity in assessment of vibration perception and/or light touch • sensitivity and specificity in assessment of grade of neuropathy • inter-rater agreement of assessment of grade of neuropathy • accuracy of risk assessment in ulcer formation • ulcer formation and amputation • time taken for sensory testing • quality of life • device-related adverse events
Cost analysis	The cost analysis will include both the 10 g monofilament and calibrated tuning fork as comparators. Use in both primary and secondary care settings should be considered Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analyses will be undertaken to address uncertainties in the model parameters, including scenarios in which different numbers and combinations of devices are needed.
Special considerations, including issues related to equality	Diabetic neuropathy is more common with increasing age and males may develop diabetic peripheral neuropathy earlier than females, but neuropathic pain causes more morbidity in females than in males. More secondary complications from diabetic neuropathy have been shown to occur in people of Hispanic or African-American family origin. People with diabetes are considered as disabled under the Equality Act 2010.

5 The evidence

5.1 Summary of evidence of clinical benefit

The sponsor's submission identified 9 studies: 4 journal papers (one was submitted as an in-press manuscript and later published during the preparation of the assessment report), 2 conference abstracts, 2 unpublished studies and a technical study. The sponsor excluded one technical study as not relevant to the decision problem, and therefore presented 8 studies that were relevant to the scope. Although the sponsor did not present a literature search strategy, a literature search by the External Assessment Centre (EAC) (assessment report 3.1.3, page 29) identified 2 additional studies (Bracewell et al. 2012, Baker 2012) as well as all of the published studies presented by the sponsor. These, with all 9 studies originally identified by the sponsor, provide a total of 11 studies for consideration.

The EAC considered that 6 of the 11 studies presented unique patient data relevant to the scope: 4 papers (Levy 2010, Bowling et al. 2012, Bracewell et al. 2012, Nizar et al. 2014) and 2 abstracts (Urbancic-Rovan 2012, Garbas et al. 2013). The EAC excluded the other 5 studies from further consideration: Bracewell *et al.* (2011) was a conference abstract which overlapped with the Bracewell *et al.* (2012) study; Baker (2012) was a commentary on Bowling *et al.* (2012) and Bracewell *et al.* (2011); and Horsfield and Levy (2013) and Horsfield and Levy (unpublished) were technical papers with no information of direct relevance to the scope. However, they contain potentially useful information which is summarized in section 5.3 of this overview. Finally, the study by Levy and Greenwood was excluded because the intervention was outside the scope (VibraTip was used by patients in their own homes).

All 6 relevant studies were diagnostic accuracy studies and the EAC used the Quality Assessment of Diagnostic Accuracy Studies tool (revised; QUADAS-2) to determine the risk of study bias and the applicability of the study to the decision problem.

Table 2 Summary of clinical evidence (adapted from Tables 3.3, 3.4 and 3.8 in the External Assessment Centre report)

Study	Study design (country)	Population	Intervention versus comparator	Diagnostic accuracy (of VibraTip)	EAC comments on study
Abbreviations used: CI=confidence interval, NDS=Neuropathy Disability Score, PPV=positive predictive value, NPV=negative predictive value, PLR=positive likelihood ratio, NLR=negative likelihood ratio					
Full articles					
Levy (2010)	Cross-sectional 'agreement' study (UK)	Patients with diabetes undergoing review in hospital or podiatry (n=100)	VibraTip vs 10 g monofilament vs 128 Hz tuning fork		No reference test used thus no diagnostic accuracy data available
Bowling et al. (2012)	Cross-sectional diagnostic accuracy study (also a measurement of intra-rater reliability) (UK)	Patients with peripheral diabetic neuropathy (varying severity) from community and hospital settings (n=83)	VibraTip (on hallux only) vs Ipswich touch test vs Neurothesiometer (>25 V threshold) vs NDS	Results for VibraTip vs reference standard Sensitivity: Neurothesiometer 100%; NDS 100% Specificity: Neurothesiometer 96.6%; NDS 90.3% PPV: Neurothesiometer 98.2%; NDS: 94.5% NPV: Neurothesiometer 100%; NDS 100% PLR: Neurothesiometer 29.0, NDS 10.3 NLR: Neurothesiometer and NDS 0	No direct comparison with the most appropriate comparator (monofilament)
Bracewell et al. (2012)	Cross-sectional diagnostic accuracy study (UK)	Patients with diabetes type 1 and 2 in secondary care (n=141)	VibraTip vs NeuroTip vs 10 g monofilament vs 128 Hz tuning fork Neurothesiometer (threshold ≥ 25 V)	10 g monofilament superior to tuning fork (p=0.0056) and NeuroTip (p=0.0022), not superior to VibraTip (p=0.3214; n=141) Sensitivity: 0.79 Specificity: 0.82 PPV: 0.75; NPV: 0.85 PLR: 4.39: NLR: 0.25	Clear presentation of diagnostic data with clearly stated cut-off (2/10 insensate sites) and most appropriate comparator

Study	Study design (country)	Population	Intervention versus comparator	Diagnostic accuracy (of VibraTip)	EAC comments on study
Abbreviations used: CI=confidence interval, NDS=Neuropathy Disability Score, PPV=positive predictive value, NPV=negative predictive value, PLR=positive likelihood ratio, NLR=negative likelihood ratio					
					(monofilament)
Nizar et al. (2014)	Cross-sectional diagnostic accuracy study (diagnostic case-control study) (UK)	Patients with type 1 and 2 diabetes recruited from specialist diabetes clinic (n=100)	VibraTip vs tuning fork (oscillation frequency not specified)	Sensitivity 92% (95% CI 80.8% to 97.8%) Specificity 94% (95% CI 83.4% to 98.7%) PPV* 94% NPV* 92% PLR 15.3 NLR† 0.09 * Calculated assuming prevalence rate of 50% † Negative likelihood ratio calculated by External Assessment Centre for completeness	Increased risk of bias as case-control study. Sensitivity of tuning fork (40%) inconsistent with other studies; neurothesiometer set at non-standard (20 V) threshold, inconsistent with all other studies (25 V)
Abstracts					
Urbancic-Rovan et al. (2012); conference abstract.	Cross-sectional 'agreement' study (Slovenia)	Patients with diabetes (n=42)	VibraTip vs 10 g monofilament vs 128 Hz tuning fork vs Tip Therm vs Neuropad	'Normal' results in 47.6% (VibraTip), 45.2% (tuning fork), 57.1% (Tip Therm), and 45.2% (Neuropad), no significant differences (p>0.05) 'Normal' result in 14.3% (10 g monofilament), significantly different (p<0.005).	No reference test used thus no diagnostic accuracy data available
Garbas et al. (2013); conference poster.	Cross-sectional 'agreement' study	Patients with diabetes mellitus (n=496)	VibraTip vs 128 Hz tuning fork	VibraTip vibration sensation impaired: VibraTip left foot 32.7%, right foot 31.3%; 128 Hz tuning fork left foot 36.5%, right foot 36.3%. No significant difference between	No reference test used thus no diagnostic accuracy data

Study	Study design (country)	Population	Intervention versus comparator	Diagnostic accuracy (of VibraTip)	EAC comments on study
Abbreviations used: CI=confidence interval, NDS=Neuropathy Disability Score, PPV=positive predictive value, NPV=negative predictive value, PLR=positive likelihood ratio, NLR=negative likelihood ratio					
	(Slovenia)			feet. Tuning fork more sensitive than VibraTip (left foot p=0.007, right foot p=0.012)	available

Levy (2010)

This was a cross-sectional study that compared three diagnostic devices in 100 patients with diabetes undergoing annual review in a hospital or podiatry clinic in the UK. The aim of the study was to measure the level of agreement between the VibraTip, a 10 g monofilament and a 128 Hz tuning fork. Agreement data between the tests were reported and the EAC analysed the results, which showed no significant difference between the tests. However, the EAC concluded that these results are of limited value in the context of the decision problem because a reference standard was not employed. The EAC also noted that the study was poorly described, that results of the statistical analyses were not reported and that the study had a high risk of bias in the index test domain (poorly described index test, such as which order the tests were applied, were the testers aware of patient reference test results, test methodology not described adequately) and in external validity.

Bowling et al. (2012)

This was a cross-sectional diagnostic accuracy study that compared the VibraTip or the Ipswich touch test with each of two reference standards: a neurothesiometer (vibration perception threshold ≥25 V) or the Neuropathy Disability Score (NDS), which is a composite outcome derived from pain sensation, vibration sensation, temperature sensation and ankle reflex (threshold score ≥ 6). People (n=83) attending diabetes outpatient clinics in hospital and community settings in the UK were assessed using all 4 methods. The results showed that both the VibraTip and the Ipswich touch test had good agreement with the vibration perception threshold (Cohen's kappa = 0.973, p<0.001) and with the NDS (Cohen's kappa = 0.921, p<0.001). The EAC calculated that relative to the neurothesiometer, the VibraTip's sensitivity was 1.0 (95% confidence interval [CI] 0.93 to 1.0) and its specificity was 0.966 (95% CI 0.822 to 0.999). The EAC considered the study to be at high risk of bias as patient selection did not appear to be randomised or consecutive and its generalisability was limited because the population studied had pre-diagnosed DPN. The EAC concluded that this study had limited usefulness in informing the decision problem.

Bracewell *et al.* (2012)

This was a cross-sectional diagnostic accuracy study that compared four index tests (VibraTip, Neurotip, 10 g monofilament and 128 Hz tuning fork) with a neurothesiometer as a reference standard. It also attempted to establish the number of insensate sites that optimised accuracy for each test. The study population was 141 patients with diabetes type 1 or 2 in secondary care in the UK. The reported prevalence of DPN in this population was 41%. The first part of the study tested intra-rater reliability of the VibraTip in a population of 18 patients with diabetes and at high risk of DPN. Results from successive readings, taken 2–3 weeks apart, demonstrated good intra-rater reliability (Cronbach's alpha = 0.88, no CI given). The main part of the study tested the comparative diagnostic accuracy of the 4 index tests compared with the neurothesiometer. Of the 141 patients recruited from a secondary care setting, 89% reported having no history of foot ulcers. The authors performed a receiver-operator characteristic (ROC) analysis to find the optimum number of insensate sites which gave the best diagnostic accuracy for each test, and found that 2 or more out of 10 were optimal for the VibraTip, 10 g monofilament and NeuroTip, while at least one site was optimal for the tuning fork. From the results provided, the EAC calculated the VibraTip's sensitivity as 0.79 (95% CI 0.67 to 0.89) and its specificity as 0.82 (95% CI 0.72 to 0.90). These results, together with the values for the 10 g monofilament and 128 Hz tuning fork, are given in table 2 below and presented graphically in the assessment report (page 67).

Table 2: Results for diagnostic accuracy of index tests from Bracewell et al. (2012) (copy of table 3.9 assessment report)

Test	Sensitivity (95% CI)	Specificity (95% CI)
VibraTip	0.79 (0.69 to 0.90)	0.82 (0.74 to 0.90)
10 g monofilament	0.84 (0.75 to 0.94)	0.83 (0.75 to 0.91)
128 Hz tuning fork	0.69 (0.57 to 0.81)	0.90 (0.84 to 0.97)

The EAC considered there to be a high risk of patient selection bias, with patient recruitment and characterisation being unclear. There was a high risk that the index test used was not generalisable because thresholds were

derived from ROC analysis. The EAC also considered that the intra-rater reliability results were prone to spectrum bias because of the relatively high rate of previous ulceration in the population. Overall, the EAC concluded that the study provided evidence for the VibraTip's having similar diagnostic accuracy in detecting DPN as the 10 g monofilament, 128 Hz tuning fork and Neurotip. However, the EAC noted that the study did not provide evidence that the VibraTip was superior to any of the other index tests, and poor reporting of baseline characteristics and results mean that the study may not be fully generalisable to all scenarios described in the scope.

Urbancic-Rovan et al. (2012)

This was a small pilot study reported as a conference abstract comparing five reference tests (VibraTip, 128 Hz tuning fork, 10 g monofilament, Tip Therm [which detects impaired skin temperature sensation] and Neuropad [described as a simple and cheap diagnostic tool for the evaluation of sweat gland function]) in 42 patients attending diabetes outpatient clinics in Slovenia. The results suggest that the 10 g monofilament had a much poorer sensitivity (positive in only 14.3% tests) compared with the other tests, including the VibraTip (positive in 47.6% of tests).

The EAC stated that patient selection, characterisation and study setting were poorly described and at high risk of bias, as was the lack of a reference test, which made calculation of diagnostic accuracy parameters impossible. The generalisability of the study to NHS practice was difficult to ascertain because of the level of reporting. The EAC also noted that the results are inconsistent with other studies which have indicated the 10 g monofilament has a much higher sensitivity. The EAC considered that the quality of reporting in this study meant that it was generally inapplicable to the decision problem.

Garbas et al. (2013)

This was a follow up to the pilot study by Urbancic-Rovan et al. (2012) and is reported in a conference poster with few details. Based in a university medical centre in Slovenia, this large study (n=496) used 2 index tests (VibraTip and

128 Hz tuning fork) to compare screening test results. The results indicate that there was no significant inter-foot variability for either of the index tests and that the tuning fork was shown to be significantly more sensitive than the VibraTip in detecting impairment of vibration sensation.

The EAC noted that neither the study setting nor details of patient selection and characteristics were reported, and that the description of how the tests were used was poorly described. The study was at high risk of bias and the lack of a reference standard meant that diagnostic accuracy data could not be obtained, limiting its usefulness.

Nizar et al. (2014)

This study compared the VibraTip and a tuning fork using a neurothesiometer as the reference standard. The study reported tests on 100 people with type 1 or 2 diabetes attending specialist clinics. Although the authors described the study as a ‘cross-sectional diagnostic’ design, it was based on a case-control design where the researchers had prior knowledge of the patients’ DPN status, and recruited them accordingly to fix the prevalence of DPN at 50%. Results from the study show that the sensitivity of the VibraTip was 0.92 (95% CI 0.808 to 0.978) and its specificity was 0.94 (95% CI 0.834 to 0.987). The authors concluded that the VibraTip is comparable to the neurothesiometer and superior to the tuning fork in terms of the accurate detection of peripheral neuropathy, and that it could be a useful screening tool in clinical practice.

The EAC considered that this study design could be subject to significant bias. The patient population was at risk of selection bias and the index test had a high risk of bias due to a lack of standard technique. The generalisability of the results was uncertain because the amplitude threshold of the neurothesiometer in this study was set at 20 V, instead of the more usual 25 V. The EAC noted that the reported results for the tuning fork from this study they were not consistent with previously published results and suggested that a suboptimal protocol had been followed. As a consequence of these concerns and other difficulties (such as the design, bias in the index test [frequency of tuning fork not stated] and operator awareness of patient DPN

status) with the quality of the study, the EAC concluded that there was serious doubt about the validity and generalisability of the results in the context of the decision problem.

5.2 Summary of economic evidence

The sponsor conducted a search of literature in an in-house database and concluded that no economic evidence was available for the VibraTip device. The EAC conducted a comprehensive literature search and agreed with the sponsor‘s conclusion.

De novo analysis

The sponsor submitted a decision tree with a 3-year time perspective which represented the flow of the entire diabetic population of the UK through the relevant patient pathways for diabetic foot inspections. The model had 2 arms: a current practice arm, where the comparator (10 g monofilament or 128 Hz tuning fork) was used to test patients, and an intervention arm, where a proportion of patients were tested with the VibraTip and the comparator was used for the remainder. The decision tree simulated patients on a pathway with defined probabilities of becoming at high risk of ulceration, developing ulceration, having continued ulceration or requiring amputation. Each stage in the model was associated with a transition probability, the number of patients in the state, and the cost of being in that state (device costs and management costs). The decision tree is represented graphically on pages 65 and 66 of the sponsor’s submission.

The EAC identified a major issue with the sponsor’s model in that it did not include any discussion of diagnostic or preventative intervention inputs. Specifically, there was no link between the clinical evidence presented and the assumptions used in the economic model. In the sponsor’s base case, as diagnostic accuracy is not applied explicitly to each test, the EAC stated that the model should be classed as a cost-minimisation analysis. Consequently, any differences in costs may be attributable only to the cost of the devices and related use, rather than any differences in diagnostic performance or from the costs of preventative management of diabetic feet.

The EAC also considered that a weakness of the decision tree structure is that the number of states increases geometrically for each time step. For instance, if a 4-year horizon had been selected then there would have been 32 outcomes in each arm rather than 16. However, a longer time period might have been more appropriate as diabetes and DPN are chronic conditions, with DPN frequently occurring years or decades after diabetes is diagnosed.

The EAC highlighted problems with the functionality of the model and also that sections were missing from the executable model, including the analysis of the 128 Hz tuning fork comparator and much of the sensitivity analyses.

Model parameters and assumptions

The sponsor provided a table listing the assumptions and parameter values used in the model (sponsor's submission, page 71). However, some specific values were not easily traceable in the references cited. The EAC has summarised the assumptions used and its interpretation of them in the assessment report (table 4.1, pages 89–93). In some cases, the EAC could not locate the specific values reported to be drawn from the references cited. In addition, the rationale for selecting certain parameters was unclear and hence the values used may be subject to selection bias. The EAC has also cross-referenced the assumptions given by the sponsor with those used in the base case of the economic model (assessment report table 4.2, pages 93–96). The EAC considered that the derivation of values for some of the parameters was not clear.

Technology and comparator costs

The sponsor's cost analysis adopts a cost minimisation approach, and so the costs per examination obtained from the technology and comparator costs are crucial. The sponsor estimated the device costs as £9.95 for the VibraTip, £15.20 for the 10 g monofilament and £28.80 for the tuning fork (all excluding VAT). The sponsor calculated the per-examination costs based on the useful life of the device and the clinic throughput:

- For the 10 g monofilament the per-examination cost was based on assumptions that each device lasts 1 year, that 2 units would be required for each clinic, and that each unit would have 10 uses per day over 3 clinics per week. This gave a per-examination cost of £0.01.
- For the tuning fork the per-examination cost was based on assumptions that each device lasts 1 year, that 2 units would be required for each clinic and, that each unit would be used 4 times an hour over a 6-hour clinic with 3 clinics per week. This gave a per-examination cost of £0.008.
- For the VibraTip the sponsor based the per-examination costs on the assumption that the battery life equated to 5000 tests, giving a cost per examination of £0.002.

The EAC did not agree with the sponsor's approach to the per-examination costs and recalculated these values (assessment report, section 4.5).

Sensitivity analysis

The base-case intervention arm assumed that the VibraTip would be used for 40% of tests for DPN (in both low and high risk groups), with the remaining 60% using 10 g monofilament or 128 Hz tuning fork. In the standard care/current practice arm, all patients received either 10 g monofilament or 128 Hz tuning fork. The sponsor conducted sensitivity analyses with proportional adoption rates for the VibraTip of 0%, 20%, 40% and 100% in the intervention arm.

The sponsor also conducted a 2-way sensitivity analysis based on an assumption that VibraTip use was associated with a 1% relative risk reduction in ulcer formation compared with comparator devices combined with a range of adoption uptake values. Given the high cost of treating ulcers and resultant amputation rates in the model, this has a material impact on costs. The EAC noted that the assumption of a 1% reduction in ulcer rates was unsubstantiated but seemed to be associated with an assumption of improved performance and ease of use with enhanced early diagnosis of DPN, and subsequent avoidance of foot ulcers. The EAC judged that the limited clinical evidence available for the VibraTip suggests equivalent or non-inferior

diagnostic accuracy to the 10 g monofilament and the 128 Hz tuning fork, and would be unlikely to result in a 1% reduction in subsequent ulceration rates.

The EAC also noted the sponsor did not present any sensitivity analyses to address the uncertainties associated with cost per examination of devices, relative diagnostic accuracies, the risks and uncertainties associated with the probability of ulcer formation and amputation, and subsequent management costs.

Base-case analysis results

The sponsor reported the aggregate costs of using the devices in the entire diabetic population (2.9 million people) over 3 years. The cumulative costs associated with each branch of the decision tree were summed for the current practice and intervention arms of the model. In the base case, with adoption of the VibraTip set at 40%, the results were £1467.86 million for the VibraTip, £1467.91 million for the 10 g monofilament and £1467.90 million for the 128 Hz tuning fork. The sponsor did not report the incremental differences in costs between the VibraTip and its comparators, but the EAC calculated these savings as £0.05 million compared with 10 g monofilament and £0.04 million compared with the tuning fork. This is equivalent to a saving of 1.7 pence per patient over 3 years compared with the use of monofilament; and a saving of 1.4 pence per patient over 3 years compared with the use of the tuning fork.

The EAC noted that the results presented by the sponsor in its submission were not the same as those in the executable model. The EAC identified the difference in the executable model was due to a £5000 discrepancy and attributed it to a mismatch between the model current practice and intervention arms (the sponsor included an unexplained £5000 correction within the model). It also highlighted that the sponsor did not provide the EAC with an executable model that included the 128 Hz tuning fork as the comparator, and so it could not replicate these results.

The sponsor also presented base-case results assuming an update of 100% of all devices and calculated the cost by multiplying the average cost per

examination of each device by the number of uses throughout the 3-year period (assessment report, page 106). The EAC judged that the underlying assumptions may be flawed and that the results should be interpreted with caution.

The sponsor also presented a ‘real-world’ analysis based on a range of assumptions including that all testing would take place in primary care settings (assessment report, page 106). The EAC concluded that this analysis did not usefully inform the decision problem.

Sensitivity analysis results

In a sensitivity analysis the sponsor varied uptake of the VibraTip (to 20% and 100% from 40%; rationale for these values was not stated), resulting in proportionate savings compared with 10 g monofilament of £17,200 for 20% adoption, £34,400 for 40% adoption and £86,000 for 100% adoption. The sponsor also reported the results for the sensitivity analysis compared with the tuning fork as £12,900, £25,800, and £64,500 for levels of adoption at 20%, 40% and 100% respectively.

For the multivariate sensitivity analysis, the sponsor assumed that the VibraTip would result in a 1% reduction in the rate of formation of diabetic foot ulcers in people who had not had an ulcer in the previous year. This resulted in savings compared with the 10 g monofilament of £3210 million (20% adoption), £6420 million (40% adoption) and £16,060 million (100% adoption). The sponsor also reported results compared with the 128 Hz tuning fork as £3180 million, £6350 million and £15,880 million for levels of adoption of 20%, 40% and 100% respectively. The EAC noted that there is no evidence to support the assumed risk reduction, and concluded that these results are not informative.

Additional cost analysis by the External Assessment Centre

The EAC found the model submitted by the sponsor to be generally unsound. The model, in its base case, had no diagnostic input and thus implicitly assumes diagnostic equivalence. Because of this, each arm of the model had

the same clinical outcomes and costs, so that only the difference in per-examination device costs contributed to the difference in aggregate costs. The EAC also noted that the two arms of the model were structurally different and, in general, the input parameters for transition probabilities and costs were not judged to be robust or transparently derived from the references provided, making it difficult for the EAC to replicate the sponsor's results. As the sponsor's base-case economic model was a de facto cost minimisation model, the costs per examination are crucial to the analysis. The EAC considered that the unit costs estimated by the sponsor were largely accurate, but that the sponsor's calculation of the per-examination costs was flawed. As such, the EAC provided additional estimates for these values.

The EAC recalculated the per-examination costs of the VibraTip and of the 10 g monofilament in a range of scenarios (assessment report table 4.5, page 112). This resulted in a cost per examination for the VibraTip ranging from £0.02, as used in the sponsor's model, to £0.0995 as used by Horsfield and Levy (2013) and by Bracewell et al. (2012). For a Bailey's 10 g monofilament (a brand used widely in the NHS), the EAC's most plausible estimate for the per-examination cost was around £0.076. The EAC considered that this approach was impossible for the tuning fork because of its unlimited useful life.

The EAC also highlighted a potentially important issue with both the VibraTip and the 10 g monofilament in that the operator may be unaware the devices are losing functionality (through battery discharge and reduced plasticity respectively). In both cases, clinical use beyond the devices' effective useful life would result in a reduced sensory force being applied to the patient and could result in increased false positives and the associated increased costs.

In summary, the EAC considered that the results of the de novo economic model did not usefully inform the decision problem. Many of the parameters and much of the functionality of the model were redundant because no difference was assumed in the diagnostic accuracies of the devices. If a cost minimisation analysis were adopted, including the per-examination device

costs only, the VibraTip might be more expensive than either comparator under heavy usage, with a plausible per-examination cost of between £0.0398 (for 4 sites per person) and £0.0995 (for 10 sites per person). This compares with a per-examination cost of £0.076 for the 10 g monofilament assuming 10 sites per person. With this in mind, the EAC concluded that an economic case for the VibraTip was not demonstrated.

5.3 Summary of technical evidence

The EAC judged that although the technical papers submitted by the sponsor did not directly relate to the decision problem, they contained useful practical information that is relevant to the clinical repeatability of the test. The EAC provided a critique of these studies in appendix 2 of the assessment report (pages 142 to 146).

Horsfield and Levy (2013)

Horsfield and Levy investigated if the nature of the vibration stimulus from the VibraTip device varied as the battery discharges through repetitive use. They measured the stimulus during three different activation pattern methods, one of which imitated the usage of the device within clinical practice. In this approach the VibraTip was subjected to 10 half-second activations at 2-second intervals, followed by 10-minute rest. This cycle was then repeated 350 times over a 10-hour working day for 5 days, allowing the device to rest overnight. Results demonstrated that over the first 1000 activations, there was no significant reduction in either frequency or amplitude of the vibrations. After 2500 and then 3500 activations, amplitude fell to approximately 74% and 65% respectively. The frequency of vibration, however, only declined to 94% of initial frequency after 3500 activations. With successive applications, the amplitude reduced more rapidly, with no initial plateau phase, until it fell to about 45% of initial amplitude after around 2000 applications. The authors concluded that with routine clinical activity, the VibraTip could provide consistent performance for many months and could test at least 100 patients with no significant reduction in frequency or amplitude of vibrations. The EAC noted that the device's instructions for use recommend a 1-second activation

when testing the diabetic foot and not the half second used in the test. Doubling the duration of each activation would potentially drain the battery more rapidly. For this reason, the EAC remained uncertain if Horsfield and Levy's conclusion would be realised in clinical practice.

Horsfield and Levy (2014; unpublished)

Horsfield and Levy also reported a set of experiments to determine the clinical consistency and reliability of the vibration stimulus application of the VibraTip and of a 128 Hz tuning fork. A manikin toe structure was modelled to mimic human bone and tissue structures, incorporating an accelerometer with which to record the frequency and amplitude of the vibration applied to the surface of the toe. Junior and senior doctors (n=21) familiar with using tuning forks but with no prior VibraTip training applied the tuning fork and the VibraTip 5 times each to the surface of the toe. The graphical presentation of results demonstrated that the amplitudes recorded from the application of the VibraTip were generally greater than those elicited by the tuning fork. Unexpectedly, the mean frequencies measured from both devices were variable. The authors concluded that although the VibraTip was as consistent a source of vibration as a standard tuning fork, reliability of the delivered vibration intensity correlated with the manner in which the devices are used.

The EAC noted that although each doctor was described as being familiar with a tuning fork, the graphical results showed that 5 of the 21 users (24%) applied only negligible stimulus to the manikin toe with the tuning fork. However, all 21 users applied a VibraTip vibration stimulus. The EAC also commented on the frequency of around 200 Hz which the VibraTip demonstrated in this study. This is higher than the 128 Hz associated with the tuning fork and 50 Hz associated with neurothesiometer. The EAC was unable to establish if the higher operating frequency of the VibraTip elicits the same physiological response as other forms of vibration perception testing.

6 Ongoing research

The sponsor stated that an ongoing study is listed on ClinicalTrials.gov (NCT01878682). However, the External Assessment Centre (EAC) noted that, as of the last published update (12 March 2014), the trial was listed as 'not yet open for participant recruitment'.

The sponsor also stated there was a study expected from the Diabetes Research Unit at Le Pitie Salpetriere Hospital in Paris, although the design and publication intention for this study is not yet known.

The EAC did not identify any other studies currently being undertaken or planned from its literature search.

7 Issues for consideration by the Committee

7.1 Clinical evidence

Quality and quantity of the evidence base

Currently, NICE guidelines for the assessment of diabetic feet recommend that the 10 g monofilament or a device testing for vibratory sensation (in practice the 128 Hz tuning fork) should be used to test for the presence of diabetic peripheral neuropathy (DPN), as part of a clinical algorithm to assess the risk of foot ulceration. The current evidence base for these specific devices is limited in terms of quantity and quality, and the guideline recommendations were developed pragmatically to reflect this.

The External Assessment Centre's (EAC's) review of the 6 diagnostic accuracy studies relating to the use of VibraTip indicated that 5 were of limited usefulness: 3 because they did not have a reference standard (Levy [2010], Urbancic-Rovan et al [2012] and Garbas et al. [2013]), 1 because it used a modified reference standard (Nizar et al. [2014]), and 1 because it recruited a population who had pre-existing DPN and its target condition was 'at-risk' feet (Bowling et al. [2012]). This left 1 study, by Bracewell et al. (2012), that the EAC considered was of reasonable quality and most closely matched the

scope. The results from this study indicated that the VibraTip test was diagnostically non-inferior to both the 10 g monofilament and the 128 Hz tuning fork. However, the EAC noted that the numbers were small (n=141) and that the diagnostic accuracy for each device was optimised using receiver-operator characteristic analysis, so it is unclear how generalisable this study is to clinical practice.

There are no data on the claimed benefits of ease of use or speed of testing, no data on the level of user variability compared to the tuning fork, and no comparative data on the level of training required with the VibraTip versus the tuning fork method of vibration perception testing.

Variability in DPN foot testing methodology

NICE clinical guidelines indicate that there is no standard approach to either the number or the location of the sites that should be tested on the diabetic foot (either for touch sensation or vibration perception). Additionally, there is no agreed cut-off for the number of insensate sites which would indicate a higher risk of DPN and result in further clinical investigation or treatment.

Cost evidence

Disjoint between clinical case and economic case

According to the EAC, the main weakness of the economic analysis submitted was that the findings from the clinical evidence were not explicitly used to influence the economic case. The clinical evidence implicitly shows that the VibraTip is equivalent to current methods (monofilament and tuning fork), which means the economic model can be considered as a cost minimisation model. The EAC stated that this may well have been the most appropriate model but that a case should have been explicitly made to support this, as it has important implications for the structure and functionality of the model.

Per-examination/per-patient cost

The EAC identified this as being important because the cost minimisation economic case submitted relies on accurate estimation of the per-examination cost of VibraTip and its comparators. Expert advice suggested that the amplitude of the vibration used to test vibration perception in humans is the most important factor. The EAC presented evidence that the useable life of the VibraTip device may be shorter than that assumed by the sponsor, and that the useable life of the comparators may be longer than assumed. Horsfield and Levy (2013) investigated the decay of the VibraTip's amplitude over time and claimed a useable life of 1000 activations, suggesting that this would easily extend up to 5000 activations before amplitude decayed to a level too low to reliably test for vibration perception. The EAC disputed this lifetime, stating that 1000 activations was more realistic.

Dysfunctional economic model

Despite requests from the EAC for further clarification, the sponsor's model as submitted remains unclear in its functionality and content. The EAC noted that many of the parameters used could not be identified in the references given and some parameters could not be identified in the model as delivered. The model and the results from the executable model were inconsistent with the economic narrative supplied and a number of the values used in the model were unexplained. The sensitivity analyses undertaken were also uninformative and failed to investigate key parameters such as diagnostic accuracy, cost per test and device useable life.

8 Authors

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NICE Medical Technologies Evaluation Programme

May 2014

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Willits I, Cole H, Arber M, et al. (2014) VibraTip for testing vibration perception in the detection of diabetic peripheral neuropathy

B Submissions from the following sponsors:

- McCallan Medical

C Related NICE guidance

- Foot care service for people with diabetes. NICE Commissioning Guide (2012)
- Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults. NICE clinical guideline CG15 (2004, updated 2011)
- Type 2 diabetes foot problems: Prevention and management of foot problems. NICE clinical guideline CG10 (2004)
- Diabetic foot problems: Inpatient management of diabetic foot problems. NICE clinical guideline CG119 (2011)
- Diabetes in adults. NICE quality standard QS6 (2011).
- The percentage of patients with diabetes with a record of a foot examination and risk classification: 1) low risk (normal sensation, palpable pulses), 2) increased risk (neuropathy or absent pulses), 3) high risk (neuropathy or absent pulses plus deformity or skin changes or previous ulcer) or 4) ulcerated foot within the preceding 15 months. NICE QOF indicator NM13 (2010).

D References

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Bracewell NJ, Scammell BE, Jeffcoate JW et al. (2011) Evaluating a new device in the assessment of peripheral sensory neuropathy in diabetes: the VibraTip study. Diabetologia 54.

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Horsfield I, Levy A (2013) VibraTip durability in clinical practice: How long does it last? British Journal of Diabetes and Vascular Disease 13: 91–5.

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Posnet J, Frank PJ (2008) The Burden of Chronic Wounds in the UK, Nursing Times 104: 44–5.

Ramsey SD, Newton K, Blough D et al. (1999) Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 22: 382–7.

Urbancic-Rovan V, M Slak M, M Hohnjec M (2012) Screening for neuropathy - do additional testing methods make sense? Diabetic Foot Study Group (DFSG) 28–30 September; Berlin-Potsdam.

Young MJ, Breddy JL, Veves A et al. (1994) The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. Diabetes Care 17: 557–60.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Ms Theresa Smyth

Nurse Consultant in Diabetes, Royal College of Nursing

Dr Edward Jude

Consultant Physician and Reader in Medicine, Society for Endocrinology

Dr Aleksandar Radunovic

Consultant Neurologist, Association of British Neurologists

Dr. Yusuf A. Rajabally

Consultant Neurologist, Honorary Senior Clinical Lecturer, British Peripheral Nerve Society

Dr Adrian Wills

Consultant Neurologist, British Peripheral Nerve Society

Mr George Dunn

Specialist Podiatrist, Society of Chiropodists and Podiatrists

Dr Paul Chadwick

Principal Podiatrist, Society of Chiropodists and Podiatrists

Mr Allister Campbell

Deputy Podiatry Services Manager, Society of Chiropodists and Podiatrists

Dr Umesh Dashora

Consultant Endocinology and Diabetes, Association of British Clinical Diabetologists

Dr John Winer

Consultant Neurologist Association of British Neurologists

Mr Neil R Baker

Principal Diabetes Specialist and Research Podiatrist, Diabetes UK

Dr Frances Game

Consultant Diabetologist, Association of British Clinical Diabetologists

Professor Kamlesh Khunti

Professor of Primary Care Diabetes and Vascular Medicine, Royal College of General Practitioners

Twelve experts commented on the technology as follows:

- Five have had direct involvement with the VibraTip: 1 had referred patients for its use; 2 managed patients who use it in another part of their care pathway; and 3 would like to use it but do not have it available to them.
- One expert is involved in ongoing research on using the VibraTip in the community and investigating its accuracy when used by different healthcare professionals; another expert had published a clinical study on VibraTip.
- Seven experts thought that the VibraTip was a minor variation on existing technologies, 4 thought it was a significant variation and 3 thought it was thoroughly novel (2 experts thought it was both a significant modification and thoroughly novel).
- All experts mentioned a selection from 10 g monofilament, tuning fork and neurothesiometer as comparators (all 12 said tuning fork, 6 mentioned the monofilament and 5 mentioned the neurothesiometer).
- All 12 experts agreed that there was no competing product.
- Three experts mentioned that it might be less expensive; 5 stated issues around the VibraTip being more reliable in terms of standardisation of testing; 1 mentioned that it was single use and disposable and 1 thought it held few benefits over existing technology.

- Four experts thought the benefits would be realisable, 1 would wait for NICE guidance and 1 needed to be persuaded of the costs before benefits would be realised.
- Outcomes to assess the VibraTip mentioned reduction in amputation or foot ulceration (3 experts) and patient satisfaction, device use, numbers of ‘at-risk’ feet detected and audit of neuropathy assessments (1 expert each).
- All experts agreed that there was little need for extra training in using the VibraTip.

Appendix C: Comments from patient organisations

The following patient organisations were contacted and no response was received.

- Black and Ethnic Minority Diabetes Association
- British Skin Foundation
- Compassion in Care
- Deaf Diabetes UK
- Deaf Diabetes UK
- Diabetes Research & Wellness Foundation
- Diabetes UK
- Elcena Jeffers Foundation
- Foot in Diabetes UK (FDUK)
- Independent Age
- Insulin Dependent Diabetes Trust
- Insulin Dependent Diabetes Trust
- Juvenile Diabetes Research Foundation (JDRF)
- Juvenile Diabetes Research Foundation (JDRF)
- Limbless Association
- National Obesity Forum (NOF)
- Participation Works
- Primary Care Diabetes Society (PCDS)
- South Asian Health Foundation
- Surya Foundation
- The Relatives and Residents Association (R&RA)
- Weight Concern
- WellChild