NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:
Evaluation title: VibraTip®
Sponsor: McCallan Medical Ltd
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Instructions for sponsors

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

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

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

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality.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

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

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

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

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

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

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

Document key

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

List of tables and figures

Please include a list of all tables and figures here with page references.

Section A – Decision problem

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

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

1 Statement of the decision problem

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

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People (adults and children) with type 1 or 2 diabetes undergoing routine foot-care checks by health care 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. The 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 sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address		

	uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	People with diabetes having routing annual checks in a primary care setting; people with diabetes having more frequent checks in a secondary care setting		
Special considerations, including issues related to equality	Diabetic neuropathy is more common with increasing age and males may develop DPN 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.		

2 Description of technology under assessment

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

VibraTip®

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

VibraTip is a device resembling a small keyring fob. When squeezed between thumb and forefinger, it 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 which touch was associated with vibration. If vibration is not perceived this may suggest the development of DPN and further investigation can be initiated. The VibraTip is intended as an alternative or replacement to the devices that are currently used in NHS clinical practice for testing foot sensory function such as the 10g 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 the battery life compared with the 10g monofilament which needs resting after every 10 full patient foot examinations.

3 Clinical context

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

VibraTip is intended for use in testing vibration perception during routine checks for diabetic peripheral neuropathy in people who have type 1 or type 2 diabetes.

Diabetes affects an estimated 3.75 million people in the UK; of which it is thought that 850,000 are 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. The current prevalence rate of 7.4% for diabetes (diagnosed and undiagnosed) is likely to rise to 8.5% in 2020 and to 9.5% by 2030, driven by demographic changes and increasing obesity.

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 by meticulous blood sugar control. Diagnosis of DPN should escalate levels of care provided and trigger foot protection strategies to prevent tissue damage.

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

NICE clinical guidelines 10 (currently being updated) and 15 (currently being updated) (for Type 2 and Type 1 diabetes, respectively) recommend a structured programme of regular (annual) foot surveillance, risk assessment and education by trained personnel, to raise awareness in patients. The annual foot examination includes a visual check, palpation of pulses and assessment of foot sensory nerve function. The sensory nerve function component of the annual foot check may include assessment of touch/pressure using a 10g monofilament or a test of vibration perception using either a biothesiometer or calibrated tuning fork. The 10g monofilament should not be used to test more than 10 patients in one session and should be rested for 24 hours thereafter.

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 foot-care specialists. The assessment will typically result in increased foot checks every 3-6 months with a vascular assessment and an assessment of footwear. For patients at particularly high risk of ulcer formation, a foot examination may be undertaken every 1-3 months, incorporating an intensive foot-care education programme and the use of specialist footwear insoles and skin and nail care. Self-monitoring and self-inspection by patients is taught and encouraged.

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

A footcare pathway which supports NICE guidance and which has been agreed by organisations of diabetologists, podiatrists, people with diabetes and other experts was issued (2013) by Diabetes UK: (http://www.diabetes.org.uk/Documents/Professionals/Education%20and%20skills/Footcare-pathway.0212.pdf). The clinical pathway involves an annual foot review for all people with diabetes, identification of any factors that may place the foot at risk and action required, based upon risk stratification. Loss of foot sensation is identified as a risk factor and the pathway indicates sensation testing using 10g monofilament or vibration.

The current GMS contract 2013-14 Quality and Outcomes Framework (QOF) guidance requires the recording of patients with diabetes who have undergone a foot examination and risk classification (includes neuropathy) in the preceding 12 months (DM indicator 012). The NICE indicator guidance for this QOF is NM13 which states –

'Patients with diabetes are at high risk of foot complications. Evaluation of skin, soft tissue, musculoskeletal, vascular and neurological condition on an annual basis is important for the detection of feet at raised risk of ulceration.

The foot inspection and assessment should include:

• identifying the presence of sensory neuropathy (loss of the ability to feel a monofilament, vibration or sharp touch) and/or the abnormal build-up of callus……'

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

Differences in performance of commercially available 10g monofilaments have been highlighted - Booth & Young, Diab Care 23 (2002) 377-384 – along with the need to 'rest' a monofilament for 24 hours after each 10 patients in order to restore its buckling resistance. This need is reflected in NICE guidance. However, we are uncertain how practical this is and how widespread this practice has become.

Vibration perception testing using a calibrated tuning fork presents an issue of user variability. Whilst the frequency of vibration may be calibrated, the more crucial amplitude of vibration is highly dependent upon how hard the device is struck (or the tines are 'twanged'). Furthermore, once activated, the amplitude then decays. In addition to potentially high variability, the patient is also subjected to cueing by sound and temperature.

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

The adoption of VibraTip would not require existing pathways of care, as outlined in 3.3 above, to be changed.

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

No changes required.

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

No changes required.

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

No changes required.

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

If VibraTips are to be used rather than monofilaments then a substitute purchase at the end of a monofilament life would be appropriate and most cost-effective. Tuning forks would continue to be used in the NHS for other tests (hearing testing, fracture identification, specialised neurological testing).

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

Although Tuning Forks would continue to be used in other screening or testing situations, one would expect purchase levels to fall going forward. As stated above, if a VibraTip is preferred over a monofilament, substitute purchasing at the end of the monofilament life would be expected minimise redundancy costs.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

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

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes – Class lla CE

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

Yes.
Class lla CE France, Germany, Romania.
Class I FDA-listed USA

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

N/A

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

Since launch in 2011 approx.4,000 VibraTips have been sold in UK. These sales have been completed via an online facility and through a network of general medical and specialised podiatry distributors. The product also features on the NHS Supply Chain. Buyers across Private, NHS Primary Care and NHS Acute settings include the following: Podiatrists, Diabetic Foot Specialists, GP's, Practice Nurses and Diabetes Nurses.

5 Ongoing studies

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

VibraTip was a winner in the Smart Solutions for Healthcare competition run by TrusTECH (the North West NHS Innovation Hub) and the 'prize' for this initiative was an investigative study conducted in an appropriate NHS facility in the North West. The study is titled 'A Study to Evaluate the Performance of the VibraTip Product by Different Community Medical Practitioners Compared to an Expert Validation by a Diabetologist'. Completion during 2014 is expected (see http://clinicaltrials.gov/show/NCT01878682 for further information).

Product has been supplied to the diabetes research unit at Le Pitie Salpetriere Hosp in Paris for their investigative purposes. The study design is unknown at this stage.

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

None known

6 Equality

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

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

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

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

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

It should be noted that people with diabetes are covered under the 2010 Equality Act. Diabetic neuropathy is more common with increasing age and males may develop DPN 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.

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

None known

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

N/A

Section B – Clinical evidence

7 Published and unpublished clinical evidence

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

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

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

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

7.1 Identification of studies

Please note: sections 7.1 and 7.2 of the submission are divided into published and unpublished data. Responses must be split accordingly.

The sponsor's review of the clinical evidence should be systematic and transparent, and a suitable instrument for reporting such as the PRISMA statement (http://www.prisma-statement.org/statement.htm) should be used and CRD should be referred to (www.york.ac.uk/inst/crd).

The strategies used to retrieve relevant clinical data from the published literature and unpublished sources should be clearly described. The methods used should be justified with reference to the scope. Sufficient detail should be provided to enable the methods to be reproduced (the External Assessment Centre must be able to reproduce the search), and the rationale for any inclusion and exclusion criteria regarding search terms should be given.

Published studies

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

Internet search facilities and specialised medical databases are the principal means by which information is gathered. Occasionally, an investigator will advise of planned publication of a study.

Unpublished studies

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

All sales (or requests for free samples) to research or specialist diabetic foot centres are noted and personally followed up. Proceedings for specialised conferences are screened for potential poster presentations that may in turn lead to study publications.

7.2 Study selection

Published studies

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

Table B1 Selection criteria used for published studies

Inclusion criteria - All available published data have been included in this review. This currently totals 9 small studies (7 published and 2 yet to be published)	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	
Exclusion criteria - None	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

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

Due to the very limited number of studies involving this device, we believe it is appropriate to include all available information.

Unpublished studies

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

Table B2 Selection criteria used for unpublished studies

Inclusion criteria - All available studies have been included in this review. This currently totals 9 small studies (7 published and 2 yet to be published)	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	
Exclusion criteria - None	
Population	
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

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

Due to the very limited number of studies involving this device, we believe it is appropriate to include all available information.

7.3 Complete list of relevant studies

Published:

1. Levy A. Preliminary data on VibraTip®, a new source of standardized vibration for bedside assessment of peripheral neuropathy. Brit J Diabetes and Vascular Disease 2010;10:284-86.

2. Bowling FL, Abbott CA, Harris WE, Atanasov S, Malik RA, Boulton AJ. A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting. Diabetic Medicine 2012;29(12):1550-52.

3. Bracewell N, Game F, Jeffcoate WJ, Scammell BE. Clinical evaluation of a new device in the assessment of peripheral sensory neuropathy in diabetes. Diabetic Medicine 2012;29(12):1553-55.

4. Nizar H, Munro N, Nightingale P, Feher MD. Diagnostic accuracy of the VibraTipTM in detection of diabetic peripheral neuropathy. The British Journal of Diabetes and Vascular Medicine 2014; in press.

5. Urbancic-Rovan V, Slak M, Hohnjec M. Screening for neuropathy - do additional testing methods make sense? Poster presented at DFSG Berlin-Potsdam, Germany, 2012.

6. Garbas M, Rovan VU, Slak M, Hohnjec M. Can we replace 128-Hz tuning fork testing by VibraTip®?, Poster presented at DFSG Barcelona 2013.

7. Horsfield I, Levy A. VibraTip durability in clinical practice: how long does it last? The British Journal of Diabetes and Vascular Medicine 2013;13(2):91-95.

Unpublished:

8. Horsfield I, Levy A. Clinical consistency of vibration sense testing: development of a manikin great toe with embedded accelerometer for testing and training. Submitted

9. Levy A, Greenwood R. Self-care and misplaced confidence. Not yet submitted 2014

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

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

The details of all published and unpublished studies that compare the technology with other treatments for the relevant group of patients should be presented using tables B3 and B4 respectively. The studies that compare the intervention directly with the appropriate comparator(s) referred to in the decision problem should be clearly highlighted. If there are none, please state this. All types of studies should be considered, including observational studies such as cohort, case series and case-control studies, and single case reports and qualitative studies when relevant to the scope.

The list of relevant studies must be complete and will be validated by independent searches conducted by the External Assessment Centre.

Published studies should be referenced by first author name and year of publication. Unpublished studies should be referenced by first author and date of report. Full details of each reference should be provided in the reference list after section 9. In addition, list any trial short names if useful.

Table B3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Levy, 2010	1	100 diabetics attending annual review clinic	Testing for peripheral neuropathy	VibraTip v 128Hz tuning fork v 10g Semmes-Weinstein monofilament
Bowling et al. 2012	2	83 diabetics attending clinic	Testing for peripheral neuropathy	VibraTip v Ipswich Touch Test v Neuropathy Disability Score v 128Hz tuning fork
Bracewell et al. 2012	3.	141 diabetic patients attending clinic	Testing for peripheral neuropathy	VibraTip v Neurothesiometer v 10g monofilament v 128Hz tuning fork v neurotip
Nizar et al. 2014	4	100 diabetic patients attending clinic	Testing for peripheral neuropathy	VibraTip v neurothesiometer v tuning fork
Urbancic-Rovan et al. 2012	5	42 diabetic patients attending clinic	Testing for peripheral neuropathy	VibraTip v 10g monofilament v 128Hz tuning fork
Garbas et al. 2013	6	496 diabetic patients attending clinic	Testing for peripheral neuropathy	VibraTip v 128Hz tuning fork

Table B4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Horsfield and Levy	8	21 medics - from F1 to consultant	Testing consistency of vibration sense testing	VibraTip v 128Hz tuning fork
Levy and Greenwood	9	60 patients in retinal screening clinic	Assessment of confidence in foot self-care	VibraTip to take home v's no VibraTip

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

The only study not represented above was a laboratory assessment of the durability of VibraTip - to find out how long the device lasts when used in a variety of different ways. A laboratory based exercise to look at consistency of output in terms of vibration frequency and amplitude over time, as the power cell is progressively exhausted. The outcome was that the device would last for many months of routine use without significantly altering its behaviour.

Ian Horsfield and Andy Levy.
VibraTipdurability in clinical practice: how long does it last?
British Journal of Diabetes & Vascular Disease 2013 13: 91

7.4 Summary of methodology of relevant studies

It is expected that all key aspects of the methodology will be in the public domain. If a sponsor wishes to submit aspects of the methodology in confidence, section 11.2 describes how to highlight confidential information.

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

Table B5 Summary of methodology for randomised controlled trials

Study name	Levy and Greenwood - Self-care and misplaced confidence
Objectives	To determine whether in addition to standard care and advice, giving a population of people with diabetes presenting for retinal screening a VibraTip to take home - not necessarily to use but certainly to 'engage with' - would enhance confidence in foot self-care and as a result, potentially improve foot safety
Location	Eye hospital retinal screening clinic - Bristol
Design	Randomised control trial. Subjects attending the retinal screening clinics were alerted to the study by a letter sent home. Diabetic patients who opted into further consideration of the study were approached by a trained member of staff while waiting in the eye clinic for their follow-up appointment to take place. This included patients who had been screened in the community and need further review. Almost all had some degree of diabetic retinopathy.
Duration of study	Follow up at 6 months
Sample size	60
Inclusion criteria	All patients who consented. Recruitment for the study of 60 patients was completed in less than three weeks.
Exclusion criteria	Those unable to understand the study
Method of randomisation	Randomised using the sealed envelope system (http://www.sealedenvelope.com/protocols.php) to either an educational package consisting of the trust's standard foot care leaflet alone, or an enhanced package containing the above but followed by a demonstration of how to test for sensory loss using VibraTip either on the patient's foot, lower leg or hand if it was inconvenient to expose the lower limb.
Method of blinding	None
Intervention(s) (n =) and comparator(s) (n =)	30 30
Baseline differences	
Duration of follow-up, lost to follow-up information	58 patients followed up at 6 months (29 each group)
Statistical tests	Means and standard deviations were reported for the groups at baseline and 6 months. Follow-up rate percentages were

	reported with 95% confidence intervals calculated using the exact binomial method. The outcome scores of health related quality of life, confidence in care, and the foot care item of the confidence in care questionnaire were analysed using an analysis of covariance (ANCOVA) to control for baseline when examining the difference between the two randomised groups. P values for the difference between the groups have not been calculated, but to aid the planning of a future trial, effect sizes with 95% confidence intervals are reported with the standard deviation coming from the ANCOVA results.
Primary outcomes (including scoring methods and timings of assessments)	

Variable	Baseline control group n=30	Baseline intervention group n=30	6 m control group n=29	6 m intervention group n=29
EQ-5D utility (Health related quality of life)	0.750 (0.259)	0.768 (0.256)	0.724 (0.344)	0.738 (0.274)
Total for confidence in self care (scored from 21 to 105)	93.4 (10.5)	90.2 (12.7)	95.6 (7.8)	92.1 (10.4)
I believe I can check my feet for sores or blisters every day (1 - 5)	4.52 (1.09)	4.50 (0.86)	4.83 (0.38)	4.43 (1.10)

Table B6 Summary of methodology for observational studies

Study name	Levy 2010 - Preliminary data on VibraTip®, a new source of standardised vibration for bedside assessment of peripheral neuropathy
Objective	To compare the sensitivity and specificity of VibraTip with tuning fork and 10g monofilament
Location	Diabetes out-patient annual review clinic and podiatry clinic in hospital - Bristol
Design	Cross sectional study with sequential testing of the three devices on either the left or right foot in random order
Duration of study	Cross-sectional
Patient population	
Sample size	100 patients
Inclusion criteria	All patients with an accessible foot
Exclusion criteria	No patients were excluded, unless lack of consent or absence of a foot to test.
Intervention(s) (n =) and comparator(s) (n =)	All patients tested with all three devices
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	kappa-statistic and McNemar's test
Primary outcomes (including scoring methods and timings of assessments)	No significant differences between the three methods

Study name	Bowling et al 2012 - A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting
Objective	To compare the Ipswich Touch Test and the VibraTip with the Neuropathy Disability Score and the vibration perception threshold (Neurothesiometer @25V) for detecting the 'at-risk' foot
Location	Diabetes out-patient clinics in hospital and the community - Manchester
Design	Cross sectional study with sequential testing of the different methods
Duration of study	Cross sectional
Patient population	
Sample size	83 patients
Inclusion criteria	Not known
Exclusion criteria	Not known
Intervention(s) (n =) and comparator(s) (n =)	All patients assessed with all methods
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	All analyses were performed using SPSS version 16.0 and Microsoft Excel 2008. Cohen's kappa was calculated. Diagnostic reliability was based on the standard scale of Landis and Koch. Sensitivity and specificity, negative and positive predictive values, negative and positive likelihood ratios measured using the method of Altman and Bland
Primary outcomes (including scoring methods and timings of assessments)	The VibraTip and Ipswich Touch Test results exhibited almost perfect agreement with the vibration perception threshold ($P < 0.001$) and the Neuropathy Disability Score ($P < 0.001$).

Study name	**Bracewell et al, 2012 - Clinical evaluation of a new device in the assessment of peripheral sensory neuropathy in diabetes**
Objective	to evaluate the device by assessing intra-rater reliability and comparing the ability of the VibraTip to detect or exclude peripheral sensory neuropathy with other bedside methods.
Location	Diabetes out-patient annual review clinic and podiatry clinic - Nottingham
Design	Cross sectional study with sequential testing of VibraTip, Neurothesiometer, 10g monofilament, 128Hz tuning fork and neurotip
Duration of study	cross sectional
Patient population	
Sample size	141 patients
Inclusion criteria	Type 1 or Type 2 diabetes patients were recruited from one secondary care-based specialist diabetes service
Exclusion criteria	Major or minor amputees were excluded if this affected the site of testing
Intervention(s) (n =) and comparator(s) (n =)	All patients tested with all devices/methods
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Cronbach's alpha using Predictive Analytics Software Statistics 18 and NCSS 2007
Primary outcomes (including scoring methods and timings of assessments)	Receiver operating characteristic curves were produced for each device and the sensitivity, specificity, predictive values and likelihood ratios for the diagnosis of peripheral sensory neuropathy were calculated. Analysis of the area under the receiver operating characteristic curves showed that the 10-g monofilament was significantly better than the 128-Hz tuning fork (P = 0.0056) and the Neurotip (P = 0.0022), but was no different from the VibraTip (P = 0.3214).

Study name	Nizar et al, 2014 - Diagnostic accuracy of the VibraTip™ in detection of diabetic peripheral neuropathy
Objective	To compare the diagnostic accuracy of VibraTip compared to tuning fork in patients with confirmed neuropathy (failure to perceive neurothesiometer stimulus at 20 volts)
Location	Diabetes out-patient clinic – Chelsea & Westminster
Design	Cross sectional observational study
Duration of study	Cross sectional
Patient population	
Sample size	100 patients - 50 DPN +ve, 50 DPN -ve
Inclusion criteria	Patients with Type 1 and Type 2 diabetes were recruited in a secondary care specialist diabetes clinic
Exclusion criteria	Not known
Intervention(s) (n =) and comparator(s) (n =)	
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Assessment of sensitivity, specificity, positive and negative predictive values and positive likelihood ratios
Primary outcomes (including scoring methods and timings of assessments)	VibraTip comparable to Neurothesiometer and more reliable than tuning fork.

Study name	Urbancic-Rovan et al. 2012 - Screening for neuropathy - do additional testing methods make sense?
Objective	To compare the screening results of VibraTip compared to tuning fork, monofilament, Tip Therm (an instrument which reveals impaired temperature sensation) and Neuropad (an evaluation of sweat gland function).
Location	Diabetes out-patient clinics – Ljubljana, Slovenia
Design	Cross sectional observational study
Duration of study	Cross sectional
Patient population	
Sample size	42 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n =) and comparator(s) (n =)	All patients tested with all devices/methods
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Methods not known from poster abstract.
Primary outcomes (including scoring methods and timings of assessments)	No significant difference between the results obtained between VibraTip, 128Hz tuning fork, Tip Therm and Neuropad – all of which may detect sensory neuropathy earlier than 10-g Semmes-Weinstein monofilament. The combined use of different screening methods increases the likelihood of early neuropathy detection.

Study name	Garbas et al, 2013 - Can we replace 128-Hz tuning fork testing by VibraTip?
Objective	Comparison of VibraTip with 128Hz tuning fork for identifying DPN
Location	University Medical Centre – Ljubljana, Slovenia
Design	Cross sectional observational study
Duration of study	Cross sectional
Patient population	
Sample size	496 patients with diabetes
Inclusion criteria	Not clear from poster
Exclusion criteria	Not clear from poster
Intervention(s) (n =) and comparator(s) (n =)	
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	Not clear from poster
Primary outcomes (including scoring methods and timings of assessments)	180 patients (right foot) or 181 patients (left foot) couldn't feel tuning fork: 155 patients (right foot) or 162 patients (left foot) couldn't feel VibraTip. The conclusion of the authors was that that finding made the 128Hz tuning fork a more sensitive test than VibraTip. However, they add that such results should be compared with biothesiometer for any firm conclusions to be drawn.

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished

report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

None meet this criterion

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

No real differences in patient populations. The population who are seen in the diabetic retinal screening clinic all had retinopathy, and had therefore had diabetes for some time. Those being seen for annual screening in the diabetes clinic and certainly those in podiatry, were a population of diabetics who probably had more advanced diabetic complications. There were no baseline differences in any of the studies. For almost all of them, patients were exposed to all testing modalities.

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

No subgroup analysis

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

These data when known are mentioned above, for each of the studies quoted.

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

There was only one randomised trial and after 6 months, when the group were re-tested, only a single patient was lost to follow up.

7.5 Critical appraisal of relevant studies

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

Table B7 Critical appraisal of randomised control trials

The randomised control trial is undergoing final analysis and write-up. Randomisation was carried out appropriately of groups that were identical at the outset. There was no subsequent blinding because the 'treatment' group were given a VibraTip device to take home with them. Almost nobody was lost to follow up. There were no 'treatments'.

Study name		
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected		

imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

All the studies in the various centres in Bristol, London, Manchester etc. were cross sectional. There were no confounding factors and the outcomes are essentially unbiased and generated by different expert centres who designed their own studies. Therefore the following table applies to all cross sectional studies:

Study name		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	
Was the exposure accurately measured to minimise bias?	Not Clear	
Was the outcome accurately measured to minimise bias?	Not Clear	
Have the authors identified all important confounding factors?	Not Clear	
Have the authors taken account of the confounding factors in the design and/or analysis?	Not Clear	
Was the follow-up of patients complete?	N/A	
How precise (for example, in terms of confidence interval and p values) are the results?	Not Clear	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.6 Results of the relevant studies

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

Table B9 Outcomes from published and unpublished studies

Study name		**Levy, 2010 -** Preliminary data on VibraTip®, a new source of standardized vibration for bedside assessment of peripheral neuropathy
Size of study groups		100 patients
Study duration	**Time unit**	Cross sectional study
Type of analysis		Comparison of sensitivity/specificity of VibraTip (VT) v's 10g monofilament (MF) v's 128Hz tuning fork (TF)
Outcome	**Name**	Detection of stimulus provided by each device
Effect size	**Value**	VT = 55/100. MF = 53/100. TF = 55/100
	95% CI	
Statistical test	**Type**	Kappa statistic and McNemar's test
	p value	No sig. difference
Other outcome	**Name**	
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Comments		Four patients detected vibration but did not feel monofilament Two patients detected monofilament but did not feel vibration. Author concludes the new device has a vibration perception threshold similar to a standard 128 Hz tuning fork and neuropathy detection was comparable to using a 10 g monofilament. The new device is rapid, reliable and hygienic.

Study name		Bowling et al, 2012 - A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting
Size of study groups		83 patients
Study duration	Time unit	Cross sectional study
Type of analysis		Compares Ipswich Touch Test and VibraTip with current gold-standard tests (Neuropathy Disability Score = or >6 or Vibration Perception Threshold of = or >25V using a neurothesiometer) to detect the 'at-risk' foot.
Outcomes	Ability to detect 'at-risk' foot	The VibraTip and the Ipswich Touch Test results exhibited almost perfect agreement with the vibration perception threshold (Cohen's kappa = 0.973, P < 0.001) and the Neuropathy Disability Score (Cohen's kappa = 0.921, P < 0.001).
Other outcomes for VibraTip compared to vibration perception threshold (VPT) and neuropathy disability score (NDS) – Altman and Bland method.	Sensitivity	Perfect: 100% VPT, 100% NDS
	Specificity	Very High: 96.6% VPT, 90.3% NDS
	Positive predictive value	Very High: 98.2% VPT, 94.5% NDS
	Negative predictive value	Perfect: 100% VPT, 100% NDS
	Positive likelihood ratio	High: 29 VPT, 10.3 NDS
	Negative likelihood ratio	0 VPT, 0 NDS
Comments		Authors conclude that VibraTip is a simple and efficient test, easy to teach, reliable and can be used in any setting. They also conclude that the VibraTip is a reliable and sensitive test for identifying the 'high-risk' foot.

Study name		Bracewell et al, 2012 - Clinical evaluation of a new device in the assessment of peripheral sensory neuropathy in diabetes
Size of study groups		141 patients comparison study
		(18 patients retested 2-3 wks later for inter-rater reliability)
Study duration	Time unit	Cross sectional study
Type of analysis	Intention-to-treat/per protocol	examination for diabetic peripheral sensory neuropathy using a Neurothesiometer (reference method), 10-g monofilament, a 128-Hz tuning fork, a Neurotip and a VibraTip.
Outcome for VibraTip (VT) vs monofilament (MF)	Sensitivity	0.79 (VT) 0.84 (MF)
	Specificity	0.82 (VT) 0.82 (MF)
	Positive predictive value	0.75 (VT) 0.78 (MF)
	Negative predictive value	0.85 (VT) 0.88 (MF)
	Positive likelihood ratio	4.39 (VT) 5.01 (MF)
	Negative likelihood ratio	0.25 (VT) 0.19 (MF)
Statistical test	Type	PASW Statistics 18 and NCSS 2007
	P value	Analysis of the area under the receiver operating characteristic curves showed that the 10-g monofilament was significantly better than the 128-Hz tuning fork (P = 0.0056) and the Neurotip (P = 0.0022), but was no different from the VibraTip (P = 0.3214).
Other outcome	Name	Inter-rater reliability
	Unit	Alpha coefficient
Effect size	Value	0.882
	95% CI	
Statistical test	Type	Cronbach's alpha calculation
	p value	
Comments		Authors conclude VibraTip can be considered a useful tool for screening for peripheral sensory neuropathy in diabetes

Study name		**Nizar et al, 2014 – Diagnostic accuracy of the VibraTip™ in detection of diabetic peripheral neuropathy.**
Size of study groups		100 patients (50 DPN +ve, 50 DPN –ve)
Study duration	**Time unit**	Cross sectional, observational study
Type of analysis		To compare the diagnostic accuracy of VibraTip compared to tuning fork in patients with neurothesiometer-confirmed (@20V) neuropathy
Outcome for VibraTip (VT) vs tuning fork (TF)	**Sensitivity 95% CI**	92% (VT) (80.8-97.8%) 40% (TF) (26.4-54.8%)
	Specificity 95% CI	94% (VT) (83.4-98.7%) 100% (TF) (92.9-100%)
Statistical test	**Type**	Not known
	p value	A statistically significant difference ($p<0.001$) between VT and TF sensitivity results for subjects +ve for neuropathy
Other outcomes	**Positive predictive value**	94% (VT) 100% (TF)
	Negative predictive value	92% (VT) 63% (TF)
	Positive likelihood ratio	15.3 (VT) ∞
Comments		The authors conclude that the VibraTip is comparable to the Neurothesiometer, and superior to the Tuning Fork, in the accurate detection of peripheral neuropathy and could be a useful screening tool in clinical practice.

Study name		Urbancic-Rovan et al. 2012 - Screening for neuropathy - do additional testing methods make sense?
Size of study groups	**Treatment**	42 patients
	Control	
Study duration	**Time unit**	Cross sectional observational study
Type of analysis	**Intention-to -treat/per protocol**	To compare the screening results of VibraTip (VT) compared to tuning fork (TF), monofilament (MF), Tip Therm (TT) [an instrument which reveals impaired temperature sensation] and Neuropad (NP) [an evaluation of sweat gland function].
Outcome	**Name**	No significant difference between VT, TF, TT, NP (all p>0.05). MF significantly inferior to other methods.
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Other outcome	**Name**	
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Comments		Methods not fully clear from poster abstract

Study name		Garbas et al, 2013 - Can we replace 128-Hz tuning fork testing by VibraTip?
Size of study groups	**Treatment**	496 patients
	Control	
Study duration	**Time unit**	Cross sectional observational study
Type of analysis	**Intention-to-treat/per protocol**	
Outcome		180 patients (right foot) or 181 patients (left foot) couldn't feel tuning fork: 155 patients (right foot) or 162 patients (left foot) couldn't feel VibraTip.
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	Not clear from poster
	p value	
Other outcome	**Name**	
	Unit	
Effect size	**Value**	
	95% CI	
Statistical test	**Type**	
	p value	
Comments		The conclusion of the authors was that that finding made the 128Hz tuning fork a more sensitive test than VibraTip. However, they add that such results should be compared with biothesiometer for any firm conclusions to be drawn.

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

7.7 Adverse events

there were no adverse events expected or recorded in any evaluations and no adverse events have been reported from current usage.

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

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

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

N/A

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

N/A

Table B10 Adverse events across patient groups

	Time period 1			***Time period 2 etc.***		
	Intervention **% of patients (n = *x*)**	***Comparator*** **% of patients (n = *x*)**	**Relative risk (95% CI)**	***Intervention*** **% of patients (n = *x*)**	***Comparator*** **% of patients (n = *x*)**	**Relative risk (95% CI)**
Class 1 (for example, nervous system disorders)						
Adverse event 1						
Adverse event 2						
Class 2 (for example, vascular disorders)						
Adverse event 3						
Adverse event 4						
CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency						

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

N/A

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

N/A

7.8 Evidence synthesis and meta-analysis

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

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

Several of the small studies compared the available methods for identifying neuropathy. In general, they found as expected that VibraTip is as good as other methods. What has not been addressed in the studies is that VibraTip is a very rapid way of assessing the presence or absence of neuropathy.

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

This would not be appropriate for a series of small observational studies

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

The most compelling advantages of VibraTip are characteristics that are difficult to address in trials. For example, VibraTip, unlike tuning forks, which tend to be stolen or locked away and neurothesiometers, which are expensive and too large and heavy to transport to the wards, is easy to carry around and therefore

much more likely to be available at the point of use. VibraTip is also bacteriologically cleaner, and is a much faster and more straightforward way to test for the presence of neuropathy.

The question then is whether when used under trial conditions, VibraTip is as good as monofilament, tuning fork and neurothesiometer. All published studies show that it is at least as good as a tuning fork or monofilament and probably as good as a neurothesiometer in identifying patients who have neuropathy. Only one trial, comparing it to a tuning fork, holds that a tuning fork is more sensitive than VibraTip. As other studies show that VibraTip and neurothesiometer (gold standard) are exactly comparable, the results of this one study (in meeting abstract form) would suggest if anything that a tuning fork is too sensitive and making diagnoses of reduced vibration sensation perception in patients who are not at risk of foot damage.

7.9 Interpretation of clinical evidence

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

As above. VibraTip is a clean, safe, easy to use, rapid, durable, and readily available source of standardized vibration that produces results similar to neurothesiometer.

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

Only a few small observational studies are available, not least because the utility of the device is self-evident.

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

Response

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

Medicine on the shop floor is very time constrained. To have utility, devices have to be available and quick, easy and reliable in use. Monofilaments change behaviour after just a few uses and are slow to use. They cannot be cleaned with a wipe because this too alters their behaviour. VibraTip is easy to transport, quick and clean. It has a built in negative control. You touch the patient without activating the device and ask whether they felt vibration. It doesn't allow for uncertainty seen with monofilament and tuning forks. If under trial conditions VibraTip comes out as equivalent, in practice, it will be preferable.

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

Any patient with diabetes or at risk of disease, trauma or drug-induced neuropathy.

Section C – Economic evidence

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

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

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

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

8. Existing economic evaluations

8.1. Identification of studies

The evaluations for the VibraTip device have been focussed on establishing its clinical utility for assessment of Diabetic Peripheral Neuropathy (DPN), against the established comparator devices as indicated in the NICE Scope document:

- **10g Monofilament.**
- **Calibrated Medical Tuning Fork (at 128 Hz).**
- **Biothesiometer, also called Neurothesiometer: this is the gold standard.**

A satisfactory demonstration of comparability provides a baseline for direct economic assessment based on the product pricing and utility. Further considerations of benefit are examined in the economic sensitivity analysis including uptake of use of the device and more effective DPN screening.

The published and unpublished literature is listed in section 7.3 with Tables B3 and B4 and discussion of the detailed findings given in sections 7.4, 7.6 and

7.8.2. The publications are listed in the References section, at the end of Section 9, with the numbering used for reference in the discussion and the sources used. A PDF copy of items 1-9 has been provided together with the Clinical Submission.

The critical conclusions from these studies irrespective of ease of use were:

- **VibraTip is of comparable performance to the Neurothesiometer.**
- **VibraTip is comparable to the 10g Monofilament.**
- **VibraTip is superior to the Medical Calibrated 128 Hz Tuning Fork.**

It is valid to note that VibraTip relies upon the amplitude of the vibration delivered in the same way as the Neurothesiometer and with a steady transmission unlike the Tuning Fork which decays in strength from the time of initiation.

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

To address the basic economic comparison the important data are the list prices of VibraTip and the comparator devices. In addition to VibraTip, the supplier figures for comparator devices were obtained from main manufacturer

and distributor list prices for the products concerned. An essential aspect was to obtain a reasoned price for such products rather than the many low cost items being offered from China and India as found in a Google search. Performance comparisons of commercially available monofilaments have demonstrated that some products are not fit for purpose [10, 11] so it is envisaged that purchasers in the UK will buy reliable products from reputable wholesalers such as Williams Medical Supplies and Canonbury Products with average list prices from these suppliers used. The figures used in the analysis are as follows, all exclusive of VAT:

- **VibraTip** at £ 9.95 – product list price as noted in the Clinical sections.
- **10g Monofilament** - £ 15.20. Ranged from £ 10 -13 and £ 25 for fully tested. There are lower cost single use products also.
- **128 Hz Medical Tuning Fork** - £ 28 used with prices ranging from £ 41.50 to £ 109.10. A Diabetic Medical Tuning Fork was £ 13.62 from Amazon!
- **Neurothesiometer** - £ 1,200 with others quoted at £ 1,176.69 to £ 1,800. Figures from **Horwell** and a range of UK and US supply companies.

Conventional database searches were not appropriate, both from the focus being on device prices and the complete listing of relevant clinical studies as demonstrated above.

The Google search terms were as the **bold product title** as above with the additional terms **Diabetic Prices** to widen or narrow the findings.

The follow up was to interrogate the company (supplier & distributor) **web sites** as identified from the internet search and contained **Application Notes**,

Price Lists and **User Product Reviews** when provided. The two specific supplier sites were: www.wms.co.uk and www.canonbury.com The US supplier of Monofilaments, **Medical Monofilaments**, which cites the FDA regulations on viability of such products was www.medicalmonofilament.com .

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Routine clinical populations selected to show test equivalence.
Interventions	Interventions were not changed as a result of the studies.
Outcomes	VibraTip equivalent to Neurothesiometer and Mono-Filament and superior to Tuning Forks.
Study design	Direct comparisons on same patients but blinded as to vibration on or off.
Language restrictions	None.
Search dates	N/A. All studies as referenced above.
Exclusion criteria	
Population	These questions are Not Applicable.
Interventions	
Outcomes	
Study design	
Language restrictions	
Search dates	

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

As noted above all the known clinical assessments have been included that are related to the actual product performance. The key clinical aspects of implementation have been taken from NHS sources and/or as quoted by NICE and for staff costs where applicable from the Unit Costs of Health & Social Care, 2013 by Lesley Curtis, PSSRU, University of Kent. The Assumptions table identifies these sources or those contained in the References section.

8.2. Description of identified studies

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

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Ref 1	Bristol	Monofilament (M/F), Tuning Fork (T/F)	100 consecutive annual review patients	As per Price Lists above	VibraTip as good as or better than comparator devices.	Rapid & reliable item that is readily available & better hygienically.
Ref 2	Manchester	Ipswich Touch, Neurothesiometer, neuropathy derived score	83 diabetic clinic patients.	As Price List with Ipswich no device	Identical to Ipswich and close to scores from Neurothesiometer. 98% PPV & 100% NPV.	Mixed operator type showed utility & clinical outcome of VibraTip.
Ref 3	Nottingham	Neurothesiometer, M/F & T/F	141 routine patients	As Price List	VibraTip equal to Gold Standard and M/F and superior to T/F.	Reliable. Same results from intra-operator use.
Ref 4	London, Warwick & Birmingham	Neurothesiometer & T/F	50 +ve & 50 –ve, by Neurothesiometer	As Price List	VibraTip comparable to the Neurothesiometer with PPV of 94% & NPV of 92% but T/F NPV of 63%.	Daily use for screening with benefits of portability & no energy needed.
Ref 5	Slovenia	T/F, M/F	42:13 female, 29 male.	As Price List	Equal performance & ease of use.	VibraTip earlier than M/F.
Ref 6	Slovenia	T/F	456: 213 Female & 283 Male	As Price List	Different results to T/F but no control for which was right.	Benefit of no cueing of touch & ease of use.
Ref 7	Bristol	Life usage study	N/A	N/A	Stable for > 5,000 activations in	Does not run down on

					routine use.	standing.
Ref 8	Bristol	User tests on …	…a big toe manikin	N/A	21 staff users of T/Fs – more consistent vibration with VibraTip.	Shows constancy & lack of user affects plus avoids cueing by patients.
Ref 9	Bristol	Self-testing option as motivation for better self-care.	Routine well established diabetics	N/A	Suggests complacency shown by diabetics may be broken down by provision of VibraTip.	Indicates that VibraTip may be useful for home use for high risk patients.

Notes: M/F is 10g Mono-Filament, T/F is 128 Hz Tuning Fork. PPV is Positive Predictive Value & NPV is Negative Predictive Value

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

Table C3 Quality assessment of health economic studies

Study name This table summarises all 9 studies noted above.		
Study design	**Primarily to demonstrate clinical utility with economic assessment possible based on device prices and outcomes.**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Focus was on demonstration of clinical equivalence & utility.
2. Was the economic importance of the research question stated?	Not Clear	Use of device could be more widespread and problems of ulcers and amputations reduced.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Not directly economic but based on clinical equivalence findings.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Compared with established methods, including Neurothesiometer as the Gold Standard but this is not portable and requires energy source.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	As per items 2 & 3 above.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not Clear	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Detailed statistical tests in several of the studies.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	As per Table C2 and Section 7.4.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Clinical effectiveness that allows application of established procedures with related costs.

12. Were the methods used to value health states and other benefits stated?	Yes	Clinical quality of Life assessed in Ref. 9.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Summarised in Table C2.
14. Were productivity changes (if included) reported separately?	No	Inferred from the equivalence and usage studies and addressed further in the Sensitivity Analysis.
15. Was the relevance of productivity changes to the study question discussed?	No	Addressed in the Sensitivity Analysis.
16. Were quantities of resources reported separately from their unit cost?	No	See Pricing Analysis.
17. Were the methods for the estimation of quantities and unit costs described?	No	See Pricing Analysis & Assumptions table.
18. Were currency and price data recorded?	No	See Pricing Analysis.
19. Were details of price adjustments for inflation or currency conversion given?	No	See Pricing Analysis & Assumptions table.
20. Were details of any model used given?	N/A	Economic Model follows later.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The “model” was as defined in each study from a clinical and usage perspective.
22. Was the time horizon of cost and benefits stated?	No	Considered in the Economic Model.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	Considered in the Economic Model and Sensitivity Testing.
27. Was the approach to sensitivity analysis described?	N/A	Only provided for clinical sensitivity not economic factors.
28. Was the choice of variables for sensitivity analysis justified?	N/A	Considered in the Economic Model and Sensitivity Testing.

29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	All the comparator devices as described in the NICE Scope document were analysed for clinical performance with economic analysis derived for the Economic Model.
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Aggregated.
33. Was the answer to the study question given?	Yes	Clinical with economic aspects inferred or derived as covered by the Assumptions table.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9. De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1. Description of the de novo cost analysis

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

The cost analysis addresses the items raised in the Scope with:

- **Comparisons versus 10g Monofilament and Calibrated Tuning Fork devices,**
- **Use in Primary and Secondary settings with impact for NHS and Social Care services.**
- **The analysis considers the current dynamics with the on-going populations of Diabetics and their different conditions. A "window of Reality" not just projecting the course of only newly diagnosed patients.**
- **Time horizon impact over 3 years is assessed.**
- **Sensitivity analysis to consider the different variables and their uncertainties.**

Patients

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

Patients are Type 1 or 2 Diabetics that are undergoing routine checks for Diabetic Peripheral Neuropathy (DPN). According to NICE Guidelines these patients should at least have annual checks but will include higher risk patients having more regular checks, at one or three monthly

intervals. In practice this is not effectively carried out – *Diabetes UK - March 5th, 2014.*

Technology and comparator

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

From the clinical studies each of the comparator devices listed in the NICE Scope document was covered. In the Economic Analysis the VibraTip device was not compared with the "Gold Standard" Neurothesiometer as this is a highly expensive device used by specialists and in research: routine use of VibraTip would not replace use of this equipment.

As noted in the Clinical section, use of a 10g Monofilament is well established as matching the Neurothesiometer in effectiveness for routine screening and monitoring of high risk patients. The reported clinical studies for VibraTip showed comparable performance to use of Diabetic Monofilament.

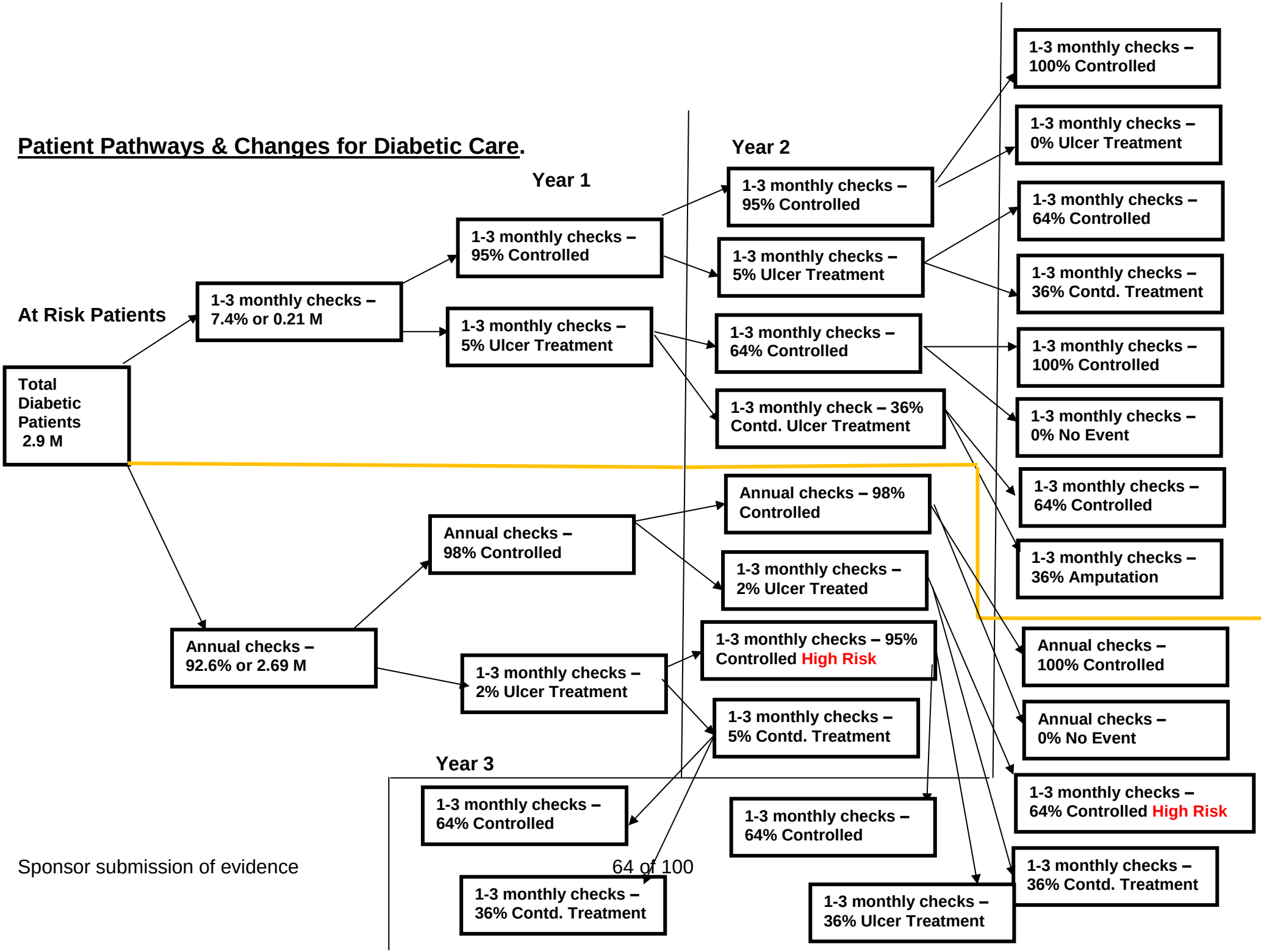
Model structure

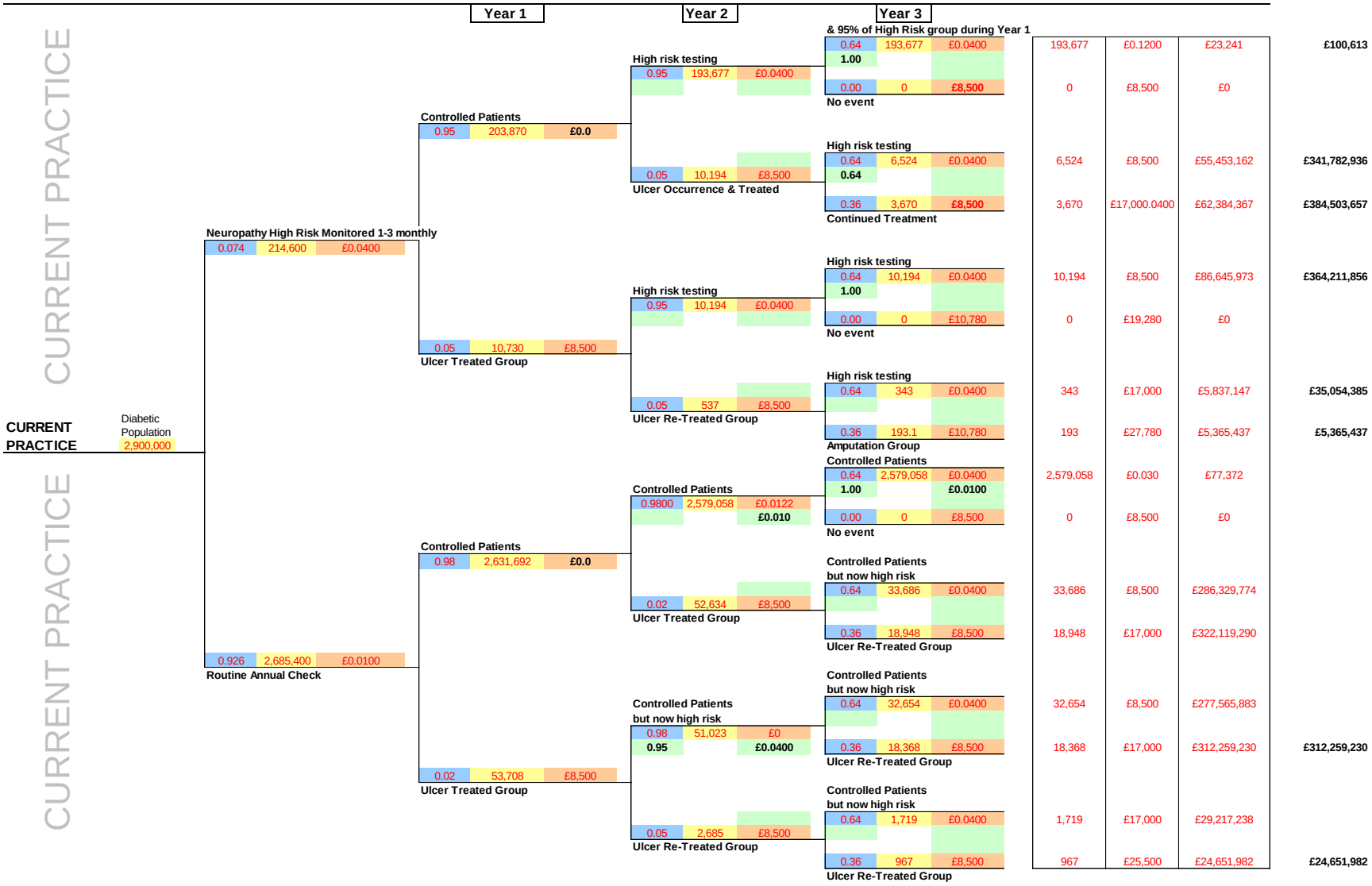
9.1.4. Provide a diagram of the model structure you have chosen.

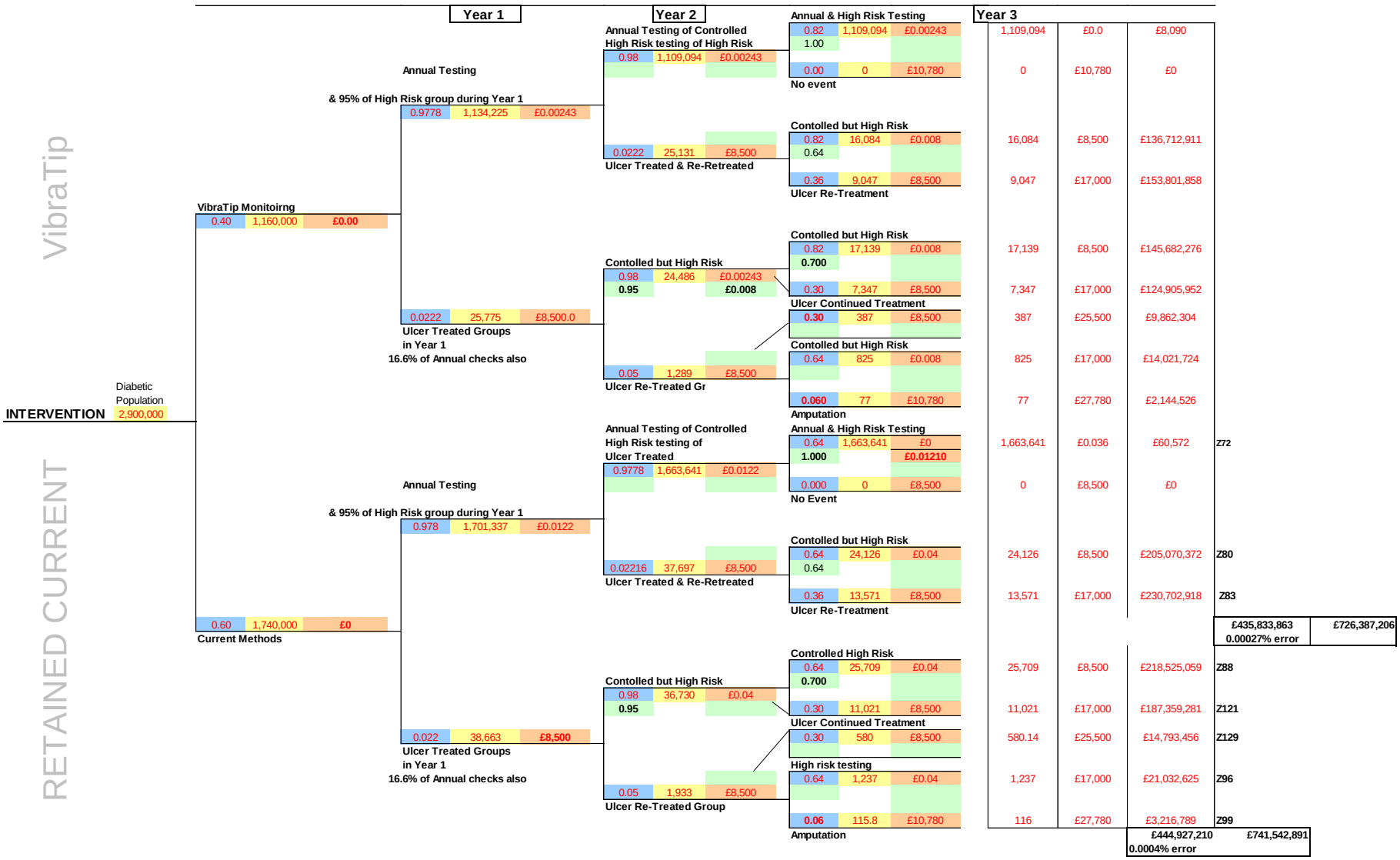
The Overview of the Clinical Pathways that are the structure for the Economic Model is given below followed by a picture of the Excel model for the current situation with the cost elements of the devices shown.

The complete Excel based model is supplied separately as requested.

Patient Pathways & Changes for Diabetic Care.




CURRENT PRACTICE
CURRENT PRACTICE
Year 1
Year 2
Year 3
CURRENT PRACTICE
Diabetic Population 2,900,000
Neuropathy High Risk Monitored 1-3 monthly
0.074 214,600 £0.0400
0.926 2,685,400 £0.0100
Routine Annual Check
Controlled Patients
0.95 203,870 £0.0
0.05 10,730 £8,500
Ulcer Treated Group
Controlled Patients
0.98 2,631,692 £0.0
0.02 53,708 £8,500
Ulcer Treated Group
High risk testing
0.95 193,677 £0.0400
0.05 10,194 £8,500
Ulcer Occurrence & Treated
High risk testing
0.95 10,194 £0.0400
0.05 537 £8,500
Ulcer Re-Treated Group
Controlled Patients
0.9800 2,579,058 £0.0122
£0.010
0.02 52,634 £8,500
Ulcer Treated Group
Controlled Patients but now high risk
0.98 51,023 £0
0.95 £0.0400
0.05 2,685 £8,500
Ulcer Re-Treated Group
& 95% of High Risk group during Year 1
0.64 193,677 £0.0400
1.00
0.00 0 £8,500
No event
193,677 £0.1200 £23,241 £100,613
0 £8,500 £0
High risk testing
0.64 6,524 £0.0400
0.64
0.36 3,670 £8,500
Continued Treatment
6,524 £8,500 £55,453,162 £341,782,936
3,670 £17,000.0400 £62,384,367 £384,503,657
High risk testing
0.64 10,194 £0.0400
1.00
0.00 0 £10,780
No event
10,194 £8,500 £86,645,973 £364,211,856
0 £19,280 £0
High risk testing
0.64 343 £0.0400
0.36 193.1 £10,780
Amputation Group
343 £17,000 £5,837,147 £35,054,385
193 £27,780 £5,365,437 £5,365,437
Controlled Patients
0.64 2,579,058 £0.0400
1.00 £0.0100
0.00 0 £8,500
No event
2,579,058 £0.030 £77,372
0 £8,500 £0
Controlled Patients but now high risk
0.64 33,686 £0.0400
0.36 18,948 £8,500
Ulcer Re-Treated Group
33,686 £8,500 £286,329,774
18,948 £17,000 £322,119,290
Controlled Patients but now high risk
0.64 32,654 £0.0400
0.36 18,368 £8,500
Ulcer Re-Treated Group
32,654 £8,500 £277,565,883
18,368 £17,000 £312,259,230 £312,259,230
Controlled Patients but now high risk
0.64 1,719 £0.0400
0.36 967 £8,500
Ulcer Re-Treated Group
1,719 £17,000 £29,217,238
967 £25,500 £24,651,982 £24,651,982


VibraTip
RETAINED CURRENT
INTERVENTION
Diabetic Population
2,900,000
VibraTip Monitoirng
0.40 1,160,000 £0.00
Current Methods
0.60 1,740,000 £0
Year 1
Annual Testing
& 95% of High Risk group during Year 1
0.9778 1,134,225 £0.00243
0.0222 25,775 £8,500.0
Ulcer Treated Groups in Year 1
16.6% of Annual checks also
Annual Testing
& 95% of High Risk group during Year 1
0.978 1,701,337 £0.0122
0.022 38,663 £8,500
Ulcer Treated Groups in Year 1
16.6% of Annual checks also
Year 2
Annual Testing of Controlled
0.98 1,109,094 £0.00243
Contolled but High Risk
0.98 24,486 £0.00243
0.95 £0.008
Ulcer Treated & Re-Retreated
0.0222 25,131 £8,500
Ulcer Re-Treated Gr
0.05 1,289 £8,500
Annual Testing of Controlled High Risk testing of Ulcer Treated
0.9778 1,663,641 £0.0122
Contolled but High Risk
0.98 36,730 £0.04
0.95
Ulcer Treated & Re-Retreated
0.02216 37,697 £8,500
Ulcer Re-Treated Group
0.05 1,933 £8,500
Annual & High Risk Testing
0.82 1,109,094 £0.00243
1.00
No event
0.00 0 £10,780
Contolled but High Risk
0.82 16,084 £0.008
0.64
Ulcer Re-Treatment
0.36 9,047 £8,500
Contolled but High Risk
0.82 17,139 £0.008
0.700
Ulcer Continued Treatment
0.30 7,347 £8,500
Contolled but High Risk
0.64 825 £0.008
Amputation
0.060 77 £10,780
Annual & High Risk Testing
0.64 1,663,641 £0
1.000 £0.01210
No Event
0.000 0 £8,500
Contolled but High Risk
0.64 24,126 £0.04
0.64
Ulcer Re-Treatment
0.36 13,571 £8,500
Controlled High Risk
0.64 25,709 £0.04
0.700
Ulcer Continued Treatment
0.30 11,021 £8,500
High risk testing
0.64 580 £8,500
Amputation
0.06 1,237 £0.04
115.8 £10,780
Year 3
1,109,094 £0.0 £8,090
0 £10,780 £0
16,084 £8,500 £136,712,911
9,047 £17,000 £153,801,858
17,139 £8,500 £145,682,276
7,347 £17,000 £124,905,952
387 £25,500 £9,862,304
825 £17,000 £14,021,724
77 £27,780 £2,144,526
1,663,641 £0.036 £60,572 Z72
0 £8,500 £0
24,126 £8,500 £205,070,372 Z80
13,571 £17,000 £230,702,918 Z83
£435,833,863
0.00027% error
£726,387,206
25,709 £8,500 £218,525,059 Z88
11,021 £17,000 £187,359,281 Z121
580.14 £25,500 £14,793,456 Z129
1,237 £17,000 £21,032,625 Z96
116 £27,780 £3,216,789 Z99
£444,927,210
0.0004% error
£741,542,891

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

The elements of the decision tree used in the Economic Model are detailed below. The probabilities were used based on best average levels as indicated in the Assumptions Table. The Device Cost items were either for the comparators (Monofilament used in the example shown) or VibraTip and varied in the sensitivity testing described below. Ulcer and Amputation costs included to assess impact of improved detection and better control that might be possible.

Product	VibraTip Neuropathy Assessment Device

The detailed components of Cost items are given in the Assumptions Table.

A "Selection Decision" has no cost but is allowed for in the pathway probabilities.

Bold Items in the Decision Tree are manually input items without changing structure of the general model.

Colum Number	Factors (Blue Cell)	Pathway Item with Unit costs (Yellow Cell for Patient Nos.)	Element Costs	Total Cost (Pink Cell)
Col. 1 Start point	2.9 M	The Total of Diagnosed Diabetic Patients 2013		
Col.2 **Selection for High Risk or Routine Checks**	7.4% 92.6%	Incidence of patients under high risk assessment Routine Assessment	4 X cost of Device 1 X cost of Device	£ 0.04 £ 0.01
Col. 3: **Year 1 Treatments for High Risk Group**	95% 5%	Controlled Patients Ulcer develops & treated – includes on-going patients	No Cost Treatment at £ 8,500	£ 0 £ 8,500
Col. 3 **Year 1 Treatments for Annual Check-up Group**	98% 2%	Controlled Patients Ulcer develops & treated includes on-going patients.	No Cost Treatment at £ 8,500	£ 0 £ 8,500
Col. 4: Year 2 **High Risk Group Controlled**	95% 5%	Controlled Patients Ulcer develops & treated includes on-going patients.	4 X cost of Device Treatment - £ 8,500	£ 0.04 £ 8,500
Col 4. Year 2 **High Risk Group with Treated Ulcers**	95% 5%	Controlled Patients Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500

Col 4 Year 2 **Annual Check Up Group Controlled**	98% 2%	Controlled Patients Ulcer develops & treated.	1 X cost of Device Treatment at £ 8,500	£ 0.01 £ 8,500
Col 4 Year 2 **Annual Check Up Group with treated Ulcers**	98% 2%	Controlled Patients but now High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500
Col. 5: Year 3 **High Risk Group Controlled**	100%	Controlled Patients No other event	4 X cost of Device No Cost	£ 0.04 £ 0
Col 5. Year 3 **High Risk Group with Treated Ulcers**	64% 36%	Controlled Patients Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500
Col 5 Year 3 **High Risk Group with Treated Ulcers but Controlled**	100%	Controlled Patients No other event	4 X cost of Device No Cost	£ 0.04 £ 0
Col 5 Year 3 **High Risk Group with Treated Ulcers in Years 1 & 2**	64% 36%	Now Controlled Patients Amputation Group	4 X cost of Device Treatment at £10,780	£ 0.04 £10,780
Col 5 Year 2 **Annual Check Up Group Controlled**	100%	Controlled Patients No other event	1 X cost of Device No Cost	£ 0.01 £ 0
Col 5 Year 3 **Annual Check Up Group with treated Ulcers in Year 2**	64% 36%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500
Col 5 Year 3 **Annual Check Up Group with Ulcer in Year 1**	64% 36%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500
Col 5 Year 3 **Annual Check Up Group with treated Ulcers in Year 1**	64% 36%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment at £ 8,500	£ 0.04 £ 8,500

40% Uptake of VibraTip – Upper Part of Decision Tree Model

Colum Number	Factors (Blue Cell)	Pathway Item with Unit costs (Yellow Cell for Patient Nos.)	Element Costs	Total Cost (Pink Cell)
Col. 1 Start point	2.9 M	The Total of Diagnosed Diabetic Patients 2013		
Col.2 **VibraTip Uptake Year 1**	40% 60%	Reasonable uptake of use for VibraTip. Input variable Retained use of Current method [**Monofilament** here]	Decision Item No Cost	£ 0.00 £ 0.00
Col. 3: **Year 1 Annual & High Risk Group VibraTip & Ulcer Treated**	97.8% 2.2%	Controlled Patients with both Annual & 95% of High Risk Group 4X/year Ulcer treated patients from High Risk & Annual checks	Annual @ £ 0.002 High Risk @ £ 0.008 Treatment at £ 8,500 plus Annual checks	£ 0.00243 £ 8,500.01
Col. 3: **Year 1 Annual & High Risk Group Current & Ulcer Treated**	97.8% 2.2%	Controlled Patients with both Annual & 95% of High Risk Group 4X/year Ulcer treated patients from High Risk & Annual checks	Annual @ £ 0.01 High Risk @ £ 0.04 Treatment at £ 8,500 plus Annual checks	£ 0.0122 £ 8,500.01
Col 4 **Year 2 Annual Check Up & High Risk Group Controlled with VibraTip**	98% 2%	Controlled Patients Ulcer develops & treated.	Annual @ £ 0.002 High Risk @ £ 0.008 Treatment at £ 8,500	£ 0.00243 £ 8,500
Col. 4: **Year 2 High Risk Group Controlled with VibraTip**	95% 5%	Controlled Patients Ulcer develops & treated includes on-going patients.	4 X @ £ 0.002 Treatment at £ 8,500	£ 0.008 £ 8,500
Col 4 **Year 2 Annual Check Up & High Risk Group Controlled with Current Method**	97.8% 2.2%	Controlled Patients Ulcer develops & treated.	Annual @ £ 0.002 High Risk @ £ 0.008 Treatment at £ 8,500	£ 0.00243 £ 8,500
Col. 4: **Year 2 High Risk Group Controlled with Current Method**	95% 5%	Controlled Patients but High Risk Ulcer develops & treated includes on-going patients.	4 X @ £ 0.01 Treatment - £ 8,500	£ 0.04 £ 8,500

Col 5 **Year 3** **Annual Check Up Group Controlled With VibraTip**	100%	Controlled Patients No other event	Annual @ £ 0.002 High Risk @ £ 0.008 No Cost	£ 0.00243 £ 0
Col 5 **Year 3** **Ulcer treated with Ulcers in Year 2 with VibraTip**	64% 36%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment - £ 8,500	£ 0.008 £ 8,500
Col 5 **Year 3** **Annual Check Up Group with Ulcer in Year 1 with VibraTip**	70% 30%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment - £ 8,500	£ 0.008 £ 8,500
Col 5 **Year 3** **High Risk Group with Treated Ulcers in Years 1 & 2 With VibraTip**	30% 64% 6%	Ulcer re-treatment or recurrence. High Risk Controlled Patients Amputation Group	Treatment - £ 8,500 4 X cost of Device Treatment at £10,780	£ 8,500 £ 0.008 £10,780
Col 5 **Year 3** **Annual Check Up Group Controlled With Current**	100%	Controlled Patients No other event	Annual @ £ 0.01 High Risk @ £ 0.04 No Cost	£ 0.0121 £ 0
Col 5 **Year 3** **Ulcer treated with Ulcers in Year 2 Current Method**	64% 36%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment - £ 8,500	£ 0.04 £ 8,500
Col 5 **Year 3** **Annual Check Up Group with Ulcer in Year 1 with Current**	70% 30%	Controlled Patients but as High Risk Ulcer re-treatment or recurrence.	4 X cost of Device Treatment - £ 8,500	£ 0.04 £ 8,500
Col 5 **Year 3** **High Risk Group with Treated Ulcers in Years 1 & 2 With Current**	30% 64% 6%	Ulcer re-treatment or recurrence. High Risk Controlled Patients Amputation Group	Treatment - £ 8,500 4 X Cost of Device Treatment at £10,780	£ 8,500 £ 0.04 £10,780

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

Assumptions Table.

Item	Unit
Diabetic Population Diagnosed	2.9 M [1]
Proportion of Patients Susceptible of developing DPN	60% [1]
Prevalence of DPN for Diabetics	7.4% [1]
Proportion of Diabetics that Develop Foot/Leg Ulcers	6% [2]
Cost of treatment for Foot Ulcers	£ 8,500 [3]
Recurrence Rate of Ulcers after treatment	10% [2]
Proportion of High Risk Diabetics resulting in Amputation	2% [3]
Cost of Amputation	£ 10,780 [4]
Amputations for Diabetic Patients	0.5% of all or 26% of Foot Ulcer group [5]
Cost of VibraTip	£ 9.95 [6]
Cost of 280 Hz Tuning Fork (Median used)	£ 28 [7]
Cost of 10g Mono-Filament (Median used)	£ 15.2 [8]
Cost of Neurothesiometer	£ 1,200 [9]
NHS Tariff for Foot Ulcer treatment for recoverable cost benefit	£ 700 + [10]
Improved diagnostic capacity versus current procedures	1-5% [11]
Cost of Death within NHS	£ 8,000 [12]
Consultation Costs – cost neutral in product comparison	£ 137 [13]
Reported pressure testing from 8,020 practices in QOF 2012/13.	85.6%[14]

Note: The Assumption references above are separate from the Clinical References given at the end of this Section C.

The Assumption Table (Ref. 2 Jeffcoate & Hennings, 2003) gives incidence of Ulcers in the Diabetic population at about 6%. The Pathway model is a snapshot of the 3 year status and picks up the incidence of Ulcers over this time span. The 6% was a figure around the level from all the papers quoted in that ref. 2. In the paper one relevant study quoted states "the cumulative 3 year incidence figure was 5.8%"!

In the **Pathway** it is assumed that Ulcer incidence would be higher with the High Risk group but that some of the Annual Check group would also develop Ulcers.

The assumptions used are designed to reflect this outcome assumption and provide an overall incidence that matches the referenced figure.

- **Year 1 – 10.7 K ulcer patients from the High Risk group with 5% incidence rate.**

  53.7 K from the Annual Check group at 2% incidence rate.
- **Year 2 – 10.2 K new ulcer patients from the High Risk group.**

  53.7 K new ulcer patients from the Annual Check group.
- **Year 3 – 20 K from recurrence patients previously treated for Ulcers but clear in Year 2.**
- **In Year 3 there is the possibility of ulcer incidence from the Controlled patients from either High Risk or Annual Check groups. This is noted as No Event and is a conservative view of the status in order to construct the Decision Tree economic Model.**
- **Total within this snapshot = 148 K or an incidence level of 5.1%.**

In the **Economic Model** from the Current Pathway position the incidence of Ulcers in the Core model from the individual cells is 146 K or 5.03%. Converting the Non-Event Cells to incidences at the appropriate level for either High Risk (5%) or Annual Check (2%) gives an incidence total of 208 K or 7.2%.

These figures show the Economic Model is a close reflection of reality and is a slightly conservative view of ulcer incidence but is a sound basis for comparison of the cost effectiveness of the different device alternatives.

Sources of Information used for assumptions:

1. NICE figures as quoted in Scope. CG10 (2004), CG 119 (2011), CG15 (2011).
2. Jeffcoate & Harding, Diabetic Foot Ulcers, Lancet, 2003 May 3362 (9368), 1545-51. Ramsay et al, Diabetes Care 22, 382-387, 1999. Boulton et al New England Journal of Medicine 2004, 352 48-55, 2004 from Manchester UK, reported 15% develop ulcers. Diabetes UK quote figure of 10%.
3. Figures used with CG 10 and CG 119 also. Posnet et al The Burden of Chronic Wounds in the UK, 2008, Nursing Times 104:3 44-45 quoted £ 5,200.
4. Figures quoted in NICE Costing Standard for In-Patient Management of Diabetic Foot, March 2011 with reference to NHS Tariff QZ11B (£ 6,759 or £ 9,405 without complications) & QZ11A (£ 13,413 or £ 13,552 with complications). Overall average of £ 10,780 used and compares with earlier figures for E115, E113 & E105 that ranged from £ 8.3 K to £ 14.5 K.
5. HES data & NICE CG 119 of 2011. See also references quoted in CG119 of Reiber *et al*, 1999 and Boulton *et al* 2005.
6. McCallan Medical Quoted figure.
7. Commercial figures from suppliers from web site searches (median used).
8. Commercial figures from suppliers from web site searches (median used).
9. Company listed prices: *Horwell, Misty Medical, Science Lab Co.*
10. NHS data. QZ 12Z for Foot Procedures and JC18Z to JC20Z range from £ 120 to £ 771 for the treatment with other costs additional.
11. From clinical studies potential from improved performance & ease of use with enhanced early diagnosis. Arbitrary 1% figure used for sensitivity analysis.
12. Scottish Cancer Therapy Network Newsletter Autumn 2003.
13. PSSU Unit costs of Health & Social Care.
14. QOF April 2012-March 2013 at http://www.hscic.gov.uk/catalogue/PUB12262

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

The economic model is designed to determine the cost benefits of using VibraTip for routine screening and monitoring of Diabetic patients for Neuropathy as a precursor or indicator of increased risk of developing an ulcer that in some cases results in amputation.

The simplicity of use of VibraTip has the potential to provide improved implementation of the NICE Guidelines for this type of test and reduced incidence of these further consequences of Diabetes by improved patient care and behaviour.

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

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	3 years	Represents an overview of assessment and progression for Diabetics.	
Discount of 3.5% for costs	3.5%	Added in final figures.	
Perspective (NHS/PSS)	NHS & Primary Care	Not differentiated overall	
Cycle length			
NHS, National Health Service; PSS, Personal Social Services			

9.2. Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 7). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

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

Primary analysis is the device cost comparisons based on the clinical performance reported in the Clinical Submission. Projections were made on possible improved outcomes due to the potential of VibraTip to be better utilised in the DPN assessment with possible improved patient care and reductions in Ulcers and perhaps Amputations.

Both improved usage of current products and varied acceptance of VibraTip are examined in the sensitivity analysis.

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

No – the three year period only was covered, but see 9.2.1 regarding relative effectiveness of the different devices.

9.2.3. Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No.

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

Not appropriate.

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

Clinical advice and opinion for this submission has been sought solely from Professor Andrew Levy of the Henry Wellcome Labs for Integrative Neuroscience and Endocrinology, University of Bristol and University Hospitals Bristol NHS Foundation Trust. Budgetary constraints have not permitted the sponsor to invest in Clinical Advisory Board activities normally associated with larger companies. Prof Levy was the obvious choice for input as he has been involved, as an employee of the product's IP owner (UH Bristol NHS FT), with the justification and development of VibraTip since its inception. Long-term commercial viability of the device may trigger royalty payments to UH Bristol NHS FT.

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

All parameters used to estimate cost are detailed in the Assumptions table above. The probabilities at each step are detailed in the explanation of the Economic Model as derived from the Assumptions table. The table C5 did not appear to be relevant for this analysis and was not completed.

Table C5 Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)	Source
Age	*A years*	*x to y (normal)*	
Overall survival	*B months*	*x to y (Weibull)*	
Cost of *[X]*	£	*x to y (gamma)*	
[Insert other relevant variables]			
CI, confidence interval			

9.3. Resource identification, measurement and valuation

NHS costs

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

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

The devices are a cost item recovered within the NHS Tariff. The consequential costs of Ulcer Treatment and Amputations are listed in the Assumptions table in 9.1.6 above.

Resource identification, measurement and valuation studies

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

Not appropriate.

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

The clinical information on both the current use of devices and the utility of VibraTip was obtained from the publications and background information cited in both the clinical sections and in 9.1.6 above & 9.2.6 below for those used directly in the economic model.

The economic model was developed and applied independently for the company by Dr David Huckle, Chief Executive of Adams Business associates. He is a Chartered Chemist with 25 years commercial experience in healthcare sectors of Pharmaceuticals, Diagnostics and Medical Devices.

He was selected for this process because of an established record in independent economic analysis for assessment of medical devices for potential use in the NHS. This HTA experience was obtained in developing economic models for the NIC technology assessment programme, including an early assessment in 2010 of VibraTip before the clinical studies were published.

The Economic Model and approach used was developed from work for the NIC in conjunction with the NHS Innovation Hubs, together with collaborative work on economic models within the MATCH programme. Since this time the basic model and related techniques have been developed and applied to a range of medical devices including a number of submissions to various NICE programmes. The model has good flexibility to address the variables required in this analysis.

An important aspect to this work was the totally independent identification of resource information and the assessment of the clinical reports used in developing the economic model and its use in the analysis.

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

Technology and comparators' costs

9.3.5. Provide the list price for the technology.

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

This economic Model is directly focussed on the various device costs and the rationale is as follows:

Product Costs Assumptions

- The comparator products require greater skill in use and additional time to perform the assessments than VibraTip. These comments are supported by all of the 9 references noted for the Economic Assessment above.
- The time to perform the necessary procedures with VibraTip can be faster than the comparator products [Ref. 1] but this is time that might not be valuably occupied and is not considered as a recoverable cost in the economic calculations.
- In the same way the ease of use, general utility and limited training required for VibraTip compared to the comparator products is not quantified for cost savings.
- The product usage costs are based on cost/test related to the usable lifetime of each comparator device as below.
- As each device has a finite life replacement of comparator products with VibraTip is assessed in the Economic Model from the level of "Adoption" of VibraTip against these other products.
- Use of the high cost gold standard Neurothesiometer is not considered in the main economic Model as VibraTip would not be used as a replacement product although the comparisons undertaken and referenced above [Table C2] showed that VibraTip gave comparable clinical performance.

Monofilament Life: 1 year.

There can be confusion on shelf life of Monofilament since this material is used in such as Sutures where 5 years is satisfactory. However, in order to comply with FDA guidelines of guaranteeing the 10 gram force range, **Medical Monofilament** as a typical manufacturer has placed a 1 year expiration date on all monofilaments for diabetic testing. Monofilaments are tested for one year and this has been taken as the average usable life.

A Medical Monofilament used for pressure testing is only suitable for 10 patients before needing a 24 hour recovery period [CG10 & Ref.10.] which means:

- **Maximum usage in the 1 year of life is 10 tests/day X 3 clinics X 50 weeks = 1,500**
- **But as a Diabetic clinic may well process more than this number it will be necessary for 2 devices to be available at any one time.**
- **At a median cost of £ 15.2 each the annual cost is £ 30.4.**
- **The cost/test for Monofilaments is (£ 15.2 X 2)/(1,500 X 2) = £ 0.010.**

A more recent study (Ref 11. Lavery LA et al.), examined the accuracy and durability of 6 widely used monofilament brands and concluded that, at best, the accepted buckling force would only remain within a usable range to evaluate 70-90 patients before needing to be replaced. As this finding does not reflect current recommendations or practice in UK we have maintained the assumption of a one year durability for each monofilament.

Tuning Forks:

There is a problem of loss due to purloining, as well as deteriorating performance. With Diabetic clinic throughput and use by multiple users on average 2 such devices will be required per year. The cost/test is then determined by

- **Time to conduct the test procedure with other examinations at best 4/hour.**
- **Total tests per 1 year = 4 Tests/Hour X 6 hour day X 3 clinics X 50 weeks = 3,600.**

- **At a median cost of £ 28 each the annual cost is £ 56.**
- **The cost/test for Tuning Forks is (£ 28 X 2)/(7,200) = £ 0.008.**
- **In this case the test numbers are limited by the availability of 1 Tuning Fork at one time as distinct from the Monofilament where the second device is to cover rest time.**

It should be remembered that the Tuning Fork in the references given above and in many other publications is inferior in clinical performance to other comparator devices and is susceptible to cueing by the noise and vibration affecting other body parts and patients detecting the “cold feeling” rather than the vibration leading to misleading clinical information. Vibration amplitude from a tuning fork is highly dependent upon the force and technique used to activate it. Furthermore, vibration decays from the moment of activation.

VibraTip:

In the Levy study [Ref. 7] battery life in normal usage was found to be at least 5,000 tests which is taken as reasonable usage although more can be expected beyond 6,000 tests. In a clinic situation as above 2 devices will be needed but the cost/test will be pro rata and:

- **Device cost at £ 9.95 for 5,000 tests the total cost is £ 19.90.**
- **The cost/test is £ 9.95/5,000 = £ 0.002.**

The **Neurothesiometer** at typical prices around £ 1,200 (e.g., **Horwell**) was not assessed as economically VibraTip would not be purchased as an alternative.

All prices are supplier list prices as noted above in the search details in 8.1.2

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

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£ 9.95 for VibraTip	McCallan Medical
Consumables (if applicable)	NA	
Maintenance cost	NA	
Training cost	Negligible	
Other costs	None	
Total cost per treatment/patient	Depends on annual (1) or High Risk (4) patients tests.	

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	Monofilament - £ 15.2* Tuning Fork - £ 28* Neurothesiometer _ £ 1,200	Williams & Cannonbury Howell
Consumables (if applicable)	NA	
Maintenance cost	NA	
Training cost	Negligible	
Other costs	None	
Total cost per treatment/patient	Depends on annual (1) or High Risk (4) patients tests.	

*** Median prices used. Monofilament from Williams at £ 16 for Bailey and £ 14.5 for a tested item with Canonbury at £15.10.**

Tuning Fork from Williams at £ 28.43 and from Canonbury at £ 27.50.

9.3.8. Health-state costs

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

Table C8 List of health states and associated costs in the economic model

Health states	Items	Value	Reference
Cost of Ulcer Treatment	**Technology cost**		QZ12Z plus JC18-20 Z and references as in Assumptions table
	Staff		
	Hospital costs		
	[Other items]		
	Total	£ 8,500	
Amputation Costs	Total figure	£ 10,780	QZ11A & QZ11B

9.3.9. Adverse-event costs

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

Table C9 is not applicable and has not been completed.

Table C9 List of adverse events and summary of costs included in the cost model

Adverse events	Items	Value	Reference
Adverse event 1	**Technology**		
	Staff		
	Hospital costs		
	[Other items]		
	Total		
Adverse event 2	**Technology**		
	Staff		
Adverse event [X]			

Miscellaneous costs

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

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

The impact matrix below addresses this item as Diabetic Clinics can be based in Hospitals, GP surgeries or other emerging sources such as Walk-In Clinics. There are opportunities for increased Primary Care examinations not only by GPs but also by Social Care and Homecare workers.

Element / Segment	Diabetic Clinics
Are there resource savings?	Yes through increased Primary Care away from Hospital clinics.
Will these rely on Patient Nos?	Individual cost benefits with less Hospital costs by earlier prevention.
Are there added value savings?	Yes – potential for increased testing with improved patient care and less incidence of ulcers and their treatment costs.
Are there savings on other purchases?	Yes: reduced treatment savings for those patients requiring amputation.
Is there Life Extension or Saving?	Almost certainly plus morbidity benefits with reduced ulcers or early warning to minimise the impact of these.
Is it Hospital saving?	Yes – reduced treatments possible.
Is it CCG or Other NHS saving?	Reduced treatment and hospitalisation possible.
Is it 3rd Level saving? Carer, Social Services, etc	Indirect and not quantified.
Are there reductions in other costs? H&S, QC, etc	Subsequent social care might be less.
Are there Training or Education Costs or Savings?	Minimal training required and demonstrated by multi-user studies reported.

9.4. Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

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

The economic analysis is primarily centred around the cost benefits of using the VibraTip device versus the comparators. In the case of the Neurothesiometer which is a high cost item no model was set out as this is a specialist instrument and VibraTip would not be used as an alternative even though its clinical utility is similar. For the Monofilament and Tuning Fork options the difficulty is that no information exists on their relative use for Diabetic Peripheral Neuropathy (DPN) assessment. Direct comparisons have been made on the basis of 100% use of each comparator and varying levels of VibraTip usage.

A major uncertainty exists on the actual implementation of the NICE Guidelines on DPN assessment: assessment using any device is not carried out for all patients and the item is often addressed in a cursory manner. The savings found with use of VibraTip will be secured on a *pro rata* basis for the figures from 100% usage. An unknown would be the increased correct pursuit of the NICE Guidelines that might accrue through the availability of an easy to use device such as VibraTip.

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

The main variable was the level of patient monitoring, with annual testing generally and more (4X per year) for high risk patients including those that have had treated ulcers and are otherwise controlled.

With the provisos noted above the variable rate of uptake of the new device was considered. It is certain that the existing procedures will continue alongside use of VibraTip and when devices have to be renewed purchase of VibraTip will become an option.

The important patient outcomes are avoiding ulcer formation and particularly that damage does not become so severe that amputation is required. The core model assumes for the direct comparison that no change is achieved in patient outcomes. The incidence of patients developing an ulcer and after treatment developing further recurrence was based on the probabilities derived from data as set out in the Assumptions table, #. 9.1.6.

The longer term incidence of amputation was also built into the model with a three year time span. For simplicity in the model it was assumed that Amputation patients would be from the High Risk group that developed an ulcer in Year 1 and continued to have recurrence or treatment in Year 2 and failed to be controlled effectively. It is known that this is not definitively the case but allows for a workable overall cost analysis of both products and outcomes.

A major reason for DPN testing is to pre-empt ulcer formation by encouraging effective patient care and behaviour. Either from increased use of the simple device or increased adherence to NICE Guidelines it is possible that ulcer incidence could be reduced. This has not yet been proved clinically but is an assumption considered in the economic analysis for potential savings; a 1% reduction in ulcer incidence was used.

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

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Adoption of VibraTip vs. Monofilament	0% or 100% of comparator	20%, 40%, 100%
Adoption of VibraTip vs. Tuning Fork	0% or 100% of comparator	20%, 40%, 100%

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis

Variable	Monofilament	Tuning Fork	VibraTip
Base case	100% use of comparator		
Adoption	100% to 0%	100% to 0%	0%, 20%, 40%, 100%
Ulcer Incidence	5% of High Risk 2% of Annual	5% of High Risk 2% of Annual	As for comparators & 4.95% of High Risk and 1.98% of Annual check group.

Table C10.3 Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution

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

As noted above the unknown variable is the extent of usage of the different comparators. The savings would be *pro rata* to the relative use of the different comparators with the additional factor that many examinations do not use any device or even rely only on patient responses to questions on foot conditions.

9.5. Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

costs

disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment

a tabulation of the mean cost results

results of the sensitivity analysis.

Base-case analysis

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

Table C11 Base-case results;

Total product outcomes costs for 2.9 M patients as per patient costs are marginally changed.

	Total for 2.9 M patient cost (£)
VibraTip	**£ 1,467.86 M**
Diabetic Monofilament	**£ 1,467.91 M**
128 Hz Tuning Fork	**£ 1,467.90 M**

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

Total product test costs for the 2.9 M patients on 100% usage over 3 years are:

- **Diabetic Monofilament at £ 134,684.**
- **128 Hz Tuning Fork at £ 107,747.**
- **VibraTip at £ 21,537.**

The precise product costs are difficult to define as Diabetic clinics vary in size and frequency across the NHS, clinicians test at differing numbers of sites and numbers of tests per device in its lifetime will vary. Using the same assumptions as used in # 9.3.6 for average test price the relative product costs are calculated using the formula:

- **(Total 3-year Test Costs/3)/Average Test Cost = Average tests per year.**
- **Average Test per year/Tests per Device = No. of device units per year.**
- **No. of Device Units per Year X Median Price = Product Cost per year.**

On this basis the relative 'theoretical' Product Costs (with units) per year are:

- **Monofilaments - £ 45.5 K (2,993).**
- **Tuning Forks - £ 33.1 K(1,181).**
- **VibraTip - £ 7.1 K (718).**

A further way of considering product costs alone is based on the 2012/13 QOF figures for 8,000 Practices where 85.6% of patients were given pressure testing. On this basis, more representative of the real world, the figures become:

- **Diabetic Population of 2.9 M but only 85.6% have Pressure testing [QOF 2012/13], i.e. 2.4824 M**

- **From the Economic Model total tests over 3 years = 13,466,363 for 2.9 M or 11,527,206 for 2.48 M at 85.6% of the total population.**

- **Average tests/year for the 2.48 M = 3,842,404 or 1.55/patient.**

- **With 8,000 practices the average performs 480 tests/year for 310 patients.**

- **With workload, life of product and resting periods it would be necessary to have 2 devices/practice of any type.**

- **Total NHS costs for 8,000 practices:**
    - **Monofilament = £ 243 K**
    - **Tuning Fork = £ 448 K. or £ 224 K if only 1 device/practice.**

- **Total NHS costs for 8,000 practices: VibraTip = £ 159 K.**

The comparison was on direct product costs alone so that tables C.12 and C.13 were not appropriate and not completed. Adverse Events are not applicable so table C.14 was not filled out.

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

Table C12 Summary of costs by category of cost per patient

Item	Cost ***intervention (X)***	Cost ***comparator (Y)***	Increment	Absolute increment	% absolute increment
Technology cost	*Xtech*	*Ytech*	*Xtech – Ytech*	*|Xtech – Ytech|*	*|Xtech – Ytech|/ (Total absolute increment)*
Mean total treatment cost	*Xtreat*	*Ytreat*	*Xtreat – Ytreat*	*|Xtreat – Ytreat|*	*|Xtreat – Ytreat|/ (Total absolute increment)*
Administration cost	*Xadmin*	*Yadmin*	*Xadmin – Yadmin*	*|Xadmin – Yadmin|*	*|Xadmin – Yadmin|/ (Total absolute increment)*
Monitoring cost	*Xmon*	*Ymon*	*Xmon – Ymon*	*|Xmon – Ymon|*	*|Xmon – Ymon|/ (Total absolute increment)*
Tests	*Xtests*	*Ytests*	*Xtests – Ytests*	*|Xtests – Ytests|*	*|Xtests – Ytests|/ (Total absolute increment)*
[Additional items]					
Total	*XTotal*	*YTotal*	*XTotal – YTotal*	*Total absolute increment*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

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

Not Appropriate.

Table C13 Summary of costs by health state per patient

Health state	Cost *intervention (X)*	Cost *comparator (Y)*	Increment	Absolute increment	% absolute increment
Health state 1	*XHS1*	*YHS1*	*XHS1 – YHS1*	*|XHS1 – YHS1|*	*|XHS1 – YHS1|/ (Total absolute increment)*
Health state 2	*XHS2*	*YHS2*	*XHS2 – YHS2*	*|XHS2 – YHS2|*	*|XHS2 – YHS2|/ (Total absolute increment)*
Health state X					
Total	*XTotal*	*YTotal*	*XTotal – YTotal*	*Total absolute increment*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

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

Not Appropriate

Table C14 Summary of costs by adverse events per patient

Adverse event	Cost *intervention (X)*	Cost *comparator (Y)*	Increment	Absolute increment	% absolute increment
Adverse event 1	*XAE1*	*YAE1*	*XAE1 – YAE1*	*|XAE1 – YAE1|*	*|XAE1 – YAE1|/ (Total absolute increment)*
Adverse event 2	*XAE2*	*YAE2*	*XAE2 – YAE2*	*|XAE2 – YAE2|*	*|XAE2 – YAE2|/ (Total absolute increment)*
Total	*XTotal*	*YTotal*	*XTotal – YTotal*	*Total absolute increment*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Sensitivity analysis results

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

Variable	Total Costs	Saving with VibraTip
Monofilament Use: Current	£ 1,467,935,122	N/A
20% VibraTip	£ 1,467,917,917	£ 17.2 K
40% VibraTip	£ 1,467,900,713	£ 34.4 K
100% VibraTip	£ 1,467,849,099	£ 86.0 K
Tuning Fork Use: Current	£ 1,467,913,607	N/A
20% VibraTip	£ 1,467,900,706	£ 12.9 K
40% VibraTip	£ 1,467,887,804	£ 25.8 K
100% VibraTip	£ 1,467,849,099	£ 64.5 K

Note. Differences for 100% VibraTip use are due to small rounding differences in the models.

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

Variable	Total Costs	Saving with VibraTip
Monofilament Use: Current	£ 1,467,935,122	N/A
20% VibraTip & 1% ulcer reduction	£ 1,464,721,492	£ 3.21 M
40% VibraTip & 1% ulcer reduction	£ 1,461,507,863	£ 6.43 M
100% VibraTip & 1% ulcer reduction	£ 1,451,866,975	£ 16.07 M
Tuning Fork Use: Current	£ 1,467,913,607	N/A
20% VibraTip & 1% ulcer reduction	£ 1,464,737,067	£ 3.18 M
40% VibraTip & 1% ulcer reduction	£ 1,461,560,528	£ 6.35 M
100% VibraTip & 1% ulcer reduction	£ 1,452,030,908	£ 15.88 M

Note. Differences for 100% VibraTip use are due to small rounding differences in the models.

The savings with the proposed benefit of availability of VibraTip are slightly higher in comparison with use of Monofilaments due to the higher unit cost per

test. However, the overall magnitude of the savings compared with either device is close, due to the relatively small product cost versus the potential savings in outcomes with reduction in incidence of ulcers. .

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

Not Applicable

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

Whatever the current usage of the comparator products, savings can be secured with use of VibraTip with no loss of clinical effectiveness for Monofilaments and with improved efficacy versus Tuning Forks.

Even at a small reduction in ulcer incidence very significant savings can be made for the NHS as well as enhancing patient wellbeing.

9.5.10. What are the key drivers of the cost results?

In this analysis the key driver is the device costs. The impact of a clinically effective but simple to use device could increase the level of adherence to the NICE Guidelines and/or reduce the incidence of Ulcers and consequential amputations by improved patient care. At present from the latest QOF report 14.4% of Diabetics do not receive Pressure testing despite the NICE Guideline.

Miscellaneous results

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

The reduction of ulcer incidence and amputations was additional to that required and was given above.

9.6. Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

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

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

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

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

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

The sub-group differences were built into the economic model based on whether the patient was considered high risk, with quarterly check-ups, and low risk, with an annual check-up. Use of the device or comparator would be at each check-up visit.

9.7. Validation

9.7.1. Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The clinical evidence and assumptions were all set out above. The internal checks for the structure of the model, particularly for values between the Current and Retained/VibraTip structures, have been left in the attached model.

9.8. Interpretation of economic evidence

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

Results were as expected from the product device price differences.

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

The data covers all applied sectors carrying out Diabetic clinics. The costs for Hospital, GP or special clinics have not been included as they are constant in this type of product cost analysis that depends for economic support on price differences.

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

The key assumption relates to the life time of each device as this impacts the cost per test and the ultimate analytical results as in #9.3.6.

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

Defining the actual usage of the comparator devices and the cases where no device is used at all, even though this aspect is ticked off as being addressed by many physicians!

Defining the actual numbers of high risk patients that actually receive 4 check-ups per year.

References

1. Levy A. Preliminary data on VibraTip®, a new source of standardized vibration for bedside assessment of peripheral neuropathy. Brit J Diabetes and Vascular Disease 2010;10:284-86.

2. Bowling FL, Abbott CA, Harris WE, Atanasov S, Malik RA, Boulton AJ. A pocket-sized disposable device for testing the integrity of sensation in the outpatient setting. Diabetic Medicine 2012;29(12):1550-52.

3. Bracewell N, Game F, Jeffcoate WJ, Scammell BE. Clinical evaluation of a new device in the assessment of peripheral sensory neuropathy in diabetes. Diabetic Medicine 2012;29(12):1553-55.

4. Nizar H, Munro N, Nightingale P, Feher MD. Diagnostic accuracy of the VibraTipTM in detection of diabetic peripheral neuropathy. The British Journal of Diabetes and Vascular Medicine 2014; in press.

5. Urbancic-Rovan V, Slak M, Hohnjec M. Screening for neuropathy - do additional testing methods make sense? Poster presented at DFSG Berlin-Potsdam, Germany, 2012.

6. Garbas M, Rovan VU, Slak M, Hohnjec M. Can we replace 128-Hz tuning fork testing by VibraTip®?, Poster presented at DFSG Barcelona 2013.

7. Horsfield I, Levy A. VibraTip durability in clinical practice: how long does it last? The British Journal of Diabetes and Vascular Medicine 2013;13(2):91-95.

8. Horsfield I, Levy A. Clinical consistency of vibration sense testing: development of a manikin great toe with embedded accelerometer for testing and training. Submitted not yet published.

9. Levy A, Greenwood R. Self-care and misplaced confidence. Not yet submitted 2014

10. ·J Booth, M Young. Differences in the Performance of Commercially Available 10-g Monofilaments. Diabetes Care. July 2000; 23(7). Accessed http://care.diabetesjournals.org/content/23/7/984.full.pdf

11. Lavery LA et al. Accuracy and durability of Semmes-Weinstein monofilaments: What is the useful service life? Diabetes Res Clin Pract. 2012 Sept; 97(3):399-404.

Appendices

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

The following information should be provided:

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

Medline
Embase

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

The following information should be provided.

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

The following information should be provided.

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

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

In addition to the searches made for clinical and product information, as in Appendix 1, the product searches were for prices and made directly from company searches on Google followed by interrogation of the various company web sites.

10.3.2. The date on which the search was conducted.

.10.3.3. The date span of the search.

Week commencing March 3rd and followed up in Week commencing March 10th 2014

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

The Google search terms were **bold product title** for each comparator with use of the additional terms **Diabetic** **Prices** to widen or narrow the findings.

The follow up was to interrogate the company (supplier & distributor) **web sites** as identified from the internet search and contained **Application Notes**, **Price Lists** and **User Product Reviews** when provided. The two specific supplier sites were: www.wms.co.uk and www.canonbury.com The US supplier of Monofilaments that cites the FDA regulations on viability of such products was www.medicalmonofilament.com .

Clinical background was based on listed publications and through general searching for **NHS, Diabetic and Diabetes Ulcer, Diabetic and Diabetes Amputation**

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

Not applicable

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

The following information should be provided.

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

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

In addition to the items noted in Appendix 3 specific search was made with follow up of referenced articles in the NICE web site with its numerous Guidelines and Assessments for products and treatments in the Diabetes area. In addition examination of sites for Diabetes UK and related NGOs was made.

10.4.2. The date on which the search was conducted.

10.4.3. The date span of the search.

Re-focussed in March 2014 for this submission and built on information obtained in 2010 and since.

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

As above

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

As above

10.4.6. The inclusion and exclusion criteria.

Not Applicable

10.4.7. The data abstraction strategy.

Not Applicable