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1 TITLE OF THE PROJECT

Skin cancer: the VivaScope 1500 and 3000 systems for detecting and monitoring skin lesions

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3 PLAIN ENGLISH SUMMARY

Skin cancer is the most common type of cancer in the UK with more than 100,000 people diagnosed each year. There are several types of skin cancer of which most are related to exposure to ultraviolet light from sunlight.

Skin cancer is usually diagnosed by a skin specialist (dermatologist) by looking at suspect moles or skin abnormalities with the help of a dermascope, a handheld microscope that works as a magnifying glass. If the skin specialist can't rule out that a skin abnormality could be cancerous it is often removed through surgery. This means that some people could have suspected moles or skin abnormalities removed that aren't dangerous, which would lead to unnecessary scars and anxiety for the patient and costs to the NHS. Some skin abnormalities are not removed and instead are monitored over some time, before a decision on diagnosis and therapy is reached.

VivaScope is a new technique that might help diagnose skin cancer and potentially reduce the number of moles and other skin changes that are removed unnecessarily, and potentially diagnose skin cancer earlier in patients that would otherwise be monitored for some time before final diagnosis of cancer is made. VivaScope might also be used to better decide how much extra skin needs to be removed during surgery to be sure that all of the cancer is gone.

The purpose of this report is to assess the benefits and harms of using the VivaScope for diagnosing skin cancer and to guide decisions around surgery to remove skin cancers. This project also looks at whether VivaScope is likely to be considered good value for money for the National Health Service.

4 DECISION PROBLEM

4.1 Objectives

1. To evaluate the clinical and cost effectiveness of the non-invasive reflectance confocal microscope (RCM) VivaScope 1500 and 3000 imaging systems, to rule out biopsy of equivocal skin lesions suspected to be malignant melanoma, basal cell carcinoma (BCC), or squamous cell carcinoma (SCC).

2. To evaluate the clinical and cost effectiveness of the VivaScope 3000 imaging system in defining the margins of melanoma, BCC, SCC, and lentigo maligna skin lesions.

4.2 Intervention technologies

The VivaScope 1500 and 3000 imaging systems are non-invasive RCMs designed to diagnose potentially malignant skin lesions. They capture highly magnified, quasi-histological images of the upper layer of the skin. They are designed to be used in conjunction with dermoscopy to investigate potentially malignant skin lesions, thus potentially providing a more accurate diagnosis leading to

fewer biopsies of benign lesions and earlier detection of skin cancers. They may also be used as a guide to surgery to provide more accurate pre-surgical margins, potentially preventing unnecessarily large scars for skin cancers in anatomic areas where tissue preservation is of importance (face, hands, feet, genitals), and reducing the risk of recurrence by more accurately identifying local metastases.

A near infrared light source is used to visualize skin structures at different horizontal levels within the upper layer of the skin.[1] The images produced are based on the reflection and scattering of light from the examined tissue section. Different cell structures lead to different reflection patterns, which are seen as shades of gray in the captured image. Melanin, haemoglobin, cellular microstructures, and collagen serve as "endogenous" contrast agents. Melanocytic lesions are therefore especially well imaged using VivaScope.

VivaScope 1500

The stationary device of the VivaScope 1500 is especially suited for use on extremities such as the back of the hand or the back. The horizontal resolution is 1.25 µm and the vertical resolution (layer thickness) is 3 to 5 µm, which corresponds to the layer thickness of normal histological examinations.[2] With the VivaScope 1500 individual images are 500 x 500 µm in size, however in total images of an area of between 1 x 1 mm to 8 x 8 mm can be captured. The imaging depth includes the upper layers of the stratum reticulare.

VivaScope 1500 is a console based unit. *In vivo* examination using the VivaScope 1500 involves applying an adhesive window on the stainless steel ring of the device, which is fixed on the skin over the lesion. The VivaScope 1500 is positioned on the tissue ring and images can be recorded. The VivaScope 1500 also includes an integrated dermatoscope.

VivaScope 3000

The handheld VivaScope 3000 is designed to access difficult to reach skin regions such as around the nose, ears, and eyes, or between fingers. It can be used for diagnosis, as well as a guide to surgery to provide pre-surgical margins of tumours. The resolution for the VivaScope 3000 is the same as for the 1500, but the individual images are 1000 x 1000 µm for VivaScope 3000 and the image depth is up to 200 µm depending on the tissue type.[2] The VivaScope 1500 and 3000 can be used as stand-alone units or together.

Diagnosis using VivaScope

VivaScope can be used for diagnosis of different kinds of skin cancer by providing detailed images that show the morphology of potentially cancerous cells.

According to the manufacturer of VivaScope the main criteria for a diagnosis of malignant melanoma include: the absence of the normal epidermis architecture, lack of delineation of the papillae (non-

edged papillae), irregular nests of atypical melanocytes, and the presence of large and highly refractile cells with prominent nucleus in higher epidermal layers.[1]

VivaScope can also be used to diagnose BCC. Five main criteria have been described by the manufacturer as characteristic BCC changes that can be identified using the VivaScope: elongated, monomorphic nuclei; polarization of these cells along an axis; pronounced inflammatory infiltrate; increased as well as dilated blood vessels; and loss of epidermal honeycomb structure.[1] In addition, tumour cell islands with peripheral palisading, distinguishable from the dermis by a dark gap, are often identified in the dermis. This optical gap formation corresponds histologically to the accumulation of mucin.

VivaScope could potentially be valuable in diagnosis of "collision tumours" with the presence of for example melanoma and BCC in the same skin lesion, and for amelanotic melanomas.[3]

The manufacturer of VivaScope has highlighted concerns about the possibility of diagnosing SCC using laser scanning microscopy (LSM) such as VivaScope, as SCCs are usually scaly because of severe hyperkeratosis.[1] This often limits the evaluation of SCC lesions as it is more difficult to capture images of structures deeper in the tissue. The manufacturer has not provided any specific criteria for diagnosis of SCC.

4.3 Target condition

Skin cancer is the most common cancer in the UK. It is commonly classified into melanoma skin cancer, which develops from pigmented cells (melanocytes) in the epidermis, and non-melanoma skin cancer, which develops from cells that produce keratin (keratinocytes).[4] Non-melanoma skin cancer can be further divided into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Malignant melanoma, SCC and BCC make up more than 95% of all skin cancers. In addition there are some more rare types of non-melanoma skin cancer including Merkel cell carcinoma, Kaposi's sarcoma and T-cell lymphoma of the skin.[5]

The main risk factor for developing most types of skin cancer is exposure to UV radiation in the form of sunlight or use of sunbeds. Other factors that may influence the risk of developing skin cancer include: age and sex, ethnicity, occupation, personal and family history of skin cancer, socioeconomic status and certain physical characteristics (light eyes or hair, fair skin which sunburn easily; having a lot of moles, unusually shaped or large moles, or a lot of freckles).[4,6,7]

4.3.1 Melanoma

In 2011, 13,300 cases of malignant melanoma were diagnosed, and around 2,200 people died from the disease in the UK.[8] However survival of malignant melanoma has been improving for the last 25 years and is now amongst the highest for any cancer. Five-year survival ranges from 100% in cases

diagnosed at the earliest stage, to 8% (men) and 25% (women) in cases diagnosed once the disease has spread. Around two-thirds of malignant melanoma cases are diagnosed at the earliest stage.[8] Like most cancers, skin cancer is more common with increasing age, but malignant melanoma rates are disproportionately high in younger people. Malignant melanoma is almost twice as common in young women (up to age 34) as in young men, but more men die from it. Malignant melanoma incidence rates have increased more than fivefold since the mid-1970s. People from the most affluent areas are more likely to be diagnosed with malignant melanoma than those from the more deprived areas. The most common sites of melanoma in men are the trunk, head and neck, and arms, whereas in women they are trunk, legs and arms.[6]

There are several different types of melanoma:

- *Superficial spreading melanoma* makes up around 70% of malignant melanomas. Initially this type usually grows outwards with low risk of metastasis, but when it eventually starts to grow down into the tissue it acquires the capacity for invasion.

- *Nodular melanoma* grows quickly and down into the skin. It may appear in areas that have only been exposed to the sun occasionally. It is usually very dark with a raised area of skin, but may not necessarily develop from an existing mole.

- *Lentigo maligna melanoma* arise from pigmented areas of the skin called lentigo maligna or Hutchinson's freckle. It most commonly appear on the face or other areas of the skin which has been exposed to the sun a lot. Lentigo maligna grows outwards very slowly, and it becomes malignant when it starts to grow down into the deeper layers of the skin. Around 10% of malignant melanomas are lentigo maligna.

- *Acral lentiginous melanoma* is a rare form of melanoma most commonly found on the palms of the hand, the soles of the feet or under or around the nails. It is the most common type of melanoma in people with dark skin.

- *Amelanotic melanoma* lacks the dark colour of usual melanomas. They usually have very little colour and may appear pink or red with light brown or grey edges. They make up around 5% of melanomas and are difficult to diagnose as they can easily be mistaken for other skin conditions.

4.3.2 Non-melanoma skin cancers

Skin cancer is the most common cancer in the UK with more than 102,000 cases of non-melanoma skin cancer registered in 2011 in the UK.[8] However there is known under-recording of non-melanoma skin cancer incidence with an estimated 30-50% of BCC and around 30% of SCC going

unrecorded. This is partly because many cases are treated in primary care or privately and are not notified to the cancer registries, and partly because most cancer registries record only the first diagnosis of BCC or SCC.[8] Since non-melanoma skin cancer registrations are known to be incomplete, they are usually excluded from incidence totals for all cancers combined. Although non-melanoma skin cancer is extremely common, in the vast majority of cases it is detected early and is not life-threatening. However, around 590 people died from non-melanoma skin cancer in 2011 in the UK.[8]

Basal cell carcinoma (BCC)

BCC is the most common type of non-melanoma making up around 75% of non-melanoma cases.[7] It develops on areas of the skin with a high sun exposure like the nose, forehead and cheeks. BCC is slow growing and rarely spreads or becomes fatal, however it can invade other types of tissue such as cartilage and bone in the nose or ears. BCCs can be divided into several subtypes based on morphology and development including nodular, superficial, morphoeic and pigmented BCCs.

Squamous cell carcinoma (SCC)

SCC is a more serious, but less common, type of non-melanoma than BCC, which has the potential to metastasize to other organs of the body.[9] Around 20% of non-melanomas are diagnosed as SCC.[7] SCC lesions often develop on sun exposed skin such as the head and neck, but they can also develop in areas of the skin that have been ulcerated for a long time, in scars, burns or in pre-existing lesions such as Bowen's disease. SCCs are usually crusty or scaly, but can also present as an ulcer without keratinisation. The appearance of SCC can make it difficult to diagnose using imaging techniques such as RCM.

4.4 Diagnosis and treatment pathway

4.4.1 Melanoma

Initial diagnosis of suspected melanoma lesions should follow the ABCD-Easy rules:[10]

- Asymmetry - the two halves of the area may differ in their shape.
- Border - the edges of the area may be irregular or blurred, and sometimes show notches.
- Colour - this may be uneven. Different shades of black, brown and pink may be seen.
- Diameter - Most melanomas are at least 6mm in diameter. Report any change in size or diameter to your doctor.
- Expert - if in doubt, check it out! If your GP is concerned about your skin, make sure you see a Consultant Dermatologist

Melanoma remains relatively uncommon in primary care settings and therefore the opportunities to develop specific diagnostic skills are limited and all suspected melanoma lesions should therefore be referred within two weeks to a multidisciplinary skin cancer team led by dermatologists, e.g. Local Hospital Skin Cancer Multidisciplinary Team (LSMDT).[10]

In secondary care assessment of suspected malignant lesions are usually done by dermoscopy. According to British Association of Dermatology (BAD) guidelines for melanoma, if malignancy cannot be excluded the lesion is photographed and then completely excised.[10] The excision biopsy should include the whole tumour with a clinical margin of 2 mm. Definitive diagnosis is then made by histopathological review of the biopsy. If malignancy is confirmed subsequent treatment options are then based on the Breslow thickness of the tumour.

In cases where it isn't possible to diagnose a lesion as a melanoma or a benign melanocytic lesion, the patient should be referred to a Specialist Skin Cancer Multidisciplinary Team (SSMDT) for clinical and pathological review.[10] A decision to treat as a melanoma should be made by the SSMDT in discussion with the patient.

Incisional or punch biopsy may be used for diagnosis of lentigo maligna or acral melanoma. However, with lentigo maligna there is a risk of subclinical microinvasion, which may be missed because of sampling errors when using incisional biopsies.

Surgery is the only curative treatment for melanoma. Following excision biopsy for diagnosis, a wider and deeper margin, based on Breslow thickness, may be needed to ensure complete removal of the primary lesion and any micrometastases.[10] Recommended surgical excision margins are summarized in Table 1. Though, the final decision about the size of the margin should be made after discussion with the patient, taking into consideration functional and cosmetic implications of the margin chosen.

Table 1. Recommended surgical excision margins

Breslow thickness	Excision margins
In situ	5 mm
< 1 mm	1 cm
1.01 – 2 mm	1-2 cm
2.1 – 4 mm	2-3 cm
> 4 mm	3 cm

For lentigo maligna and other *in situ* melanomas the aim is to excise the lesion completely with a clear histological margin after which no further treatment is then required. However, in current clinical guidelines there are no recommendations for the excision margin for lentigo maligna.[10] There may also be clinical situations where treatment by other methods such as radiotherapy, or observation only may be appropriate.

4.4.2 Basal cell carcinoma (BCC)

Nodular BCC may be removed in primary care by suitably qualified GPs. However, if there is uncertainty around the diagnosis or if the BCC is of any other subtype it should be referred to a LSMDT.[11] In most cases dermatologists can make a confident diagnosis of BCC by visual examination of the lesion, which may be helped by dermoscopy. If there is uncertainty around the BCC diagnosis or around the subtype of BCC, which may influence prognosis or treatment selection, diagnosis should be confirmed by biopsy and histology. The aim of treatment of BCC is to remove the tumour while resulting in a cosmetic outcome that is acceptable to the patient.[11]

The treatment options for BCC depends on if the lesion is classified as low- or high-risk of recurrence following treatment, which depends on a range of prognostic factors including:

- Tumour size (increasing size indicate a higher risk of recurrence)
- Tumour site (lesions on the central face, especially around the eyes, nose, lips and ears, are at higher risk of recurrence)
- Definition of clinical margins (poorly defined lesions are at higher risk of recurrence)
- Histological subtype (certain subtypes leads to a higher risk of recurrence)
- Failure of previous treatment (recurrent lesions are at higher risk of further recurrence)

Techniques that do not allow histological confirmation of tumour clearance are generally only used for low-risk BCC lesions. These include cryosurgery, curettage, radiotherapy, topical treatments such as imiquimod, and photodynamic therapy. The exception is radiotherapy which is also used for high-risk BCC. Surgical excision is widely used to treat both low- and high-risk BCC.[11]

4.4.3 Squamous cell carcinoma (SCC)

All SCC presented in primary care should be referred, under the two week rule, to the local SSMDT, which will establish diagnosis histologically.

The majority of SCC tumours are low risk, but it is essential to identify the around 5% of SCC tumours that are high risk.[9] SCC tumours are deemed low or high risk based on several prognostic factors that may influence their metastatic potential, including: tumour site, size, thickness and level of invasion, rate of growth, aetiology, degree of histological differentiation (subtype), and host immunosuppression.[9] However, the malignant behaviour of SCC tumours vary greatly.

The aim of treatment is complete removal of the primary tumour and any metastases. The success of treatment is highly dependent on definition of tumour margin. The gold standard for tumour margin

identification is histological assessment. However, determining tumour extent may be challenging, particularly when the margins of the tumour are ill-defined or any metastases are discontinuous from the primary tumour. Locally recurrent tumours may arise either due to failure to treat the primary tumour, or from local metastases.[9]

Surgical excision (including Mohs' micrographic surgery for high risk tumours) is the primary treatment option for the majority of SCCs. The advantage of surgical excision is that it provides tissue for histological examination, which allows assessment of the adequacy of treatment and for further surgery if necessary. Other treatment options include curettage and cautery, and cryosurgery for small, well-defined, low-risk tumours, and radiotherapy for non-resectable tumours with ill-defined margins.[9]

4.5 Place of intervention in diagnosis and treatment pathway

VivaScope may be used in secondary care settings in conjunction with dermoscopy to rule out biopsy of skin lesions suspected of malignant melanoma, lentigo maligna, BCC, or SCC. It may also be used to diagnose skin cancer in patients with equivocal skin lesions who would otherwise been sent home for watchful waiting, and used to define the margins of melanoma, BCC, SCC, and lentigo maligna skin lesions to guide surgical excision.

4.6 Relevant comparators

In clinical practice lesions suspected of malignancy are assessed by visual examination of the lesion followed by dermoscopy by an experienced dermatology specialist. Similarly decisions on tumour margin delineation are based on visual assessment of the lesion followed by dermoscopy by an experienced dermatology specialist.

5 REPORT METHODS FOR ASSESSING THE OUTCOMES ARISING FROM THE USE OF THE INTERVENTIONS

A systematic review will be conducted to summarise the evidence on the clinical effectiveness of VivaScope 1500 and 3000 for the assessment of potentially malignant skin lesions and for delineation of excision margins of malignant skin lesions. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care(12) and in the NICE Diagnostic Assessment Programme manual.[13]

5.1 Inclusion and exclusion criteria

5.1.1 Population

Study populations eligible for inclusion will be:

Diagnosis

People referred for assessment of equivocal skin lesions suspected of malignant melanoma, lentigo maligna, BCC, or SCC.

Delineation of lesion margins

People presenting with melanoma, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or lentigo maligna who require tumour margin delineation for excision surgery.

5.1.2 Setting

The relevant setting is secondary care.

5.1.3 Intervention

Diagnosis

Assessment of the lesion by dermoscopy and VivaScope 1500 or 3000 by an experienced dermatology specialist.

Delineation of lesion margins

Assessment of the lesion by dermoscopy and VivaScope 3000 by an experienced dermatology specialist.

5.1.4 Comparators

The comparator eligible for inclusion for the assessment of both diagnostic accuracy and delineation of lesion margins will be visual assessment of the lesion followed by dermoscopy and clinical judgement by experienced dermatology specialist.

5.1.5 Reference standard

The reference standard for the assessment of diagnostic accuracy will be histopathology of the excised skin lesion.

5.1.6 Outcomes

If the evidence permits the following outcomes will considered:

Diagnosis

- Diagnostic accuracy
- Time to test result
- Test failure rate, e.g. imaging failure
- Number of scans deemed impractical because of the site of the lesion

- Number of biopsies performed and repeat biopsies
- Morbidity associated with biopsy such as pain and swelling
- Extent of scarring and associated psychological impact
- Adverse events from biopsy including infections
- Adverse events from false test results including patient distress and sequelae
- Health related quality of life

Delineation of lesion margins

- Time to result
- Imaging failure rate
- Number of scans deemed impractical because of the site of the lesion
- Number of surgical procedures/surgical stages
- Morbidity associated with excision surgery such as pain and swelling
- Recurrence rates
- Extent of scarring and associated psychological impact
- Adverse events from surgery including infections
- Health related quality of life

5.1.7 Study design

The following types of studies will be included:

- Randomised controlled trials or observational studies, where participants are assigned to dermoscopy plus VivaScope or dermoscopy for diagnosis or skin lesion delineation, and where outcomes are compared at follow-up.
- Test accuracy studies assessing the test accuracy of VivaScope and/or dermoscopy with standard histology of biopsy as the reference standard.

The following study/publication types will be excluded:

- Pre-clinical and animal studies
- Reviews, editorials, and opinion pieces
- Case reports

5.2 Search strategy

The searches will combine terms for the condition and terms for the technology being assessed. For the technology we will use both generic terms (e.g. reflectance confocal microscope) and terms for the specific product (e.g. VivaScope). The search strategy will be refined by scanning key papers identified during the review, through discussion with the review team, clinical experts and information specialists.

Electronic sources to include: MEDLINE, EMBASE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, the NHS Economic Evaluation Database (NHS EED) and CENTRAL).

Ongoing and unpublished studies will be searched for using: clinicaltrials.gov, controlled-trials.com, clinicaltrialsregister.eu.

Relevant reviews and guidelines will be identified through searching additional resources, including Clinical Evidence, National Institute for Health and Clinical Excellence (NICE) website, NIHR Health Technology Assessment Programme, NHS Evidence - National Library of Guidelines, SIGN Guidelines, the Guidelines International Network website.

Reference lists of included papers will be assessed and the abstracts from key conference proceedings, to be identified in consultation with clinical experts, will be screened, where possible, for additional relevant studies. No limits relating to date, language or study design will be applied to the searches.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form, and independently checked by another. Information extracted will include details of the study's design and methodology, intervention and comparator tests, reference standard, baseline characteristics of participants, and outcome measures, including clinical outcome efficacy and any adverse events. Where there is incomplete information, if time constraints allow, attempts will be made to contact authors with a request for further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

5.4 Quality assessment strategy

The quality of included studies will be assessed by one reviewer and independently checked by another. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of diagnostic studies will be assessed using the QUADAS-2 tool,[14] according to recommendations by the *Cochrane Handbook for Diagnostic Test Accuracy Reviews*.[15] The quality of clinical effectiveness studies will be assessed according the study design; randomised controlled trials will be assessed according to recommendations by the CRD and the Cochrane Handbook for Systematic Reviews of Interventions[16,17] and recorded using the Cochrane Risk of Bias Tool, cohort studies will be assessed using the Newcastle-Ottawa Scale.[18]

5.5 Methods of analysis/synthesis

Details of results on clinical effectiveness and quality assessment for each included study will be presented in structured tables and as a narrative summary. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated.

For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study.

6 REPORT METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

6.1 Identifying and systematically reviewing published cost-effectiveness studies

A systematic review of the literature will be undertaken in order to identify

- published economic evaluations addressing the research questions
- studies reporting resource use and cost data associated with the care pathways of suspected skin cancer, including lentigo maligna, that could be utilised in primary economic modelling;
- utility studies that provide data on the health-related quality of life (HRQoL) of people with (suspected) skin cancer including lentigo maligna that can be used for the estimation of quality-adjusted life years (QALYs) in primary economic modelling.

6.1.1 Search strategy

Searches for economic evaluations will be undertaken in the databases listed in section 5.2. The search strategy will combine terms capturing the condition (skin cancer including lentigo maligna), the intervention (VivaScope) and relevant comparators (dermoscope, surgical excision and biopsy) with health economic and health-related quality of life terms. The health economic and health-related

quality of life terms will aim to capture the study designs of interest (cost-utility, cost-effectiveness, cost studies) as well as studies reporting preference-based HRQoL data.

The search for economic evidence will not be limited to the interventions and comparators listed above, in order to allow identification of studies that report care pathways and costs associated with the assessment and management of skin cancer, including lentigo maligna, that could support the development of an economic model. Moreover, model-based economic evaluations that assess interventions for the prevention, assessment and management of skin cancer including lentigo maligna will be sought in order to gain an insight into the modelling methods in the area of skin cancer. These studies will not be subject to formal assessment but may be used to assist in the overall development of a new decision-analytic economic model with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty.

No language, date or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and meta-analyses will be searched for additional references. The details of the search strategy are presented in full in Appendix 10.1.

6.1.2 Inclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion in the review by two reviewers using the following criteria:

For the assessment of cost effectiveness studies:

- intervention or comparators according to the scope of the assessment
- secondary settings
- full economic evaluations (cost-utility, cost-effectiveness, cost-benefit and cost-consequence) that assess both costs and outcomes associated with the interventions of interest will be included; economic evaluations will be considered if they utilise clinical effectiveness data from randomised or non-randomised clinical trials, prospective cohort studies or systematic reviews and meta-analyses of clinical studies. Economic analyses that utilise clinical data from studies with a mirror-image or other retrospective design will not be considered.

For the identification of resource use or cost data on skin cancer including lentigo maligna:

- the review will focus on UK-based studies but if no sufficient data are identified, non-UK studies will be reviewed

For the identification of utility data

- only studies reporting utility data elicited using a generic or a condition-specific preference-based measure, vignettes or self-report and a validated, choice-based technique for valuation (i.e. time trade-off or standard gamble) will be considered
- utility data need to refer to specific health states associated with the condition of the study population through the care pathway.

6.1.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. All relevant data from economic evaluations (such as study population, intervention and comparator, outcome, type of analysis, perspective, discounting & cost year, results including uncertainty) and from studies reporting utility data (including definition of health states & population reporting HRQoL, valuation method and population providing valuations , health state utility scores) will be presented in respective data extraction tables. Reasons for exclusion of potentially relevant studies will also be documented.

6.1.4 Quality assessment strategy

All published economic evaluations identified within the review that address the research questions and any economic evaluations submitted by manufacturers to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against NICE's reference checklist for economic evaluations[19] together with the Philips checklist[20] on mathematical models used in technology assessments. Each economic evaluation will be assessed by one health economist and the details of the assessment will be checked by a second health economist.

6.1.5 Presentation of the findings of the systematic economic literature review

A narrative summary and the accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations, utility studies and studies reporting relevant resource use and/or cost data.

6.2 Development of a health economic model

In addition to the systematic review of relevant existing economic evaluations, which will adopt the methods described above, 2 broad economic models will be constructed to assess the cost effectiveness of

1. the VivaScope 1500 and 3000 for the diagnosis of skin cancer, including lentigo maligna, in people with equivocal skin lesions following dermoscopy, relative to current practice
2. the VivaScope 3000 in defining the margins of diagnosed skin cancer, including lentigo maligna, prior to surgical treatment, relative to current practice

The diagnosis model will aim to assess the overall cost effectiveness of VivaScope 1500 and VivaScope 3000, assuming that both devices will be available for the diagnosis of equivocal lesions but each will be used as appropriate according to the location of the equivocal lesion to be examined.

The structure of the models will be determined by the relevant care pathways associated with identification, assessment and management of skin cancer and the availability of relevant clinical, utility and cost data. The model structures may be further informed by relevant economic evaluations undertaken for other NICE guidance or identified in the published literature; all structural assumptions will be documented and accompanying rationales provided.

Each model will consider separately the different types of skin cancer (i.e. BCC, SCC, melanoma, potentially lentigo maligna), as the accuracy of VivaScope in diagnosis and margin delineation as well as the treatment pathways and associated costs and outcomes vary across different types of skin cancer. However, total costs and outcomes associated with VivaScope and current practice for each type of skin cancer will be combined, if possible, by weighing according to the proportion of each type of skin cancer in the study population, so that overall costs and outcomes associated with VivaScope and current practice across all types of skin cancer are estimated.

The economic analyses that were undertaken to inform the NICE public health guidance on the prevention of skin cancer[4] have utilised data on the QALY loss in the general population from melanoma and non-melanoma skin cancer arising from premature mortality and from morbidity associated with non-fatal cases. They have also utilised data on the cost per case of melanoma and non-melanoma skin cancer to the NHS. These data on QALY loss and cost per skin cancer case will be reviewed and, if possible, updated and utilised in the economic models (in particular in the diagnosis model) as appropriate.

The diagnosis model will consist of an identification pathway part (Vivascope 1500/3000 or current practice for lesions with equivocal findings at dermascopy), potentially an assessment pathway part regarding margin delineation for excision where appropriate (which will be informed by evidence from the margin delineation model), and a treatment pathway part (treatment according to type/stage of skin cancer); appropriate pathways will be designed for all potential outcomes following

identification, i.e. true and false positives, and true and false negatives. The treatment pathway of cases of skin cancer will be ideally informed by relevant updated information on QALY loss and associated costs per case of skin cancer, as reported in the economic analyses undertaken for the NICE public health guidance on the prevention of skin cancer. Alternatively, if this is not possible, the endpoints of the assessment pathway for each type of skin cancer may be entered into a 'treatment pathway' Markov model, which will follow people over lifetime. A proposed structure of the economic models is provided in Appendix 10.2.

The perspective of the analyses will be that of the NHS and personal social services. The measure of outcome will be the QALY. The time horizon of the models will ideally be over lifetime, so as to capture the progress of skin cancer, potential future recurrences and mortality. If no appropriate data are available to allow a life time horizon, a time horizon that captures the progress of the disease from the time of intervention until the endpoint of one 'episode' of the disease (i.e. from identification/ assessment until treatment and follow-up monitoring up to discharge) will be attempted.

The clinical effectiveness parameters required for the economic models will be informed by the review of the clinical effectiveness literature outlined in Section 5. In addition, parameters such as estimates of quality of life (utility data) will be informed by the published literature identified in the systematic review. In cases where parameters that are required to populate the model are not available from studies identified in the HRQoL literature review, expert clinical opinion will be used to identify utility data from similar indications that may be used as proxy utility data. In accordance with NICE methods guidance, utility values will be ideally based on EQ-5D data that have been converted to utilities using the UK TTO tariff;[21] if no such data are available, preference will be on utility data reported in studies that have elicited utility values from the public using a choice-based method, as recommended by NICE.[19] Mapping of condition-specific measure data to EQ-5D values will be considered on a case-by-case basis, using the University of Oxford Health Economics Research Centre's database of mapping studies.[22]

The cost-effectiveness of the interventions will be estimated in terms of the incremental cost per additional QALY gained. As appropriate, cost data will be obtained from national sources such as the NHS reference costs,[23] the British National Formulary,[24] national Unit Costs of Health and Social Care,[25] and other published sources. Costs associated with the intervention (VivaScope 1500 and 3000) will be provided by the manufacturer. Costs will consist of intervention costs (e.g. equipment and maintenance costs, staff training and staff time for the procedure and monitoring), procedure costs including biopsy, histological examination and surgery, costs of management of adverse events associated with the interventions, biopsies, surgery and other forms of therapy, and costs associated with the treatment pathways following correct (i.e. true negative and true positive cases) and incorrect

(false negative and false positive) diagnosis, which include costs of surgery, hospitalisation, and treatment of skin cancer. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.[19] Any assumptions used in the models and any parameter values utilised will be based on the literature if possible and supplemented by clinical expert opinion as required.

To take account of the uncertainty around the input parameter estimates, probabilistic analyses will be undertaken; that is, all relevant input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the models' results. The outputs of probabilistic sensitivity analysis will be presented in a cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. In addition, uncertainty will be explored through deterministic one-way sensitivity analysis. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity on cost-effectiveness results will be explored in subgroup analyses.

7 HANDLING INFORMATION FROM THE COMPANIES

{All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than XXXX. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.}

{Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets).}

8 COMPETING INTERESTS OF AUTHORS

None.

9 TIMETABLE/MILESTONES

Milestone	Date to be completed
Draft protocol	11/09/2014
Final protocol	06/10/2014
Progress report	05/01/2015
Draft assessment report	02/03/2015
Final assessment report	30/03/2015

10 APPENDICES

10.1 Clinical effectiveness and health economics search strategy

10.1.1 Clinical terms

Medline (OvidSP)

1. ((skin* or melano* or cutaneous* or sarcoma* or "non melanoma") adj3 (secondar* or neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumo?r* or malignan* or metastas* or lesion*)).mp.
2. ((superficial* adj2 melanoma*) or SSM or nodular* melanoma* or lentigo* maligna* or lentiginous* melanoma* or (Hutchinson* adj2 freckle*) or melanoma* in situ or acral* lentiginous* melanoma* or amelanotic* melanoma*).mp.
3. exp skin neoplasms/
4. exp melanoma/
5. (non melanoma* or BCC or gorlin* syndrome* or rodent ulcer* or basalioma* or NMSC*).mp.
6. ((basal or basocellular* or basosquamous*) adj2 (carcinoma* or cancer* or neoplasm* or tumo?r* or epithelioma* or malignan*)).mp.
7. ((squamous adj2 (carcinoma* or tumo?r* or cancer* or neoplasm* or epithelioma* or malignan*)) or Bowen* disease* or squamous* cell* carcinoma* in situ or SCC).mp.
8. exp carcinoma, basal cell/
9. exp carcinoma, squamous cell/
10. exp Neoplasms, Basal Cell/
11. exp Basal Cell Nevus Syndrome/
12. exp eyelid neoplasms/
13. Kaposi* sarcoma*.mp.
14. Merkel* cell* carcinoma*.mp.
15. (T*cell lymphoma* or cutaneous* T*cell lymphoma* or CTCL or primary* cutaneous* lymphoma*).mp.
16. or/1-15
17. (((CSLM or laser microscop* or confocal microscop* or confocal scanning microscop* or reflec*) adj confocal adj microscop*) or RCM or confocal laser scanning microscop* or reflectan*-mode confocal microscop*).mp.
18. exp Microscopy, confocal/
19. vivascope*.mp.
20. exp Dermoscopy/
21. (Dermatoscop* or dermascop* or dermoscop* or (epiluminescen* adj microscop*) or skin* surface* microscop*).mp.
22. or/17-21

23. 16 and 22

10.1.2 Health economics terms

Economic filter – costing studies and economic evaluations

Medline & Embase (OvidSP)

1. Health Economics.mp
2. Economic evaluation.mp
3. exp Costs and Cost Analysis/
4. cost benefit analysis/
5. exp models economic/
6. exp fees/
7. exp budgets/
8. (economic adj2 burden).tw.
9. (expenditure* not energy).tw.
10. Cost Effectiveness Analysis.mp
11. (unit cost or unit-cost or unit-costs or unit costs or drug cost or drug costs or hospital costs or health-care costs or health care cost or medical cost or medical costs).tw.
12. Cost Minimization Analysis.mp
13. (cost adj2 (util$ or effective$ or efficac$ or benefit$ or consequence$ or analys$ or minimi$ or allocation$ or control$ or illness$ or affordable$ or fee$ or charge$)).tw.
14. (decision adj1 (tree* or analys* or model*)).tw.
15. (econom* or price* or pricing or financ*or fee* or pharmacoeconomic* or pharmaeconomic* or pharmaco-economic*).tw.
16. ((value or values or valuation) adj2 (money or monetary or life or lives or costs or cost)).tw.
17. Markov*.tw
18. or/1-17

Economic filter – HRQoL

Medline & Embase (OvidSP)

1. Quality of Life/
2. ((quality adj3 life) or life quality or QOL).ti,ab.
3. (HRQL or HRQOL or HRQol).ti,ab.
4. (value adj2 life).ti,ab. or exp Value of Life/
5. (life adj2 qualit$3).tw.
6. (quality-adjusted life year$1 or QALY or QALYs or quality adjusted life year$1).ti,ab. or exp Quality-Adjusted Life Years/

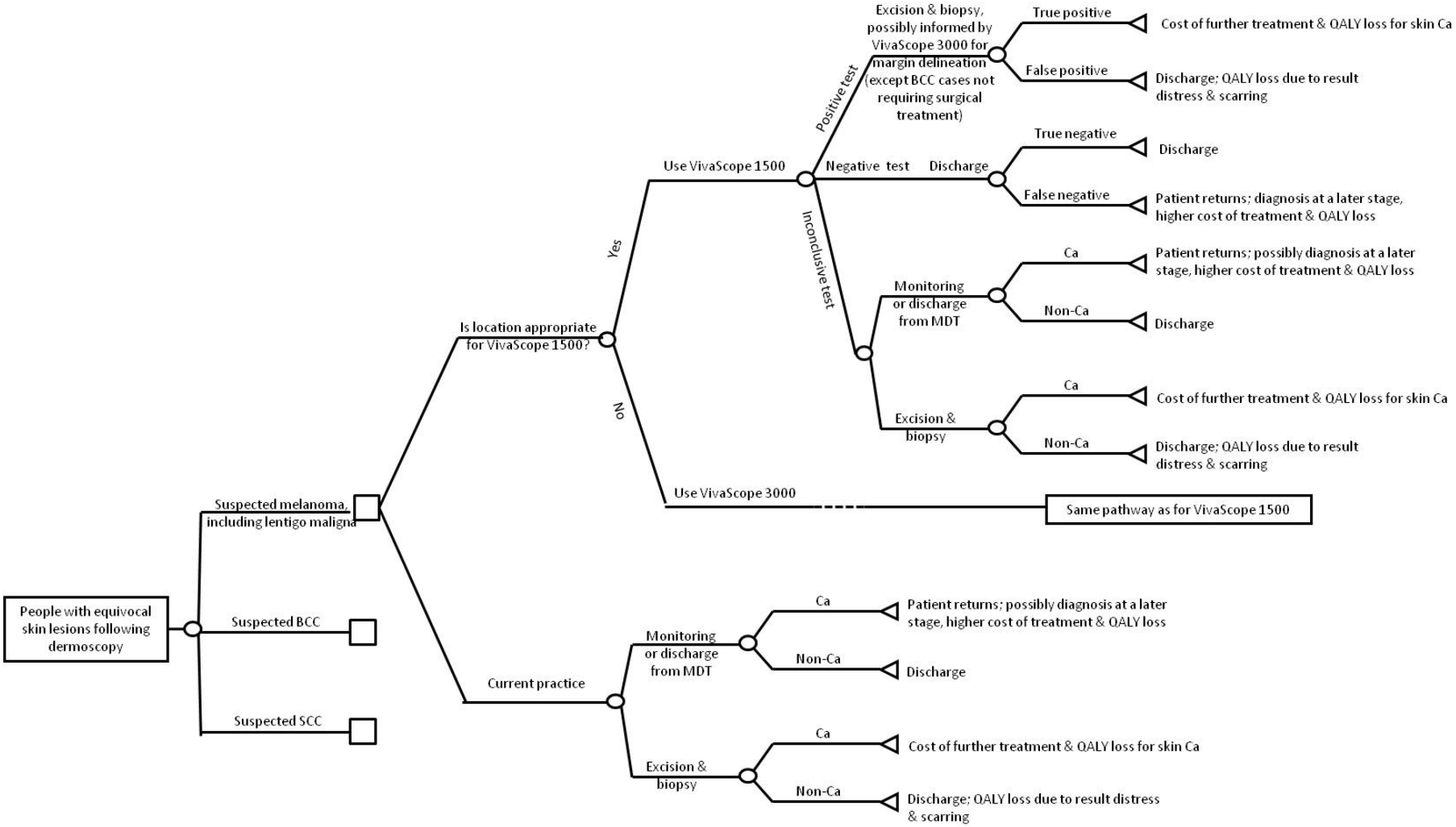
7. daly.ti,ab.
8. (disabilit$3 adj2 life).ti,ab.
9. exp Health Status Indicators/
10. (sf36 or sf-36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf6d or sf 6d or sf-6d or short form 6d or shortform 6d or sf six dimension$1 or short form six dimension$1).tw
13. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.
14. (sf16 or sf 16 or sf-16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
15. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.
16. (euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.
17. (hye or hyes or health$ year$ equivalent$).tw.
18. hui$1.tw.
19. (willing$ adj2 pay).tw.
20. (willing$ adj2 accept).tw.
21. standard gamble$.tw.
22. (health adj3 (utilit$3 or value$2 or preference$2)).tw.
23. (visual analog$3 scale or VAS).tw.
24. patient preference$2.tw.
25. (person$ trade-off or person$ trade off or PTO).ti,ab.
26. (Contingent value or contingent valuation).ti,ab.
27. discrete choice.ti,ab.
28. health status.ti,ab. or exp Health Status/
29. ((quality adj3 wellbeing index) or QWB).ti,ab.
30. (health utilities index or HUI).ti,ab.
31. (time trade off or time tradeoff or TTO or time trade-off).ti,ab.
32. (utility or utilities).ti,ab.
33. disutil$.ti,ab.
34. disability.tw.
35. (wellbeing or well-being or well being or qwb).ti,ab.
36. quality of well being.tw.

37. quality of wellbeing.tw.

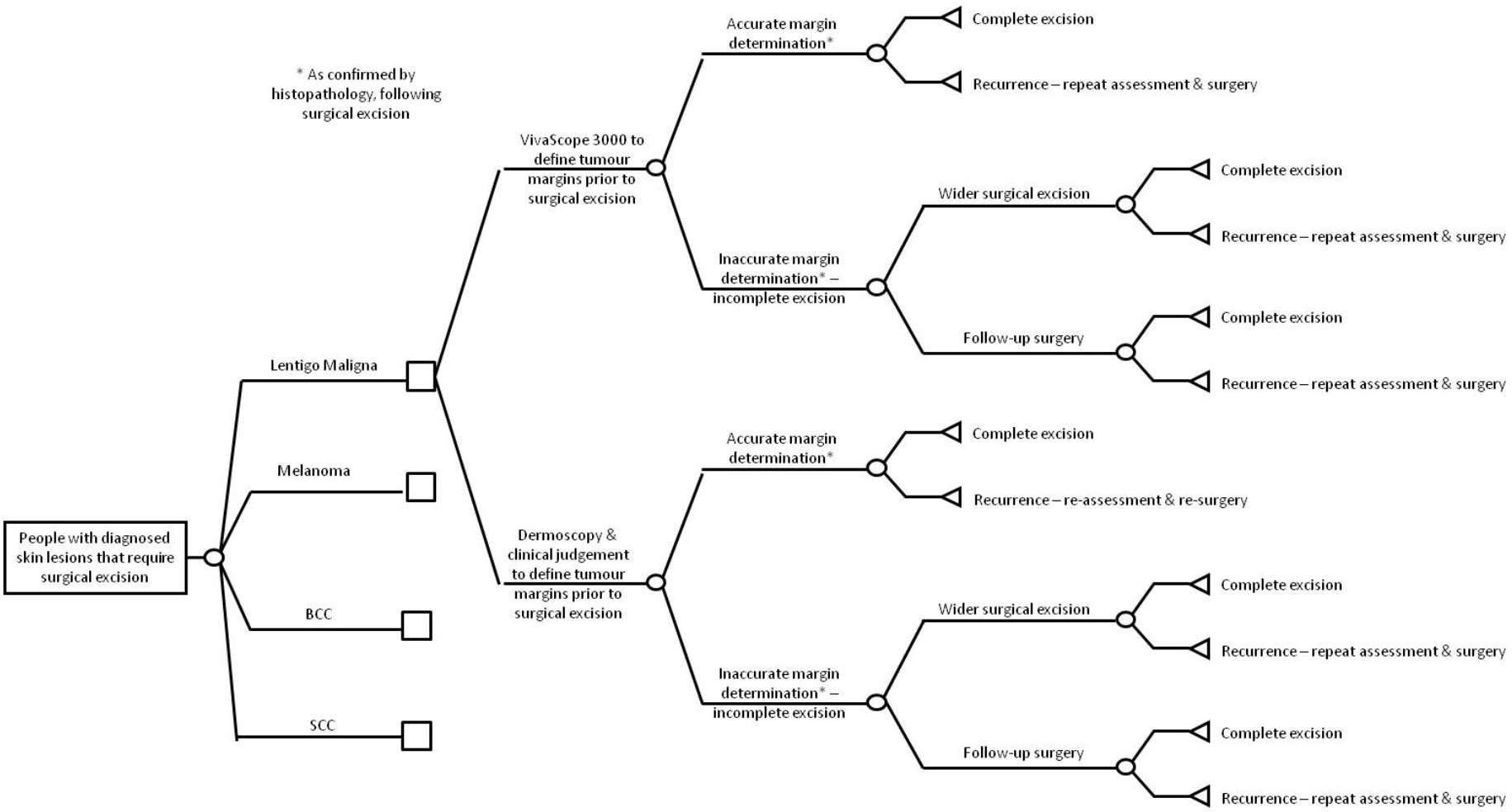
38. Or/1-37

10.2 Proposed economic model structures

A. Diagnosis model



B. Margin delineation model



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Additional information that is needed by NETSCC, HTA and NICE.
Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

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Timetable/milestones

- A Progress Report (to NETSCC, HTA who forward it to NICE within 24hr) will be submitted 5 January 2015
- The Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 30 March 2015