Funding acknowledgement
This project was funded by the NIHR Health Technology Assessment (project number 16/166)

1. PROJECT TITLE: 16/166 HTA CET, Evidence Synthesis Full Form, closing 5 April 2017

Title: **Optimal surveillance strategies for AJCC stage I cutaneous melanoma post primary tumour excision: an evidence synthesis and economic evaluation**

Abbreviations:
ACP: Association of Cancer Physicians; AJCC: American Joint Committee on Cancer; BAD: British Association of Dermatology; BAPRAS: British Association of Plastic, Reconstructive and Aesthetic Surgeons; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CT: Computerized tomography; Embase: Excerpta Medica Database; EVPI: Expected value of perfect information; EVPPI: Expected value of partial perfect information; FN: False negative; FP: False positive; HMIC: Health Management Information Consortium; HSROC: Hierarchical summary receiver operating curve; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio; ILI: Isolated limb infusion; ILP: Isolated limb perfusion; MEDLINE: Medical Literature Analysis and Retrieval System Online; MRI: Magnetic resonance imaging; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NPV: Negative predictive values; OS: Overall survival; PET: Positron emission tomography; PFS: progression free survival; PPV: Positive predictive values; PROSPERO: International prospective register of systematic reviews; PSA Probabilistic sensitivity analyses; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: Quality adjusted life year; RCT: Randomised controlled trial; REMARK: Recommendations for tumour marker prognostic studies; SIGN: Scottish Intercollegiate Guidelines Network; SLNB: Sentinel lymph node biopsy; SMR: Society of melanoma research; TN: True negative; TP: True positive; VOI: Value of information; WTP: Willingness to pay

SUMMARY OF RESEARCH

Design: Identifying optimal care pathways for surveillance of patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour through systematic review of relevant literature and synthesis of identified evidences. Results will be reported narratively for different surveillance strategies, with meta-analysis of prognostic and diagnostic tests and economic modelling of the effectiveness, and cost-effectiveness different surveillance strategies for patients with AJCC stage I melanoma. Future research needs will be informed by value of information analysis.

Setting: Community, primary care, hospital outpatient and hospital inpatient.

Target population: Patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour

Health technologies to be considered: All interventions relevant to the patients with melanoma and the NHS delivered in the community, primary care or in hospital.

Outcome measures: The primary outcome is overall survival (OS) defined as patient survival until death from any cause following primary treatment. Secondary outcomes include: number of detected recurrence and metastasis, prognostic performance of biomarkers and risk models (i.e. ability of the biomarkers and risk models to predict the future development of recurrence and metastasis disease) and diagnostic performance of tests in detection of recurrence and metastasis. For the economic model the primary outcome is incremental cost per quality adjusted life years from the perspective of the NHS and Personal Social Services.

Search strategy: Multiple databases will be searched, including but not limited to: MEDLINE, EMBASE, CINAHL and Cochrane Library. Further focused searches will be conducted to identify cost and utility data required for the economic evaluation.

Systematic Review: Identified titles and abstracts will be examined and full text papers of studies that potentially meet the inclusion criteria will be sought. These will be assessed for inclusion by two independent reviewers, with

disagreements resolved by discussion or arbitration by a third researcher. Depending on study type, included studies will be independently assessed for risk of bias and their quality appraised using a variety of previously validated checklists. Data on all components of differing surveillance strategies and their effectiveness will be tabulated and described in a narrative review. If possible, meta-analyses will be carried out using random-effects models for the primary outcome (OS) as well as for prognostic and diagnostic performance of the tests. Heterogeneity will be explored through consideration of study populations, methods and interventions, by visualisation of results and, in statistical terms, by the chi -squared test for homogeneity and the I^2 statistic. Evidence of small study biases such as publication bias will be examined by funnel plots.

Economic evaluation: Data from the systematic reviews and the meta-analyses will be combined in a decision analytic model. This model will be used to describe the logical and temporal sequence of events following the implementation of alternative surveillance and follow up strategies and will be used to determine relative effectiveness and cost of alternative strategies. We will also assemble the different types of data required for populating the economic model from focused searches for specific pieces of data and if necessary by analyses of existing data sets. Point estimates of costs, quality adjusted life years (QALYs) and incremental cost per QALY will be estimated. Cost-effectiveness acceptability curves will be used to represent the imprecision surrounding estimates of cost -effectiveness. We will conduct value of information (VOI) analysis to demonstrate whether more research in that area is worthwhile.

Research timetable: Research project will be conducted over 15 months. Month 1 first expert panel will convene;1-2 protocol(s) developed, agreed and registered on PROSPERO; 2-7 Main elements of the systematic reviews; 2–5 Model structure developed and agreed; 5–8 Additional model data requirements identified, synthesised and model populated; 7-10 meta-analyses; 10-11 meta-analysis and model integrated; 13–15 Final report written.

Expertise in team: We are an experienced multidisciplinary team with experience and expertise in: the development and evaluation of screening, diagnostic and monitoring technologies; mathematical and statistical modelling (Vale, Javanbakht, Bryant); clinical researcher in fields of melanoma (Ellis, Lovat and Nasr) and evidence synthesis/systematic review methodology (Vale and Nyakang'o) and we can draw upon valuable patient perspective provided by Steward, Lucas and Walker, our PPI co-applicants. The team will be supported by an advisory group comprising relevant leading clinical and methodological experts.

Flow diagram: see section 9.

2. PLANNED INVESTIGATION

2.1 Research objectives

The aim of this research is to evaluate effectiveness and cost-effectiveness of different surveillance strategies of patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour. We will meet our aim by undertaking a comprehensive evidence synthesis to assess the clinical effectiveness and cost-effectiveness of different surveillance strategies and follow-up regimens of patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour. This will include meeting the following objectives:

1- To identify different strategies for surveillance and follow-up after surgical excision of primary cutaneous tumour and review the evidence on their effectiveness and cost-effectiveness
2- To determine the prognostic performance of biochemical and biophysical markers and risk models used to determine the prognosis and risk stratification of patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour
3- To determine the diagnostic performance of tests used within surveillance and follow-up strategies in detecting recurrence and metastatic diseases in patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour.
4- To develop a decision analytic model to estimate the effectiveness and cost-effectiveness of the surveillance and follow-up strategies after surgical excision of primary cutaneous tumour
5- To undertake value of information (VOI) analysis to assess the need for further primary research.

How we will meet these objectives is described in detail in Section 3 below.

2.2 Background

Cutaneous melanoma is the 5th most common cancer in the UK, and the leading cause of cancer related death in 20-35 year olds (1). There have been great advances in the earlier detection of primary melanoma through increased public awareness, the adoption of dermatoscopic examinations and a rapid "2 week wait" referral system

in the UK (2). There is also widespread belief that earlier detection of metastatic disease results in improved overall patient outcomes (3). At present, however, there is no internationally accepted standardised model of follow-up of patients diagnosed with cutaneous melanoma, with wide variations in care across North America, Australia, Europe and the UK (4).

Primary melanomas are staged according to the American Joint Committee on Cancer (AJCC) staging criteria (5). These encompass Breslow depth (the depth of invasion of the tumour into the skin), mitotic rate (the number of dividing tumour cells as a marker of overall activity) and the presence of ulceration (loss of epidermis overlying the tumour) to allow risk stratification based on the likelihood of disease progression. AJCC staging of primary cutaneous tumours is described in Box 1.

Box 1: AJCC staging of primary cutaneous tumours

AJCC Ia
- <1mm Breslow thickness, no ulceration, mitoses <1 per mm^{-2}

AJCC Ib
- <1mm Breslow with ulceration or mitoses ≥1 per mm^{-2}
- 1.01 – 2mm, no ulceration

AJCC IIa
- 1.01 – 2mm Breslow with ulceration
- 2.01 – 4mm Breslow without ulceration

AJCCIIb
- 2.01 – 4mm Breslow with ulceration
- > 4mm Breslow without ulceration

AJCCIIc
- > 4mm Breslow with ulceration

AJCC stage I disease encompasses both Ia and Ib disease and represents the thinnest tumours with the lowest risk of mortality at ~14% over 10-years (5). Stage II disease encompasses thicker, but localised tumours. Stage III/IV patients have evidence of local and distant metastases, with 2-year mortality up to 82% in stage IV disease, although with the introduction of new chemotherapeutic agents this is now falling. With low rates of metastasis, and early physiological stage of tumour development, targeting AJCC I melanomas for appropriate and individual follow-up strategies would potentially allow the greatest health economic benefits. The limited evidence available suggests that patients at the lowest risk of disease recurrence may not need intensive clinician follow-up as is generally recommended (6), whereas patients at higher risk following surgical or drug treatment would benefit from more intensive require future surveillance to detect recurrent or metastatic disease early. This project seeks to systematically review and meta-analyse evidence for the various elements that underpin an ideal model of follow-up, thus allowing recommendations to be made on future care models for AJCC I melanoma in the UK. With the rapid increase in melanoma rates it is paramount that the UK develops a robust, evidence based model of follow-care for the majority of affected patients i.e. patients with AJCC I disease. The increase in diagnostic accuracy, development of potential prognostic biomarkers, new radiological modalities and introduction of personalised systemic treatments suggest we are entering a "golden age" of melanoma care, much of which has been driven by the UK. However, without a robust, evidence based framework for implementation of such interventions the potential health and economic benefits will be significantly diluted.

The main problem faced by patients, health care workers and NHS priority setting is that available evidence on clinical- and cost-effectiveness for component parts has not been systematically analysed and synthesised (7). By undertaking such analysis, this project will systematically review available evidence for clinical effectiveness of available and future prognostic and screening tools, and via economic modelling determine if particular follow-up sequences may be offered to patients based on individual characteristics to allow clinically and cost-effective, strategies.

Through the evidence synthesis work proposed, we aim to highlight areas deficient of evidence to allow proposals for future research priorities. This will follow a systematic review of the data available, but also, through discussions with stakeholders, that make up the research team and advisory group who we will engage throughout the project to ensure that the various requirements of these individuals are met as far as the data generated and resources requested allow. Our final conclusions will be disseminated as widely as possible to allow the UK to maintain its position as a leading centre of melanoma research, with our findings "exported" from the NHS to the other major health services of the world.

2.2.1 Outcome measures to assess effectiveness of surveillance of AJCC stage I melanoma patients after primary surgery

On-going surveillance of patients following diagnosis, and initial surgical treatment of AJCC I melanoma is undertaken to monitor for the development of further primary melanoma, local recurrence, in transit, regional or distant metastasis. Surveillance recommendations vary worldwide according to the country of residence of the patient, primary melanoma disease stage, and the specialty of the reviewing clinician, which may be a dermatologist, a surgeon or a community practitioner (8). This wide variation underlines the lack of concrete evidence for any particular surveillance strategy.

The range of potential interventions/investigations used as part of a surveillance strategy also vary in AJCC I patients. An important surveillance strategy is education of the patient to allow them to identify any new lesions of concern or signs of recurrence, in one study by Hoffman et al, 24% of the 127 patients who developed their first relapse had never participated in the follow up programme or had prematurely ceased follow up or had completed their follow up process. This data demonstrates the often erratic and unpredictable course of the disease. In the same study, 68% of first relapses were detected due to follow-up activity (9).

Regular clinical history and examination is the mainstay of most surveillance guidelines. Again, the recommended clinician undertaking such examinations varies, as does the setting of these reviews; with recommendations for either primary or secondary (in-hospital) based appointments. Specific radiological examination of patients is also recommended in some guidelines for follow-up of stage I melanoma (9). Routine use of such modalities aims to detect the development of regional and distant metastases as early as possible; theoretically, even before these become clinically apparent. However, if a patient is found to have clinical evidence of metastases then another sub-set of radiological modalities such as USS, CT and PET-CT may be used. These methods allowed targeted biopsy of the relevant melanoma deposits to allow histopathological assessment of the tissue (the use of these tool as part of a diagnostic aid rather than a surveillance modality is only addressed in this study as a small component of the economic model, when that model needs to consider management of metastases).

The use of any radiological intervention has to take into account a number of factors, namely the sensitivity and specificity of the procedure, the false positive rate, including incidental findings which ordinarily would have not been identified, the associated side effects of radiation exposure, the cost of the service, staffing requirements and the available evidence that such interventions have an overall positive impact on patient care and satisfaction – an area of understanding that is often lacking from guidelines (8-11). Table 1 outlines the variability of surveillance practices worldwide.

Table 1 Stage I melanoma specific surveillance by country during years 1 to 5 after primary excision (adapted from Cromwell et al. (8))

Number of clinical visits					
	Australasia	**Canada**	**Germany**	**UK**	**USA**
Years 1-2	1-2	2-4	3-4	2-6	1-3
Year 3	1-2	2-4	3-4	2-3	1-3
Years 4–5	1-2	2-4	2	1-2	1-3
Self-examination					
Years 1-5	Yes	Yes	Yes	Yes	Yes
Routine diagnostic imaging					
Years 1-5	Sonography of regional nodal basin	Chest x-ray, bone and liver-spleen scan	Chest x-ray, CT/MRI, and PET	Photography, abdominal sonography, chest radiography	Chest x-ray, CT of chest, abdomen and pelvis

The British Association of Dermatologists Revised UK guidelines for the management of cutaneous melanoma 2010 (12), advise that patients who have stage I melanoma are followed up to detect signs of recurrence after history and examination. This surveillance is undertaken as such:

- Patients with stage IA melanoma should be seen two to four times over up to 12 months, then discharged
- Patients with stage IB melanoma should be seen 3-monthly for 3 years, then 6-monthly to 5 years

There are no recommendations for the routine use of any radiological modality; only guidance that these can be implemented if required in symptomatic patients.

There are currently no biomarkers in routine use in any guidelines for stage I disease. Lactate dehydrogenase blood levels are validated for use in patients with evidence of metastases only (13), and there is increased application of serum S100B, but once again only in patients with evidence of metastatic disease (14). The overall measures to assess the effectiveness of surveillance strategies for stage I melanoma must encompass an evidence base for each of the following elements:

- Person(s) undertaking surveillance
    - Patient, dermatologist, surgeon, primary care physician, specialist nurse, combination of practitioners
- Site of surveillance
    - Patient's home, primary/community care, secondary care setting
- Availability/clinical utility of prognostic biomarkers for further disease stratification
- Interval timing of review appointments
- Length of overall surveillance
    - Immediate discharge, 1-year, 5-years, 10-years, life
- Routine radiological interventions
    - Which modalities, how often
- Assessment of clinical benefit from surveillance strategy
- Acceptance of any model by melanoma patients and service providers
- Value for money

2.2.2 Summary of effectiveness of interventions used in the surveillance of AJCC stage I melanoma patients after primary excision

As with much of the background to our proposed study, there is a lack of consistent evidence for the effectiveness of any particular intervention as part of a surveillance strategy in AJCC stage I patients. In a review of the effectiveness of surveillance in localised primary cutaneous melanoma conducted by Francken et al (11), the main conclusion demonstrated that history taking and physical examination resulted in the most sensitive, and cost-effective method to detect tumour recurrence in AJCC stage I and II patients. However, many studies included in this review were retrospective; so suffering from the disadvantage that data collection for the study is heavily reliant on a good level of previous data entry, and there is a greater chance of missing data which may skew and alter results. Another major disadvantage is the inability to control for other factors that might differ between the studies, for example public healthcare provision versus private healthcare provision (15). A single centre, prospective study consisting of 1460 patients with AJCC I melanoma was undertaken in Germany in 2003 (10). This study followed the German Society of Dermatology guidelines 1994, which are more intensive when compared to current British guidelines. AJCC I patients were reviewed as follows:

- History, full skin and lymph node examination every 3 months for 5 years, then 6 monthly up to 10 years
- Abdominal ultrasound, chest x-ray and blood investigations (full blood count, erythrocyte sedimentation rate, renal function, liver enzymes, lactate dehydrogenase) were performed every 12 months.
- Within the first 5 years, ultrasound of the resected tumour scar, lymphatic drainage area and regional lymph node were performed once a year.

In patients with Stage I melanoma who eventually developed distant disease, routine investigations initially identified the metastasis in varying proportions:

- physical examination in 55.6% of patients
- lymph node ultrasound in 16.7%
- chest x-ray in 11.1%
- CT scans in 5.6%
- Abdominal ultrasound detected no metastasis in such patients

2.2.3 Summary of effectiveness of interventions used to treat metastatic disease

The surgical management of primary cutaneous melanoma remains the gold standard of initial treatment, however, once metastases of the primary tumour have occurred the outlook for patients was once bleak. Over the last five years there have been rapid developments in the therapeutic options available for metastatic disease, with accompanying improvements in patient related outcomes. These developments have been so rapid that we are

currently in the follow up period for many drug trials and as such we will be unable to draw full conclusions of the effectiveness of these systemic therapies for a few years until all of the available data sets have been collated.

Metastatic disease encompasses:

- Satellite lesions – skin, or subcutaneous deposits within 2cm of the primary tumour
- In transit metastases – occur further than 2cm from the primary tumour, but before the regional lymph node
- Nodal micrometastases – metastatic deposits only evident following histopathological analysis of sentinel lymph node biopsy tissue or reginal lymph node dissection
- Nodal macrometastases – metastatic deposits within regional lymph nodes that are either clinically apparent or found on histopathological assessment of regional lymph node dissection
- Metastases to distant skin, subcutaneous tissue, lymph nodes or other visceral sites/organs

Localised metastatic disease is broadly distinguished based on the distance of spread and the total metastatic tumour bulk (AJCC Staging criteria (5)):

- IIIA
    - 1 – 3 local lymph nodes with micrometastases (diagnosed on sentinel lymph node biopsy (SLNB) or node dissection
- IIIB
    - 1 – 3 local lymph nodes with macrometastases (clinically palpable lymph node involvement or within node dissection)
    - In transit metastases/ satellite lesions with no metastatic lymph node involvement
- IIIC
    - ≥4 local lymph nodes involved
    - In transit metastases/ satellite lesions with frank metastatic lymph node involvement

"In-transit metastases" covers a wide range of clinical presentations, ranging from localised, small melanoma deposits that are easily amendable to further surgery, or >100 deposits of bulky melanoma tissue. In such cases, the clinical decisions are made based on the extent and technical feasibility of treatment.

One of the most established therapies for in-transit metastases include isolated limb perfusion (ILP), and isolated limb infusion (ILI). Both of these therapies involve the isolation of a limb's vasculature, with the addition of an anti-tumour agent into this closed system. The aim of therapy is to allow anti-tumour concentrations of the chemotherapeutic agent, without the associated systemic side effects. Traditionally, ILP/ILI has been carried out using melphalan, but recently has been carried out with the addition of tumour necrosis factor. Overall, although tumour response rates range from 64 – 93% (16, 17) the median survival post treatment is still only 2 years (18). There is currently no suggestion that ILP/ILI can be used in localised melanomas without any evidence of frank metastatic disease.

For metastatic deposits in lymph nodes (either following detection after SLNB or nodal biopsy) the most common therapy is for a lymhadenectomy (with or without post-operative radiotherapy (19)) of the involved lymph node basin. This has significant morbidity attached to the procedure and there is still a great deal of debate as to the expected benefit, if any, for patients undergoing such procedures in terms of overall melanoma survival (20, 21).

Distant metastases, encompassing stage IV disease (5), rely on systemic therapeutic options. This has arguably seen the greatest recent advances in understanding of melanoma biology and the addition of a raft of new therapeutic agents. The mainstay of chemotherapy for stage IV melanoma was once dacarbazine, with objective response rates in the range of only 10%, with a median survival of only 7-9 months (22).

The newer systemic agents can be categorized by their mode of action as either targeting the MAP Kinase signalling pathway, or via immune checkpoint blockade. A multitude of clinical trials have been undertaken assessing the benefits of each group as first line systemic therapy in patients with metastatic disease (usually AJCC IIIC and above); either as monotherapy or combined with another agent affecting the same pathway. Results to date have been impressive, and are broadly outlined in Table 2. The contemporary and shifting debate is around the order in which these drugs should be exploited to reap the greatest benefits for patients (23-38).

Table 2 Overview of median outcomes of different systemic medication regimes

Drug Regime	6 month PFS*	1 year OS*

BRAF inhibitor	56%	64.4%
BRAF inhibitor + MEK inhibitor	71.6%	74.5%
PD-1 inhibitor	51%	71.9%
CTLA-4 inhibitor	31%	65%
CTLA-4 inhibitor and PD-1 inhibitor	68%	73%

** OS: overall survival; PFS: progression free survival*

The vast majority of chemotherapeutic agents are aimed at patients with evidence of distant disease progression. Generally, patients with AJCC IIIC and above are eligible for treatment with these agents either in a therapeutic or trial setting (39). With the long-standing hypothesis that earlier introduction of systemic therapies results in better response rates it is predicted that with a better understanding of melanoma biology it may be possible to introduce systemic agents before there is clinical evidence of metastasis. Such adjuvant regimes are being studied, but in limited numbers (40). A search of clinicaltrials.gov revealed 37 trials actively recruiting to studies of adjuvant therapy in melanoma, but only three of them allowed entry for high risk primary melanoma defines as either AJCC IIB (NCT02425306) or over 4mm Breslow depth (NCT01259934, NCT02656706). One of the limiting factors of the initiation of the earliest systemic therapy possible is the lack of prognostic biomarkers in localised melanoma. The 5-year survival of patients with AJCC IIB disease is around 70%, suggesting that without better markers of disease risk, 70% of patients may be exposed unnecessarily to the side effects of chemotherapy with no overall benefit.

2.2.4 Summary of cost-effectiveness data

An initial search yielded five cost-effectiveness studies for melanoma (41-45), none of which took a UK NHS perspective. Losina et al (45) used a Markov model to evaluate the cost-effectiveness of different visual screening strategies for malignant melanoma over a lifetime time horizon from a US third party payer perspective. They considered four screening strategies: a routine non-dermatologist physician visit once every five years, a single screening by a dermatologist, a biennial screening by a dermatologist, and an annual screening by a dermatologist. They considered three populations: a general population, a population having a first-degree relative with a history of melanoma, and a population having more than one first-degree relative with a history of melanoma. While they differentiated between the various stages of melanoma, one weakness was that their categorisation of melanoma was not contemporaneous as they followed the AJCC 5th Edition Cancer Staging Manual (46) (published 1997) instead of the AJCC 6th Edition (47) (published 2002) where changes were made to the classification of melanoma based on Breslow thickness. The population defined in the analysis is also different from our target population.

Krug et al (41) studied the cost-effectiveness of surveillance strategies using either fluorodeoxyglucose positron emission tomography-computer tomography (FDG PET-CT) scan or whole body CT to diagnose pulmonary metastases from melanoma. They used a Markov model, with a time horizon of 10 years taking the perspective of the Belgium health care payer. Due to large variation in surveillance regimes and a lack of international consensus, they based their model on a conventional biannual surveillance visit for the first five years and annual visits thereafter. However, the population evaluated was for patients with resected high risk cutaneous malignant melanoma (stage IIc and III) and is different from our population of interest.

Freedberg et al (44) developed a decision analytic model to evaluate the cost-effectiveness of a visual screen by a dermatologist compared to no screening, from a third party payer perspective over a lifetime horizon. They found that the visual screen strategy to be cost-effective. However, they modelled a one-time screen instead of a screening regime. In addition, the population in the study are defined as high risk (people who burn easily, or with a family history of skin cancer, or have extensive sun exposure, or have higher than average number of moles) instead of patients with resected stage I melanoma.

Mooney et al (43) conducted a cost-utility analysis from a US healthcare payer perspective comparing usual follow-up to usual follow-up with life-long annual chest x-rays for local, regional or metastatic recurrence in a hypothetical cohort of patients diagnosed with intermediate-thickness local, cutaneous melanoma. The study used a 4 Markov model and a 20-year time horizon. The model estimated an additional cost per patient of $755 and an increase in QALYs of 0.035 resulting in an incremental cost effectiveness ratio (ICER) of $215 000.

The study by Basseres et al (42) used retrospective cohort data for patients examined at a French dermatology department from 1981 to 1991 to study the cost-effectiveness of surveillance methods for the detection of metastases after treatment for stage I melanoma. However, there was a high dropout rate of 42% and hence significant bias could have been introduced. The costs in the study were not discounted and it was not clear which

year they relate to. In addition, the AJCC classification for stage I melanoma has changed since this study was published.

Overall, this evidence base shows there are few published economic evaluation studies on post-treatment surveillance for melanoma and even fewer specifically for post-treatment surveillance of stage I melanoma. The categorisation for stage I melanoma based on Breslow thickness has changed between the AJCC 5th and 6th Editions and this may mean older published studies are no longer be relevant. None of the studies adopted a UK perspective and the results are not applicable to the study question posed.

2.3 Why is this research needed now?

Melanoma is the deadliest of skin cancers. 17,000 patients are diagnosed with melanoma each year in the UK alone (1). Thankfully, once surgically removed from the skin the majority of melanomas are cured, however up to 30% of all primary melanomas progress to metastatic disease with an associated extremely poor survival rate of only 5 – 15% s (5); as a consequence, there are some 2500 melanoma associated deaths in the UK annually. The incidence of melanoma is also increasing worldwide, and internationally Australia and New Zealand have the highest melanoma rates in the world with the Queensland incidence rate of 71 cases per 100,000 (2009-2013), vastly exceeding rates across Australia and worldwide. Melanoma rates in Australia have doubled over 20 years from 1986–2006 and are still on the rise. In Australia, 1 in 14 men and 1 in 24 women will be diagnosed with melanoma at some point in their lifetime(48). In the UK, there is an overall 7% predicted increase of diagnoses in the UK by 2035 (1), rates of melanoma are rising by up to 5.5% per year in the 20 – 45 year-old age group, the 3rd highest internationally (49); this will continue to put an increasing burden an already stretched UK National Health Service.

Although the surgical treatment of primary melanoma is effective and long established, there has been a rapid pace of change recently with the addition of earlier investigatory techniques such as sentinel lymph node biopsy, various radiological modalities, as well as a raft of advances with the treatment of metastatic disease. However, a structured, uniformly adopted, evidence based model of patient follow-up after initial diagnosis is lacking. Current guidelines vary across the world, with most developed using anecdotal evidence and expert opinion. These are usually based on the assumption that earlier detection of metastatic disease results in improved overall outcome, but often do not take a wider, holistic view of the patient pathway to identify a model that incorporates all of the elements used in the diagnosis and management of the condition. Thus, they may fail to adequately capture physical, psychological consequences and costs of these strategies.

The proposed project will take an overarching view of the model of care for patients with the most common stage of melanoma, AJCC 1, which accounts for up to 60% of diagnoses. This will encompass evidence around currently available, and predicted future prognostic histopathological indicators at the time of diagnosis, thus potentially allowing further refinement of risk-stratification of patients. These data will then be used to assess the optimal, evidence based, frequency and duration of clinical and radiological follow-up regimes. We will also develop an understanding of the most appropriate care providers for individual patients based on their disease characteristics, including the implications of increased patient education or evaluation in primary care via General Practitioners or when Dermatological, Surgical or Oncological expertise are most appropriate. We will seek to determine the impact on of different surveillance strategies on patient survival, psychological and physical well-being, as well as on costs and cost-effectiveness By conducting a rigorous evidence synthesis we will seek to inform the development of a robust future model of AJCC I melanoma care in the UK, to achieve the best health outcomes for patients, within resources available to the NHS.

3. RESEARCH METHODS

This research will be divided into two consecutive phases; the first involving the synthesis of extant literature and a second phase in which a *de novo* economic model will be developed. This model will be informed by the findings from Phase 1 along with focused searches on clinical effectiveness of different treatment options for recurrent and metastatic melanoma and other databases for economic data e.g. costs and utilities.

3.1 Systematic Reviews

The first phase of this project will consist of three systematic reviews:

i) A systematic review to identify different surveillance and follow-up strategies for stage I melanoma patients following surgical excision of the primary cutaneous tumour and their clinical effectiveness in terms of overall survival, detecting melanoma recurrence, new primaries, or metastasis.

ii) A systematic review of the prognostic accuracy of the biochemical and biophysical biomarkers and risk models used (alone or in combination) for the prediction of recurrence, new primary tumours or metastasis for patients with AJCC stage I melanoma following surgical excision of primary cutaneous tumour.

iii) A systematic review of the diagnostic accuracy of the tests/clinical exams used to detect recurrence and metastases in patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour.

The first step will be to develop, revise and register full research protocols for each systematic review in the PROSPERO database. The protocols will set out detailed descriptions of the processes and methods to be followed including, the study selection criteria, data extraction, quality appraisal, and synthesis methods. In this way, it will be possible for us to compare the final review results to their respective protocols. These reviews will be conducted in line with the guidance contained in the handbooks published by the Cochrane Collaboration (50) and Centre for Reviews and Dissemination (51).

Search methods

Search strategies will be developed for each review by an information specialist in collaboration with clinical experts, the investigators and, where appropriate, the wider project advisory group. The searches will comprise of relevant free text terms, MeSH headings/database-specific thesaurus terms as needed, in combination with a variety of search filters to identify particular study designs. Boolean operators (AND, NOT, OR) will be used to join search terms given the underlying conceptual similarities between reviews (e.g. the condition of interest, melanoma) a list of common search terms is presented in Table 3. Examples of the search filters that may be applied for the different reviews are shown in Table 4.

Table 3: Sample MEDLINE search terms for common concepts related to melanoma and surveillance

	MEDLINE
Melanoma	1 exp Melanoma/ 2 melanoma$.tw. 3 (skin adj2 (melanoma or tum$r*)).tw. 4 (cutaneous adj2 (melanoma or tum$r*)).tw. 5 (malignant adj3 melanoma).tw. 6 or/1-5
Surveillance	1 (monitor* or surveill*).tw. 2 ((follow adj2 up) or follow$up).tw. 3 (evidence-based adj3 (follow adj2 up or follow$up)).tw. 4 (evidence-based adj3 surveill*).tw 5 exp Public Health Surveillance/ or exp Population Surveillance/ 6 or/1-5
Screening	1 mass screening.tw. or exp Mass Screening/ 2 exp Biopsy/ or biops*.tw. 3 exp Genetic Testing/ 4 (biomarker* or (bio* adj3 marker*)).tw. 5 ((antibody or cell or cancer or gene*) adj5 (test* or screen* or surveill*)).tw. 6 or/1-5

Table 4: Sample search filters for the MEDLINE database (source: NICE Guideline [NG50], July 2016)

Study design	Search terms
Randomised Clinical Trials (RCTs) and other trials	1 randomized controlled trial.pt. 2 controlled clinical trial.pt. 3 randomi#ed.ab. 4 placebo.ab. 5 randomly.ab. 6 clinical trials as topic.sh. 7 trial.ti. 8 or/1-7
Diagnostic studies	1 exp "sensitivity and specificity"/ 2 (sensitivity or specificity).ti,ab. 3 ((pre test or pretest or post test) adj probability).ti,ab. 4 (predictive value* or ppv or npv).ti,ab. 5 likelihood ratio*.ti,ab. 6 likelihood function/ 7 (roc curve* or auc).ti,ab. 8 (diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. 9 gold standard.ab. 10 or/1-9
Prognostic studies	1 predict.ti. 2 (validat* or rule*).ti,ab. 3 (predict* and (outcome* or risk* or model*)).ti,ab. 4 ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. 5 decision*.ti,ab. and logistic models/ 6 (decision* and (model* or clinical*)).ti,ab.

	7 (prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. 8 (stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab. 9 roc curve/ 10 or/1-9

Multiple databases will be searched, including but not limited to: MEDLINE, EMBASE, CINAHL, and the Cochrane Library. In the first instance, there will be no restrictions on the language or country of publication, subject to the availability of translation resources. Retrieved references will be imported into separate EndNote libraries except in the event of significant study overlap between reviews, when references will be combined to prevent duplication of screening. Any identified duplicates within the references will be removed prior to study selection. Additional studies will be identified through forward and backward citation chaining, which involves mining the reference lists of relevant systematic reviews and selected papers for relevant material. Grey literature will also be obtained from databases such as OpenGrey and from the websites or relevant organisations such as Cancer Research UK (http://www.cancerresearchuk.org/about-cancer/melanoma) and Melanoma UK (http://www.melanomauk.org.uk/). Where appropriate, authors identified from trial registers will also be contacted to provide relevant unpublished reports or data.

I. Review one: clinical effectiveness review of alternative surveillance strategies

Search strategy: The searches for this review will include terms related to melanoma, surveillance, and follow-up strategies. During scoping we identified a high-quality pre-existing systematic review published by Cromwell et al. (8) that sought to identify the range of stage-specific surveillance practices for melanoma patients. To avoid duplication of work, we will restrict our searches for this review to studies published since 2011; minimising overlap. Scoping searches performed in March 2017, covering 2011 to date, suggest 7000 records.

The review by Cromwell et al had a broader population inclusion criteria, as they did not restrict their review to stage I melanoma patients. They included 104 articles in their review. We will extract these 104 citations and screen using our own inclusion and exclusion criteria. The subset of articles which meet our narrow inclusion criteria will form the foundation for our review. We believe that the studies selected by Cromwell et al. are a likely representation of the evidence-base for surveillance strategies in this patient population for that timespan. Therefore, our proposed approach will achieve efficiencies without reducing the overall quality of our study.

Screening: Two reviewers will independently assess each identified study for inclusion. The titles and abstracts of the retrieved references will be read, after which the full papers of all studies meeting our criteria will be obtained. Any disagreements at this stage will be resolved either by discussion between the reviewers or with arbitration from a third member of the study team.

The following inclusion criteria will be used:

***Population**:* Adults treated for AJCC stage I cutaneous melanoma. Studies that combine patient populations (e.g. all stages of disease) will only be included in cases where it is specified that the test/data applies also to stage I patients. Studies that do not specify a patient population will be included in the first instance pending confirmation from study authors, where possible.

***Intervention**:* Any surveillance or follow-up strategies relevant to this patient population.

***Comparator**:* Any comparator that allows for the assessment of relative clinical effectiveness e.g. no surveillance, alternative strategy.

Outcomes: Detection of recurrence, new primary tumours /metastases, patient survival.

***Timing**:* Post-resection of the primary cutaneous tumour.

***Setting**:* All settings will be eligible for inclusion, regardless of whether the study was conducted in primary, secondary, or tertiary care.

***Study design*:** Randomised controlled trials (RCTs), other non-randomised trials including quasi-experimental, comparative observational studies that address bias in their analyses.

Data extraction: Data extraction forms will be created and piloted on a subset of included studies prior to use. After any necessary adjustments, one reviewer will undertake the data extraction of included articles. The completed extraction forms will be checked for accuracy and consistency by a second reviewer, with any disagreements resolved through discussion or by a third member of the study team.

Risk of bias and methodological quality assessment: The quality of included papers in each review will be assessed independently by a reviewer and will be checked by a second reviewer. Any disagreements will be resolved through discussion or with arbitration from a third member of the study team. Critical appraisal tools will vary depending on the type of study included per review; a preliminary list of tools listed by study design is presented in Table ***5:*** 5. However, this is not a comprehensive list and any checklist deemed most appropriate at the time of performing the review will be considered for use. Any selected tools will be modified or adapted to specific study types as needed.

Table 5: List of sample critical appraisal tools by study design

Study design	Quality assessment tool
RCTs	Cochrane Risk of Bias (52)
Cohort studies	Newcastle-Ottawa Scale (53)
Non-randomised trials	ROBINS-I (Risk of Bias In Non-randomised Studies of Interventions) (54)
Grey literature	AACODS (55)

Data analysis: In recognition of AJCC staging criteria changes in past decades, we will illustrate the range of existing surveillance and follow-up strategies in the form of one or more tabular summaries. These tables will outline various strategy characteristics including: applicability to stage I patients, staging criteria used in the study, the frequency and duration of follow up and the setting/regions in which these strategies are followed. Where possible, we will seek to categorise these data by any identified common characteristics to provide a more coherent presentation of findings.

To determine the clinical effectiveness of different surveillance strategies, all collected data will be synthesised narratively in the first instance. Adjustments and calculations will also be performed at this point for any significant differences in the staging criteria reported by the included studies. If sufficient clinically and methodically similar studies are available, we will conduct meta-analyses to pool outcomes in the review. For time-to-event data (e.g. overall survival, time to recurrence etc), we will pool hazard ratios (HRs) and for dichotomous outcomes (e.g. death from any cause if not possible to report HRs), we will pool risk ratios (RRs). Initial searches have not revealed any studies which have combined and reviewed the overall risk of adverse events caused by surveillance strategies used in melanoma care, for example the adverse events which may be caused by contrast reaction secondary to performing a sentinel lymph node biopsy. Random-effects models will be used for all meta-analyses with inverse variance weighting, and the overall results will be displayed graphically in the form of a forest plot. Data from RCTs will be pooled separately from data from other non-randomised studies, to account for variations in the robustness of different study designs. If possible, sensitivity analyses will also be performed to determine the impact of study quality on the overall results. Funnel plots will be used to test for publication bias.

II. Review two: prognostic accuracy review

Search Strategy: This systematic review will combine an analysis of the accuracy of both: (i) prognostic biochemical and biophysical biomarkers, and (ii) prognostic risk models. However, we anticipate that the use of a prognostic study filter will retrieve eligible studies for either review; therefore, only one search will be conducted, combining search terms for melanoma, biomarkers, risk models and prognosis. Scoping searches performed in March 2017 with no restrictions on publication dates suggest a library of approximately 9200 records.

Screening: Two reviewers will independently perform screening in stages: after selecting studies based on their titles and abstracts, the full texts of these papers will be obtained and read in full to confirm their eligibility. Any disagreements at this stage will be resolved either by discussion between the reviewers or through the involvement of a third party. Each reviewer will apply the following criteria to screen the retrieved studies:

Population: Adults treated for AJCC stage I cutaneous melanoma. Studies that combine patient populations (e.g. all stages of disease) will only be included in cases where it is specified that the test/data applies also to stage I patients. Studies that do not specify a patient population will be included in the first instance pending confirmation from study authors, where possible.

***Index/comparator tests*:** Any relevant biochemical or biophysical markers used during patient surveillance to predict the likelihood of recurrence, new primary tumour or metastasis.

***Reference standard*:**	Any professionally-recognised biomarker used as an indicator for the likelihood of recurrence, new primary tumour or metastasis – we expect that this test will differ depending on the site (e.g. local vs distant metastases)
Outcomes:	(i) Ability of the biomarkers to predict the future development of recurrence and metastasis disease (ii) Predictive accuracy of the risk model in relation to recurrence and metastasis occurrence
***Timing*:**	Post-resection of the primary cutaneous tumour.
***Setting*:**	All settings will be eligible for inclusion, regardless of whether the study was conducted in primary, secondary, or tertiary care.
***Study design*:**	(i) Prospective or retrospective cohort studies that report on any type of prognostic biomarkers related to melanoma progression and provide sufficient time-to-event data to allow for the construction of 2x2 tables or the calculation of hazard ratios and their standard errors/confidence intervals. (ii) Studies using statistical methods to present or validate models used (a) to predict suitable melanoma outcomes of interest, and, (b) to group patients based on their risk of developing such outcomes (risk prediction models).

We will define prognostic markers as those that facilitate the stratification of patients by the likely eventual outcome of their disease. Studies on predictive biomarkers, those that indicate which subgroups of patients would likely benefit from specific treatments, will not be included. Non-empirical studies will also be excluded. To determine eligibility, we will only consider biomarker studies that are REMARK-compliant, in line with accepted reporting standards.

Data extraction: Appropriate data extraction forms will be created and piloted on a subset of included studies prior to use. The type of data extracted will include participant characteristics, type of tumour markers, reference tests and participant outcomes. Because extraction of hazard ratio data for prognostic biomarker tests is not typically straightforward, we will apply the established methods of extracting or estimating these data, as reported by multiple authors (56-58). After any necessary adjustments, one reviewer will undertake the data extraction of all include articles. The completed extraction forms will be checked for accuracy and consistency by a second reviewer, with any disagreements resolved through discussion or by arbitration from a third member of the team.

Risk of bias and methodological quality assessment: The quality of included papers in each review will be assessed independently by a reviewer and will be checked by a second reviewer. Any disagreements will be resolved through discussion or by a third party. The REMARK tool (59) will be used to critically appraise all included biomarker studies, whereas risk prediction models will be assessed using the CHARMS checklist (60).

Data analysis: i) Pooled estimates of hazard ratio data from all included studies providing sufficient data will be obtained using a random effects meta-analyses conducted in STATA; this model will account for between-study heterogeneity in effect estimates which is likely to be present. Statistical heterogeneity will be assessed using the tau-squared statistic (which provides an estimate of between study variance) and the I^2 statistic (which gives the percentage of total variability in data due to heterogeneity). Funnel plots will be created to investigate the likelihood of small study biases such as publication bias. ii) Existing risk prediction models will be identified and their predictive accuracy compared to inform the development of the *de novo* economic model.

III. Review three: diagnostic test accuracy review for test used during surveillance

Search strategy: The searches for this review will be conducted using terms for melanoma, post-treatment and diagnostic accuracy. Scoping searches performed in March 2017 with no restrictions on publication dates suggest a library of approximately 3000 records.

Screening: Each paper's relevance to this review will be determined independently by two reviewers. This will involve selecting seemingly appropriate titles and abstracts from the EndNote library of retrieved citations, then reading the full texts of the selected papers to check that they report the appropriate data. Any disagreements at this stage will be resolved by discussion between the reviewers or by arbitration from a third member of the team. Each study will be evaluated for eligibility using the following criteria:

***Population*:**	Adults treated for AJCC stage I cutaneous melanoma. Studies that combine patient populations (e.g. all stages of disease) will only be included in cases where it is

	specified that the test/data applies also to stage I patients. Studies that do not specify a patient population will be included in the first instance pending confirmation from study authors, where possible.
Target condition:	Melanoma recurrence or metastases.
Index/comparator tests:	Any tests used to detect the recurrence of melanoma or the presence of metastases, whether local or distant.
Reference standard:	Any test used to provide a definitive diagnosis of melanoma recurrence or metastasis (e.g. biopsy and histopathologic examination)
Outcomes:	True positive (TP), False positive (FP), True negative (TN), False negative (FN), Sensitivity, Specificity, Positive predictive values (PPV), Negative predictive values (NPV).
Timing:	Post-resection of the primary cutaneous tumour.
Setting:	All settings will be eligible for inclusion, regardless of whether the study was conducted in primary, secondary, or tertiary care.
Study design:	Diagnostic test studies - RCTs or other study designs (e.g. cohort, nested case-control) that report adequate data to allow for the construction of a 2x2 table of outcomes either directly or indirectly. Non-empirical studies will be excluded.

Data extraction: Suitable data extraction forms will be created and piloted on a subset of included studies prior to use. The type of data extracted will include participant characteristics, type of tumour markers, reference tests and participant outcomes. After any necessary adjustments, one reviewer will extract relevant study details and reported results on diagnostic accuracy. The completed extraction forms will be checked for accuracy and consistency by a second reviewer, with any disagreements resolved through discussion by arbitration from a third member of the team.

Quality assessment: The quality of included papers in each review will be assessed independently by a reviewer and will be checked by a second reviewer. Any disagreements will be resolved through discussion or by a third party. The QUADAS-2 tool (61) will be used to critically appraise all included studies, as recommended in the Cochrane Handbook for Diagnostic Test Accuracy Reviews (62).

Data analysis: Depending on the sufficiency and availability of data, hierarchical meta-analytic models will be used to summarise the diagnostic test accuracy data for each test type in STATA. Studies that use a range of diagnostic accuracy thresholds will be summarised using the hierarchical summary receiver operating curve (HSROC) model, which attributes between-studies differences to threshold variation. It allows the meta-analyst to investigate heterogeneity between studies while taking into account both within- and between-study variability and thus avoids the need for separate meta-analyses using a range of different methods often applied to subsets of the data. Studies that use a common threshold will be summarised using the bivariate model. The output from the HSROC model will be plotted in STATA to obtain a summary receiver operating characteristic (ROC) curve. From this, feasible operating points will be identified to obtain estimates of possible combinations of sensitivity and specificity. For the bivariate model, the output will be summary estimates of sensitivity and sensitivity. Given the susceptibility of diagnostic accuracy tests to small study biases such as publication bias, funnel plots will also be created to assess this risk.

Where feasible, sensitivity analyses will be performed to investigate whether meta-analysis results are dependent on study quality (as informed by the finding of the quality assessment described above).The need for additional sensitivity analyses may be identified during the review; these will be carried out to understand their implications on review conclusions.

3.2 Economic model

3.2.1 Model structure

As described in Section 2.2.4 none of the existing economic evaluations have addressed this question from a UK perspective. Therefore, we propose to develop a de novo economic model to estimate the costs, long-term effects and relative cost-effectiveness of alternative surveillance strategies. Since surveillance can be considered as an event undertaken at discrete intervals and repeated over time, we will represent this in a Markov model. The economic model will describe the pathway of care of individuals from the excision of the initial tumour and different forms of ongoing surveillance and follow-up strategies are initiated. This encompasses their longer-term costs and consequences, including those that might arise from any subsequent recurrence, metastasis and new primary tumours. Events will be explicitly mapped through care pathways, and will be linked by logical and mathematical relationships. We will use the model to provide the estimated costs and outcomes over a specified

time period for a cohort of patients treated for AJCC stage I melanoma. The economic model perspective will be that of the UK NHS.

Results from the systematic review of surveillance strategies and diagnostic and prognostic tests and risk prediction models will be used to define the components of different surveillance strategies in terms of frequency, duration and tests that need be used within each surveillance strategy in the model ***Figure 1***. Results from previous systematic reviews of surveillance strategies of patients with melanoma indicate that there are big variations in terms of surveillance intervals and diagnostic imaging and laboratory evaluations especially for early stage melanoma (8). Therefore, to describe the variation in current surveillance and follow-up practice in the UK and to inform the feasible alternative surveillance strategies, we will also do a survey of dermatologists, surgeons and radiologists to identify the most feasible surveillance strategies in the UK. Results from previous studies show that about 60% of recurrences and 50% of new primary tumours would be detected by the patient or partner with no delay in diagnosis (63, 64), therefore we will also model different scenarios where opportunistic diagnosis and unscheduled visits are incorporated into the care pathway.

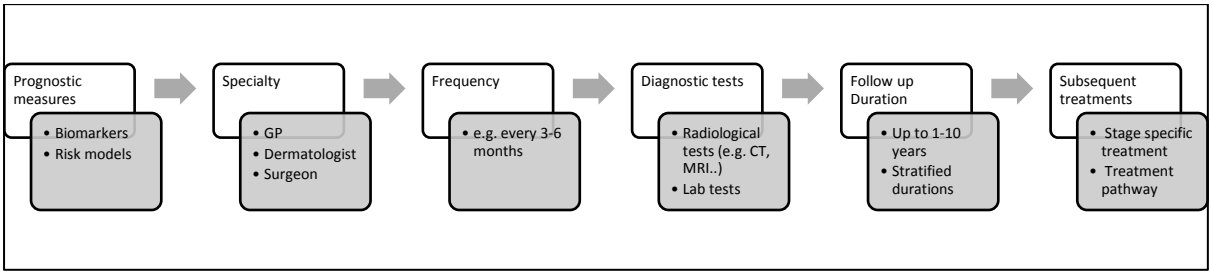

Figure 1 Main components of the surveillance strategies to define care pathway for patients with AJCC stage I melanoma after surgical excision of primary cutaneous tumour

3.2.1 Model structure

We will assemble the different types of data required for populating the economic model from the systematic reviews performed in the previous section, and focused searches for specific pieces of data and analyses of existing data sets. We will derive information on diagnostic and prognostic performance of different types of tests from the systematic reviews (**Figure *2***). It is also proposed to use a previously collected dataset to explore the natural progression of the disease in order to inform the economic model. Below we have detailed the sources of different inputs for the model.

Derivation of cost data: The costs of different surveillance strategies will comprise of cost of inviting patients for screening, the surveillance test (e.g. MRI, clinical examination), health-care professional time (e.g. GP consultation, clinical examination), further invasive tests (e.g. core biopsy or other biomarker tests) and treatment (e.g., radiotherapy, drug treatment). We will obtain the health resource utilization data from review of the previously published economic evaluation studies and the models submitted for HTA appraisal. However the identified studies are unlikely to provide all required data. With the help of relevant members of the expert group and a further search of the literature such as previous clinical guideline of melanoma (65), we will seek information on the resources required to provide surveillance and subsequent management of the disease. Unit costs for healthcare services will be obtained from standard sources such as NHS Reference Costs (66), the British National Formulary (medication) (67) and Unit Costs of Health and Social Care (68) for contacts with primary care. Discounting will be applied to costs and outcomes at 3.5% per the National Institutes of Health and Care Excellence (NICE) reference case (69).

Derivation of health utilities: The primary purpose of the economic model will be to inform decision-making in a UK setting. Given that earlier diagnosis and treatment of melanoma will affect not only survival but also quality of life, we will seek to assess the impact on quality of life through the incorporation of health-state utility weights. These will be combined with estimates of survival to estimate QALYs for different surveillance strategies. Recent guidance suggests that estimates of QALYs should ideally be based on generic health-state valuation methods using UK population tariffs (69). Therefore, health utility values associated with each health states (e.g. disease free, local metastasis, nodal metastasis, etc) will be obtained through the review of economic studies. Priority will be given to studies that have reported utility values using generic measures such as EQ-5D or SF-6D for UK patients. The mean QALYs for each intervention will be calculated by multiplying amount of time patients spend in each health state with its associated health utility value in the Markov model.

Derivation of treatment effects: The clinical effectiveness of standard treatment options for recurrence, metastasis and new primary tumour post-treatment for melanoma are required to assess the cost-effectiveness of different surveillance strategies. Since the main objective of this study is to find optimal surveillance strategies in terms of cost effectiveness, identifying and synthesising all studies for clinical effectiveness of all treatment options is beyond the scope of the project. We will search local, national or international bodies such as NICE and the Scottish Intercollegiate Guidelines Network (SIGN) to identify relevant guidelines for melanoma treatment. We believe that the best available summary of the clinical effectiveness for treatments of melanoma cancer for early, locally advanced and advanced disease are provided within the guidelines. In order to inform the economic model a previously collected dataset may be used to supplement the literature on melanoma progression.

3.2.3 Model outputs/sensitivity analysis

The different surveillance strategies will be evaluated through a cost-utility analysis (CUA) using the model developed. The joint estimates of costs and effects will be combined in an incremental analysis between different strategies, and presented as the point estimate of mean incremental cost-utility ratio (ICER) for each comparator. The ICER will be calculated as the difference in costs divided by the difference in effects (QALYs) between different surveillance strategies. To identify the optimal strategy, the net monetary benefit (NMB) framework will be used.

Deterministic and probabilistic sensitivity analyses (PSA) will be used to explore the effect of uncertainty surrounding parameter values on estimates of cost-effectiveness. PSA will be carried out using Monte Carlo simulation where model inputs for each parameter are randomly selected from predefined distributions and the results recorded. This process will be repeated for a large number of iterations to produce a distribution of results from the model. These results will be presented graphically using the cost-effectiveness plane and cost-effectiveness acceptability curves. The distribution for each parameter will be defined by considering the mean, standard error and anticipated shape of the distribution.

3.2.4 Value of information analysis

The maximum amount policy makers should be willing to invest to eliminate uncertainty in the decision will be informed by the expected value of perfect information (EVPI). The EVPI evaluates the expected cost of current uncertainty by accounting for both the probability that a decision based on existing evidence is wrong and for the magnitude of the consequences of making the wrong decision. The EVPI for individual parameters (or groups of parameters) - the expected value of partial perfect information (EVPPI) – will be estimated. The EVPI and EVPPI calculations identify which parameters have the greatest overall impact on decision uncertainty and can inform the direction of future research. Population size will be calculated based on the previous studies. After conducting the PSA, EVPI will be calculated. The most cost-effective surveillance strategy based on expected estimates of costs and QALYs, the level of decision uncertainty (the error probability for this strategy) and the magnitude of the consequences will be reported.

3.3 Ethical arrangements

Main part of this study will be involved in searching and synthesising secondary data sources therefore ethical approval is not required for this work. But in order to inform the economic model a previously collected dataset may be used to supplement the literature on melanoma progression. Permission has been given by the data holder, Dr Rob Ellis. Patient samples in these cohorts was either developed from tissue samples collected prior to the Human Tissue Act 2006, or following full ethical agreement (REC 08/H0906/95+5). All data sets used for this proposed study are completely anonymised, with no patient identifying features involved in analysis and the relevant Ethics Committee will be informed to confirm that the data can be used for research purposes. The data will be anonymised and we will follow the guidance laid out in the MRC Ethics Series Personal Information in Medical Research and Section 60 of the Health and Social Care Act regarding use, storage and investigator responsibilities. We will also seek NHS Research Ethics Committee advice and approval, as appropriate, for the study and we will abide by the 1998 Data Protection Act.

3.4 Management of the project

Rob Ellis will co-ordinate and supervise all aspects of the research project. The project will be managed through a steering group, comprising all co-applicants, which will be responsible for strategic leadership and to ensure the project will be delivered according to plan. The steering group will meet (in person or via phone conference) on a monthly basis. The day to day running of the project will be the responsibility of Rob Ellis and Luke Vale reflecting the division of responsibilities between evidence synthesis methodology (Luke Vale) and Topic expertise (Rob Ellis).

4. DISSEMINATION AND PROJECT OUTPUTS

A full account of our research will be published in the journal Health Technology Assessment. In addition, we anticipate that this research will result in at least three peer-reviewed journal articles, targeting the Lancet for the main results of the review of clinical effectiveness and the European Journal of Health Economics for the economic evaluation. We anticipate that a further paper reporting further systematic review results will also be published in specialist clinical journals of dermatology, plastic surgery and radiology.

The research will also be presented at meetings of appropriate learned societies such as the Society of Melanoma Research (SMR), Melanoma Taskforce, National Cancer Research Institute Skin Cancer Clinical Studies Group, British Association of Dermatology (BAD), British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS), Royal College of Radiologists and the Association of Cancer Physicians (ACP).

We will work with the press officers at South Tees NHS Foundation Trust and Newcastle University to publicise the results of our work to local and national news media; we have strong ties to ITV who have already shown interest in the findings of this study.

Key to the study is the role played by practitioner and service user members of the research team. We will consult with them and a wider group of doctors, specialist nurses and patients who have been diagnosed with AJCC I melanoma informing them about the study and inviting their comments on how the project can be improved. In so doing we will be encouraging those involved to engage with the project so that they will more readily contribute to meetings in the latter stages of the project where we will be asking for their input to help the research team in generating ideas for dissemination.

The expected outputs of the research will include: peer reviewed journal publications; presentations to professional societies and information to patients, practitioners and the NHS. As noted in the preceding section the whole report will be published in a Health Technology Assessment. Key elements of the research will be included in papers submitted for publication in scientific journals. For the main results around evidence of clinical effectiveness and recommendations for future melanoma care this will be a generalist journal such as the Lancet. Other elements of the review will be published in specialist clinical journals to inform practitioners interested in other review findings, including those relating to interventions provided by specialists. Publication of the economic component will be sought in a health economics journal to make it more accessible to those interested in this evidence. Similarly, we will take opportunity to present the research at meetings of appropriate learned societies including the SMR, Melanoma Taskforce, National Cancer Research Institute Skin Cancer Clinical Studies Group, BAD, BAPRAS and the National Cancer Research Institute Cancer Conference. These meetings provide another means of informing practitioners of the new evidence.

As the first in-depth review of the follow-up of AJCC I patients our findings will certainly influence future national guidelines. Presentation of our data at national meetings involving the key individuals/group in the development of national guidelines (Melanoma Taskforce, Melanoma Focus, BAD) will aid inclusion in future follow-up guidelines, with a specific target of inclusion within the Melanoma: assessment and management NICE guidelines.

5. PROJECT TIME TABLE AND MILESTONES

In the first month of this 15 month project we will convene our advisory group, comprising the project team, PPI collaborators and expert advisors. This initial meeting will focus on the protocol for the systematic reviews and care pathway development and agreement of our management plan for communications throughout the project. The protocol(s) will be completed, agreed and registered on PROSPERO by the end of month 2. The main components of the systematic reviews will be completed by month 7, at which point description of different surveillance strategies and the meta-analysis/synthesis of prognostic and diagnostic tests will take place from month's 7-10. Concurrently, from month 2 onwards the model structure will be developed, this will be agreed by the advisory group. From month 5-8 the additional model data will be identified and synthesised and will be used to populate the model. In months 10-11, the results of meta-analyses and model will be integrated. From month 11-13, model analysis and VOI analysis will be undertaken. All analyses will be presented at an advisory group meeting in month 13. In parallel, from 10-12 a draft report will be written and presented to the advisory group in month 13. The remaining time will be spend finalising the report and consulting with the advisory group and co-applicants on findings and recommendations.

Month Task:
1 Advisory group convened
1-2 Protocol developed, agreed and registered on PROSPERO

2-7 Main elements of the systematic reviews
2–5 Model structure developed and agreed
5–8 Additional model data requirements identified, synthesised and model populated
7-10 Meta-analyses
10-11 Meta-analysis and model integrated
11–14 Model analysis and value of information analysis undertaken
11–13 Initial draft report written
13 Results presented to advisory group
13–15 Final report written

6. EXPERTISE AND EXPERT PANEL

We are a multidisciplinary team with experience and expertise in: the development and evaluation of screening, diagnostic and monitoring technologies; mathematical and statistical modelling; clinical researcher in fields of melanoma and evidence synthesis/systematic review methodology. **Dr Rob Ellis** (principle investigator) is a consultant dermatologist within the South Tees NHS Foundation Trust. His main clinical interest is melanoma and as such he runs a weekly Melanoma Screening Clinic and is the deputy chair of the South Tees Specialist Skin Cancer MDT, as well as being a member Melanoma Taskforce, Melanoma Focus Group and the Northern Cancer Network Skin Cancer Specialty Group. He holds an Honorary Clinical Senior Lecturer post at Newcastle University and is heavily involved in translational work around novel skin cancer diagnostic and prognostic biomarkers, and associated targeted therapies. He will be involved in the day-to-day management of the study, as well as acting as a clinical expert. **Prof Luke Vale** (co-investigator) is an expert in the design and conduct of all aspects of evidence synthesis projects and has considerable experience of leading collaborative projects. He will be responsible for the methodological components of the project and will support the PI. **Dr Mehdi Javanbakht**, is a senior research associate at Newcastle University. He has experience in both economic evaluation and economic modelling. He will supervise the health economics researcher in the completion of the economic model and VOI analysis, drafting of the final report and subsequent publications. **Dr Brenda Nyakang'o** (co-investigator) is a systematic reviewer working within the Evidence Synthesis Team at Newcastle University's Institute of Health and Society. She will be the lead reviewer in the first phase of this project. **Prof Penny Lovat** (co-investigator), Professor of Cellular Dermatology and Oncology leads a translational research group at Newcastle University and is an internationally acknowledged expert in biomarker and novel 'targeted' drug development in melanoma. Penny has considerable experience of leading collaborative research projects including those as part of an EU consortium and led the research leading to the present application. She will support the PI in project management and consideration of biomarker utility. **Dr Batoul Nasr** (co-investigator) is a Dermatology Registrar in the Northern Deanery, she is completing a Masters of Clinical Research at Newcastle University and is also an Associate Clinical Researcher based in Dermatological Sciences at the same university. Her research interest is skin cancer, she has contributed to the writing of the application and will support the PI and non-clinical members of the team in relation to clinical interpretation of data. **Mr Andy Bryant** is an experienced statistician with research interests in meta-analysis. He will lead on the meta-analysis components. **Mrs Pam Walker** (co-investigator), is a TV News Journalist and Presenter. She was diagnosed with stage Ia melanoma in 2016. She has since taken an active role in local melanoma research. Her work as a Broadcast Journalist over the past 30 years has involved previous reporting on medical conditions, research and development. **Mrs Rachel Lucas** (co-investigator) was diagnosed with stage I melanoma. Her first-hand experience of the condition will allow her to contribute valuable views from a patient's perspective, and she has previously been involved in other melanoma research projects. Rachel's background is in business and marketing and she currently works as a marketing consultant in the dental industry. **Mr Paul Steward** (co-investigator) has a background in Finance and 15-years Board level experience in the NHS. Paul was diagnosed with a malignant melanoma in 2015 and has assisted Newcastle University closely in melanoma research over the last 12 months.

In addition to the co-applicants described above, an expert advisory panel will be convened at the start and towards the end of the project to discuss the proposed direction of the study and in the later meeting to discuss key findings. The members of the group are: **Prof Ruth Plummer,** is a clinical professor of experimental cancer medicine and her clinical work focuses on the systematic therapies for skin cancer. She will advise on clinical and methodological aspects of the study. **Dr Ed Carling** is a consultant in cytopathology and histopathology and he will advise on the interpretation of pathology evidence. **Dr Tim Cunliffe** is a GP with a Specialist Interest in Dermatology and Skin Surgery. He is a founding member of the South Tees NHS FT Melanoma Screening Clinic, author of the Primary Care Dermatology Website www.pcds.org.uk and has worked with a number of national organisations including NICE, where he has acted as part of the review body for the existing NICE guidelines on melanoma. He will provide an important link to policy as well as providing a primary care perspective. **Dr Joanne Fletcher (Radiologist)** is a consultant radiologist with a special interest in oncological imaging. She will advise in the interpretation evidence on imaging modalities. **Dr Janine Graham** is a consultant oncologist

working with in the South Tees Foundation Trust. She has a specialist interest in melanoma and as such runs a weekly melanoma clinic. She is also a member of the South Tees specialist skin cancer MDT. She has a keen interest in clinical trials and is Principle Investigator on a number of non-commercial and commercial trials. She is also lead for clinical trials within the oncology department at James Cook hospital. She will advise on the clinical management of melanoma. **Mr Tobian Muir** is a Consultant in Plastic and Reconstructive surgery with a specific interest in electrochemotherapy of advanced cancer and primary BCC/SCC. Electrochemotherapy treatment has been provided to patients since July 2007. Mr Muir was vice-chairman of the international INSPECT (International network for sharing practice in electrochemotherapy) steering committee 2008-2011, and remains as active member. He will advise on the surgical aspects of melanoma management. **Sr Caroline Brownless** is a Senior Macmillan skin cancer nurse with 20 years of cancer experience, specialising in skin for 8 years. She is involved in supporting skin cancer patients through their cancer journey and developing the service to ensure high standards of care. She has undertaken primary research within skin cancer and has been involved in cancer clinical trial recruitment and data collection. She will provide an important nursing perspective on possible changes to cancer perspective. **Sr Helena Hinde** is a dermatology cancer nurse specialist, with 10 years of experience in skin cancer and surgery area. She has been working with patients on a day to day basis. She will provide a link between patients and the team and bring a nursing perspective to the team with regard to melanoma care in the UK. **Mr Stuart Horswell** is a Principal Informatician at the Francis Crick Institute, with fifteen years' experience working in the fields of medical and cancer research. He has a particular interest in the application of biostatistical and mathematical approaches to the study of cancer evolution, heterogeneity and treatment. He will provide advice on the interpretation of statistical methods used in biomarker studies.

7. SERVICE USERS

It is vital for a project of this kind to have service user involvement. To indicate the importance we attach to this we have included three people each of whom has personal experience of melanoma and who are already engaged with the applicants in improving the care for those with melanoma. To demonstrate the importance these people are included as co-applicants and they have commented and advised on this application. It is the intention that they have input to the project as it progresses but particularly to be involved in discussions around whether the research is likely to meet service user needs and how it could be best modified to do so. This will be facilitated by ongoing engagement through the project management meetings. We intend that there will be a user-led section (roughly half the meeting will be devoted to this) to the final advisory group meeting to discuss the results of the study and recommendations for policy and practice.

8. JUSTIFICATION OF SUPPORT REQUIRED

The proposed research will involve three systematic reviews which will need a team of efficient and skilled reviewers to ensure that this work is completed to the highest standards. The staff costs to complete the systematic reviews and the economic component will be based at Newcastle University. We estimate that we will need two reviewers (11 months and 5 months for the first and second reviewer) for a total of 15 months to undertake this work and ensure it is completed to the highest standard. We have also estimated that we will need the equivalent of 2 months funding from an information specialist to design and conduct the necessary searches. The quantity of staff time required to complete the systematic reviews has been informed by numerous previous evidence synthesis projects that co-investigators (Luke Vale and Mehdi Javanbakht) have been involved in and consideration of the size of the evidence base as informed by previous research and our scoping searches.

Statistical time and health economics time reflects the potential complexity of the meta-analyses and economic modelling. In particular for both elements of analysis the number of comparators and variations within the comparators as well as methodological challenges in combining different measures of the same outcome and synthesis of diagnostic and prognostic measures. We have therefore costed about 6 months of a statistician (Andrew Bryant) time to undertake the meta-analyses. The health economics work will be undertaken by two experienced economists (Mehdi Javanbakht (2 months) and a RA, with the latter costed at 11.5 months), spread over the duration of the project. In addition, both the systematic reviews and economic evaluation of the work will be supported and supervised by Luke Vale who has been costed at 2.5% FTE to allow time to undertake this aspect of the project. In addition to these staff costs further staff costs have been included for clinical collaborators (Rob Ellis 20% FTE, Penny Lovat and Batoul Nasr both 2.5% FTE. 15 day funding has been included for each PPI co-applicant. Further costs are included to support the project management, meeting costs, office supplies, equipment and dissemination of the research.

9. Flow diagram

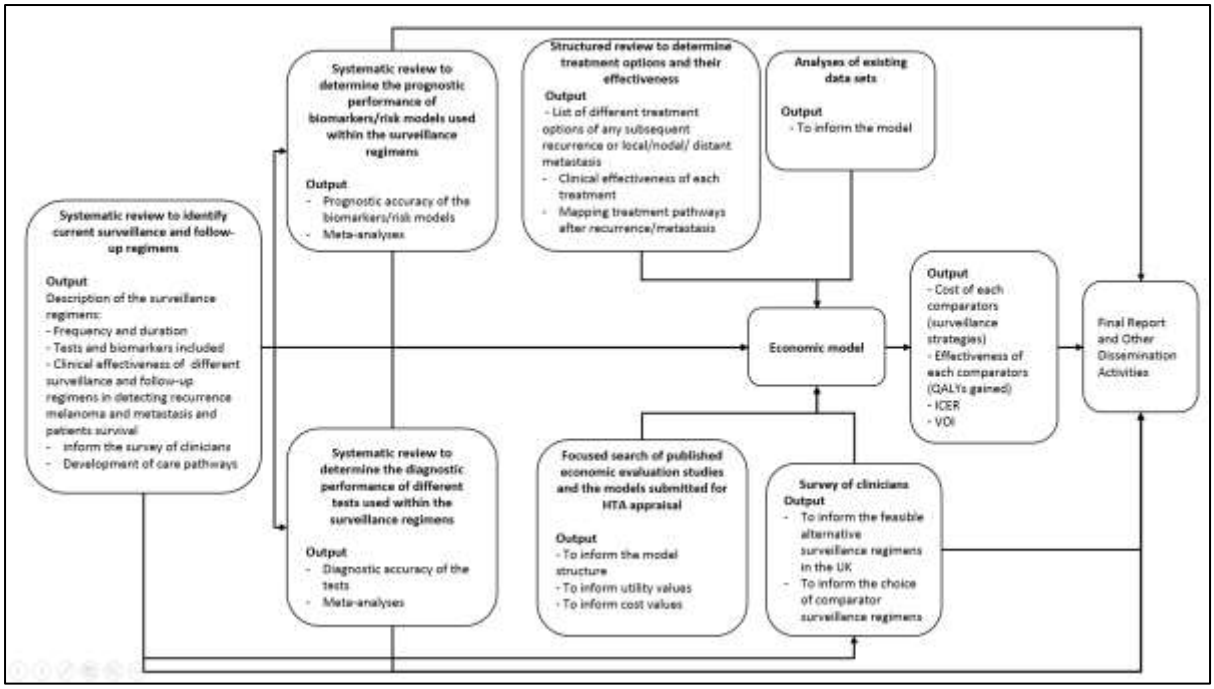

Figure 2 The evidence syntheses and model development flow diagram

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