Detailed project description

Full title: Understanding the effectiveness, cost-effectiveness and current use of cancer diagnostic tools to aid decision-making in primary care

Summary of Research: Cancer survival in the UK is lower than the European average for many cancer types(1). Reducing the time to diagnosis is a potential area where improvement in cancer survival could be made(2). Primary care has a major role here, and earlier identification of individuals who have cancer could lead to improved patient quality of life and survival. Cancer diagnostic prediction models have been developed for this reason. They are formal combinations of multiple predictors (including clinical and non-clinical characteristics) from which the probability of a specific diagnosis can be calculated for individual patients(3), and aim to help doctors in estimating probabilities and potentially influence their decision making(4). Tools beyond the NICE suspected cancer guidelines(5) are available to help GPs in their cancer diagnostic decision making. Examples of these tools include an electronic system, known as QCancer, which is based on the findings of diagnostic prediction models by Hippisley-Cox and colleagues(6, 7); and mouse mats, desk flipcharts and an electronic system, collectively known as Risk Assessment Tools (RATs), based on the findings of diagnostic prediction models developed by Hamilton and colleagues(8, 9). There is some evidence to suggest increased referrals/investigations are associated with use of these tools(10); however, no systematic review of the effectiveness of these or other tools has been done, nor has there been any exploration of their cost-effectiveness.

We aim to review the evidence on the effectiveness and cost-effectiveness of such tools, use decision-modelling (for a particular cancer type) to explore the trade-offs between patient outcomes and the impact on NHS resources and costs, and explore the extent to which GPs currently have access to and use cancer diagnostic tools.

The main components of the project will include a systematic review of the effectiveness and cost-effectiveness of cancer diagnostic tools in terms of patient outcomes (Systematic Review 1). As we do not anticipate a great deal of evidence for such tools available in the literature, to assess the likely availability of tools in the near future, we will supplement Systematic Review 1 with a systematic review of studies evaluating the development and validation of diagnostic prediction models (Systematic Review 2). We will use decision analytic modelling to explore uncertainty in the likely impact of using the tools identified in Systematic Review 1 within the context of the NHS for a particular cancer type. These impacts will include patient outcomes and NHS resource use and costs. We will also update a previous systematic review investigating the impact of reducing time to diagnosis and/or treatment on patient outcomes conducted by co-applicants Neal, Lewis and Hamilton(11). We believe this particular issue is both critical to an understanding of whether diagnostic tools could impact on patient outcome, and a key parameter in the decision analytic modelling, linking short- and medium-term effects of the diagnostic tools with longer term outcomes if direct evidence of effect on patient outcomes does not exist. We will conduct a survey of GPs to estimate the proportion of GPs with access to diagnostic cancer tools, and the proportion stating they use these tools. We will then estimate the effect that the use of the risk assessment tool has upon 2 week wait (2WW) referrals by linking the information from the GP survey to the 2WW referral rates reported by practice by Public Health England (using the unique GP practice code). Given that impact of the tool on the 2WW referral rates is also likely to be affected by other confounding variables, such as the patient population and practice characteristics, we will control for this confounding by using propensity scores matching in this analysis. As part of the NHS constitution, patients with suspected cancer have a right to be seen by a specialist within two weeks of the GP referral(12). Findings from this will also inform parts of the decision analytic model.

For the decision model, we have chosen colorectal cancer to illustrate a best case where we believe there are good a priori reasons why diagnostic tools in primary care may be effective and cost-effective. Although limiting exploration to one cancer type for reasons of feasibility may restrict generalisations to other cancer types, this project will help identify key evidence that currently exists for different cancer types, and gaps in the literature which further research could help inform. If effectiveness and cost-effectiveness results are favourable for colorectal cancer, the modelling approach could be extended to other cancers, but would be most difficult where well developed and validated disease treatment models did not exist, such as for pancreatic cancer or upper gastro-intestinal cancer. The difficulty arises because the modelling approach depends on linking evidence on short-term outcomes, such as time to diagnosis, to evidence on the effectiveness of management and treatment effects.

The key principle underlying our project is to provide an answer to the questions posed in the brief in a focused and timely manner. To do this, we are harnessing researchers who are already in post and ready to start as soon as the project has been approved. We have necessarily had to make decisions on which features of the wider problem to investigate in order to maximise the impact of research in a shorter period.

Background and Rationale: Cancer survival in the UK is lower than the European average for most cancers, e.g. 5-year survival for stomach cancer is 17.2% in the UK vs European average of 25.1%, colon cancer is 51.8% in UK vs European average of 57%(1). Efforts to reduce the time to make a cancer diagnosis have the potential to improve prognosis(13), since earlier diagnosis is associated with earlier stage at diagnosis(14), and earlier treatment is associated with improved survival(2). There is also the potential to reduce presentation via emergency admissions, and prevent the poorer survival associated with that route of diagnosis(15). National cancer screening programmes in the NHS (for breast, bowel and cervical cancer), and the National Awareness and Early Diagnosis Initiative (NAEDI) (to increase public awareness on the signs and symptoms of cancer (16)) are intended to improve early diagnosis. As many individuals go through primary care as a route for diagnosis(15), efforts here could improve cancer survival.

Cancer diagnosis in primary care is not straightforward. Symptoms of cancer are commonly seen but mostly have non-cancer origins(5). Of those individuals referred from primary care via the 2-week wait referrals for suspected head and neck cancer, approximately 9% were ultimately diagnosed with cancer(17). The type and presence of symptoms can vary greatly (16), and it is not surprising that patients can have multiple GP consultations before being referred, especially for those cancers that have less well-known signs and symptoms(18). Thus, tools to help improve cancer diagnosis in primary care have great potential to impact on diagnoses and subsequent treatment options, leading to better outcomes for patients.

Diagnostic prediction models combine multiple predictors, such as symptoms and patient characteristics, in order to obtain the risk of the presence or absence of a disease within an individual patient(3, 4). These prediction models can then be used to develop diagnostic tools (such as a website risk calculator, or mouse mat containing estimates of risk depending on characteristics) to assist doctors in estimating probabilities and potentially influence their decision making(4). To evaluate diagnostic prediction models, there are three important stages, or types of studies: prediction model development, prediction model validation, and assessment of the impact of prediction models in practice (generally implemented as diagnostic tools). The first two are often conducted as part of the same study, and are generally evaluated using a single cohort design. These types of studies are commonly found in the diagnostic prediction literature, with some studies also reporting results of an external validation(19). To assess the impact of the prediction model (the third stage), comparative studies are required to evaluate the ability of the tool to guide patient management. In the literature on prediction models in general, very few

diagnostic prediction models that are developed go on to be evaluated for their clinical impact(19).

Tools currently available to GPs to help cancer diagnosis, beyond the NICE guidelines for suspected cancer referral(5), are based on diagnostic prediction models:

1) The Risk Assessment Tool (RAT) developed by Hamilton (co-applicant on this project) and colleagues which provides estimates of cancer risk for 17 cancers based on symptoms alone,

2) The Qcancer tool, which estimates the risk of 10 cancers based on symptoms and patient characteristics, such as age, smoking status, and body mass index.

There are clear differences in the derivation of RAT and Qcancer. RAT used a case-control design to predict likely cancer diagnosis while Qcancer used a cohort design. Many of the Qcancer prediction models have subsequently been externally validated and reported to have good diagnostic performance(20-24). There has, however, been no comparison of the effectiveness of these diagnostic tools in clinical practice.

Hamilton(10) reported an increase in cancer referrals and investigations associated with the introduction of RATs as a mouse-mat and desk flipchart for lung and colorectal cancer, and an increase in the awareness of GPs of cancer symptoms, especially those symptoms that are less known in that cancer(25). More recent evaluation of an electronic version of RATs for lung and colorectal cancer highlighted the potential issue of prompt overload from the system, cautioned on potential variation in data used by the tool, and the extent to which the aid might increase pressure on secondary care due to increased referral (a finding which could be generalised to all such diagnostic tools)(26).

An Australian study using simulated GP consultations explored the implementation of an aid based on Qcancer(27). They found that GPs agreed that the diagnostic aid was potentially useful in practice, but noted that different GPs interpreted the same set of symptoms differently, leading to inconsistent estimates of risk from the Qcancer aid. In collaboration with NAEDI, Macmillan Cancer Support developed, with BMJ Informatica, and evaluated the introduction of an electronic clinical decision system (eCDS) containing RAT and Qcancer for colorectal, lung, oesophago-gastric, pancreatic and ovarian cancers. They found that the impact of eCDS varied across practice, from no impact on referrals to increased referrals and investigations in other practices(28), with use of eCDS leading to further investigation or referral of the patient which would not have occurred otherwise in 19% of cases.

However, there is very little evidence on whether these tools have led to increased or quicker cancer diagnoses and ultimately to impacts on patient quality of life or survival. A study protocol for a RCT to evaluate eCDS for symptoms indicative of stomach cancer has recently been published(29). Other diagnostic prediction models have been developed in the UK, such as that reported by Iyen-Omofoman(30) for lung cancer and the Bristol-Birmingham equation for colorectal cancer(31), plus those developed outside of the UK such as BLINK in Australia for skin cancer(32) and that developed in the US for ovarian cancer(33), that may have the potential to be useful in the NHS context. However, little is known about whether and how these diagnostic prediction models and tools impact on patient outcomes, and would impact on NHS resources.

Although we are unclear about the evidence on the effectiveness of these diagnostic tools to impact patient quality of life and survival, a systematic review by co-applicants(11) (Neal, Lewis, Hamilton) found a large number of studies looking at the impact of reducing diagnostic and/or treatment intervals for cancer on patient outcomes. Only a small number of studies were found to be of high quality, and there was substantial variation in the type of intervals evaluated and the

findings within and between cancer types. Compared to other cancer types, studies within colorectal, breast, head and neck, testicular cancer and melanoma suggested that shorter time intervals were associated with improved patient outcomes. However, for each of these cancer types there were also studies reporting no association between time interval and patient outcome.

We will add to the existing literature by conducting a systematic review of the effectiveness and cost-effectiveness of diagnostic tools in improving patient outcomes, including the timing of diagnoses, cancer stage at diagnosis, quality of life, survival and NHS resources (Systematic Review 1). Given that we are familiar with work in this area, and trends in research on diagnostic prediction models in general(19), it is anticipated that there may be a limited number of studies evaluating the effectiveness or cost-effectiveness of these diagnostic tools. Therefore, we will supplement this systematic review with a systematic review of studies reporting on the development and validation, including estimates of accuracy where available, of diagnostic prediction models fitting our definition (Systematic Review 2). This corresponds to the first and second type of study design above.

It will be important to consider the possible trade-offs between the costs and harms, and the inherent uncertainty, of using these diagnostic tools in primary care. For instance, will the tools lead to additional referrals and investigations, and will the potential benefit, in terms of quicker or increased diagnoses, outweigh the costs of additional tests and referrals? Alternatively, could the prediction tools be no better than clinical judgement for identifying those with cancer, but better at identifying those without cancer, and therefore potentially lead to a decrease in the number of referrals, but improved confidence in the clinical decision and reassurance for the patients who do not have cancer? Due to such uncertainty, we will use decision analytic modelling to extrapolate the available effectiveness evidence, and explore the impact on resource use, costs and patient outcomes of using specific cancer diagnosis tools. The decision model will allow us to explore this uncertainty and comment on the likely effectiveness and cost-effectiveness of tools in a specific cancer type representing a best case example of their use. To understand the extent to which reducing times to diagnosis and/or treatment could impact on patient outcomes, we will supplement the systematic review of effectiveness of the diagnostic tools by updating the review by co-applicants Neal, Lewis and Hamilton(11) on impacts of patient outcomes associated with reducing diagnostic and/or treatment intervals.

We will also add to the existing evidence by conducting a survey of GPs to ascertain whether they have access to cancer diagnostic tools, and whether they use them to inform their decision-making. This survey will build on an on-going (as yet unpublished) survey being conducted at University of Exeter (by co-applicants Hyde and Hamilton) on the use of decision tools for cancer diagnosis in primary care.

The findings of the proposed project will shed light on the current use of cancer diagnostic tools, the amount of effectiveness evidence available for these tools, and where gaps in the evidence exist; in addition, it will explore the uncertainty in their impact on patient outcomes and NHS resources, and identify where investing in further research would be most useful.

Evidence explaining why this research is needed now: Cancer diagnostic tools to aid decision-making in primary care in the NHS are readily available to GPs in electronic form. Part funded by the Department of Health, Macmillan Cancer Support with BMJ Informatica have made the RAT and Qcancer tools available within 2 GP electronic patient record systems EMIS and Vision INPS: QCancer in the EMIS, and RATs in Vision INPS. Through this, Qcancer is now integrated in over 4000 practices, covering 12 cancer types. Currently, RAT covers 6 cancer types and has just been rolled out across Scotland via Vision INPS, but will be expanded by Macmillan to 17 cancer types (all published).

There is also emerging evidence, from an on-going study at the University of Exeter surveying regional GPs on their use of such tools in cancer diagnosis, to suggest that these diagnostic tools are used by GPs (study by co-applicants Hyde and Hamilton, and as yet unpublished). Based on the published literature, we are aware of some of the pros and cons associated with GPs using these diagnostic tools in practice(10, 25, 27); however, what is lacking is an exploration of the effectiveness and cost-effectiveness of these diagnostic tools either compared to each other or to routine practice without their use. It is important to look at the potential impacts of these tools not just on the number of referrals or further testing their use may lead to, but also on the diagnoses made, patient quality of life and survival, and NHS resource use. NICE specifically addressed eCDS in their 2015 advice(5), but stated there was insufficient evidence to support eCDS as a platform for delivery of cancer knowledge.

Now is the most appropriate time to start exploring the impact of these tools on patients and the NHS. We know that diagnostic prediction models other than those behind RATs and Qcancer have been developed(30, 31), but it is unclear whether these have the potential to be of use within the NHS. Comprehensively reviewing the evidence on the existence, effectiveness and cost-effectiveness of diagnostic prediction models will help identify gaps in the evidence, and help to summarise what has already been investigated. Using decision analytic modelling, we will explore the trade-offs and uncertainty in the use of these diagnostic tools. We have chosen a specific cancer type to model - colorectal cancer - based on criteria to help identify the cancer type where use of such tools might offer greatest opportunity for patient benefits – a best case example. Moreover, compared to other cancer types, colorectal cancer is an area where there is a great deal of evidence to help inform the decision analytic model.

We need to better understand the patient and NHS impacts of using these diagnostic tools in primary care. This will allow better recommendations to be made on cancer referrals, including which tools might be better in different circumstances. As these tools may be used in the presence of screening programmes, and existing efforts to improve cancer awareness in the general population, evaluation of the effectiveness and cost-effectiveness of these diagnostic tools will be considered in light of this.

Aims and objectives:

Aims: to review the effectiveness and cost-effectiveness of cancer diagnostic tools in primary care, and understand the extent to which existing tools are currently used in the primary care setting in the NHS.

Objectives:

1. Summarise the effectiveness and cost-effectiveness of symptom-based diagnostic tools that could be used to inform cancer diagnosis decision-making in primary care **(Systematic review 1)**

   This will be supplemented by a systematic review to identify studies reporting the development, validation or accuracy of any diagnostic prediction model that could be used as a tool to help cancer diagnosis in primary care **(Systematic review 2)**

2. Use decision analytic modelling to explore uncertainties in the cost-effectiveness of using such diagnostic tools, including impacts on health service resource use, costs and patient outcomes in colorectal cancer **(Decision-model)**

   The findings of Systematic Review 1 will directly inform the decision analytic model. The model will also be informed by an update of a previous systematic review conducted by co-

applicants Neal et al(7), which will provide evidence on the impact of reducing time to cancer diagnosis and/or treatment on patient outcomes **(Update systematic review)**

The decision analytic model will also be informed by additional reviews conducted using a systematic approach consistent with good modelling practice(34), to identify the values and ranges for other model parameters such as accuracy of the diagnostic tools (also identified in Systematic Review 2), utilities, resource use and costs.

3. Understand the extent to which GPs currently have access to cancer diagnostic tools and are using them in primary care to inform their decision-making **(Survey).** This will be linked to data on 2 week wait referral rates for suspected cancer to estimate the likely impact of using diagnostic tools on 2 week wait referrals.

Health technologies being assessed: Diagnostic tools are diagnostic prediction models used in clinical practice. We make a clear distinction between these two, and thus define the intervention in two steps:

(1) Any statistical 'model' predicting the probability or risk that a patient currently has cancer based on a combination of known features for a patient. These features are defined to include symptoms which are self-reported by the patients, or identified within primary care via routine testing (such as full blood count, urine dipstick testing). Features may also include patient characteristics in addition to symptoms. Examples include the prediction modelling by Hippisley-Cox and co-authors(6, 7), and the models by Hamilton and co-authors (9, 35). (These are referred to as prediction models)
(2) Any tool that allows a prediction model for cancer to be incorporated into clinical practice, e.g. mouse-mats for the Hamilton models, Qcancer electronic system for Hippisley-Cox models. (These are referred to as diagnostic tools)

Any tool used for cancer screening of asymptomatic patients, or tools used to predict future risk of cancer in asymptomatic patients will be excluded.

Target population: We define the target population as individuals presenting to primary care with symptoms that could indicate cancer. These symptoms could be self-reported by the patient, or identified within primary care via routine testing (such as anaemia identified from a full blood count test).

Setting context: The setting is defined as primary care in the UK, which can include general practice, NHS dental services, community pharmacies and opticians working for the NHS. We acknowledge that outside of the UK, primary care may be hard to define, and we will discuss any uncertainties with the project team, and refer to our expert advisory group for advice when necessary. For **Systematic Reviews 1 and 2**, and the **Update Systematic Review** we will search for evidence beyond the UK setting that may have the potential to be appropriate to the UK. We will determine appropriateness of any non-UK evidence found to the UK setting in discussion with our expert advisory group and thoroughly justify our decisions. The decision modelling will be restricted to the NHS perspective, justifying any use of evidence from outside the UK. The GP survey will be restricted to primary care.

Research plan: The research plan has been designed to efficiently address the research brief in as timely a manner as possible. To this end we have targeted our research plan to address key aspects of the wider problem (as opposed to all possible dimensions) using experienced staff who is already in post. The research plan also maximises the use of existing models, minimising the need to develop time-consuming treatment management decision analytic models where they do not already exist, and will use efficient methods of searching to update a systematic review.

The systematic reviews will follow good practice guidelines(36), including CHARMS(37) for diagnostic prediction models. All systematic reviews will be registered with PROSPERO and reported using PRISMA(38). The decision-model(s) will be developed in accordance with good practice guidelines(34), and reported using CHEERS(39). The survey will be design and conducted in line with good practice guidelines, and reported using Burns et al(40).

Objective 1: Summarise the effectiveness and cost-effectiveness of tools that could be used to inform cancer diagnosis decision-making in primary care

Systematic review 1

Aim: To systematically review the existing evidence on the effectiveness and cost-effectiveness of cancer diagnostic tools to aid decision-making in primary care.

Systematic review 2

Aim: To systematically review the literature to identify studies reporting the development, validation or accuracy, of diagnostic prediction models that could be used to help cancer decision-making in primary care.

Systematic Reviews 1 and 2 will be conducted in tandem using the same search strategy but different inclusion and exclusion criteria. Below we first summarise the literature search that will be used for both systematic reviews, and then describe the specific inclusion and exclusion criteria, data extraction and risk of bias assessment separately for each systematic review.

Literature search: Study identification will be led by systematic searches of key bio-medical bibliographic databases, including MEDLINE, Web of Science, Cochrane Library. Sensitive searches will be undertaken to identify published studies reporting the use of tools or prediction models to help cancer diagnosis in primary care. A draft scoping search for MEDLINE is provided for illustration of the likely number of hits expected. As this is a draft it will be further refined at the start of the project with additional input from the project team members and the expert advisory group.

---------- DRAFT SCOPING SEARCH ----------

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present Search Strategy:

1. (Cancer$ or neoplasm$).ti,ab,kw. or exp Neoplasms/	3116058
2. (tool or tools or aid$ or model or models or checklist or check list or rule or rules or algorithm$).ti,ab,kw.	2736089
3. (predict$ or assessment or risk$ or diagnos$ or decision or decision-support or prognosis or prognoses).ti,ab,kw.	4564027
4 (primary care or general practice or family practice or (primary adj3 (healthcare or health care))).ti,ab,kw. or exp General Practice/ or primary health care/ or General Practitioners/	190415
5. 1 and 2 and 3 and 4	1333

These searches will be supplemented by searches of named tools (i.e. Qcancer) or diagnostic prediction models. Bi-directional citation searches(36) will also be undertaken to identify further published and unpublished studies on specific diagnostic tools or prediction models. Supplementary search techniques will be key to our approach, and to identifying unpublished studies. The project team will work with the expert advisory group to identify researchers, study

authors, and groups developing, validating and evaluating tools and prediction models, and we will make contact to identify any unpublished or on-going work. Study identification will be led by a senior information specialist (CC) and the process will be developed with the project team and the expert advisory group.

Selection of studies: Against the inclusion and exclusion criteria, two reviewers (BG + RL) will independently screen titles and abstracts from the searches. Those included on title and abstract will then be screened on their full-texts, independently by the two reviewers. Disagreements at either stage will be discussed by the two reviewers, and, if not resolved, a third reviewer (CH) will independently make the final decision. Pilot screening will be undertaken for the first 100 hits to ensure all reviewers are interpreting the inclusion and exclusion criteria in the same way.

Studies will be included in Systematic Review 1 if they fulfil the following criteria:

- Population: symptomatic patients attending primary care
- Intervention: any diagnostic tool used to provide an estimate of the risk of current cancer based on patients' symptoms (with or without patient characteristics)
- Comparator: standard care for the setting/country in which the evaluation was undertaken, or another cancer diagnostic tool
- Outcome: any patient related or economic outcome measure including the number of cancer diagnoses, time to cancer diagnosis, stage of cancer at diagnosis, resection rates, patient health-related quality of life (and other patient reported outcome measures), survival, resource use, cost per quality-adjusted life-year (QALY), cost per diagnosis.
- Study design: any comparative design will be included, e.g. randomised controlled trial (RCT), controlled before-after, and interrupted time-series. If we do not find a great deal of evidence using these study designs we will broaden our inclusion criteria to include any type of evaluation, for example studies analysing national trends in cancer diagnosis before and after diagnostic tools became available to use.

Studies will be included in Systematic Review 2 if they fulfil the following criteria:

- Population: symptomatic patients attending primary care
- Intervention: any diagnostic prediction model that estimates the risk of current cancer based on patients' symptoms (with or without patient characteristics)
- Outcome: estimates of risk associated with symptoms (including odds ratios, hazard ratios), and/or details on the development, validation or accuracy of the tool.
- Study design: any design for the development or validation of tools using symptoms (and patient characteristics) to predict current risk of cancer diagnosis

For Systematic Review 2, multiple studies may report the development and validation aspects of particular prediction models (e.g. the development and internal validation of the prediction model by Hippisley-Cox is reported in one paper (41) and external validation is reported in a separate paper (20)). We will therefore collate all studies related to each specific prediction model regardless of whether they refer to the development or validation of that tool.

For both systematic reviews we will exclude studies developing, validating or evaluating diagnostic prediction models or tools outside primary care, or studies in a screening setting or any other setting with asymptomatic patients. A great deal of information will be required to critically appraise the included studies, and so studies only published as conference abstracts, or where their full-text cannot be obtained will be excluded. (We have included costs for inter-library loans.) Only studies in English will be included, but the searches will not be restricted to English language in order to gauge the potential language publication bias.

Data extraction: Standardised forms will be used to extract relevant data from each included study. One reviewer (BG) will conduct data extraction, which will then be checked by a second reviewer (RL and/or CH). Pilot data extraction will be undertaken to ensure the standardised forms are sufficient. For Systematic Review 1, items to be extracted will include study design, country of origin, sample size, patient recruitment (with inclusion and exclusion criteria), characteristics of the tool (including whether based on symptoms alone or other features in addition to symptoms), cancer type(s), definition of outcomes, main results including confidence intervals, subgroup analyses. For Systematic Review 2, we will follow the CHARMS checklist(37) and extract details on: study design, sample size, number of participants with specific cancer, recruitment (including inclusion and exclusion criteria), participant characteristics, country, features of the tool (based on symptoms alone, symptoms and patient characteristics), how symptoms/characteristics are defined and measured, cancer type(s), definition of primary and secondary outcomes, how and when outcomes are assessed, main results (including model performance, validation and estimates of risk), symptoms/characteristics included in final tool. For both systematic reviews, we will attempt to contact study authors for further clarification and/or information where necessary.

Critical appraisal: For Systematic Review 1, we will use the Cochrane Risk of Bias Tool(42) or an adaptation of this (developed by Cochrane Effective Practice and Organisation of Care (EPOC) group) to assess potential features of different study designs that may lead to biased estimates of effectiveness. For Systematic Review 2, we will use the PROBAST checklist (anticipated to be published end of 2016) to critically appraise the included studies(43).

Synthesis: For both systematic reviews we expect a great deal of heterogeneity between included studies in terms of the diagnostic tool or prediction model evaluated, the setting and country, cancer type(s), and outcome measures. Therefore we anticipate a narrative review of the findings from the included studies for each systematic review. For Systematic Review 1, we will narratively synthesise the evidence by subgrouping studies and describe their key components, e.g. cancer location, population, intervention, comparator, study design. We will explore reasons for heterogeneity and highlight important differences and similarities between the studies and their results. This will be aided by the tabulation of the key components and results. In the unlikely event that there is less heterogeneity between studies than we would expect, we will use random effects meta-analysis models to summarise the outcomes across studies of similar aim and design. For Systematic Review 2, to synthesise the evidence identified we will group and tabulate studies by the prediction model to summarise the current evidence base for that prediction model. Multiple prediction models for the same cancer location will be compared, and differences and similarities in their development, validation and/or accuracy will be discussed. This approach will allow us to provide an authoritative list of cancer diagnosis prediction models sufficiently validated to be considered for use by primary care, with a summary of the elements of that validation, and accuracy of the prediction model, if that information is found.

Systematic Reviews 1 and 2 will be undertaken by BG and RL who are both experienced at conducting systematic reviews generally and in areas closely related to this topic, and will be supported by CH and RN in particular. CC (senior information specialist) will lead the literature searches and JL will help with document retrieval. CC, CH and JP have worked successfully on a number of systematic reviews together. Co-applicants on the project who have been involved in the development of any cancer diagnostic aid or prediction model will not be involved in the assessment of studies referring to that aid or prediction model.

Objective 2: Use decision analytic modelling to explore uncertainties of using such diagnostic tools, including health service resource use, costs and patient outcomes in colorectal cancer

Decision modelling

Aim: to use decision modelling to explore the uncertainties regarding the effectiveness and cost-effectiveness of tools to aid cancer diagnosis decision-making in primary care in the NHS. We will link empirically demonstrated impacts on short- and medium-term outcomes to the effects of treatment to estimate the impact on longer term outcomes. As we do not anticipate a great amount of evidence to inform assessment of the cost-effectiveness of the use of risk tools, we expect to use the model to demonstrate the uncertainty inherent in the current evidence base, and show what likely impact use of the tools in clinical practice may have on patient outcomes and NHS resources. Due to uncertainty in the evidence, we do not expect the primary role of the decision modelling to be the estimation of the single most likely point estimates of costs per QALY associated with each diagnostic tool. Instead, we will use the decision model and the evidence that is available, to explore the likely range of costs per QALY, and ask questions about the likely impact of the diagnostic tools given the current lack of evidence. We specifically want to investigate the following hypotheses, and the decision analytic model will be designed to allow these questions to be examined:

- Will the benefit to patients identified earlier by diagnostic tools who are confirmed as having cancer outweigh any disutility in extra patients referred for further investigation who do not have cancer?
- Could a cancer diagnostic tool be considered cost-effective if it reduces the period of extreme anxiety for patients (with or without cancer), even if it made no impact on patient outcome, by expediting investigation and management in patients with cancer minimising a period of extreme anxiety?
- What are the possible impacts on patient quality of life or survival if use of diagnostic tools reduces time to diagnosis?
- How big an improvement in quality of life would be needed to warrant use of these tools if there are no survival impacts associated with the diagnostic tools? Would this quality of life improvement be justifiable given the evidence we have?

We also want to develop a decision model which can be used as a template for modelling the effect of diagnostic tools in cancers other than colorectal cancer. Furthermore, we will aim to develop a model which anticipates evidence development and can be used alongside any studies measuring impact on patient outcome directly in the future to explore implications for cost-effectiveness. We will also be able to use the model to identify the parameters where uncertainties contribute most to the overall decision uncertainty about the cost-effectiveness of decision tools and where additional research might be targeted using expected value of partial perfect information(44-46). If considered effective and cost-effective, now or in the future, the model could also be developed to assess the budget impact of introducing cancer diagnostic tools in different populations.

Cancer type(s): As part of this project it is not feasible to model the impact of diagnostic tools for all common cancer types for which diagnostic tools exist. Instead we have chosen to model one common cancer, colorectal cancer, based on criteria below to provide a best case example of where the diagnostic tools could impact on patient outcomes:

- Tools exist – to compare diagnostic tools to each other and to no tool, we need tools to be available for the specific cancer type. RAT(8, 47)and Qcancer(48) both cover colorectal cancer, as do other diagnostic prediction models, for example the Bristol-Birmingham

equation(31). Systematic Reviews 1 and 2 will help to identify further diagnostic tools and prediction models for colorectal cancer meeting our inclusion criteria.

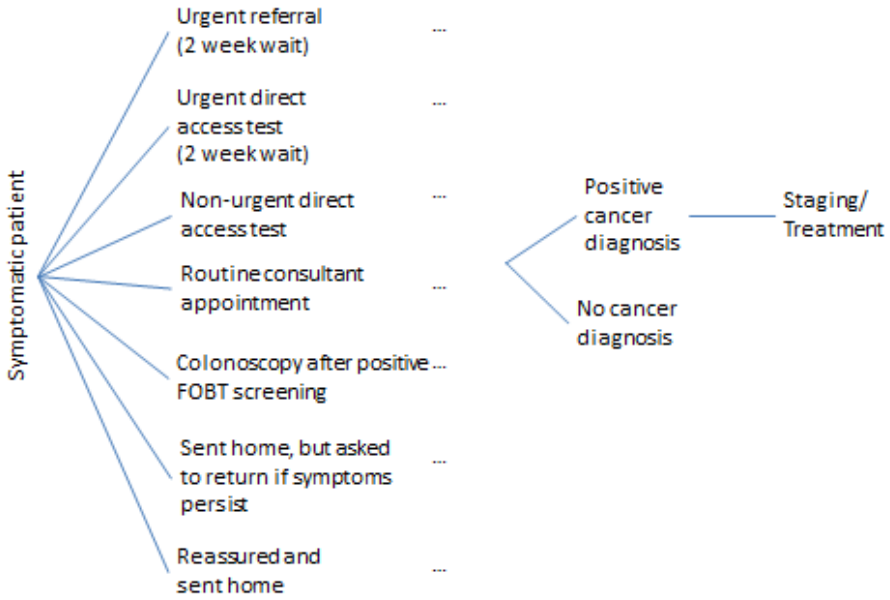
- Common cancer - colorectal cancer is estimated to be the 3rd most common cancer in the UK, contributing to 11% of cancers in women and 13% in men(49).
- Whole disease models exist - it is not realistic to develop new decision analytic models for common cancers as part of this project when the development of such models has been funded previously, and have face validity. Recent decision models are available in the literature mainly for breast, lung and colorectal cancer (including Murphy(50) who looked at the introduction of the faecal immunochemical test to the Bowel Screening programme, and the colorectal model developed for NG12(5)). However, we intend to use the decision-analytic model that was developed by Whyte(51) to evaluate the cost-effectiveness of public awareness campaigns to increase knowledge of the signs and symptoms of colorectal cancer. In principle investigators should allow us to use their model and will adjust their model to help answer questions on the likely impacts of using diagnostic tools to help cancer diagnosis in primary care.
- Wide agreement on patient management – to evaluate the impact of the diagnostic tools it will be important that there is wide agreement on the treatment and management of individuals to minimise, where possible, uncertainties elsewhere in the clinical pathway. Colorectal cancer is a cancer where there is wide agreement on the treatment and management of individuals.
- Evidence that use of diagnostic tools changes practice – to explore the impact of the tools it will be important to identify a cancer type where evidence has shown where and what impact the diagnostic tools might have. A number of studies assessing the impact of RATs have looked at colorectal cancer and reported that increased cancer referrals and investigations for colorectal cancer were associated with use of tools(10, 25, 26).
- Evidence that change in practice impacts patient outcomes – it is not enough that increased referrals and investigations are associated with use of the tools, there also needs to be evidence that earlier diagnosis could impact on patient outcomes. This might be in leading to earlier stage at diagnosis, higher resection rates, improved survival, as well as improved quality of life of patients. In their review of evidence on the association between diagnostic and/or treatment intervals and patient outcomes, Neal et al identified colorectal cancer as one of the cancers with evidence that earlier time to diagnosis/treatment is associated with improved patient outcomes. More recent studies, which were not included in the systematic review by Neal have reflected this(52, 53).

Interventions: Any diagnostic tool or prediction model used in primary care identified in Systematic Review 1 or 2 that has the potential to be relevant to the NHS. This will include RATs(8, 47), Qcancer(48), and Bristol-Birmingham(31). We anticipate variation in the amount of effectiveness evidence identified from Systematic Review 1, therefore diagnostic tools having a greater evidence base will be given priority in the modelling. Where relevant we will compare different tools to each other as well as to the comparator.

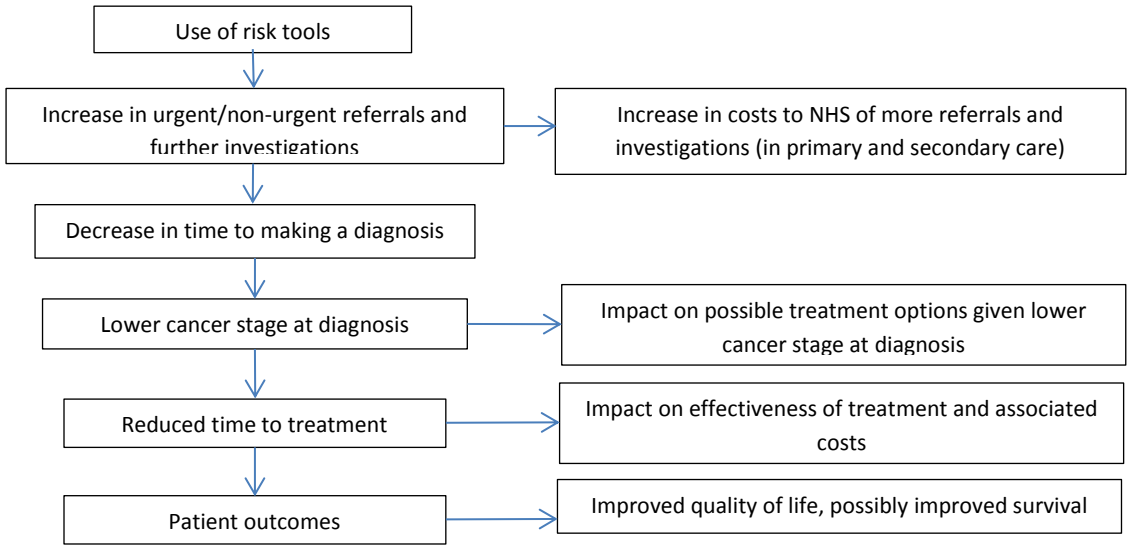
Comparator: strategies for decision-making which are not informed by cancer diagnostic tools. This will include the national screening programme for colorectal cancer, and use of the NICE guidelines for suspected cancer(5).

Model structure: The decision model developed by Whyte et al(51) models the natural history of colorectal cancer, from the progression of cancerous lesions through the Dukes' stages, which are linked to treatment costs. It has a state-transition structure and is implemented in MicroSoft Excel. The model was developed to evaluate the cost-effectiveness of a campaign to increase public awareness of signs and symptoms of colorectal cancer. It includes the national screening

programme currently running in the NHS in England and Wales of biennial guaiac faecal occult blood test (FOBT) for men and women aged 60-74 years. The model by Whyte relates to the general population >30 years old. Therefore we may need to adjust certain parameters so that the decision model fully reflects our target population (individuals with symptoms attending primary care) and is relevant to the target population for the diagnostic tool (e.g. a diagnostic tool may only be intended to apply to those aged >40 years). We will model the pathway that a patient presenting to primary care with symptoms indicative of colorectal cancer could take. This part of the model will take the form of a decision tree, based on the simplified tree below:



The probability of these events occurring will depend on the symptom profile of individuals presenting to primary care and whether a diagnostic tool is used, and, if so, which is used. The decision tree will be added to the front-end of the state-transition model by Whyte, so that the short-term costs and patient impacts of using diagnostic tools can be linked to the longer term treatment and management costs and outcomes. The possible impacts on patient outcomes and NHS costs are shown in the diagram below.



It is likely that evidence to inform this part of the model will be found in Systematic Review 1 for the specific diagnostic tools. As we do not anticipate finding a great deal of evidence on the longer-term impact of using the diagnostic tools, to link between short- and long-term outcomes, we will update the systematic review of the impacts of diagnostic and/or treatment delay on patient outcomes conducted by co-applicants (NEAL, LEWIS, HAMILTON) – see Update Systematic Review below. It is prohibitively expensive to use systematic reviews to identify evidence to inform all model parameters such as utilities, resource use and costs. However, consistent with good modelling practice(54) we will use as rigorous methodology as possible, justifying any decisions, to provide the most valid estimates and ranges for them. Although accuracy is often an important aspect of tests (which a diagnostic prediction model is), we are unlikely to identify a great deal of evidence on the accuracy of diagnostic prediction models. Instead the modelling will capture the clinical impacts of the use of diagnostic tools, focussing on effectiveness beyond accuracy, which will capture the impacts for those falsely referred for cancer diagnosis.

Analysis: The decision analytic model will allow us to see how benefits, harms and costs of using diagnostic tools interact in the short term, and how short term benefits may be translated into long-term benefits in patient outcomes. We will also explore the impact of using different risk thresholds as criteria for patient management actions. For example, currently the 3% threshold for eCDS is advised, but the decision model will permit an exploration of the trade-offs of increasing or decreasing this threshold. We will undertake deterministic one-way sensitivity analyses to explore uncertainty in the evidence and the modelling assumptions. We will also undertake a number of probabilistic sensitivity analyses for different scenarios and plan to use expected value of information to explore decision uncertainty by comparing the expected costs of uncertainty against the costs of collecting additional information to eliminate or reduce uncertainty(46). In our study we will focus on expected value of partial perfect information, which aims to estimate the expected value of eliminating uncertainty on one or more parameters involved in taking a decision(45) (based on the assumption of NICE's £20,000-£30,000 willingness to pay threshold per QALY)(55, 56).

Not only will the decision model be used to explore uncertainties in the existing evidence, it will also allow inputs from future RCTs to be incorporated, allowing for ease of update when such evidence becomes available. As such the decision model will also be useful for updating the evidence in future.

As experienced decision-modellers, AML & JP will lead the decision modelling. They will be supported by AS and CH, with help from CC, BG and RL to identify and review relevant evidence for the model. As well as clinical input from RN, WH, and our expert advisory group, outputs from a PPI workshop will help to inform the clinical pathways and events that patients may experience and therefore should be modelled.

Update Review

Aim: to update a previous systematic review conducted by co-applicants (NEAL, LEWIS, HAMILTON) assessing the evidence linking the durations of different intervals in the diagnostic process to clinical outcomes. This will cover all cancers and any type of diagnostic interval, grouped according to accepted definitions (patient, primary care, secondary care, and combinations).(57) Findings from this update will inform the decision analytic modelling, supplementing the evidence of effectiveness on specific diagnostic tools from Systematic Review 1. Although the decision modelling will be limited to colorectal cancer, understanding how reductions in time to diagnosis and/or treatment affect patient outcomes in other cancers will allow consideration of the likely impact of using diagnostic tools in those cancers, but also

provide a greater evidence base on the likely impact that could be expected from reducing time to diagnosis and/or treatment. The protocol of the existing review is registered with PROSPERO (CRD42014006301),(58) and the findings published by Neal(11).

Literature search: The review was last updated in 2013. On the basis of scoping searches, we anticipate that the process of updating the literature searches (2013-Current) will result in screening approximately 25,000 studies. We therefore propose an alternative and pragmatic approach to updating this review. We plan to: i) forwards citation chase all studies included in the original review and double-screen this output, and ii) contact our expert advisory group and all corresponding authors of studies included at full-text (where e-mail contact can be made) to identify any other published or in-press studies that meet our review criteria, and to validate our list of included studies. This pragmatic updating approach will be evaluated to some extent by comparing relevant studies identified during the previous update searches (2010-2013, which identified 24907 references) conducted by Neal, to an approach of forwards citation chasing for that same period. Thus the approach will also generate novel methodological work in the field of information science and updating systematic reviews. As the main purpose of this update is to inform the decision model, uncertainty in the evidence will be explored using the model.

Selection of studies: Two independent reviewers (BG + RL) will screen the titles and abstracts of all the records identified by the searches for relevance, and then assess the potentially relevant records that are retrieved in full-text, for inclusion. Disagreements will be resolved by discussion or, if necessary, taken to a third reviewer (AML or CH).

Studies will be included if they fulfil all of the following criteria:

- Include symptomatic patients with primary cancers (screening- and biomarker-detected cancers will be excluded).
- Investigate at least one diagnostic delay interval.
- Report data on survival, morbidity, quality of life, stage, or extent or severity of disease at diagnosis.
- Available as a full text paper in English.

For cancers other than colorectal, included articles must address the waiting time paradox (see Critical appraisal below). For articles focusing on colorectal cancer, no inclusion criteria based on quality will be applied, however all included studies will be critically appraised.

Data extraction: This will be undertaken by one reviewer and checked by another (RL + BG), and will include data on the study aims, study design, population, location, setting, number of participants sampled and subsequently recruited and analysed, definitions of time duration, data collection methods, outcome measures used and the authors' conclusions. The main results will also be extracted, including the methods used for assessing the association between interval and outcomes, statistical significance, confidence intervals, and any subgroup analysis.

Critical appraisal: The methodological quality of included studies will be assessed using the same bias assessment tool used and reported in the publication for the initial review.(58) Bias assessment will also include identifying studies that address the so-called 'waiting time paradox', as they are likely to be of higher analytic quality.(11) The waiting time paradox stems from the fact that patients with aggressive cancers tend to present with earlier and more pronounced symptoms, and will in turn receive a different medical priority. However, they have poor prognosis as the cancer is aggressive. Patients with advanced cancer or poor performance status also tend to be diagnosed and treated promptly, for the same reason. This leads to confounding by severity of disease (or the 'sicker quicker' effect). Studies that address the waiting time paradox will be defined as: 'articles that undertake an analysis or sub-analysis that specifically includes or excludes patients who are either diagnosed very quickly (for example within 4-8 weeks, although

this will vary between cancers), or have very poor outcomes (such as deaths within a short time after diagnosis, for example within 4-8 weeks).' Papers that simply reported that the 'waiting time paradox' may have confounded their data will not be included in this subset. Bias assessment will be undertaken by two independent reviewers, with disagreements taken to a third person.

Synthesis: A narrative synthesis is planned due to expected variation between studies as found in the original review. We will follow the approach of the previous systematic review and group identified studies by cancer location and whether the analysis considered patient outcomes such as survival, stage of disease or other outcomes. As the motivation for conducting the Update Review is to inform the decision model, we will be able to explore and quantify the impact of heterogeneity between studies from the Update Review using the model. A key output will be identifying the association between reduced diagnostic and/or treatment delay and improved patient outcome, which will feed directly into the decision analytic model and permit an exploration of the variation in findings from different studies.

RL will lead the update review having been involved in the original systematic review with RN and WH. CC will design and run the searches, including contacting authors. BG and AML will help with the screening, and CH, RN and WH will provide additional support where needed. We have included resource for additional help with screening for this review should it be necessary.

Objective 3: Understand the extent to which GPs have access to such tools and are using them to inform their decision-making for cancer diagnosis

Survey

Aims: A cross-sectional, quantitative, survey design will be used to estimate current practice regarding the availability and use of cancer diagnostic tools in primary care in the UK. Additional aims are to inform aspects of the Decision Modelling, including:

1. Estimates of the 2-week-wait (2WW) referral rate at the practice level in England (using nationally collected data(59)) for:
   a. GP practices with no access to a cancer diagnostic tool (i.e. standard care, the comparator)
   b. GP practices where at least one GP has access to, and uses, cancer diagnostic tools (i.e. using the intervention)
2. Identifying how the cancer diagnostic tool is used in the rare occasions where cancer is suspected; for example:
   a. identification of cancer risk in patients, audit, discussion of cancer risk with patients
   b. preferences around decision support content, format and medium
   c. where diagnostic tools best fit within the decision and referral process in primary care

Design: The cross-sectional survey will be planned and conducted in line with the reporting checklist for self-administered surveys of clinicians.(40) The target population consists of general practitioner practices in the UK. The GPs surveyed in the practice will be GP partners/principals, and sessional GPs (includes salaried and locum GPs). Additional surveys will be included for GP registrars, and these will be analysed separately. The survey will build on an existing online survey – *Cancer Referral Decision Support: GP survey* – conducted within the University of Exeter in 2016 by Hyde and Hamilton. We will pilot our survey with 36 participants of that survey who expressed an interest in follow-up and will use the pilot to develop data collection strategies that minimise missing data in the main survey. However, we will conduct a postal survey to ensure that: 1) we obtain a representative sample of GPs across the UK and 2) we can

determine an accurate response rate.(60) The survey will consist of main questions asking about the availability and use of the tool, and be followed by optional additional questions focussing on how GPs use the diagnostic tool in the rare occasions when a cancer may be suspected, e.g. refer to it during consultations, use as an audit tool.

Inclusion criteria: GP practices in the UK and the GP partners/principals and sessional GPs (includes salaried and locum GPs) working there.

Exclusion criteria: GPs who have retired or who are not currently practising.

Sampling: A random sample of GP practices in the UK will be obtained from Binley's (www.binleys.com), a commercial company established in 1992. They maintain a database of the 46,000 GPs in the UK that is re-verified twice a year (in January and July). Binley's supports The Royal College of General Practitioners in maintaining its membership list. Response rates are increased by incentives(60) and in our experience, the simplest (and cheapest) method of doing this is to offer a charitable donation. We suggest £7.50 for the first 400 questionnaires returned which is included in the costs of the project.

Estimation of sample size: The sample size calculation for the survey will be inflated by a factor of 1.03 to account for the effect of the cluster design, assuming an intra-class coefficient of 0.01 and four GPs per practice.(61, 62) A sample size of 392 GP practices would be large enough for a 95% confidence interval to have a margin of error of no more than 5%. Assuming a response rate of 40%(63), the questionnaire will be sent to 900 GP practices.

Survey administration: Personalised communication, incentives and follow-up will be used to maximise the response rate.(40, 60, 64) Regarding missing data, the survey will identify which GP practices have failed to respond and which GPs within a practice have not responded.

Survey outcomes: The survey will collect information on the following:

1. The response rate for the main questions
2. The response rate for the optional additional questions
3. The proportion of GP practices and GPs who have access to a cancer diagnostic tool – used to estimate the national figure
4. The proportion of GP practices and GPs who have access to, and use, a diagnostic tool – used to estimate the national figure
5. Qualitative responses focusing on identifying how the diagnostic tool is integrated with the 2WW referral form and how the tool is used; for example, identification of cancer risk in patients, audit, discussion of cancer risk with patients

Estimating the effect of the diagnostic tools: The 2WW referral rates for suspected cancer for responding practices in England are available through Public Health England. We will link the information form the GP survey to the 2WW referral rates using the unique GP practice code. We will estimate the impact on the 2WW referral rates by stratifying GPs into those:

a. that have access to, but do not use, a cancer diagnostic tool
b. where at least one GP has access to and uses a diagnostic tool
c. where none of the GPs has access to a diagnostic tool

For suspected colorectal cancer, these data will be used in the decision analytic model to consider the impacts of the 2WW referral rates, especially in the comparator strategy (standard care) of no use of diagnostic tools.

Controlling for confounding: It is likely that the characteristics of GP practices that choose to download the diagnostic software may vary from those that choose not to. In such instances, it would be important to suppress the effects of other confounding variables, such as differences in

patient population or staff characteristics that may influence both the likelihood of downloading diagnostic software and referral rates. There are a number of approaches that try to control for confounding variables in observation data, such as propensity scores(65, 66) that can be applied to adjust for differences. In this study we define propensity as the practice's probability of downloading the software given the complete set of all information about that GP practice and the patients they serve. Practices may have the same or similar propensity scores, yet some will have downloaded the diagnostic tool and others not. An assumption of propensity score analysis is that a fair comparison of the rates of referral can be made between practices with similar propensity scores who either did or did not download the diagnostic tool.

Missing data and data imputation: Our data collection procedures have been designed to minimise missing data; for example, thorough and careful pilot work and the use of a short survey questionnaire. But where necessary we will use multiple imputation of GP responses to correct for bias that may result from GP survey responses that are missing at random, rather than missing completely at random. In these analyses we will conduct further sensitivity analyses to consider alternative assumptions about the missing data mechanisms.(67)

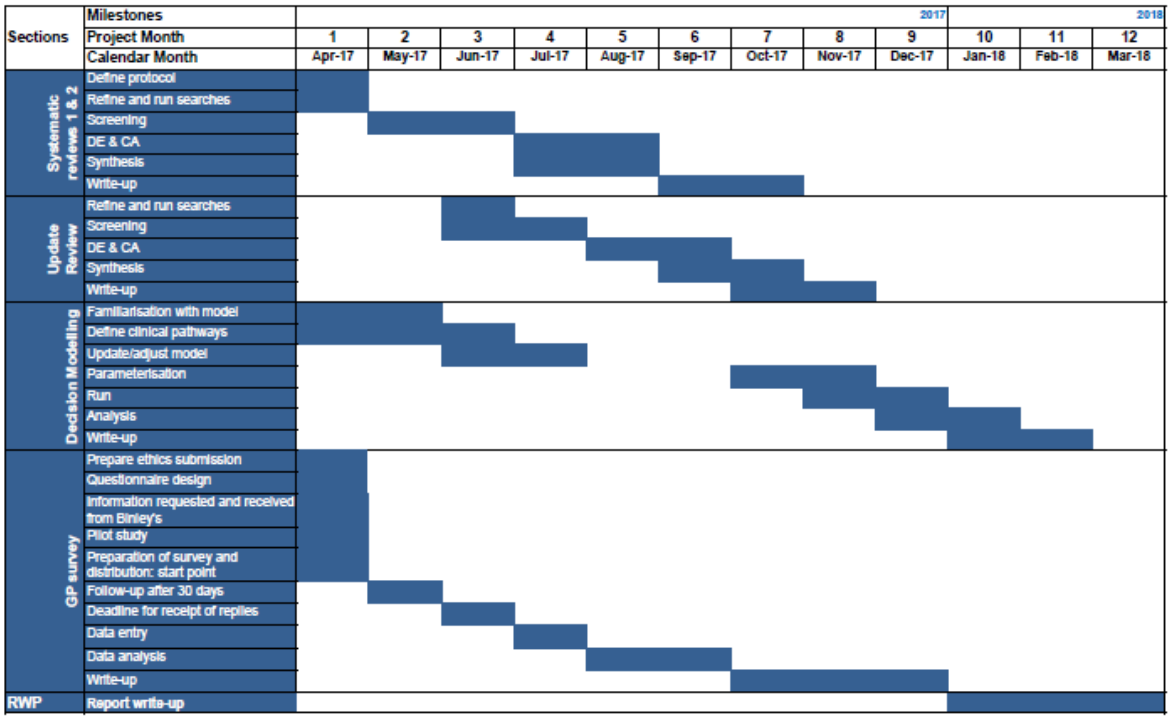
SP will lead the survey. She will be supported by CH and WH who are currently involved in a pilot of this survey to GPs (N>120). AML and AS will also provide additional support where needed. JK will assist SP by providing administrative support specifically for the survey.

Dissemination and projected outputs: As there are a number of beneficiaries to this project (including patients, GPs, secondary care practitioners, decision-makers, researchers and methodologists), we will take a number of routes to disseminate our work, including:

- Open-access peer-review
- Presentation and networking at national conferences
- Via existing links to engage an international audience
- Via our expert advisory group and patient or member of the public joining in the project team
- Exploiting existing links co-applicants have with Macmillan, the Royal College of GPs, Cancer Research UK, policy research in the Department of Health, NICE clinical guidance
- Via GPs participating in the survey

Plan of investigation & timetable: The Gantt chart below details the timing of the work for this project. The project will take 12 months to complete (1st Apr 2017 – 31st Mar 2017). The deliverables will be completion (including write-up) of:

- Systematic Reviews 1 and 2 at 7 months
- Update Review at 8 months
- Survey at 9 months
- Decision Modelling at 11 months
- The HTA report at 12 months.



Project management: AML and RL are co-PIs and they will jointly manage this project on a day-to-day basis; JP is also a co-PI and will join the management group once she returns from maternity leave in early 2018. An initial meeting consisting of all co-applicants, plus BG, JL and JK, and members of the expert advisory group will be held in Exeter at the start of the project. After this initial meeting, monthly project team meetings will be held via teleconference to update and discuss progress. Any additional meetings will be arranged as and when necessary. BG, RL and CH will have to work closely on the systematic reviews and update review, and will use email and teleconferences to allow effective collaborative working. We have also included costs for visits by Exeter-based researchers to Bangor (and vice versa) for such meetings.

An expert advisory group will be formed and include Dr Brian Willis (University of Birmingham – GP and clinical researcher), Dr Cliff Jones (Macmillan National GP Cancer Lead for Wales), Prof Debbie Sharp (University of Bristol – Professor of Primary Care) and a consultant at the Royal Devon and Exeter Healthcare NHS Trust. As well as attending the initial meeting, we will consult members of the expert advisory group as and when needed to assist with uncertainties arising during the project.

Approval by ethics committees: The GP survey will require ethics approval from the University of Exeter Medical School ethics committee. The committee meets every 2 months. Once we have confirmation of the approval of this project, preparation for the ethics submission will begin as soon as possible, and we will request a slot at the earliest available meeting after the start of the project.

Patient & public involvement: Considering the sensitive nature of this topic, we see patient and public involvement as essential to this study. The overarching aim for this involvement is to ensure that the study trajectories are informed by patients' perspectives as well as other stakeholders. We plan to do this in two ways.

First, we will involve patients and the public in the development of the protocol for the systematic review of the effectiveness of tools **(Systematic Review 1)** to ensure that the review captures patient relevant outcomes. Early in the project will we set up two meetings where we present the research question and discuss with them the main sections of the protocol. The main focus of these discussions will be on the outcomes, and we will facilitate targeted discussions followed by prioritisation via voting. The nature of discussions at these two meetings might mean that patients will want to inform other aspects of the protocol. While we will not actively seek this, we intend the meetings to be of a nature of openness and responsiveness to the views and perspectives of the public/patients. We will hold a third meeting to inform discussions on the **Decision Model**, making sure that the relevant patient pathways are well-defined.

Second, we will recruit one patient or one member of the public to be part of the project team. The role of that individual will be to help with the general management of the project, as well as to advise on areas of uncertainty throughout the 12 months of the project. These areas are likely to include assisting in defining the clinical patient pathways relevant for the decision model, ensuring the model captures relevant patient outcomes, but also contributing to the uncertainties in the design of the GP survey. Having patient and public involvement in the project team will give us another perspective on the research, and its aims and outputs. As part of the project team, we hope that public and patient involvement will assist in the dissemination of our findings to interested groups and networks. We have included payment and travel costs for an individual to attend up to 3 project meetings, and further payment and travel costs to meet with the co-PI (AML) at the beginning of the project to discuss expectations and training and support.

At the Institute for Health Research we have a CLAHRC public and patient involvement team. Linked to the PPI team, is the Peninsula Public Involvement Group (PenPIG) which consists of members of the public, service users and carers. We will work closely with the PPI team to identify individuals from PenPIG or via other links (such as the Clinical Research Network or Health Watch) who are interested and best placed to be involved in the project either in assisting with the development of the systematic review protocol or in being part of the project team. At the Institute for Health Research we have expertise in systematic review, decision-modelling and survey research, and will provide support to individuals involved in the project on aspects of methodology as well as research more generally. The PPI team is working with other researchers on involvement in HTA and we will draw on their expertise on this too.

Expertise and justification of support required: We have a team with highly relevant clinical and methodological expertise. AML, JP, RL, BG and CH are experienced systematic reviewers in related areas of tests and cancer diagnostics. While CC is a highly experienced information scientist. AML, JP, AS and CH are also experienced in the development, analysis and interpretation of decision modelling. SP and WH have extensive experience of the methodology to develop cancer diagnostic tools, and WH and RN have highly relevant clinical and research experience in the area of cancer diagnostics which will be invaluable through the project.

Dr Antonieta Medina-Lara (Co-Pi, Senior Lecturer in Health Economics; University of Exeter) is an experienced economist with specialisation in health economics, decision modelling, randomised controlled trials, experimental economics, applied micro-econometrics and. She has wide experience in disease areas such as Cancer, Rheumatoid Arthritis, Viral Encephalitis, Meningitis, Malaria, HIV/AIDS and Tuberculosis has been involved in projects in Belgium, Burkina Faso, France, Ghana, Italy, Kenya, Malawi, South Africa, Tanzania, Uganda, UK and Zimbabwe. She has been a primary investigator and collaborator of several UK and international projects including EU-funded, DFID and NIHR research projects.

Dr Jaime Peters (Co-PI, Senior Research Fellow; University of Exeter) is an experienced decision modeller, systematic reviewer and medical statistician. She has 7 years' experience of developing decision models including the evaluation of a prediction model to identify individuals likely to have monogenic diabetes(68), and a methodological review of economic evaluations of prediction models.

Miss Ruth Lewis (Co-PI, Research Fellow; Bangor University) has extensive experience in the methodology and conduct of systematic reviews. Over the last 15 years she has been involved in a number of systematic reviews funded by NIHR, HTA programme, Cancer Research UK, DoH (England) and the Welsh Government. She has also conducted evidence reviews to underpin National Institute for Health and Care Excellence (NICE) Cancer guidelines (including colorectal cancer), and is an author on a number of Cochrane reviews.

Dr Bogdan Grigore (Associate Research Fellow; University of Exeter) has expertise in systematic review methods within the HTA context, particularly in relation to tests. He has worked closely with JP and CH in previous projects.

Dr Sarah Price (Co-applicant, Research Fellow; University of Exeter) works closely with WH and has extensive experience of the methodology used to model the symptomatic presentation of cancer in primary care. She is currently working on a university-funded project to identify the national and international impact of the Hamilton risk assessment tools. In July, she starts work with AS and WH, on a CRUK-funded project evaluating the impact of NICE guidelines for suspected cancers on the timeliness of cancer diagnosis and cancer survival.

Mr Chris Cooper (Co-applicant, Senior Research Fellow (Information Science); University of Exeter) has a background of identifying studies and study data for systematic reviews and decision models in HTA, public health and social science reviews. Chris is currently undertaking a PhD (part-time) that seeks to explore the use of pragmatic search techniques for study identification in complex reviews. CC has worked closely with JP and CH in previous projects. He will also assist AML, JP and BG in identifying further relevant evidence to inform the decision modelling.

Prof Richard Neal (Co-applicant, Professor of Primary Care Medicine; Bangor University) has been at the forefront of cancer diagnostic research for 15 years. RN will provide clinical expertise to all parts of the project, in addition to his knowledge of the research in this area. He led the previous systematic review(7) that will be updated. He will provide support to RL, especially for the update review, and also to AML and JP in the development, analysis and interpretation of the decision modelling.

Prof Chris Hyde (Co-applicant, Professor of Public Health and Clinical Epidemiology; University of Exeter) has expertise in health technology assessment with a particular interest in the effectiveness and cost-effectiveness of tests including risk assessment tools. He has supervised many systematic reviews and health economic models and has worked closely with BG, JP and WH in the past. He is also currently involved in a GP survey on whether and how risk assessment tools for cancer are being used. CH will provide systematic review, decision modelling, survey and general HTA support and advice to AML, JP, BG, RL and SP throughout the project.

Prof Anne Spencer (Co-applicant, Associate Professor; University of Exeter) is an experienced health economists specializing in developing methods for health outcome measurement (including clinical guidelines), economic evaluation and economic modelling. She currently working with operational researcher to incorporate health economics into their health service delivery models [NIHR-SDO programme Grant 141908 Sept 2015-Feb 2017]. AS is also leading the analysis on a Cancer Research UK funded project with WH to measure the impact of the

NICE 2015 suspected cancer guidelines on times to diagnosis, stage at diagnosis, treatment with curative intent and survival using the Clinical Practice Research Datalink (CPRD) with an ONS and Cancer Registry link [Cancer Research UK Grant C56843/A21550 July 2016-January 2018]. AS will provide support in all areas of the project, particularly to AML and JP on the decision modelling.

Prof Willie Hamilton (Co-applicant, Professor of Primary Care Diagnostics, University of Exeter) has been at the forefront of cancer diagnostic research for 15 years. WH will provide clinical advice on the use of tools to aid cancer diagnosis in primary care. He has worked closely with CH, AS, RN and RL in cancer diagnostic research. Because his role may be perceived as a conflict of interest he will absent himself from the analyses, and if the funder wishes, from production of the outputs.

Jen Kew (Administrator, University of Exeter) will provide administration support to SP for the GP survey.

Jenny Lowe (Administrator and Information Officer, University of Exeter) will provide general administration support for the project and help with document retrieval for the systematic reviews and decision model.