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STUDY PROTOCOL

Effectiveness and cost-effectiveness of gynaecological surveillance for women with Lynch syndrome: systematic reviews and economic evaluation

Version 1.0

26th February 2020

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1 List of abbreviations

AE	Adverse event
CA125	Cancer antigen 125
CRC	Colorectal cancer
DALY	Disability-adjusted life year
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LS	Lynch syndrome
MMR	Mismatch repair
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PAG	Project Advisory Group
PPI	Patient and public involvement
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
WP	Work package

2 Study summary

2.1 Version history

Version	Date	Details
1.0	26th February 2020	This is the original protocol prepared from the detailed research plan approved by the NIHR HTA board with the following changes: • Details of ethics and registrations • Removal of the "Success criteria and barriers to proposed work" section • Additional detail for Work Package 1

2.2 Project timings

- Start: 1 April 2020
- End: 30 September 2021
- Duration: 18 months

2.3 Funding acknowledgement and disclaimer

This project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference NIHR129713). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

2.4 Ethics

The Chair of the University of Exeter College of Medicine and Health Research Ethics Committee (Professor Ruth Garside) has confirmed this project does not require ethical review (Chair's Action Review RG/CB/CA381).

2.5 Roles and responsibilities

Chief Investigator

- Dr Tristan Snowsill, University of Exeter

Co-Investigators

- Dr Helen Coelho, University of Exeter
- Mr Simon Briscoe, University of Exeter
- Professor Emma Crosbie, University of Manchester
- Professor Claire Hulme, University of Exeter
- Dr Neil Ryan, University Hospitals Bristol NHS Foundation Trust
- Mrs Tracy Smith, Lynch Syndrome UK

Additional people involved

- Dr Kate Boddy, University of Exeter (patient and public involvement expert)
- Ms Leala Watson, University of Exeter (administrator)
- Dr Fiona Lalloo, Manchester University NHS Foundation Trust (clinical expert)

2.6 Registration

The clinical effectiveness review (Work Package 1) is registered on PROSPERO (CRD42020171098).

2.7 Summary of Research

This study aims to determine the effectiveness and cost-effectiveness of surveillance for gynaecological cancer in women with Lynch syndrome (LS), a hereditary cancer syndrome caused by pathogenic variants of DNA mismatch repair (MMR) genes. The objectives are to conduct systematic literature reviews of the clinical effectiveness and cost-effectiveness of gynaecological surveillance and of the impact of surveillance and cancer on health-related quality of life (HRQL), and to conduct an economic evaluation of gynaecological surveillance using decision analytic modelling.

The study benefits from patient involvement: a core member of the Project Advisory Group is a well-networked PPI co-applicant with relevant life experience and a workshop to be attended by ten women with LS is scheduled for the beginning of the project, at which patients will help to refine the methods and plans for dissemination. We will recruit two additional patient representatives to the Project Advisory Group from the workshop.

The systematic review of clinical effectiveness aims to address three broad research questions: what is the clinical effectiveness of different gynaecological cancer surveillance strategies in LS; what is the ability of those strategies to detect gynaecological cancers in this population; and what harms are associated with those strategies (including pain and adverse events)? To address these questions, the review will consider a number of outcomes (survival, mortality, treatment response, cancer stage at diagnosis, fertility,

detection rates, interval cancers, incidental findings, accuracy, adverse events) and will include randomised, non-randomised and observational studies. Study populations will be women with LS and interventions will include hysteroscopy, directed endometrial biopsy, undirected endometrial biopsy, ultrasound and biomarkers. Studies will be identified and quality assessed following best practice guidance for systematic reviews. Evidence will be synthesised narratively and pooled if justified.

The systematic review of cost-effectiveness aims to address: is gynaecological cancer surveillance in LS cost-effective; what factors significantly affect the cost-effectiveness of surveillance; and, how is surveillance modelled?

The systematic review of HRQL aims to address: what is the impact of gynaecological cancer on HRQL; what is the impact of gynaecological cancer surveillance on HRQL; what is the impact of risk-reducing gynaecological surgery on HRQL? The review will focus on preference-based measures of HRQL.

The economic evaluation aims to address: is gynaecological cancer surveillance in LS cost-effective; how much uncertainty is there surrounding the cost-effectiveness of surveillance; what are the sources of uncertainty; how much value would there be in reducing that uncertainty? The evaluation will estimate the costs and consequences of difference gynaecological surveillance strategies. It will be a cost-utility analysis with health consequences measured in quality-adjusted life years (QALYs). It will be based on a whole disease model which is conceptualised following good practice guidance and parameterised from the best available sources, including the systematic reviews. Uncertainty will be explored through sensitivity analyses and a value of information analysis will be conducted to estimate the potential value of further research.

Through discussion with the advisory group, and at the PPI workshop, we will explore how the findings can inform clinical guidelines, identify key questions for future research, co-create non-scientific summaries of the findings to share through social media, submit open access papers to internationally recognised academic journals, present the findings at scientific conferences and make the economic model open access on Open Research Exeter or open source on GitHub.

The potential impacts from the study are patient benefit (if surveillance is found to be effective and cost-effective then more women are expected to be offered it) and NHS savings (if surveillance is not found to be cost-effective then surveillance is expected to be offered to fewer women).

The study will take 18 months, with the systematic reviews completed in the first seven months. The project team includes methodological experts with a track record of publications relating to LS and clinical experts with experience of research in LS and in developing clinical guidelines.

3 Background and Rationale

Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by pathogenic variants in the DNA mismatch repair (MMR) genes. Although mostly undiagnosed, around 1 in 300 people are born with variants causing LS. LS confers a higher lifetime risk and earlier onset age of developing colorectal, endometrial and ovarian cancer. Depending on which MMR gene is affected, the cumulative risks by age 70 can exceed 50% and 20% for

endometrial and ovarian cancer (1-3), compared to cumulative risks of 1.3% and 1.0% by age 70 in the general population (4). The treatment for endometrial cancer in women with LS is typically removal of the uterus and ovaries and may also include chemotherapy and radiotherapy. Ovarian cancer is also associated with morbidity and mortality (5).

Two main interventions are available to manage the gynaecological cancer risk in LS: risk-reducing surgery (removal of the uterus and ovaries) and surveillance. Some patients may have surveillance initially and then have risk-reducing surgery. In addition, chemoprevention with aspirin (6) and hormone therapy (7) may be considered, as well as lifestyle changes.

Gynaecological surveillance can identify precancerous lesions in the uterus for which there are fertility-sparing treatments. Surveillance may also be able to identify ovarian cancer in early stages where management options could maintain fertility or allow egg harvesting.

Gynaecological surveillance has been estimated to cost the NHS £473 per year for a woman with LS (8). Later stage gynaecological cancers can be costly to treat, e.g. Stage 3 ovarian cancer costs twice as much to treat as Stage 1 cancer (9). If surveillance is not effective, or is not sufficiently effective to justify its cost, NHS resources can be spent elsewhere to achieve meaningful benefits for patients.

Surgery is widely offered, since its effectiveness is well-documented (10), typically at age 40-45 when most women have completed their families (11). This prevents women from becoming pregnant and artificially brings on menopause, which can detrimentally affect health-related quality of life (HRQL) and long-term health unless managed with hormone replacement therapy. In some cases women do not have risk-reducing surgery because of technical difficulties due to past surgery for colorectal cancer (CRC), high anaesthetic risk due to medical comorbidities, or patient preferences (12).

Some NHS providers offer surveillance for gynaecological cancer in women with LS not undergoing risk-reducing surgery, others do not due to a lack of evidence-based guidelines and resource constraints. Some women opt to pay privately for surveillance, but not all women can afford this.

3.1 Evidence explaining why this research is needed now

Due to recent NICE guidance on identifying LS (13), more women will have a diagnosis of LS and need to manage their gynaecological cancer risk. Evidence is needed to determine which interventions are effective and cost-effective to reduce the morbidity and mortality from gynaecological cancer and to contribute to the NHS Long Term Plan goal of improving early diagnosis of cancer (14). Surveillance is a preferred option for patients for managing cancer risk, but good quality estimates of its effectiveness and cost-effectiveness have not been produced.

NICE has recommended testing for LS in people diagnosed with CRC (DG27), and are assessing testing for LS in women with endometrial cancer (GID-DG10033). By testing relatives each case of cancer can result in many people being diagnosed with LS. The number of women identified as having LS is expected to rise steadily: full implementation of DG27 would lead to >2000 new individuals per year diagnosed with LS, with over half being women (8). Many women will discover they have substantial gynaecological cancer risk but have limited information about whether surveillance is effective, or will find they cannot access surveillance. At the moment there are no NICE Clinical Guidelines for the

management of LS – the results of this work could inform the development of such guidelines.

A key recommendation from the recent Manchester International Consensus Group meeting was “further research is required to establish the value of gynecological cancer surveillance in Lynch syndrome” (15). The Group considered that if there is equipoise in the literature then primary research could be pursued, so an assessment of the literature and the use of an economic model to determine the value of future research is timely.

3.2 Published evidence and ongoing research

We searched (September 2019) for existing systematic reviews of gynaecological surveillance in MEDLINE using the search strategy in Figure 1 and the Centre for Reviews and Dissemination systematic review study design filter (16) (50 citations identified). We adapted the search strategy in Figure 1 to search CENTRAL (Cochrane Library) for relevant ongoing controlled trials (11 records identified) and PROSPERO for relevant ongoing systematic reviews (one record identified).

The most recent well-conducted systematic review of studies of gynaecological surveillance in women with LS was published in 2011 (17). At least 8 new studies have been published since then (15). A 2016 systematic review considered evidence for ovarian but not endometrial surveillance (18). Existing reviews have identified potential for benefit from gynaecological surveillance (detection of early stage cancer and premalignant lesions) but were not able to make evidence-based recommendations for or against surveillance.

A review currently being undertaken for a NICE Diagnostics Assessment of testing for LS in women with endometrial cancer includes a sub-question relating to the effectiveness of gynaecological surveillance, but this will only consider controlled trials and does not consider study designs to evaluate the test accuracy of surveillance technologies or uncontrolled designs which may be able to provide good quality evidence on benefits and harms (19). It also will not answer the question of whether surveillance is cost-effective.

Two economic evaluations of gynaecological cancer risk management in LS have been conducted in the USA (20, 21). The studies, published in 2008 and 2011, used Markov models and concluded risk-reducing surgery was cost-effective and surveillance alone would be dominated by risk-reducing surgery alone. One study suggested a combined approach of surveillance from age 30 followed by risk-reducing surgery at age 40 would be most effective but not cost-effective (20). The studies have limitations: they were published before good estimates of the cancer risks in LS were described; they relied on estimates of screening effectiveness from non-LS cohorts (mainly post-menopausal) which could introduce bias; one study assumed no benefit of surveillance for ovarian cancer. There may also be substantial differences in costs and other parameters between the US and the UK.

3.3 What this research will add

This will be the first comprehensive health technology assessment of gynaecological surveillance in LS. Existing reviews and economic evaluations have had restricted scopes and little evidence synthesis has been conducted since 2011. It will provide an independent characterisation of how effective and cost-effective surveillance is and will estimate the value of further primary research through value of information analyses. By adopting a whole disease modelling approach and making the model freely available, the research will continue to generate knowledge after its completion.

NHS clinical practice, which is currently inconsistent across providers in whether surveillance is offered, will be able to be based on an up-to-date assessment of the benefits and costs of surveillance. This should reduce inconsistencies, either by encouraging more providers who may currently be sceptical about surveillance to offer it to particular groups of patients, or by empowering providers to make decisions to discontinue services with the support of clear evidence on effectiveness and cost-effectiveness.

4 Aims and objectives

The primary aim is to determine the effectiveness and cost-effectiveness of gynaecological cancer surveillance in women with LS, with secondary aims to investigate which women may benefit most and to identify whether further primary research is needed.

The objectives are to conduct:

- Systematic reviews of clinical effectiveness and cost-effectiveness studies of gynaecological surveillance **(Work Packages 1 and 2)**
- A systematic review of preference-based utility values for health states related to gynaecological cancer in LS **(Work Package 3)**
- An economic evaluation of gynaecological surveillance using an economic modelling approach **(Work Package 4)**.

Detailed objectives and research questions for each work package are provided below.

5 Research Plan / Methods

5.1 Target population

The research will focus on adult women with LS, that is, women who either:

- Have confirmed constitutional pathogenic variants in the MMR genes *MLH1*, *MSH2*, *MSH6* or *PMS2*; or,
- Have been diagnosed with LS or are suspected of having LS in the absence of confirmatory testing.

5.2 Health technologies being assessed

We will assess strategies for gynaecological cancer surveillance in women with LS which may include a number of different modalities.

5.2.1 Hysteroscopy and directed biopsy

An endoscopic technique for inspecting the uterine cavity (in this case to identify endometrial neoplasia) by inserting a hysteroscope via the cervical os. Hysteroscopy can allow for directed biopsy (targeted extraction of tissue for pathological examination). It can often be performed in outpatient or office settings with no anaesthesia or analgesia, although in some cases local or general anaesthetic may be used.

5.2.2 Undirected biopsy

Techniques for sampling the endometrium without visualising the interior of the uterus. Numerous samples are taken from different parts of the endometrium. Aspirate biopsy (e.g. Pipelle) is typically conducted in an outpatient or office setting while dilatation and curettage (D&C) is conducted under sedation or general anaesthetic in an inpatient or day case setting.

5.2.3 Transvaginal ultrasound

An ultrasound probe is inserted into the vagina in order to visualise organs in the pelvic cavity, which can identify signs of endometrial and ovarian malignancy (e.g. increased endometrial thickness).

5.2.4 Transabdominal ultrasound

An ultrasound probe is pressed against the abdomen to visualise the uterus and ovaries to identify malignancies.

5.2.5 Cancer Antigen-125 (CA-125)

A blood serum biomarker which is raised in around 90% of women with advanced ovarian cancer. NICE recommends that serum CA-125 of 35 IU/ml or greater is an indication for further investigation in women with symptoms of ovarian cancer [NICE CG122].

5.2.6 Timing

Surveillance is typically conducted at 1- or 2-year intervals, and is typically initiated between the ages of 25 and 35 years (2, 15).

5.2.7 Comparators

Hysterectomy with bilateral salpingo-oophorectomy is commonly used in clinical practice to all but eliminate the risk of endometrial and ovarian cancer (10), but is an operation under general anaesthetic that can carry surgical risk (particularly with women who have had prior surgery, e.g. for CRC) and artificially brings on menopause in pre-menopausal women.

There is evidence from a retrospective cohort study that prolonged use (≥1 year) of hormonal contraceptives lowers the rate of endometrial cancer in women with LS (7).

Symptom awareness, optionally reinforced by annual clinical review, has been recommended by a consensus group (15), along with rapid access to investigation for suspicious signs and symptoms.

5.3 Work Package 1 (WP1): Systematic review of clinical effectiveness

5.3.1 Work Package Objectives

The review will seek to evaluate:

- The clinical effectiveness of different gynaecological cancer surveillance strategies in LS; *Specifically:*

    1. Do gynaecological surveillance strategies improve mortality, survival, cancer prognosis, treatment response and fertility in people with LS?
    2. Do gynaecological surveillance strategies improve early diagnosis (i.e. stage at diagnosis) in people with LS?

- The ability of those strategies to detect gynaecological cancers in LS; *Specifically:*

    3. What are the cancer detection rates/incidence rates (malignancies and pre-malignancies) for gynaecological surveillance strategies in people with LS?
    4. What are the cancer detection rates/incidence rates for gynaecological surveillance amongst *asymptomatic* women with LS?
    5. What is the incidence of interval cancers amongst people with LS taking part in gynaecological surveillance programmes?

6. What are the incidental detection rates of other medical findings (e.g. ovarian cysts) amongst people with LS undergoing gynaecological surveillance?
7. What are the diagnostic test accuracies of different gynaecological surveillance strategies for people with LS?
8. What are the test failure rates for gynaecological surveillance procedures in LS?

- The harms associated with those strategies (including pain and adverse events). *Specifically:*

9. What are the rates (and severity) of adverse events (including pain) observed in different gynaecological surveillance strategies amongst people with LS?
10. What risk-factors impact the occurrence (and severity) of adverse events amongst people with LS undergoing gynaecological surveillance?

5.3.2 Search strategy

Bibliographic database searches will be designed by an information specialist (SB) in consultation with the review team. CENTRAL (via the Cochrane Library), CINAHL (via EBSCO), MEDLINE and Embase (both via Ovid) and Web of Science (Clarivate Analytics) will be searched. A draft MEDLINE search is provided in Figure 1.

#	Searches	Results
1	Lynch syndrome.tw.	2664
2	(HNPCC or hereditary nonpolyposis colorectal cancer or hereditary non polyposis colorectal cancer).tw.	3051
3	Colorectal neoplasms, hereditary nonpolyposis/	4251
4	(Amsterdam adj3 criter$).tw.	549
5	or/1-4	6174
6	((endometr$ or uter$) adj3 (sampl$ or biops$)).tw.	8089
7	((transabdominal or transvaginal) adj3 ultraso$).tw.	7797
8	hysteroscop$.tw.	6281
9	(CA-125 or CA125).tw.	8350
10	(gyn?ecolog$ adj3 (screen$ or surveill$)).tw.	636
11	(endometr$ adj3 (screen$ or surveill$)).tw.	507
12	(ovar$ adj3 (screen$ or surveill$)).tw.	1724
13	or/6-12	30777
14	5 and 13	164

Figure 1: Draft search strategy (MEDLINE)

The review is registered on PROSPERO (CRD42020171098).

To identify further studies, forward and backward citation chasing from included studies using Scopus (Elsevier) and/or Web of Science (Clarivate Analytics) will be conducted, and the following conference proceedings published in the previous three years will be scrutinised (European Society of Gynaecological Oncology, Society of Gynecologic Oncology, European Hereditary Tumour Group, International Gynecologic Cancer Society, Royal College of Obstetricians & Gynaecologists). Ongoing trials will be identified through the clinical trials databases ClinicalTrials.gov and the WHO ICTRP.

5.3.3 Inclusion criteria

To be eligible for inclusion in the review studies must fulfil the following criteria:

Population: Adult women (age 18 or over) with LS (this includes women confirmed to have constitutional path_MMR and women with suspected LS due to family history and demonstrated MMR deficiency).

Intervention: The following surveillance strategies, either alone or in combination (with each other or with comparators), will be eligible for inclusion: hysteroscopy and directed biopsy, undirected biopsy, ultrasound (transvaginal or transabdominal), and cancer antigen-125 testing. Studies will not be excluded on the basis of the surveillance schedule.

Comparators: Where controlled trial designs are identified, comparators may be no surveillance, or alternative surveillance strategies (e.g. symptom awareness via discussion of red-flag symptoms with a gynaecologist followed by self-monitoring; or a regular gynaecologist review to discuss symptoms/changes, check signs and possibly do manual examination). Surveillance strategies may be compared with surgical prevention (e.g. hysterectomy with bilateral salpingo-oophorectomy) or with hormonal contraceptives.

For diagnostic test accuracy studies, any eligible intervention may be used as a reference standard for another intervention. However, studies using cancer diagnosis as a reference standard will primarily be sought.

Outcomes: In order to ensure that all research questions are addressed, studies evaluating (at least one of) all-cause mortality, cancer-specific mortality, cancer survival, cancer treatment response, fertility, cancer stage, cancer detection rates (in symptomatic and asymptomatic women), interval cancer rates, incidental medically important findings, diagnostic accuracy (sensitivity, specificity, positive and negative predictive values, likelihood ratios), test failure rates, adverse event rates and severities (including pain/discomfort), risk factors impacting adverse events, or health-related quality of life, will be eligible for inclusion in the review.

Study design: Suitable study designs have been identified for each of the research questions detailed above, and include randomised trials (all questions), non-randomised controlled trials (all questions), prospective and retrospective comparative observational designs (all questions), prospective and retrospective non-comparative observational designs (questions 3-6 and 8-10), diagnostic test accuracy designs, including any design from which relevant 2x2 data can be ascertained (question 7), surveys, interviews and studies primarily collecting data using VAS or Likert-type scales (questions 9 and 10). For all questions, case reports, opinion pieces and editorials will be excluded. Studies not published in English, or only published in abstract form, will be excluded. Systematic reviews will not be eligible for inclusion in the review, but will be used to check for other eligible studies. No limits will be placed on publication dates.

5.3.4 Study selection

Two reviewers (HC and SB) will independently screen titles and abstracts against the inclusion criteria to identify records to retrieve as full texts. All retrieved full texts will be independently screened by two reviewers (HC and SB) to determine eligibility. At both stages of screening, disagreements will be resolved by discussion (with involvement of a third reviewer (TS) if necessary). Screening will be managed in EndNote (version X8.2 or later; Clarivate Analytics, Philadelphia, PA).

5.3.5 Data extraction and risk of bias assessment

Data from included studies will be extracted into bespoke extraction forms (in MS Excel), which will be piloted by the lead reviewer prior to use. Refinement of these forms will involve consultation with Patient and Public Involvement (PPI) representatives. Data items to be extracted will cover information about the publication (authors, years, journal title), study characteristics (including setting, design, funding sources), participant characteristics, methods (including all PICO items as appropriate to the study design), and results for each outcome (for all time-points provided in the publications). Each study will be labelled according to which of the review questions are being addressed.

Risk of bias will be assessed at the study level using appropriate tools for the study design, e.g. RoB-2 for randomised trials {Sterne, 2019 #55}, ROBINS-I (22) for non-randomised comparative effectiveness studies, the relevant CASP checklist for observational studies {Critical Appraisal Skills Programme, 2020 #56} and QUADAS-2 (23) for diagnostic accuracy studies. Outcomes for which risk of bias might differ will be identified and the assessments will be adapted for each outcome as appropriate.

Both data extraction and risk of bias assessment will be performed by one reviewer (HC or SB) and checked by a second (HC or SB). Study authors will be contacted if any inaccuracies or inconsistencies are found in key outcomes data, but only if the study was published within the last 5 years.

5.3.6 Synthesis of evidence

Narrative synthesis of study methods and results will be conducted, supported by cross-tabulation. For clinical outcomes (such as all-cause mortality, cancer-specific mortality, cancer survival, cancer treatment response, fertility, cancer stage, cancer detection rates, interval cancer rates, and incidental medically important findings) random effects meta-analyses will be conducted, in Stata (version 15 or later; StataCorp LLP, College Station, TX), where there are sufficient numbers of clinically and methodologically homogeneous studies providing data on that outcome. Statistical inconsistency will be assessed as appropriate, using the I^2 statistic.

For test accuracy data, sensitivity, specificity, positive and negative predictive values, likelihood ratios and prevalence will be calculated for each study as a minimum. If studies display sufficient clinical and methodological homogeneity, meta-analysis will be conducted following guidance in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy {Macaskill, 2010 #54}.

If data permit, the following subgroups (of participants and/or studies) will be considered in any narrative or quantitative synthesis: participant age (and/or pre- or post-menopause status), MMR gene affected, participant ethnicity, frequency and age of commencement of surveillance, diagnostic status (e.g. confirmed by mutation testing, suspected by family history criteria), previous gynaecological or colorectal surgery, women for whom risk reducing surgery is not considered appropriate (particularly those with previous CRC), other previous cancer, family history of gynaecological cancer. Additional subgroups to be considered may be identified from the PPI workshop.

All decisions on whether meta-analyses should be conducted, and which studies should be included in any meta-analyses, will be made by two reviewers in a consensus discussion.

5.4 Work Package 2 (WP2): Systematic review of cost-effectiveness

5.4.1 Work package objectives

The review will seek to:

- Summarise the existing evidence for the cost-effectiveness of gynaecological cancer surveillance; specifically:
    1. What are the costs associated with gynaecological cancer surveillance?
    2. What are the benefits associated with gynaecological cancer surveillance (in natural units, QALYs, DALYs or monetary terms)?
    3. What is the incremental cost-effectiveness ratio associated with gynaecological cancer surveillance?
- Identify factors affecting the cost-effectiveness of gynaecological cancer surveillance; specifically:
    4. Which model input parameters or measured outcomes significantly affect the cost-effectiveness of gynaecological cancer surveillance?
    5. Which structural assumptions significantly affect the cost-effectiveness of gynaecological cancer surveillance?
- Inform the development of a new economic model (WP4); specifically:
    6. How is gynaecological cancer surveillance modelled?

5.4.2 Search strategy

The results of the bibliographic database searches conducted for WP1 will be used in this work package. Filters for economic evaluations will not be used as the number of citations is expected to be manageable, and not applying a filter would be expected to increase the sensitivity of the search.

Forward and backward citation chasing will be conducted on included studies.

5.4.3 Inclusion criteria and study selection

Studies will be eligible for inclusion in this review based on the following criteria:

Population: Women with LS.

Interventions and comparators: Must include gynaecological surveillance and at least one comparator.

Outcomes: Costs and health outcomes; health outcomes may be measured in natural units (e.g. cancer deaths avoided), in utility-based units (e.g. QALYs) or in monetary terms.

Study designs: Cost-effectiveness, cost-utility, cost-consequences and cost-benefit analyses will be eligible for inclusion. Studies may be based on measured or modelled costs and outcomes.

Studies not reported in English, or only reported in abstract form, will not be eligible for inclusion. Study selection will be performed in the same manner as in WP1 but conducted by TS and the postdoctoral research fellow to be appointed.

5.4.4 Data abstraction and quality assessment

Bespoke data abstraction templates will be designed (TS) and piloted prior to use. Quality assessment will be supported by established quality assessment tools for economic evaluations (24, 25), supplemented by quality items deemed important a priori for this review (e.g. are separate cancer incidences modelled for different MMR mutations, are cancer incidence estimates subject to ascertainment bias, are effectiveness estimates for surveillance from an LS population, are cancer survival estimates from an LS population). Data abstraction and quality assessment will be conducted by one reviewer and checked by a second.

5.4.5 Synthesis of evidence

Narrative synthesis will be performed, supported by cross-tabulation of study characteristics and findings. Costs will not be converted into a common currency or inflated to a common price year, but indicative cost-effectiveness thresholds will be presented.

5.5 Work Package 3 (WP3): Systematic review of utility values

5.5.1 Work package objectives

The review will seek to address the following research questions:

- What is the impact of endometrial or ovarian cancer on preference-based HRQL? Including:
    1. What is the relationship between stage of cancer and other pathological features and HRQL?
    2. What are the impacts of different cancer treatments?
- What is the impact of gynaecological surveillance on preference-based HRQL?
    3. Are there differences between alternative technologies?
    4. What is the duration of the impact?
    5. Can impacts be mitigated through anaesthetic use?
- What is the impact of risk-reducing gynaecological surgery on preference-based HRQL?
    6. Does the impact depend on which organs (uterus, ovaries or both) are removed?
    7. Does the impact differ for vaginal, laparoscopic or abdominal hysterectomies?
    8. What is the duration of the impact?
    9. Does the impact differ between pre- and post-menopausal women?
    10. Can impacts be mitigated through hormone replacement therapy?

5.5.2 Search strategy

Bibliographic database searches for MEDLINE, Embase and Web of Science will be designed by an information specialist (SB) with input from a health economist (TS) and clinical experts. Search terms for LS will not be included as it is anticipated that insufficient studies will exist focussed on LS. The Tufts Cost-Effectiveness Analysis Registry (26) will also be searched for utility weights. Forward and backward citation chasing will be conducted on included studies.

5.5.3 Inclusion criteria and study selection

Studies will be eligible for inclusion in this review based on the following criteria:

Population: Women with endometrial or ovarian cancer or women undergoing gynaecological surveillance or women who have had risk-reducing gynaecological surgery. It is anticipated that insufficient studies will exist conducted with participants with LS, so studies where the population does not have or has not been tested for LS will be eligible for inclusion.

Outcomes: Studies using generic preference-based HRQL tools and techniques will be included, e.g. EQ-5D, SF-6D, standard gamble, time trade-off. Studies only using non-preference-based measures (e.g. FACT-G, visual analogue scale, McGill Pain Questionnaire) will not be eligible for inclusion.

Study type: Primary studies and literature reviews will be eligible for inclusion.

Studies not reported in English, or only reported as abstracts, will be excluded. Study selection will be performed in the same manner as in WP1 but conducted by TS and the postdoctoral research fellow to be appointed.

5.5.4 Data abstraction and quality assessment

Bespoke data abstraction templates will be designed (TS) and piloted prior to use. Quality assessment will be performed using an established set of quality assessment criteria for health state utility values (27).

5.5.5 Synthesis of evidence

Narrative synthesis will be conducted supported by cross-tabulation of study characteristics and findings. Where subgroups exist with substantially different HRQL (e.g. different stages or grades of cancer) these will be explored.

5.6 Work Package 4 (WP4): Economic modelling

5.6.1 Work package objectives

The economic evaluation seeks to evaluate:

- The cost-effectiveness of gynaecological cancer surveillance strategies; specifically:
    1. What are the costs of various gynaecological cancer surveillance strategies compared to each other and compared to no surveillance and to risk-reducing surgery at various ages?
    2. What are the relative benefits of gynaecological cancer surveillance strategies?
    3. Which, if any, gynaecological cancer surveillance strategies would be considered cost-effective at standard UK cost-effectiveness thresholds?
- The uncertainty in the cost-effectiveness estimates; specifically:
    4. What is the effect of uncertainty surrounding input parameters on cost-effectiveness?
    5. What is the effect of structural uncertainty on cost-effectiveness?
- The factors which most affect cost-effectiveness; specifically:
    6. What is the impact on cost-effectiveness of parameters relating to the effectiveness of surveillance?
    7. What is the impact on cost-effectiveness of the cost of surveillance?
    8. What is the impact on cost-effectiveness of the HRQL associated with cancer, surveillance and risk-reducing surgery?

9. Is surveillance more/less cost-effective for particular subgroups?

- The value of future research which could reduce uncertainty; specifically:

10. What is the expected value of perfect information about all aspects relating to gynaecological cancer surveillance in LS?
11. What is the expected value of partial perfect information about specific aspects (including the risk of cancer, the effectiveness of surveillance, the impacts on HRQL)?
12. How do the expected values of information compare to the expected costs of corresponding research?

The economic evaluation is a critical component of the study as it has the potential to produce policy-relevant conclusions even if there is no clear evidence for the effectiveness of surveillance and can indicate what effect size would be necessary for surveillance to be cost-effective.

5.6.2 Methodology

A decision analytic model will be built with the advantage of considerable prior experience in this area (8, 28-30). It will be conceptualised based on existing models in LS and discussions with clinical and patient experts, following good practice modelling guidance (31). Model parameters will be drawn from the best available sources (32) including the results of WP1–3.

Health outcomes will be measured in quality-adjusted life years (QALYs) and an NHS–personal social services perspective will be adopted. A lifetime horizon will be used and costs and QALYs will be discounted at 3.5%. The evaluation will follow the NICE reference case (33).

A whole disease modelling approach (34) will be adopted so the effect of upstream, downstream and concomitant interventions on the cost-effectiveness of gynaecological cancer surveillance can be assessed. This will likely mean a Markov approach is insufficiently flexible and an alternative approach (e.g. individual patient simulation) will be needed (35). A whole disease modelling approach is justified because the identification and management of LS are not simple interventions. For example, the cost-effectiveness of surveillance will clearly depend on the availability of competing alternatives, but will also depend on concomitant risk-reducing measures (e.g. aspirin). There are also a spectrum of cancer risks associated with pathogenic variants in different MMR genes, so the methods used to identify people with LS (e.g. whether an age limit is imposed on reflex testing) will affect who could be eligible for surveillance.

The model boundary (34) will include at least all women with LS (whether it is diagnosed or not) and the model will include the preclinical natural history of gynaecological cancer, diagnosis of LS (e.g. following CRC or diagnosis in a relative), surveillance, diagnosis and treatment for gynaecological cancer, and death. The model will include a representation of the stage of gynaecological cancer because the hypothetical mechanism for surveillance improving outcomes is to detect cancer in earlier stages. The model will incorporate certain behavioural features, such as women choosing to defer risk-reducing surgery until they have completed childbearing.

The key interventions and comparators for the decision problem in the economic evaluation will be gynaecological cancer surveillance, risk-reducing gynaecological surgery and no action. Key concomitant interventions will include colonoscopy and may include aspirin.

Costs for surveillance and risk-reducing surgery will be estimated using unit costs from the NHS national schedule of reference costs (36). Costs for the diagnosis, treatment and management of gynaecological cancer will be estimated from the best available sources (32), which may include clinical expert advice.

QALYs will be estimated by applying health state utility values to health states within the model. The health state utility values will principally be produced by WP3. Adjustments for age, sex and comorbidities may also be made based on published literature.

5.6.3 Analysis

A fully incremental cost-effectiveness analysis will be conducted, producing incremental cost-effectiveness ratios (ICERs). The base case analysis will assume that women are diagnosed with LS following CRC and following diagnosis of relatives with LS.

Key subgroups will be considered:

- Women for whom risk-reducing surgery is not considered appropriate (disproportionately those with prior CRC)
- Different MMR genes (e.g. risk-reducing measures in women with pathogenic *PMS2* variants may be less cost-effective)

Uncertainty will be explored through one-way sensitivity analyses of individual parameters, probabilistic sensitivity analysis and scenario analyses (e.g. use of aspirin, structural assumptions, time horizon). Particular attention will be paid to parameters relating to the effectiveness of surveillance and health-related quality of life. Value of information analyses will be conducted to estimate the value of future research which could reduce parameter uncertainty (37), indicating whether further primary research into the effectiveness of gynaecological surveillance is warranted or if there is sufficient evidence to make decisions.

6 Dissemination, Outputs and anticipated Impact

6.1 Outputs

The anticipated outputs described in this section are subject to discussion and refinement at the PPI workshop on 5 April 2021.

6.1.1 Publications

In addition to the NIHR monograph, we will prepare and submit publications to internationally recognised journals with immediate open access options on the findings of the systematic review of clinical effectiveness (WP1) and the model-based economic evaluation (WP4).

6.1.2 Conference presentations

We will present interim findings of the project at the Lynch Syndrome UK patient conference in Q1/Q2 2021 and submit findings and conclusions to a prominent European scientific conference in Q3/Q4 2021 (e.g. HTAi, ESMO, ESGO, ISPOR).

6.1.3 Patient materials

We will co-create summaries of the findings suitable for patients and families in multiple formats (e.g. PDF pamphlets for use in clinical settings, snippets suitable for sharing on

social media, written summaries for websites) and share these on social media and through relevant organisations (e.g. Lynch Syndrome UK and Eve Appeal).

6.1.4 Open access/open source economic model

The economic model produced in WP4 will be made open access on Open Research Exeter (allowing anyone worldwide to access it) or open source on GitHub (additionally making it possible for anyone worldwide to contribute to future developments).

6.1.5 Implications for clinical practice

While the report will not make recommendations for clinical practice, it will outline the implications of the research findings for clinical practice. There are a number of existing guidelines on the management of gynaecological cancer risk in LS (38-41), and the findings of the research will be emailed to the corresponding authors of those guidelines in case updates are planned.

6.1.6 Recommendations for future research

The research will be able to highlight important areas where further research would be valuable by evaluating the body of existing research (identified primarily in WP1 and WP3) and comparing it with the information needs of patients. The value of information analysis in WP4 will be very valuable in identifying which research may be needed to support decision makers when cost-effectiveness is a key consideration.

6.2 Dissemination plan

Our primary means to engage with patients is through our relationship with the charity Lynch Syndrome UK (LSUK). Mrs Smith (PPI co-applicant) is a trustee of LSUK. We will present our research plans at the April 2020 LSUK annual conference, and present preliminary findings at the 2021 annual conference. We will prepare materials for LSUK to share on social media (including their Facebook group with >1,900 members) and content for their website (which is an educational resource used by patients) to summarise the findings of our research. We will also seek to engage with patients with the help of the charity Eve Appeal, who have agreed in principle to share and discuss our research findings on social media. We will also contact Cancer Research UK to offer updates for their webpages on screening for endometrial and ovarian cancers.

By the time we produce our results NICE will have two guidelines specifically focussed on LS: DG27 (testing for LS in people with CRC) and GID-DG10033 (testing for LS in people with endometrial cancer); as well as at least two other relevant guidelines: CG122 (ovarian cancer recognition and initial management) and NG12 (suspected cancer recognition and referral). We will register as stakeholders for these guidelines so that we can feed the findings of our research into any updates of those guidelines.

We will reach out to clinicians who have the most significant interactions with women with LS in regard to gynaecological cancer risk management: gynaecologists and genetic counsellors. Most people diagnosed with LS have appointments with genetic counsellors to discuss what LS means for them and their family and what their options are for managing the risks caused by LS. We will prepare PDF leaflets suitable for printing which explain the findings of our research in a manner suitable for patients to read, and we will write clinical updates for publication in the newsletters of the relevant professional organisations.

We will reach the wider public through the news media with the assistance of the University of Exeter press office.

The outputs of this research are expected to enter the health and care system through two routes: patient-led and clinician-led. Patient-led activities include advocacy by patient charities (LSUK and Eve Appeal) and direct education of clinicians by patients supported by appropriate materials. Outputs can also enter the health and care system through professional societies for gynaecologists (Royal College of Obstetricians and Gynaecologists [RCOG]) and genetic counsellors (Association of Genetic Nurses and Counsellors, British Society for Genetic Medicine). Dr Ryan is a committee member of the RCOG Genomics Task Force.

We currently have an excellent relationship with LSUK (Tracy Smith, PPI co-app, is a trustee of LSUK).

We will produce suitable materials for dissemination through each of these channels, including printable PDF leaflets for patients and short updates for clinicians to be included in professional society newsletters.

These materials will be released under Creative Commons licenses.

6.3 Possible barriers for further research, development, adoption and implementation

The possible barriers to the incorporation of the findings of this research to clinical practice are budgetary constraints (resistance to implementing effective and cost-effective interventions because they incur additional costs which may not be suitably reimbursed), staffing and clinic constraints, and resistance to discontinuing interventions in those already receiving them (especially if the intervention is effective but not cost-effective).

Future research into the effectiveness of gynaecological cancer surveillance in women with LS (if needed) may face other barriers. Experimental studies (RCTs or cluster RCTs) are expected to be expensive due to the need for large numbers of participants and long follow-up to achieve statistical power, and the cost of the intervention. Observational studies (e.g. prospective registries, retrospective cohort studies) also require large numbers of people to be identified, good quality data on the surveillance and other risk-reducing measures employed, and advanced statistical techniques (which may involve untestable assumptions) to produce estimates at low risk of bias.

6.4 Anticipated impact

If surveillance is found to be effective and cost-effective the main impact will be patient benefit through changes in NHS service. More women with LS should be offered gynaecological surveillance, which could lead to better cancer outcomes and patients feeling reassured. Women currently paying privately for surveillance should be able to continue to benefit from surveillance but without significant personal expense. The timescale of these effects will likely depend on the budget impact of surveillance as a higher budget impact may result in a need for specific commissioning arrangements. The scale of benefits will depend on how effective surveillance is found to be and how many women with LS take up surveillance.

If surveillance is not effective and/or cost-effective the main impact will be changes in NHS service resulting in savings. The research may also help women to make better informed decisions about whether they wish to pay privately for surveillance.

7 Project / research timetable

The project will run from 1 April 2020 (start of Month 1) to 30 September 2021 (end of Month 18). The PPI workshop takes place on 5 April 2020 (early Month 1) to allow refinements to the systematic reviews (WP1–3). Key milestones in the project will be: 31 October 2020 (WP1–3 complete except for update review [WP1] and writing up for the final report, conceptual model for WP4 complete) and 31 May 2021 (WP1 update review complete and WP4 model implemented and parameterised). The Project Advisory Group will monitor progress in respect of these milestones.

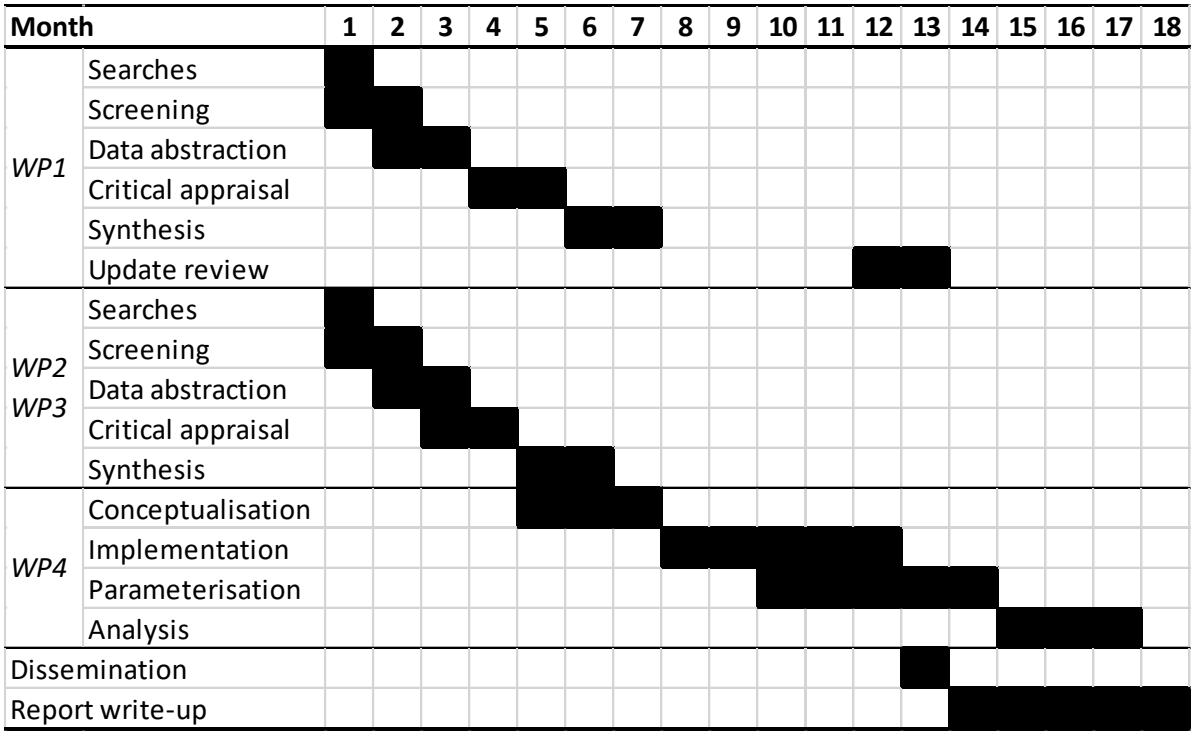

Figure 2: Project monthly timeline

8 Project management

The project will be overseen by the Project Advisory Group, which will be chaired by Prof Hulme and will have Mrs Smith, Dr Crosbie, Dr Lalloo, and two additional patient representatives as members. The Project Advisory Group will meet eight times at the University of Exeter (Months 1, 3, 5, 7, 10, 13, 16 and 18). The research team will report its progress and planned actions at these meetings. The Project Advisory Group will support the research team with expert advice (methodological, clinical and patient), ensure that conclusions from the PPI workshop are carried through the project, and ensure the successful completion of the project. The Project Advisory Group will have discretion to recruit additional members.

There will be monthly meetings of the research team to maintain connections between work packages and give opportunities for the research team to ask or prepare questions for clinical and patient experts. These meetings will coincide with Project Advisory Group

meetings when applicable. When the Project Advisory Group is not meeting, teleconferencing will be used.

Each work package will have an associated weekly meeting to be attended by individuals working on those work packages. The lead investigator will be present at all work package meetings where possible.

Mentoring arrangements will be in place for Dr Snowsill to support him in his first time as a lead investigator on an individually funded project. Prof Hulme will provide formal mentoring through the University of Exeter's One Step Beyond programme, and Dr Snowsill's line manager, Prof Antonieta Medina-Lara will provide informal mentoring. Dr Snowsill will have a minimum of six mentoring meetings with each of Prof Hulme and Prof Medina-Lara over the course of the project.

The postdoctoral research fellow to be appointed for health economics (working on WP2–4) will be offered mentoring through the One Step Beyond programme.

9 Ethics

The project is not expected to entail any ethical or other regulatory issues as it deals with published evidence from the scientific literature and other data sources in the public domain. The PPI planned does not require specific ethical approval in accordance with NIHR Involve.

10 Patient and Public Involvement

Patient and Public Involvement (PPI) has been key to the development of this proposal and will be vital in delivering research which is scientifically rigorous and meets the needs of patients, the public and the NHS.

10.1 PPI in developing the proposal

Our research team includes a PPI co-applicant, Mrs Smith, who is a trustee of the patient charity LSUK. Mrs Smith has reviewed and commented on this proposal at the outline and full application stages, and has consulted the LSUK Facebook group (which she moderates and has >1,900 members) about their views on the proposed research. This consultation provoked over 200 responses, with many respondents saying they thought it was important women with LS received gynaecological surveillance as well as colorectal surveillance, and that their experience with the NHS had included limited awareness of the gynaecological risks in LS. Many had paid for surveillance privately as a result.

The Plain English Summary of our proposal was reviewed by the Peninsula Patient Involvement Group (PenPIG), the user involvement group of the NIHR CLAHRC South West Peninsula, with a specific focus on readability. This resulted in a number of changes.

10.2 PPI throughout the project

We ensure PPI throughout the project by the inclusion of three patient representatives on the Project Advisory Group (see *Project management*), one of whom is Mrs Smith and the other two are to be recruited at a PPI workshop which will take place at the start of the project (on 5 April 2020). We will provide mentorship and support to PPI contributors before and after PAG meetings, addressing queries, language and documentation.

The workshop is attached to the LSUK annual conference and will be promoted in advance to maximise attendance (which will be capped at 10 participants). The workshop will be

facilitated by an experienced PPI researcher (Kate Boddy), and will seek to: 1) inform participants about the research project; 2) obtain insights from the patients about the outcomes they consider to be important and whether particular groups of patients may have different experiences; 3) explore perceptions on the best way to share the results to patients and the public.

The results of the workshop will directly into the systematic review of clinical effectiveness (WP1), by refining the strategies for study selection, data abstraction and narrative synthesis. They will also help to guide the dissemination activities. The patient representatives on the Project Advisory Group will help to ensure that the results of the PPI workshop are represented in the research conducted.

Throughout the project we will adhere to the INVOLVE guidelines and reimburse PPI members according to INVOLVE recommendations.

11 Project / research expertise

Dr Snowsill (Post-doctoral Research Fellow in Health Economics; Grade F) is a health economist with multiple publications of economic evaluations in LS, including two NIHR-commissioned health technology assessments (8, 28-30). He led a health technology assessment of lung cancer screening (42). He has twice been invited to speak at international consensus meetings on LS, and been invited to speak at five LSUK conferences. Dr Snowsill will supervise all aspects of the research project, in particular leading WP2–4. Dr Snowsill will be supported through mentoring arrangements with Prof Hulme and Prof Antonieta Medina-Lara (see *Project management*).

Dr Coelho (Post-doctoral Research Fellow in Systematic Review; Grade F) is a systematic reviewer with experience of systematic review in LS (8, 28, 43). Dr Coelho has substantial systematic review experience in health technology assessment and beyond, e.g. (44-46). She has supervised and trained numerous junior reviewers and leads an MSc module on Systematic Reviews for Policy and Practice at the University of Exeter. Dr Coelho will lead WP1.

Mr Briscoe (Information Specialist; Grade F) is an information specialist and systematic reviewer at the Exeter HS&DR Evidence Synthesis Centre. He has previously been the information specialist for a systematic review in LS (8, 43) and has contributed to the development of systematic review methods through his contribution to the Cochrane Handbook of Systematic Reviews (47). Mr Briscoe will design and conduct literature searches for the systematic reviews (WP1–3) and supplementary searches for the development of the economic model (WP4) and be the 2nd reviewer for WP1.

Dr Crosbie is a clinical senior lecturer and consultant gynaecological cancer surgeon as well as a previous NIHR Clinician Scientist. Dr Crosbie co-organised the Manchester Consensus Meeting on the Gynaecological Manifestations of Lynch syndrome (15). Her research focuses on the screening, prevention and early detection of gynaecological cancers. Dr Crosbie has led eight clinical trials recruiting >1800 women and has co-authored several systematic reviews. Dr Crosbie will provide expert clinical advice and sit on the Project Advisory Group.

Dr Ryan is an Obstetrics and Gynaecology Registrar whose PhD included literature reviews and primary studies of gynaecological cancer in LS (48-50). Dr Ryan co-organised the

Manchester Consensus Meeting on the Gynaecological Manifestations of Lynch syndrome (15) and is a LSUK clinical advisor. He is a committee member of the RCOG Genomics Task Force and the European Hereditary Tumour Group. Dr Ryan will provide expert clinical advice.

Prof Hulme is a Professor of Health Economics who will act as senior support to the project and will chair the advisory group. Prof Hulme's expertise lies in economic evaluation and she has extensive HTA experience. She was health economic methodological lead for the NIHR Diagnostic Evidence Co-operative in Leeds and has supported and mentored first time PIs on NIHR projects in the past as well as sitting on advisory and project delivery boards including the NIHR Commissioning Board. She currently sits on a NIHR Programme Grants for Applied Health Research Sub-Committee and the NIHR Invention for Innovation (i4i) Programme for the Challenge Awards Real World Implementation panel. Prof Hulme has been a mentor for early and mid-career academics and researchers for over a decade and is a member of the University of Exeter One Step Beyond Mentor Scheme.

Dr Fiona Lalloo is a consultant in cancer genetics. She is a former chair and current committee member of the UK Cancer Genetics Group and a committee member of the Clinical Genetics Society. She has contributed to several key clinical guidelines relating to Lynch syndrome, including from the Manchester Consensus Meeting on the Gynaecological Manifestations of Lynch syndrome (15) and from the British Society of Gastroenterology (BSG) / Association of Coloproctology of Great Britain and Ireland (ACPGBI) / United Kingdom Cancer Genetics Group (UKCGG).

Mrs Smith is a patient and trustee of LSUK. She brings a wealth of personal experience and strong networking potential to the project. Mrs Smith cannot have risk-reducing surgery for gynaecological cancer due to previous surgery for CRC and she has paid privately for gynaecological cancer surveillance in the past. Mrs Smith has reviewed this proposal at both stages. During the project Mrs Smith will: share her expertise and experience of LS; share any insights she has as a trustee of LSUK and moderator of the Facebook support group; be part of the Project Advisory Group alongside Prof Hulme, Dr Crosbie and two additional patient representatives; help with dissemination activities, particularly those relating to materials for patients and materials to be shared through LSUK.

We will recruit a health economic modeller for this project. They will conduct the systematic reviews of cost-effectiveness studies (WP2) and utilities (WP3), and will contribute to the conceptualisation, implementation and parameterisation of the economic model (WP4). They will be supervised by Dr Snowsill and will be offered mentoring through the University of Exeter One Step Beyond scheme.

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