Short title: Colonoscopy check-up in people with Lynch syndrome

Full title: Prevalence, determinants, and challenges of adherence with colonoscopy check-up in people with Lynch syndrome: a questionnaire-based study

Study protocol, version 1.4, 7 September 2023

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Clinical queries

Clinical queries should be directed to Emma Robbins who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

Cancer Research UK is funding the study.

This protocol describes the 'Colonoscopy check-up in people with Lynch syndrome' study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act, and other regulatory requirements as appropriate.

Table of Contents

Glossary of abbreviations

Abbreviation	Definition
BCSP	Bowel Cancer Screening Programme
BSG	British Society of Gastroenterology
CaPP3	Cancer Prevention Project 3
VCQ	Views, experiences, and challenges of colonoscopy check-up questionnaire
CRC	Colorectal cancer
CSPRG	Cancer Screening and Prevention Research Group
DSP	Data Security and Protection
GCP	Good Clinical Practice
IG	Information Governance
LS	Lynch syndrome
MLH1	MutI homolog 1
MMR	Mismatch repair
MSH2	MutS homolog 2
MSH6	MutS homolog 6
NHS	National Health Service
PMS2	PMS1 homolog 2, MMR system component
QR	Quick response
REC	Research Ethics Committee

Keywords

Lynch syndrome, colorectal cancer, colonoscopy.

Study summary

Short title: Colonoscopy check-up in people with Lynch syndrome.

Full title: Prevalence, determinants, and challenges of adherence with colonoscopy check-up in people with Lynch syndrome: a questionnaire-based study.

Design: Questionnaire-based study.

Aims: To examine, among people with Lynch syndrome (LS) in the LS research registry pilot study ('registry pilot'):

- the proportion who are adherent with 2-yearly colonoscopy check-up
- individual, social, and healthcare-related determinants of non-adherence with colonoscopy check-up
- the most important challenges to having colonoscopy check-up from the patient perspective

Outcome measures: The primary outcome measure is participant non-adherence to 2-yearly colonoscopy check-up. The secondary outcome measure is the four most important challenges to having colonoscopy check-up for participants.

Population: People in the LS registry pilot.

Eligibility: People with LS in the registry pilot who have provided consent to be involved in future research and are aged ≥25 will be eligible. People who have had surgery involving removal of their rectum will not be eligible.

Duration: One year.

Introduction

Background

LS is the most common hereditary colorectal cancer (CRC) syndrome, responsible for over 1,100 CRCs each year in the UK, representing 2-3% of all CRCs.[1] It is caused by germline pathogenic variants in the coding sequence or regulatory domain of the mismatch repair (MMR) genes Mutl homolog 1 (*MLH1)*, MutS homolog 2 (*MSH2)*, MutS homolog 6 (*MSH6)*, and PMS1 homolog 2, MMR system component *(PMS2).* The most commonly implicated genes are *MLH1* and *MSH2*, accounting for ~90% of LS cases.[2] The pathogenic variants disrupt the DNA repair system, resulting in the accumulation of DNA replication errors and promotion of malignant progression over time.[1] People with LS have a high lifetime risk of CRC, estimated as high as 40-50% for *MLH1* and *MSH2* pathogenic variant carriers,[3-5] compared with 6-7% in the general population.[6] Furthermore, people with LS have an increased risk of developing CRC at an early age (<50 years).[5]

Given their high risk of CRC, people with LS are recommended to have regular check-up colonoscopies ('colonoscopy check-up'). Colonoscopies examine the inner lining of the colorectum to aid detection of CRC at early, more treatable stages, as well as CRC prevention through removal of polyps (CRC precursor lesions). Colonoscopy check-up is associated with reduced CRC mortality among people with LS.[7] The British Society of Gastroenterology (BSG), together with the Association of Coloproctology for Great Britain and Ireland and United Kingdom Cancer Genetics Group, have developed guidelines for the management of LS (the 'BSG guidelines').[8, 9] The 2010 BSG guidelines recommended that people with LS have colonoscopy check-up at least every 2 years, from age 25 years until age 70–75 years or deemed inappropriate due to comorbidity.[8] The updated 2020 guidelines recommend colonoscopy check-up every 2 years until age 75 years, starting at age 25 and 35 years for *MLH1* / *MSH2* and *MSH6* / *PMS2* pathogenic variant carriers, respectively.[9]

The care of people with LS varies greatly across the UK, with many not having the recommended colonoscopy check-up.[10-12] Very few studies have examined determinants of adherence with colonoscopy check-up in people with LS; three studies conducted >10 years ago in the US, Canada, and the Netherlands identified patient history of CRC, attitudes towards colonoscopy, and risk perceptions; knowledge of LS among healthcare staff; and the continuity and coordination of care as being important.[13-15] A recent study from the Netherlands found that lower educational attainment and a history of <5 colonoscopies were associated with non-adherence with colonoscopy check-up, and that bowel preparation was perceived as the most burdensome aspect of the colonoscopy process by patients.[16]

Rationale for the current study

Data are urgently needed on determinants of colonoscopy check-up adherence in people with LS in the UK, considering the differences between countries in healthcare funding, capacity, access, and performance;[17] and patient health-related attitudes and behaviours.[18, 19] Additionally, further studies are needed to understand the psychological, social, and healthcare-related determinants of colonoscopy check-up adherence in people with LS.

From April / May 2023, the National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) is assuming responsibility for performing the colonoscopy check-up in people living with LS in England.[20] While the aim is to provide a reliable recall system for LS colonoscopy check-ups, many challenges might remain for those living with the condition; for example, challenges due to a lack of coordination among different aspects of their care; difficulties with attending colonoscopy check-up appointments (time, financial, travel issues, etc.); a lack of support, information, or knowledge of LS among healthcare staff; negative views and experiences of the bowel preparation and colonoscopy procedure; or the overall burden of living with LS and lifelong colonoscopy check-up. Therefore, it remains crucial to understand

the current care and experiences of people with LS and identify what needs to be improved and which challenges addressed.

The Cancer Screening and Prevention Research Group (CSPRG) at Imperial College London is performing a LS research registry pilot study (https://lynchregistry.org.uk/) (the 'registry pilot'). The registry pilot is recruiting people with LS who are living in England and participating in the Cancer Prevention Programme 3 (CaPP3) trial (http://www.capp3.org/). The present study described in this protocol will investigate the prevalence, determinants, and challenges of adherence with colonoscopy check-up among people with LS in the registry pilot.

Study objectives

The primary objective of this study is to determine the proportion of people in the registry pilot who are adherent with 2-yearly colonoscopy check-up. Secondary objectives will be to examine individual, social, and healthcare-related determinants of non-adherence with colonoscopy check-up, and the most important challenges to having colonoscopy check-up from the patient perspective.

Study design

This study will collect data from ~170 participants using a questionnaire. The study will last approximately one year from administering the questionnaire to sharing the results with participants.

The primary outcome measure is participant non-adherence to 2-yearly colonoscopy check-up. The secondary outcome measure is the four most important challenges to having colonoscopy check-up for participants.

Participant entry

This study will include people who are in the LS registry pilot. The registry pilot is recruiting people who have a confirmed genetic diagnosis of LS[9] and are aged >18 years, living in England, and participating in CaPP3. Recruitment into the registry pilot began in November 2022 and is expected to be complete by November 2023. The registry pilot is expected to recruit ~230 people.

Inclusion criteria

People in the registry pilot who have provided consent to be involved in future research and are aged ≥25 years (above the minimum recommended age for colonoscopy check-up in the UK)[8, 9] will be eligible for this study.

Exclusion criteria

People who have had surgery involving removal of their rectum, and so would not have endoscopic check-up, will not be eligible for this study.

Adverse events

Safety reporting is not applicable for this non-interventional, questionnaire-based study.

Assessment and follow-up

This study does not involve any assessments or follow-up. The end of the study will be when we share the summary of the results with participants (see *Publication policy*).

Regulatory issues

Ethics approval

The study coordination centre has obtained approval from the xxx Research Ethics Committee (REC). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent

We will obtain informed consent from all participants. For those completing the paper version of the questionnaire, we will obtain consent through a paper consent form included in the study pack (see *Study materials*). Two copies of the consent form will be provided; participants will be asked to complete both copies and return one to the study team and retain the other for their records.

For those completing the online version of the questionnaire, we will obtain e-consent via a consent form embedded within Qualtrics before the first page of the questionnaire (https://www.imperial.ac.uk/staff/tools-and-reference/web-guide/tools/qualtrics/, see *Study materials*). The form includes the consent declarations with tick boxes. Each form, accessed through a unique web link/QR code, will be recorded with a unique ID and date/time-stamp when submitted. This will enable linkage of consent data to the respective participants. We will email participants a copy of their e-consent form if their email address is stored in the registry pilot database. For those without an email address in the database, we will print and mail them a copy of their e-consent form. We will have mailing addresses for all participants in the registry pilot, whereas we will have email addresses only for those who provide their email address on the registry pilot consent form.

Participants can withdraw their consent at any time, without having to give a reason; this will not affect their healthcare in any way. They can withdraw by contacting the study team; contact details are given on the invitation letter, participant information sheet, and questionnaire. If a participant withdraws their consent or asks for data collected about them for the study to be erased, or if it comes to our attention at any point that a participant has lost capacity to consent during the study, we will withdraw the participant from the study and delete all identifiable data. We will retain data which is not identifiable. A log will be kept of all withdrawal and data erasure incidents.

Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be pseudonymised (see *Data protection and participant confidentiality*).

Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Sponsor

Imperial College London will act as the main Sponsor for this study.

Funding

Cancer Research UK is funding this study.

Audits

The study may be subject to audit by Imperial College London under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice (GCP) and the UK Policy Frame Work for Health and Social Care Research.

Study management

The day-to-day management of the study will be co-ordinated through the CSPRG.

Publication policy

We will publish a lay summary of the results on the registry pilot website (https://lynchregistry.org.uk/) by the end of 2024. We will mail the results summary to participants who opt in to receiving the results in this way (which they can do by selecting this option on the first page of the questionnaire). We will collaborate with the patient representatives to develop a plan to disseminate the results. Preliminary ideas include sharing the results via our contacts at Lynch Syndrome UK and presenting the results at the Lynch Syndrome UK annual patient conference; leveraging our network of collaborators which consists of clinical and academic experts in LS; using our Twitter account (@CSPRG_Imperial) to engage with the LS community online; publishing a blog article with Bowel Cancer UK; and publishing in a peer-reviewed journal.

Data sources

The questionnaire for this study is called the 'Views, experiences, and challenges of colonoscopy check-up questionnaire'. We will refer to it as the 'VCQ' in this protocol. We will analyse data collected by the VCQ, together with a few additional pieces of information previously collected, with informed consent, as part of the registry pilot and stored in the registry pilot database. This will include colonoscopy check-up data, data on MMR pathogenic variants, dates of LS diagnosis, and data collected by the registry pilot baseline health and lifestyle questionnaire (the 'baseline questionnaire'). For everyone in the registry pilot, we will have data on check-up colonoscopies performed after the date of recruitment into the registry pilot. We will additionally have data on previous check-up colonoscopies for those who consented to the storage of their past data on the registry pilot consent form; early indications show that everyone recruited into the registry pilot so far has consented to this.

We will administer the VCQ to those eligible towards the end of 2023 / early 2024. This will mean that the VCQ is administered within approximately one year of completion of the baseline questionnaire. Exposure variables (see *Exposures*) will not likely change in this time interval. The VCQ therefore does not reassess exposures already assessed in the baseline questionnaire.

In personal communication with St Mark's Hospital (London), it was noted that most people in the registry pilot will not have their first colonoscopy check-up through the BCSP by the end of 2023. Our timeline will, for the most part, allow us to capture participants' perspectives and experiences before the BCSP transition happens. A few people might have their first BCSP-colonoscopy before completing the VCQ; we can identify them by examining the timing of colonoscopies in the registry pilot database and take it into account in our analyses.

Data collected by the VCQ will be stored in a study-specific database. Both the registry pilot database and the study-specific database were developed by the CSPRG Data Analyst / Developer (see *Study team*).

Outcome measures

The primary outcome measure is participant non-adherence to 2-yearly colonoscopy check-up. This will be assessed through examination of colonoscopy check-up data stored in the registry pilot database. Participant's check-up colonoscopies will be grouped into visits; a check-up visit might comprise a single or multiple colonoscopies performed to completely examine the colon and remove any detected polyps.

We will classify adherence on a case-by-case basis using all available data; the following rules will be used as a guide. In general, participants will be classified as adherent if the mean interval between their three most recent check-up visits, and between their last check-up visit and questionnaire completion, is ≤2.5 years, or as non-adherent if the mean interval is >2.5 years.[16] The ≤2.5 year cut-off allows for six months on top of the recommended interval because some delay is inevitable. We expect that a six-month buffer will suffice; however, if observed intervals are systematically longer than expected, indicating that delays are mostly due to non-patient factors (e.g., scheduling by hospitals), we will consider allowing for further time beyond 2.5 years. We will conduct sensitivity analyses to examine how the results vary when using cut-offs that are more or less stringent than our default cut-off. We will examine COVID-19-related disruptions (occurring from ~2020-2022) in the colonoscopy check-up data and through data collected by the VCQ (in the 'Your history of colonoscopy check-up' section). For participants with fewer than three recorded past check-up visits, we will examine the timing of any recorded colonoscopies, date of LS diagnosis, and VCQ data to determine whether they should be classified as adherent or non-adherent. Participants' age and MMR pathogenic variant will be taken into account because BSG recommendations for starting and stopping colonoscopy check-up consider these factors.[8, 9] For participants who have had surgery to remove part or all of their colon, we will count check-up by flexible sigmoidoscopy to be appropriate.

The secondary outcome measure is the four most important challenges to having colonoscopy check-up for participants. The VCQ asks participants to select their most important challenges (maximum of four) from a provided list, relating to the coordination and continuity of care, issues with booking and attending check-up appointments, availability of support and information, and attitudes towards and experiences of the bowel preparation and colonoscopy procedure. The list was developed by working with the patient representatives (see *Patient involvement*) and Dr Kevin Monahan, Dr Christian von Wagner, and Laura Monje-Garcia (see *Study team)*.

Exposures

Demographic and socioeconomic variables

Age, sex, ethnicity, educational attainment, employment status, and socioeconomic status are of interest because they are associated with adherence with colonoscopy and screening examinations for CRC.[14, 16, 21, 22, 24-32] The baseline questionnaire collects data on age, sex, and ethnicity. The VCQ includes questions to assess educational attainment and employment status (in the 'About you' section). It also includes a question on age for reasons described below (see *Data protection and participant confidentiality*). We will assess socioeconomic status via Index of Multiple Deprivation scores which we will identify from participants' postcodes; postcodes will be collected as part of the registry pilot.

Personal and family medical history

Personal and family medical histories are of interest because they might affect health seeking behaviours (e.g., they might be 'cues to action'[33, 34]) or the ability to attend colonoscopy check-up.[31, 32, 35-38]

The baseline questionnaire collects data on participants' smoking behaviour, comorbidities (e.g., diabetes), and history of cancer (including CRC but also other types), colectomy, colorectal polyps, or inflammatory bowel disease. The baseline questionnaire also assesses participants' family history of LS, other hereditary CRC syndromes, and cancer. These variables are not assessed again in the VCQ.

Psychological, social, and healthcare-related variables

The VCQ includes Likert-type scales to assess psychological, social, and healthcare-related variables that might influence adherence with colonoscopy check-up (in the 'Your views, experiences, and challenges of living with LS and having colonoscopy check-up' section). This includes participants' perceived susceptibility to CRC, perceived severity of CRC, perceived benefits of having colonoscopy

check-up, fatalistic beliefs, risk compensation (e.g., trying to manage CRC risk through chemoprevention rather than colonoscopy check-up), stigma associated with having a colonoscopy, support from family / friends, and previous experiences with colonoscopy check-up. We identified these variables by reviewing existing relevant research,[13-15, 21, 22, 24-34, 38-42] and working with the patient representatives (see *Patient involvement*) and Dr Kevin Monahan and Dr Christian von Wagner (see *Study team).*

Self-reported history of colonoscopy check-up

The VCQ assesses participants' history of colonoscopy check-up (in the 'Your history of colonoscopy check-up' section). This includes how often participants have been recommended to have colonoscopy check-up, which we will compare with how often they are actually having it as recorded in the colonoscopy check-up data. Additionally, it assesses how participants travel to a hospital for their check-ups and the type of bowel preparation and sedation they use,[16] considered important by the patient representatives. The VCQ also assesses any delays to check-ups, including both COVID-19-related and unrelated delays, to aid our classification of colonoscopy check-up adherence.

Study materials

We developed the VCQ following guidance on questionnaire development.[43-55] We reviewed existing research examining factors associated with adherence with colonoscopy check-up in people with LS and with colonoscopy and screening examinations for CRC.[13-16, 21, 22, 24-32, 38-42] This informed our selection of exposure variables, the type of questions and response options that we include in the VCQ, and the questionnaire layout and length. The VCQ is eight pages long which will allow us to gather the necessary data but not over-burden participants.

The CSPRG Data Analyst / Developer created an online version of the VCQ using Qualtrics, a tool to build online questionnaires which is supported by Imperial ICT (https://www.imperial.ac.uk/staff/tools-and-reference/web-guide/tools/qualtrics/). Participants will be able to choose between completing the paper or online version of the VCQ. Both versions have the same questions; the only difference is the format. Providing the option to complete the VCQ online will hopefully help to increase response rates, particularly among younger people, while providing a paper version is important to ensure that those without internet access or unfamiliar with technology are not disadvantaged. The VCQ was reviewed by Dr Kevin Monahan, Dr Christian von Wagner, Laura Monje-Garcia, and all members of the CSPRG, as well by Dr Fiona Lalloo (Consultant in Clinical Genetics and Clinical Head of the Genomics Division, Clinical Genetics Service, Manchester Centre for Genomic Medicine), Kate Green (Database Manager, Clinical Genetics Service, Manchester Centre for Genomic Medicine), and Catherine Willis (LS Genomics Nurse / Genetic Counsellor, University Hospital Southampton NHS Foundation Trust). We incorporated their feedback to improve the clarity, accessibility, and relevance of the questionnaire.

We pre-tested the VCQ with five of the six study patient representatives (see *Patient involvement*). This involved holding one-on-one meetings online with the representatives, during which they completed the VCQ and 'thought aloud' as they did so. Two representatives tested the online version of the questionnaire, while the remaining three representatives tested the paper version. They shared what they thought was being asked by the questions, their reactions, any uncertainties and difficulties that arose, and suggested additions and improvements. The main changes made to the VCQ based on the representatives' feedback are summarised below (see *Patient involvement*).

We developed the invitation letter and participant information sheet with input from Dr Kevin Monahan, Dr Christian von Wagner, Laura Monje-Garcia, and the patient representatives. A downloadable PDF version of the participant information sheet will be available on the registry pilot website (https://lynchregistry.org.uk/). We did not need to translate the study materials into other languages

because participants will be selected from among those in CaPP3 and living in England, all of whom can read and write in English.

The participant information sheet and paper versions of the consent form and VCQ will be sent by mail to eligible people in a study pack. The study pack will contain a freepost envelope (addressed to the CSPRG) for the VCQ to be returned in. Each VCQ will be linked with a unique ID (see *Participant recruitment and data collection*). Unique IDs will be written on the paper version of the VCQ. For the online consent form and VCQ, a unique web link (corresponding to the unique ID) and a quick response (QR) code will be provided on the front page of the paper VCQ; participants will need to type the web link into their internet browser or scan the QR code on their computer or mobile phone. Web links will be kept short to minimise the likelihood of participants typing them in incorrectly. Additionally, after submission of the consent form/VCQ, the corresponding web link will expire to prevent more than one participant using the same web link or one participant submitting the consent form/VCQ more than once. Participants are reminded, in the participant information sheet and questionnaire, to not share a photocopy of the paper version or the weblink/QR code with anyone else.

Participant recruitment and data collection

Everyone in the registry pilot will have a unique ID assigned to them. We will compile a list of unique IDs for those who are eligible for the present study. The IDs will serve as the link between the study materials and each individual. All eligible people will be sent the invitation letter and then, within the following week, the study pack. The invitation letter will be sent by mail or email depending on the person's preferred method of contact indicated on the registry pilot consent form. The study pack will be sent by mail only for reasons described below (see *Data protection and participant confidentiality*).

People will be invited to complete the VCQ, either the paper or online version, and to return / submit it within three weeks. As each VCQ will be linked with a unique ID, it will be possible to identify those who have not returned / submitted their VCQ.

We will send a first reminder to people who do not respond within four weeks of the study pack being sent (allowing for an additional one week on top of the specified three-week period). The reminder will comprise a reminder letter and replica of the study pack. The reminder letter will ask people to complete and return / submit the VCQ within two weeks.

We will send a second reminder to those who do not respond within three weeks of the first reminder being sent (allowing for an additional one week on top of the specified two-week period). This reminder will comprise a reminder letter only, but people will be able to order another study pack if they have lost theirs by contacting the study team. People who do not respond within three weeks of the second reminder being sent will not be included in the study (Figure 1). We use normative messages in the reminder letters to encourage non-responders to respond (e.g., implying high levels of response among invitees).[56]

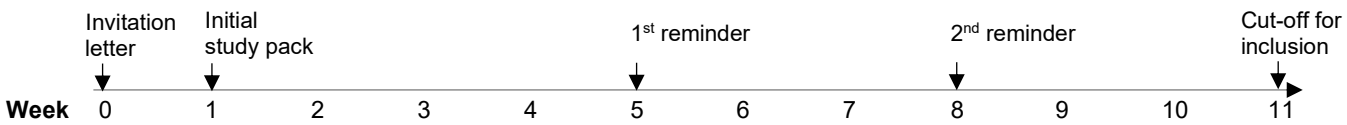

Figure 1. Timeline of the study

Data entry and coding

Emma Robbins will enter data from paper VCQs, which have been completed and returned, into the study-specific database, using a secure application such as Oracle Application Express to access the database. The CSPRG Data Analyst / Developer will upload data collected via the online VCQ into the study-specific database. Emma will clean and code the data using standard operating procedures. The CSPRG Data Analyst / Developer will independently code a random sample (10%) of the questionnaires and cross-check their data entries with Emma's. Any discrepancies will be discussed and resolved.

Statistics and data analysis

Sample size

Of the ~230 people expected to be recruited into the registry pilot, we estimate that 90% will be eligible for the present study, of whom we estimate that 80% will complete and return the questionnaire, giving a total of ~170 study participants. We are estimating a high response rate to the questionnaire because early indications show that everyone recruited into the registry pilot so far has responded to the baseline questionnaire. We assume that 30% of study participants will be classified as non-adherent with colonoscopy check-up. This is informed by personal communication with St Mark's Hospital, London, and a study examining adherence with colonoscopy check-up in people with LS on the Manchester Familial Colorectal Cancer Registry in 2011.[12] Under this assumption, there will be a total of ~50 events which will be sufficient for our planned analyses.

Data analysis

We will compare demographic variables between people who respond to the VCQ and those who do not, and between those who complete the paper versus online version of the VCQ, using χ^2 tests.

We will calculate the percentage of participants classified as non-adherent with 2-yearly colonoscopy check-up. We will describe the distribution of the number of past check-up colonoscopies among participants using percentages. We will identify the four most important challenges to having colonoscopy check-up by examining the frequency of selections for each challenge in the provided list.

We will describe the distribution of demographic, socioeconomic, and medical variables among participants using percentages. We will categorise the Likert-type scale ratings for psychological, social, and healthcare-related variables and describe them using percentages. We will examine associations between the ratings and demographic, socioeconomic, and medical variables using χ^2 tests.

We will examine non-adherence with colonoscopy check-up by demographic, socioeconomic, medical, psychological, social, and healthcare-related variables and by number of past check-up colonoscopies using χ^2 tests. We will further explore associations using logistic regression; we will consider variables with p-values <0.2 in univariable models for inclusion in a multivariable model to identify variables independently associated with non-adherence with colonoscopy check-up. To avoid overfitting, we will include a maximum of one variable per 10 observed events in the multivariable model; with 50 participants anticipated to be non-adherent, this would allow inclusion of five variables. Collinearity between variables will be assessed by a correlation matrix.

We will conduct all analyses in Stata/IC V.17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, Texas, USA: StataCorp LLC). We will use a significance level of 0.05.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study.

Patient involvement

We are working with six patient representatives, who have personal lived experience of LS, throughout the research cycle to ensure the patient voice, preferences, and needs are at the centre of the research (Figure 2). We recruited the representatives through social media (Twitter: @CSPRG_Imperial), engagement with Lynch Syndrome UK and Bowel Cancer UK, and at the Lynch Syndrome UK annual patient conference in 2022.

We are conducting the patient involvement according to guidance from the National Institute for Health Research (NIHR).[57] Emma Robbins (PhD student, see *Study team*) is the main point of contact for the patient representatives; she has completed training in patient involvement at Imperial College London.

Patient involvement to date

The representatives reviewed the study protocol, confirming that it addresses questions important to people with LS and that the methods for recruiting participants, obtaining informed consent, and data collection are appropriate and ethically acceptable. We incorporated the representatives' suggestions of additional important factors to assess in the VCQ; to include a foreword from a representative in the invitation letter encouraging completion of the questionnaire; and to enclose all documents being mailed to participants' home addresses in blank envelopes as an additional precautionary measure.

The representatives reviewed the invitation letter and participant information sheet and gave suggestions to ensure that the documents are clear and concise, will be easily understood by study participants, and cover all important issues.

The representatives played a crucial role in the development of the VCQ. They participated in a group workshop to identify the key challenges of having colonoscopy check-up for people with LS. The challenges they identified are included in the VCQ; participants completing the questionnaire will indicate whether each challenge applies to them and will select up to four challenges that they consider the most important.

Additionally, five of the six representatives participated in the pre-test of the VCQ as described above. The following is a summary of the main changes made to the VCQ based on the representatives' feedback:

- We added new text to specify that the questions pertain to experiences since being diagnosed with LS.
- We added new text to inform participants that they can skip questions they prefer not to answer and can cross out and change their answers.
- We removed a question asking participants about the frequency of their colonoscopy check-ups because this was identified as difficult to answer.
- We added new questions asking participants how they travel to and from the hospital for colonoscopy check-ups and what type of sedation and bowel preparation they use.
- We added extra responses to questions assessing experiences of colonoscopy check-up during the COVID-19 pandemic and other delays to check-up, to capture all possible experiences.
- We reworded statements assessing perceptions of CRC risk, benefits of colonoscopy check-up, and fatalistic beliefs for clarity.
- We reworded statements assessing the support participants receive from people close to them to avoid causing distress to individuals with limited support.

- We added a new statement to assess participants' satisfaction with the timeframe in which biopsy results are shared after colonoscopy check-up appointments.
- We reworded several statements describing the challenges of having colonoscopy check-up for clarity.
- We added new challenges including the impracticalities and side effects (nausea/vomiting) of the bowel preparation process and geographical/travel issues related to accessing a hospital for colonoscopy check-up.
- We revised the instructions for one question to allow participants to select up to four challenges they find most important, instead of limiting them to three.
- We improved the response selection method for a question in the online questionnaire that was found to be cumbersome.
- We added new text to provide an explanation for why 'About you' questions are included.

Future patient involvement

As mentioned above, the patient representatives will attend a future workshop to interpret the study findings, check whether our interpretations are appropriate and represent the patient perspective, and develop a research dissemination plan. We will also work with the representatives to develop a lay summary of the results.

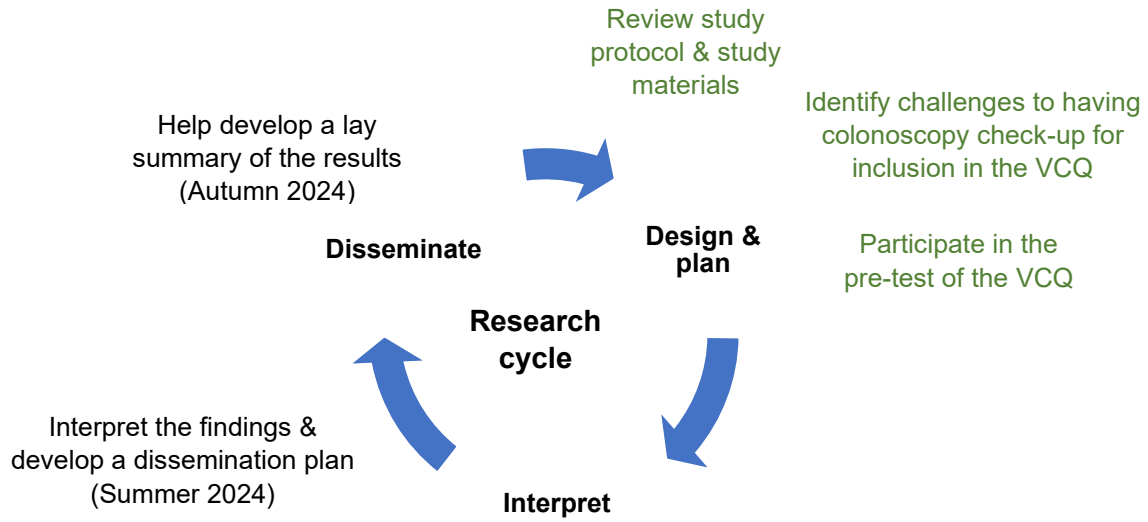

Figure 2. Patient involvement activities for the study

Activities conducted to date are in green, future activities are in black.

Data protection and participant confidentiality

The study will comply with data protection laws as specified in the Data Protection Act 2018 and the General Data Protection Regulation 2016/679. The study will be conducted under the auspices of the CSPRG, which has a proven track record of securely storing data from large national studies and trials, ensuring participant confidentiality is protected. All data will be handled in accordance with the CSPRG Information Governance (IG) Policy and NHS England Data Security and Protection (DSP) Toolkit which meet requirements for the storage and processing of patient information as set out by the Department of Health and Social Care. They detail numerous precautions to ensure patient data are kept safe and secure, including secure software development practices, firewalls, access restrictions, encryption, and security audits.

The study will use data stored on two Oracle databases, the registry pilot database and the study-specific database, both of which are encrypted and have access restrictions imposed (Oracle Corporation, Redwood City, California, USA). Patient identifiable information will be stored in the registry pilot database but not the study-specific database; the former will be accessible to the CSPRG Data Analyst / Developer only, while the latter will be accessible to the CSPRG Data Analyst / Developer and Emma Robbins. The study-specific database will be accessed using a secure application such as Oracle Application Express.

We will follow the Caldicott Principles and guidance from the NHS Code of Confidentiality to preserve participant confidentiality throughout all stages of the study. We will pseudonymise personal data and will only handle identifiable information when strictly necessary for the study, such as to send out the invitation letter, study pack, and reminders. Specific details outlining how we will maintain participant confidentiality are given below.

The CSPRG Data Analyst / Developer will assess participant eligibility by reviewing information in the registry pilot database on dates of birth (to calculate age), any previous colorectal surgery, and whether consent was given to be contacted about future research. The CSPRG Data Analyst / Developer and Emma will collaborate to identify people who have had surgery to remove their rectum and should be excluded; the CSPRG Data Analyst / Developer will create a pseudonymised file with unique IDs and colorectal surgery information, encrypt it, and save it on the CSPRG's secure drive with access restricted to the two of them. Emma will review the information and highlight IDs for exclusion. The CSPRG Data Analyst / Developer will compile a list of unique IDs for every eligible person and a file containing information linking the unique IDs to patient identifiable information. The file will be encrypted and saved in a secure location on the CSPRG's secure drive. Only the CSPRG Data Analyst / Developer and Emma Robbins will have access to the file and they will access it only when strictly necessary. The CSPRG's secure drive is compliant with Imperial College policies.

The file with the linkage information will be accessed to send out invitation letters, study packs, reminders, and copies of participants' completed consent forms, and to mail the results summary to those who opt in to receiving the results in this way. If a person notifies us that they do not wish to participate in the study, we will access the file to identify their unique ID and make a note against their ID in the study-specific database to not contact them further.

Participants completing the paper consent form and VCQ will be asked to return the two documents in separate envelopes. This will keep completed VCQs separate from personal details in consent forms, ensuring that VCQs cannot be attributed to participants. The e-consent form, embedded within Qualtrics, does not request any patient identifiable information, ensuring no patient identifiers are transmitted in Qualtrics (https://www.imperial.ac.uk/staff/tools-and-reference/web-guide/tools/qualtrics/). Each form, accessed through a unique web link/QR code, will be recorded with a unique ID and date/time-stamp when submitted. This will enable linkage of consent data to the respective participants.

The VCQ does not ask participants for identifiable information. It requests age as an open response rather than asking for date of birth. Therefore, it will not be possible to attribute a completed VCQ to a participant without knowing the information linking unique IDs to patient identifiers. It would be possible to attribute a completed VCQ to a participant if they sent it back to us by email; our decision to send study packs by mail rather than email will minimise the likelihood of this happening. As an additional precautionary measure, we will enclose all documents being mailed to participants' home addresses in blank envelopes with no postmark showing they are from the CSPRG or Imperial.

Pseudonymised data from consent forms and the VCQ will be entered into the study-specific database. For each unique ID, the CSPRG Data Analyst / Developer will crosscheck the age provided in the VCQ against the date of birth recorded in the registry pilot database. This will help to identify whether

participants have been accurately matched between the questionnaire and their records in the registry pilot database via the unique IDs.

Paper consent forms and questionnaires, which have been completed and returned by participants, will be stored in locked filing cabinets in the CSPRG office at St Mary's Campus (London). The physical security of the CSPRG office is maintained by Imperial's Head of Security. The building has turnstiles covering the main entrance which are manned 24 hours a day by security officers. All entrances to the building are monitored by video surveillance cameras and the building is patrolled 24 hours a day. The building and CSPRG office are accessible only with a campus radio frequency identification card. Access to the office is granted only to members of the CSPRG and essential ICT, security, maintenance, and cleaning staff.

The planned analyses will require data stored in the registry pilot database, some of which are potentially identifiable. The CSPRG Data Analyst / Developer will compile the required pseudonymised data into an Excel file which will be encrypted and saved in a secure location on the CSPRG's secure drive, with access restricted to the CSPRG Data Analyst / Developer and Emma Robbins (Microsoft Corporation. 2023. Microsoft Excel: Version 2208). Emma will import the pseudonymised data from Excel into Stata for analysis (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, Texas, USA: StataCorp LLC).

We will publish anonymised, aggregated results and apply disclosure control measures where necessary to ensure anonymity is maintained. For example, we will aggregate data in table cells with small counts to prevent the potential identification of individuals. As a general rule, counts of five or below will be considered as small counts.

Potential risks to participants

It will be our utmost priority to safeguard the wellbeing and safety of participants, including those who participate in the study and the patient representatives. We will minimise the potential risks to participants in the following ways.

A personal data breach is a potential risk. Possible consequences include emotional distress, loss of control over personal data, identity theft and fraud, and discrimination. We have policies and precautions in place to ensure that participant data are safe and secure, as described above. If a breach of confidentiality occurs, all participants will be notified as soon as possible using their given contact details.

Other potential risks include emotional distress caused by completing the VCQ. To minimise this risk, we pre-tested the VCQ with the patient representatives and removed and reworded questions/statements that the representatives thought could make participants feel uncomfortable, worried, or upset. For example, we reworded statements assessing whether participants receive support from people close to them based on feedback from two representatives, to avoid making individuals with limited support feel upset or discouraged. Additionally, we reduced the number of 'About you' questions based on feedback that these types of questions can seem unnecessary or intrusive. The VCQ now only asks participants for their age, education level, and employment status, which are essential for our analyses and not covered by other questions.

In the participant information sheet, we highlight the possible risk of experiencing emotional distress because of the VCQ and let participants know that they are free to skip any questions they prefer not to answer or stop the questionnaire at any time. If participants experience emotional distress because of the VCQ and feel that they need support, we recommend they seek support from a healthcare professional or via an NHS mental health helpline. We also let participants know that they can contact us at any time, for any reason, and we can provide details of relevant support services if needed.

An inevitable risk of participation is loss of time. To minimise the loss of time to participants, we have kept the VCQ as concise as possible while still ensuring the collection of necessary information. Completing the VCQ will take approximately 15 minutes. The five patient representatives who participated in the questionnaire pre-test commented that the number of questions and time required to complete the VCQ is optimal.

There is a risk of emotional distress for the patient representatives; for example, a representative might experience anxiety about how people with LS are currently being cared for when they review the study findings. We ensure that the representatives are informed of possible risks prior to the patient involvement activities and that they know they can contact us at any time, for any reason. As above, we will provide details of relevant support services if needed.

There are no risks of physical harm associated with completing the VCQ. For the patient representatives, there are risks of physical harm associated with attending in-person workshops (e.g., from first aid, fire, or security related hazards). Before all in-person activities, we perform a risk assessment and implement any risk mitigation strategies.

Potential benefits to participants

Potential benefits to participants include being part of research that has the potential to help improve the care of people with LS. Study participants and patient representatives will provide insight into the views, experiences, and challenges of people with LS in living with the condition and having colonoscopy check-up. This will identify what changes need to be made to improve experiences of colonoscopy check-up for people with LS and help overcome the challenges that they face. Participants may experience a sense of fulfilment knowing that their contributions could help improve services and experiences for present and future generations of families with LS. This sentiment was emphasised by a patient representative during their review of the study protocol. Additional benefits for the patient representatives might include new skills, knowledge, and relationships among themselves and with the study team.

Study team

Professor Amanda Cross is a Professor of Cancer Epidemiology (School of Public Health) and the Head of Section for Gastrointestinal Surgery and Head of the CSPRG (Department of Surgery and Cancer) at Imperial College London. She is an expert in CRC screening and prevention and has many years' experience in leading nationwide, multisite studies and trials. As Chief Investigator of the study described in this protocol, Professor Cross is responsible for overseeing the study; ensuring necessary approvals and appropriate measures to protect participant data, confidentiality, and wellbeing are in place; and providing guidance on all aspects of the study from its design to statistical analysis.

Emma Robbins is a PhD student in the CSPRG. Before starting her PhD in 2021, Emma was a Research Assistant for the CSPRG for four years, gaining expert knowledge relating to CRC screening and prevention. She received training in questionnaire-based research during her MSc in Public Health (London School of Hygiene & Tropical Medicine) and has completed training in patient involvement (Imperial College London). Emma is leading the study described in this protocol as part of her PhD research. She has led the development of the protocol and study materials and questionnaire, and is responsible for designing and conducting the patient involvement activities, performing the statistical analyses, and writing-up the study findings.

Paul Greliak is a Clinical Trial Manager for the CSPRG. He has over 10 years' experience in the field of cancer, including a tenure at the Thames Cancer Registry (Kings College London), and expertise in managing trials, with previous experience within the Clinical Trials Section at the Cancer Research UK

Imperial Centre and the Imperial Clinical Trials Unit. Paul provided input on this study protocol (particularly related to participant recruitment, consent processes, and regulatory issues), as well as input on the study materials. As the Clinical Trial Manager for the LS registry pilot, Paul will continue to provide information and insight from the registry pilot, as well as overall support on study management and regulatory issues.

Salman Shahrezaei is a Data Analyst and Developer specialist in the CSPRG. With an MSc in Software Engineering (Kingston University) and over 15 years' experience as a System Analyst and Developer for an internationally recognised company, he has expertise in delivering Oracle-based solutions and optimising database design and data management. Salman provided input on this study protocol (particularly related to data storage, management, and protection). He developed the online version of the study questionnaire, as well as the LS registry pilot database and study-specific database detailed in this protocol. Salman is responsible for managing these databases; this involves systems administration and security, liaising with data providers to gather clinical data, designing data-processing applications, and maintaining compliance with CSPRG IG policies.

Kate Wooldrage is an experienced medical statistician with over 15 years' experience with the CSPRG and expert knowledge in the field of CRC. As the CSPRG's senior statistician, Kate leads the statistical analysis on many of the group's studies and trials. She provided input on this study protocol (particularly related to the sample size, outcome measure definition, and statistical analysis plan). She will provide support for the statistical analyses and contribute insight in interpreting the findings.

Mariano Kälfors is the Project Manager for the CSPRG. He has extensive experience in project management having held positions as a Programme Manager with the National Cancer Research Institute and a Project Manager with the World Cancer Research Fund. Mariano provided input on this study protocol (particularly related to regulatory issues and patient involvement) and on the study materials, as well as guidance and support with the patient involvement. He will continue to provide overall support to ensure the study is completed on time and in accordance with this protocol.

Dr Christian von Wagner is an expert in behavioural science, particularly related to CRC screening. He is a Reader in Behavioural Science and Health at University College London, with many years' experience in assessing patient understanding of cancer, perceptions and preferences regarding screening, and engagement with participant information materials. Dr von Wagner provided input on this study protocol (particularly related to the selection of exposure variables, participant recruitment, and patient involvement activities), study materials, and questionnaire. He will contribute insight in interpreting the study findings.

Dr Kevin Monahan is a clinical expert on LS. He is a Consultant Gastroenterologist and Endoscopist at the St Mark's Centre for Familial Intestinal Cancer, where he leads the Lynch Syndrome Clinic and Family Cancer Clinic and manages the Polyposis Registry and the Bobby Moore Database for people at familial risk of CRC. Dr Monahan is also an Honorary Clinical Senior Lecturer at Imperial College London. Dr Monahan provided input on this study protocol (particularly related to the outcome measure definition and selection of exposure variables), study materials, and questionnaire. He will contribute insight in interpreting the study findings.

Laura Monje-Garcia is a clinical expert on LS. She is the National Lead Nurse for the National Lynch Syndrome Project, a Nurse Practitioner and Clinical Research Fellow at the St Mark's Centre for Familial Intestinal Cancer, and an Honorary Member of the School of Public Health, Imperial College London. Laura is also a trainee health psychologist and has been working with patients living with inherited conditions since 2012, currently conducting research into the psychological impact of living with inherited CRC. Laura provided input on the study materials and questionnaire and will contribute insight in interpreting the study findings.

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