CANCER RESEARCH UK

Dennis and Mireille Gillings Foundation

UNIVERSITY OF EXETER | MEDICAL SCHOOL

FULL/LONG TITLE OF THE STUDY

A pragmatic cluster randomised controlled trial assessing the clinical effectiveness and cost-effectiveness of electronic risk-assessment for cancer for patients in general practice (ERICA)

SHORT STUDY TITLE / ACRONYM: Electronic Risk Assessment for Cancer (ERICA)

PROTOCOL VERSION NUMBER AND DATE:
Version 4.0 Dated 3rd September 2021

RESEARCH REFERENCE NUMBERS

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REC REF: 19/LO/0615
CRN Portfolio - CPMS ID 41736

SPONSOR: University of Exeter
Sponsor Protocol Reference: 1819/19

This protocol has regard for the HRA guidance

Signature Page

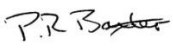
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date: 03/09/21



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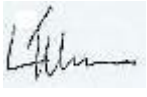
Statistician:

Date: 03/09/21

Signature: 

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Contents

List of Abbreviations

AE	Adverse Event
CAG	Confidentiality Advisory Group
CCG	Clinical Commissioning Group
CI	Chief Investigator
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCDS	electronic Clinical Decision Support
eRAT	electronic Risk Assessment Tools
ExeCTU	Exeter Clinical Trials Unit
GCP	Good Clinical Practice
HRA	Health Research Authority
HCRW	Health and Care Research Wales
ISRCTN	International Standard Randomised Controlled Trials Number
LHB	Local Health Board
MHRA	Medicines and Healthcare products Regulatory Agency
NCRAS	National Cancer Registration and Analysis Service
NHS R&D	National Health Service Research & Development
NIHR	National Institute of Health Research
ODR	Office for Data Release (within NCRAS)
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
RAT	Risk Assessment Tool
RCT	Randomised Control Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
WCISU	Welsh Cancer Intelligence and Surveillance Unit

Trial summary

Title	A pragmatic cluster randomised controlled trial assessing the clinical effectiveness and cost-effectiveness of electronic risk-assessment for cancer for patients in general practice (ERICA)
Aim	To assess the clinical and cost effectiveness of electronic Risk Assessment Tools (eRATs) for cancer compared to usual care for patients in general practice.
Objectives	To compare the effects of eRATs against usual care on cancer staging at time of diagnosis, cost to the NHS, patient experience of care, and service delivery models.
Design	The study is a pragmatic cluster RCT. Practices will be randomised 1:1 to receive either the intervention (access to the suite of eRATs) or usual practice. The clusters will be practices. There will also be embedded process and health economics evaluations along with a parallel study modelling the impact of eRATs on NHS service delivery.
Intervention description	The eRATs are electronic clinical decision support tools embedded into the general practices' principal clinical system. They work by collating relevant Read-coded symptoms, supplemented by existing routine blood tests already in the GP's clinical system, which are then assessed for the possibility of cancer using published algorithms developed by Hamilton and colleagues. There are six eRATs of interest to the study (lung, colorectal, oesophago-gastric, bladder, kidney, and ovary) and they are housed within a Macmillan-sponsored Clinical Decision Support Tool. The eRATs have two main ways of working. Firstly, a prompt appears on screen when a patient has a risk of any one of the studied cancers of 2% or higher. Secondly, the clinician may specifically open a 'symptom checker' which lists the relevant symptoms of each studied cancer, allowing the patient's symptoms to be added and the risk of cancer to be (re)calculated.

Funding and Support in Kind

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
The Dennis and Mireille Gillings Foundation	£2,000,000.00
University of Exeter	£200,000.00
Cancer Research UK	Funding administrative support via CanTest – approx. £25,000
NIHR CRN	Support instrumental for the recruitment of practices
Macmillan Cancer Support	Macmillan financed the development of an electronic Clinical Decision Support (eCDS) Tool which originally contained five eRATs (lung, pancreas, colorectal, ovarian, oesophago-gastric). The research grant from the Gillings Foundation has financed the development of two further eRATs (kidney and bladder) which will be housed within the eCDS tool (The study will focus on all eRATs except pancreas; i.e. six out of the seven eRATs).

Role of Trial Sponsor and Funders

The University of Exeter is the trial sponsor.

The study sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research proceeds and approve any modifications to design, obtaining requisite regulatory authority.

The sponsor will assume responsibility for operating the management and monitoring systems of the research. Some of these activities may be undertaken by Exeter Clinical Trials Unit by arrangement through the Chief Investigator and Exeter CTU, and these will be notified to the Sponsor. Any amendments will be checked and authorised by the Sponsor before submission to regulatory authorities.

Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- Where appropriate the research has been reviewed and approved by an NHS Research Ethics Committee and/or the Health Research Authority Approval Programme.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.
- Organisations and individuals involved in the research agree the division of responsibilities between them.

• Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
• There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.
The sponsor plays no role in the design of this study, and will have no role in data analysis or interpretation, or writing up of findings of the study.

The trial funders are providing finance to run the trial. None of the funders will be involved in the design or conduct of the trial, analysis of data, or interpretation of findings. With respect to dissemination strategies, the terms and conditions of all funders will be honoured and respected.

Roles and Responsibilities of Trial Management Groups and Committees

Trial Steering Committee (with Data Monitoring Committee responsibilities)

The responsibilities of the Trial Steering Committee (TSC) will be to review the main study protocol and any amendments, monitor and supervise the trial towards its interim and overall objectives, review relevant information from other sources, and to help resolve problems brought by the Trial Management group (TMG). The TSC will therefore provide overall independent supervision for ERICA on behalf of the funders and the University of Exeter (sponsor) to ensure that the trial is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice (GCP). Meetings will be held at regular intervals determined by need and not less than twice a year. Routine business will be conducted by telephone, videoconference, and email.

The TSC will also operate as the Data Monitoring Committee (DMC). The ERICA trial is considered to be low risk to patients. Participants may experience an adverse incident following referral for investigations (e.g., a consequence of colonoscopy). There are no mechanisms for recording adverse incidents because the trial design focusses on the recruitment of practices and not patients *per se* – patients will be unaware that they are in a trial, with their outcome data accessed via routinely collected data from cancer registries. However, the process evaluation will explore AEs retrospectively via interviews in a subset of the patients for whom the eRATs were used on. There will also be a time lag between patients 'entering the trial' and data availability from cancer registries. The time lag will be such that data will only be available once practices have completed data collection. Therefore, interim analyses to assess whether the trial was (in)effective, and to support a decision whether to stop the trial early, would be unnecessary as data collection (and practice participation) would have already ceased. Accordingly, the TSC will function as a DMC with the role to primarily monitor the overall conduct of the ERICA study. When operating as the DMC, the members will meet independently of the research team (though supported by the trial statistician). At least one of the bi-annual TSC meetings will have a closed-door meeting where the DMC will review study progress.

Trial Management Group

A Trial Management Group has been established and includes those responsible for the day-to-day management of the trial and those supporting the delivery of the trial and associated stakeholders, including representatives of the Local Clinical Research Networks (LCRN) and Macmillan. The group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The group will meet regularly (monthly in the first instance, until recruitment has completed) in person and/or by phone or over the internet (via MS Teams).

Core Study Team

The core study team (CI, TM) will meet weekly during the study. Day-to-day running of the trial will be the responsibility of the Trial Manager (TM). The TM will have access to the ExeCTU suite of standard operating procedures (SOPs) and will ensure that the trial is run in compliance with all relevant SOPs (e.g., assessment, processes and reporting, data management, study staff health and safety).

Background and rationale

The health challenge of cancer

An estimated 10,000 annual UK cancer deaths would not occur if the UK matched the outcomes of other European countries.(1) Most of the difference relates to diagnostic delay.(2) The NHS Long Term plan, published in January, 2019, specifically targets an increase in the percentage of cancer patients whose cancer is stage 1 or 2 (curable) to rise from the current 54% to 75% by 2028.(3) This requires major changes in the way cancer is diagnosed. Within general practice, where the core problem exists of identifying the patient who may have a cancer explaining their symptoms, there has been an enormous increase in research efforts, much by the Exeter team. These studies were aimed at identifying which symptoms of possible cancer actually matter.(4) The main outputs from them have been Risk Assessment Tools (generally abbreviated to RATs); these give precise estimates of the chance of an underlying cancer as a percentage figure. This figure can be calculated for single symptoms (e.g. the risk of cancer of the lung with coughing blood is 2.4%), as pairs of symptoms (coughing blood accompanied by loss of weight is 9.2%) or as repeated symptoms (a re-attendance with coughing blood is 17%).(5) We have published RATs for the 17 most common adult cancers, accounting for nearly 90% of the total cancer burden. These papers have been highly influential: two have won Research Paper of the Year;(6, 7) more importantly, they strongly underpinned the NICE 2015 guideline revision.(8) Indeed, 100 of the 220 recommendations in NICE 2015 can be traced back to RATs studies.

Do RATs work?

RATs themselves have evolved. The initial versions were in paper, mouse mat, calendar, or web-based forms; they increased cancer diagnostic activity, but the formats did not allow close integration with GPs' clinical systems.(9) In partnership with Macmillan, the UK cancer charity, electronic versions for seven major cancers (lung, colorectal, pancreas, oesophago-gastric, bladder, kidney and ovary) have been developed. These eRATs have been integrated into the GPs' clinical software, for two of the main UK GP software providers, with two other major providers almost ready to host them. The eRATs prompt the GP when the risk of one or more of these cancers is above 2%. They have been downloaded by 1,000 of the UK's 10,000 practices, though actual usage is largely unknown. Macmillan commissioned two internal studies of eRATs, which examined practitioner acceptability: these reports were positive, but did not address important clinical outcomes, such as stage at diagnosis or survival.(10, 11) A pilot feasibility trial of the oesophago-gastric eRAT is ongoing.(12) Although important, findings from this study will be restricted to the single eRAT. Crucial questions regarding the clinical effectiveness and usability of multiple eRATs remain.

One major aspect of the eRAT research that is outstanding relates to cost-effectiveness, as there is very little health economic evidence to date. This is crucial: annual NHS spending on cancer diagnosis is approximately £1bn.(13) Observational data suggests that expedited cancer diagnosis may be clinically effective, but there is no data to examine cost-effectiveness. What work has been published has been judged to be of very poor quality, or simplistic.(14) A carefully designed clinical trial is now needed to address the following question: what is the clinical effectiveness and cost-effectiveness of

electronic decision support embedded within primary care IT systems in the early diagnosis of symptomatic cancer?

Trial aim and objectives

The overarching aim of the trial is to assess the clinical and cost effectiveness of electronic Risk Assessment Tools (eRATs) for cancer compared to usual care for patients in general practice. The specific objectives of this study are to compare the effects of eRATs (vs usual care) on: cancer staging at time of diagnosis, cost to the NHS, patient experience of care, and service delivery.

Methods

Design

The study is a pragmatic cluster RCT, supported by Exeter Clinical Trial Unit (ExeCTU). Practices will be randomised 1:1 to receive either the intervention (access to the suite of eRATs) or usual practice. The clusters will be practices (and we have a working definition of 'practice' based upon whether electronic medical records are shared or independent between 'satellite' or 'umbrella' practices), as it is unrealistic to offer eRATs to individual GPs, and even if we could there would be considerable contamination within any practice. There will also be embedded process and health economics evaluations along with a parallel study modelling the impact of eRATs on NHS service delivery. Although the intervention is implemented at the practice level, some process and resource use measures and all main trial primary and secondary outcomes relate to individual patients.

Intervention

Justification of cancer sites

RATs are available for 17 adult cancers, each varying in their incidence, ease of diagnosis, amenability to treatment and proportion presenting as an emergency. We elected to study cancer sites a) which were common; b) which by the time symptoms have occurred there remains a reasonable chance that curative treatment is possible; and c) with a significant percentage of patients presenting as an emergency. An additional consideration was the current length of the primary care interval, which our team has studied in depth. (15) Using these criteria, six cancer sites appeared particularly worthy of inclusion. These are shaded green in Table 1. This shading captures approximately half of all cancers. eRATs are available for all. Shaded orange are six comparator cancers for examining any spill over effects.

The eRATs

eRATs have been developed in partnership with Macmillan with a view to making them available to practices who host EMIS, or SystmOne principal clinical software systems. The eRATs are being developed by a specialist IT team: Informatica Systems Ltd, who will use the risk calculators developed by Hamilton and colleagues. (5, 7, 16-20) The eRATs are a medical device and Informatica Systems Ltd have performed the necessary conformity assessment (UKCA) which has been registered with the MHRA (Application reference: 2021082601213536). The eRATs will be packaged within Macmillan's electronic Clinical Decision Support (CDS) software tool. Practices will access the software via a new cloud-based software system called Skyline R1. Skyline has been designed to facilitate more simple

and efficient integration into GP clinical systems. The older host of the software, Audit+, which this trial originally sought to use, became untenable when the new NHS software framework (GP IT Futures) came into effect in early 2020. New policies effectively meant that the software was no longer freely available to GP practices. Skyline will appear on the GP IT Futures software catalogue in late 2021. However, the ERICA team have agreed to purchase directly from Informatica Systems Ltd all licences needed for the trial, so there will be no cost to GP practices and is within the study research budget (offset against savings during the pausing of the study).

As part of the Macmillan Clinical Decision Support Tool practices will also have access to the QCancer (21) cancer risk tool. QCancer is also embedded into the EMIS system. On all accounts it resides dormant, requiring manual switch on. The QCancer algorithm is not subject to investigation in this study and all participating practices will be asked to not use it during the duration of the trial.

The UKCA marking of the Skyline version of eRATs has been completed and was received by the MHRA on 26th August 2021, with the device due to be available on the market later in the year. Informatica are planning to stagger the installation in Q3/4 2021 after the piloting process in several GP practices is complete.

For the trial, the eRATs should be available first in SystmOne and EMIS. These clinical systems account for over eighty percent of the GP surgeries in England. The Macmillan suite will contain an eRAT for each of the six cancer sites that are of interest in this study – lung, colorectal, bladder, kidney, ovarian, and oesophago-gastric – plus an eRAT for pancreatic cancer, which is not being studied (see Table 1 justifying the selection of cancer sites). The six cancers cover a range of proportions currently diagnosed at an early stage, increasing the generalisability of the trial result.

The eRATs have multiple functions. The first function is the *'prompt'*. This part collates relevant Read-coded symptoms and blood tests from the previous 12 months of information in the patient's medical record, which are then assessed for the possibility of cancer using algorithms developed by Hamilton and colleagues. A risk score is generated. This is performed simultaneously for all eRATs within the suite. A prompt (pop-up), displaying the risk score(s), appears on screen when a patient has a risk of 2% or higher for at least one of the studied cancers. The second function is the *'symptom checker'*. The GP can choose to explore the possibility of cancer further during the consultation with the patient by accessing the symptom checker directly, or from the prompt. The symptom checker displays the patient demography, and relevant Read-coded and blood test result data from the previous 12 months. The relevant symptoms of each studied cancer appear as a checklist, along with the option of noting whether there has been a repeat attendance with the same symptom. This allows the GP to add symptoms: the risk of cancer is then automatically (re)calculated.

Table 1 Justification of the cancer sites

Cancer site	Ranking by incidence	Ranking by curability (22)[1]	Percentage diagnosed at stage 1 or 2(23)[2]	Percentage emergency admissions (24)	Notes
Breast	1	1	71%	5%	Although a RAT exists, breast cancer diagnosis is dominated by breast lump, and rapid diagnosis is the norm, with little gap between UK and Europe.(25)
Prostate	2	9	50%	10%	There is an easy primary care test for prostate cancer (PSA), and usage is high for men with lower urinary tract symptoms. Furthermore, there is considerable doubt of the value of early diagnosis in this cancer.
Lung	3	13	21%	39%	Very common, poor prognosis cancer. It's important we study 'difficult' cancers as well as the 'easier ones'(26)
Colorectal	4	6	40%	26%	Very common cancer, with the strongest evidence supporting early diagnosis.(4)
Oesophagus	5=	15		22%	These are generally merged as the main diagnostic test is the same
Stomach	5=	17		33%	
Melanoma	6	3		3%	No RAT exists, as the diagnosis is primarily visual
NHL	7	14		27%	This could be merged with Hodgkin's if desired as the two RATs are similar(27, 28)

[1] This paper includes some rare cancers, which is why not all rankings appear in this table.
[2] This paper only reported five cancers, explaining omissions. For these cancers missing data ranged from 10-18%, so the 'true' Stage 1 and true percentage is probably higher.

Kidney	8	4		25%	Common intra-abdominal cancer.
Larynx	9	7		6-11% across the various subtypes	This merges many cancers, and only a larynx paper RAT is available.(29)
Brain	10	17		62%	No RAT is available, and highly unlikely that expedited symptomatic diagnosis will help.
Bladder	11	5		19%	Common cancer, with moderate evidence that delay matters
Pancreas	12	18		50%	Common cancer, but currently highly unlikely that expedited symptomatic diagnosis will help.(30)
Leukaemia	13	16		25-54%	There is an easy test in primary care, and using a RAT would complicate a simple diagnostic process
Uterus	14	2		8%	Although low emergency percentage, very high on curability ranking.(30) It is dominated by a single symptom, with referral of women with post-menopausal bleeding rapid currently
Ovary	15	12	37%	32%	Relatively rare, but high profile.

The clinician may also access the symptom checker directly from the Macmillan CDS tool bar (although for this to work the GP must already think that the patient has symptoms raising some concerns of cancer and wants to use the tool as an aid to clinical judgement in deciding a course of action). On reviewing the risk score from the prompt and/or symptom checker, the GP then decides the best course of management, which may be: clinical review in primary care, the ordering of test/investigations, or referral into secondary care.

A third *'risk* stratification' function exists, which will not be encouraged. This function allows periodic audits of the entire patient list for individuals whose existing symptom patterns appear to put them above the 2% threshold. This function is unpopular with doctors due to the number of false-positives.(31) Embedded within all eRATS will be links to authoritative guidance regarding the early diagnosis of cancer, NICE NG12,(32), Macmillan's abbreviated NICE guidance(33) and Cancer Research UK guidance. (34)

Training practices in using eRATs

Training in use of the eRATs will largely be performed via a host of short, pre-recorded videos that will be available online. We expect each GP practice to nominate a practice 'research champion', who will be the main point of contact for the ERICA team. The research champion, likely to be a GP, will co-ordinate the training within the practice. There will also be system-specific walkthroughs targeted at GPs, showing them how to use the prompt and symptom checker functions of the eRATs. We will also provide a FAQs video. This video will provide more clinically pertinent information and guidance including: what an eRAT score means; informing GPs how the eRATs relate to NICE guidance; the implication of the eRATs on the number of referrals into secondary care; whether GPs are obliged to act on a risk score; the medico-legal risks of using eRATs; and whether GPs need to adjust the way they take notes.

We anticipate training to be relatively straightforward - development work (10, 11) did not raise significant concerns - but should individual GPs or practices experience problems, Informatica, trial and CRN staff will be available. The research team will also operate a 'help line' to support GPs or practice computer staff and facilitate troubleshooting. All phone calls will be logged so that we can capture helpline use. All practices will undergo a two month 'settling in' period prior to the start of data collection.

Duration of intervention

Recruitment started in August 2019 and is expected to finish December 2021, including the installation of the eRATs software. The formal start of the intervention window will be 01/01/2022 (although some practices may have delayed installation) and will close for all intervention practices on 31/12/2023.

Usual care

Patients presenting to the control practices will experience the GP's usual diagnostic approach. Usual care is being used as a comparator for this study to help determine the actual benefits above normal practice. GPs in control practices will have no specific on-screen prompt to cancer guidance though they may have access to hard-copy (e.g. paper or mouse mat) versions of the Risk Assessment Tools. Control practices that have acquired (but have never used) the Macmillan electronic CDS tool will be required to ensure the eRATs and alternative cancer risk tools remain inactive (switched off) for the duration of the trial. We will document control practice use of RATs and access to and use of eRATs via an interim questionnaire completed within the first 12 months of the trial and exit questionnaire completed at the end of the trial. As for intervention practices, trial time will formally begin for control practices on 01/01/2022 and end on 31/12/2023.

Data collection window

Outcome data for all practices will be obtained for the two-year period from 01/03/2022 to 29/02/2024. This data collection window is lagged behind the trial time window (01/01/2022 to 31/12/2023) in order to a) provide some time for practices to become accustomed to how the intervention functions prior to data collection, and b) to have a two month window following the end of the intervention window in order to capture outcome data on patients seen at the end of that window.

Sample size

There are 130,000 new diagnoses of the six included cancers in the UK annually. As each of our six cancer sites has different proportions diagnosed at an early stage, we have based the sample size calculation on a relative improvement in staging, using an odds ratio of 0.8 for a cancer being diagnosed at Stage 3/4 in the intervention arm compared to the control arm. This difference is quite large, and equates to an absolute reduction of 4.8% in the intervention arm as an incidence-weighted figure across the six cancers. A much smaller improvement would still be worth having, but would necessitate an impossibly large trial.

As this is a cluster-RCT, an inflation factor has to be added: we have used an inter-cluster correlation coefficient, based on our previous work, of 0.05. With an average cluster size of 23 patients with a diagnosed cancer with recorded stage during 2-year follow-up (i.e. a duration of 2 years of using the intervention), and a coefficient of variation for cluster size of 0.7, the design effect becomes 2.66. For an individually randomised trial with 90% power and an alpha threshold of 0.05, the sample size would be 2,049 patients per arm. Adding in the design effect, this becomes 5,497 patients, requiring 239 practices per arm, and 478 practices in total. Due to changes in practice structure (such as practice mergers, closures or divisions), we anticipate the loss of up to 10% of recruited practices over the course of the trial; to account for this loss of practices will recruit a target of 530 practices overall. Thus, we expect to recruit 530 primary care practices and anticipate an average of 23 patients per practice with a cancer diagnosis of interest with recorded stage across a two year period, leading to collection of routine data from 12,190 patients in total.

Inclusion & exclusion criteria

To be included in the trial, practices must host either EMIS, or SystmOne principal clinical systems. Only practices completing an agreement to engage with the research processes and the intervention/control arms will be eligible; in the agreement the practice will confirm that a practice meeting has taken place and at least fifty percent of their GPs have agreed to participate in the trial. A practice must also have two week wait referral rate data available. If a practice is planning to merge or restructure over the course of the trial (to the extent that the practice size will change by at least 10%) they will not be permitted to participate. See the section “Managing practice splits and mergers in analyses” for how we will handle such events that occur during the study period that were not known *a priori*.

The Covid-19 pandemic resulted in an increase in undiagnosed cancers in the community. In response to this the Department of Health and Social Care and the Cancer Alliances encouraged GPs to use

electronic tools to help identify and manage cancer. There are risk stratification and safety netting tools available. Practices who are using cancer risk tools will be eligible to take part as long as the risk tools do not automatically alert GPs to the risk of cancer. Practices using cancer risk tools with automatic alerts will not be permitted to take part in the trial due to the potential for contamination with ERICA eRATs.

Practice recruitment

A total of 530 primary care practices across England will be recruited, supported by the Clinical Research Network and strategic media releases to raise awareness of the trial. We will initially target research active practices as they typically engage in and have the necessary infrastructure to support research. If recruitment numbers need to be bolstered we will open up recruitment to non-research active practices. Practices who also have the Audit+ tool installed, but who are not using eRATs, will also be targeted.

Recruitment will take a multi-stage approach: i) an email will be sent to all practices identified by the LCRN as hosting a principal clinical system that the eRATs can operate within (i.e., EMIS, SystmOne). We expect to send emails to around two-thirds of the practices across England. We will record the number of practices approached. The email will summarise the study and will signpost the reader to the trial website to view GP information and the complementary suite of recruitment videos. The recruitment videos will provide a summary of the trial and the core activities that the practice will need to perform. Practices will be asked to register an expression of interest (EOI) and to identify a 'practice research champion' to be the primary contact for the research team. Practices can either contact the research team directly by telephone, via the research website, or via the LCRN. ii) Four weeks after sending the email, if no EOI has been received, a follow-up email will be sent. All expressions of interest and any practices declining to participate will be logged for monitoring purposes. Practices' reasons for declining to participate will be captured where possible. iii) Practices who record an expression of interest will be asked to hold a practice meeting to discuss the trial; the meeting will be led by the practice champion and supported by the research team, LCRN or Macmillan, if required. iv) Practices will complete an agreement to participate in the trial confirming the practice meeting took place and at least fifty percent of their GPs agreed to participate in the trial.

Patient recruitment

Patients are not being recruited into this trial - patient consent is not being sought for the use of the eRATs during the consultation. This is because the tools are used at the discretion of the GP to support their clinical decision making. Other randomised controlled trials of interventions in primary care have taken this approach, including the ECASS pilot trial of the Oesophago-Gastric eRAT (12, 35, 36). Practitioners will still adhere to usual clinical guidelines – the eRATs will simply prompt them to consider the possibility of cancer – the GP should manage them based on the most clinically appropriate way. To promote patient awareness of the practice's participation in the ERICA trial, posters will be displayed at all participating practices (i.e. in the intervention and control arms). A selection of patients will be recruited to the nested process evaluation and health economics studies (see below).

Randomisation

This is a pragmatic, cluster RCT. The 530 practices will be randomised using a 1:1 ratio into one of two trial arms: usual diagnostic practice (control) and usual diagnostic practice plus access to the suite of Macmillan electronic risk assessment tools (eRATs) (as the intervention), for a total of 265 practices per arm. Randomisation will be remote and web-based, conducted by an independent member of the staff at the Exeter Clinical Trials Unit, overseen by the CTU statistician (not the trial statistician). The sequence of randomisation will be computer generated. To ensure there is balance between the trial arms regarding practices' propensity to refer patients for cancer investigation, we will minimise the randomisation by age-sex standardised two week wait referral ratio (the best available proxy) in national tertiles. We will use simple randomisation to allocate the first 50 practices (~10% of the total target), and then apply minimisation by two week wait referral ratio tertile, taking into account the previous allocations to inform the minimisation algorithm. To promote allocation concealment, all allocations using the minimisation algorithm will retain a stochastic element.

Once the randomisation has been performed, the research team will inform the practice of their allocation outcome. Although this randomisation with minimisation approach should make it almost impossible for the study team to predict the trial arm allocation for practices being processed (i.e., interested and undergoing screening), to ensure allocation concealment the last ten practices to be recruited will be randomised simultaneously – i.e., we will delay randomisation until we have ten final practices signed up to the study.

Blinding

Given the nature of the interventions, it is not possible to blind GPs or the GP practice to treatment allocation. Similarly, the trial team overseeing the day-to-day management of the trial will not be blinded. The data analysis will be carried out by the trial statistician who is blind to treatment allocation and all primary outcome data are objective assessments of clinical outcome.

Outcome measures

Primary outcome

Outcome measures will be captured at patient-level, using data routinely collected or linked to by the National Cancer Registration and Analysis Service (NCRAS). The primary outcome, forming the basis of the sample size calculation, is whether a patient diagnosed with one of the six cancers during the follow-up period is diagnosed at stage 1/2 (early – cure likely) or stage 3/4 (advanced – cure not likely). This division of staging is commonly used, and is a targeted metric in the highly influential Independent Cancer Taskforce (ICT) report, is used in National Cancer Intelligence Network (NCIN) metrics, forms part of the Public Health Outcomes Framework and comprises 20% of the Quality Premium pay-for-performance measure.(37, 38) The target in the 2019 NHS Long Term Plan is for stage 1 and 2 cancers at diagnosis to comprise 75% of the total by 2028. The current UK figure is 54% (for all cancers other than non-melanoma skin cancer), and is rising by 1-2% per annum.(39) For our six cancers, the current incidence-weighted percentage at an early stage is 35% (this lower proportion further justifying the selection of these six cancers).

Secondary outcomes

A range of secondary outcomes will be examined:

- The stage at diagnosis of a further six cancers without eRATs (coloured orange in Table above) will be explored and compared between intervention and control practices. This is to investigate the possibility of a 'spill-over' effect whereby eRATs are associated with increased diagnostic activity beyond the eRAT cancers.
- Operational measures:
    i. The practice's number of patients diagnosed with the six eRAT cancers combined, and the total number of cancer cases (excluding non-melanoma skin cancer).
    ii. The number of patients investigated or referred under the two week wait system or equivalent for the six eRAT cancers combined, and in total (using waiting times data).
- Route to diagnosis (this can be identified by Routes to Diagnosis Dataset,(24) which uses Hospital Episode Statistics data). Specifically, we will investigate the cancer diagnosis via the following routes: emergency attendance, two week wait referral, GP referral, and "other". We will collect this information for each of the six eRAT cancers, and for the six comparator non-eRAT cancers.
- Two week wait performance measures (using waiting times data), for the six eRAT cancers combined (restricting the sample to patients from relevant pathways) and for all cancer referrals:
    i. Whether a patient on a two week wait pathway received a diagnosis of cancer. This will also allow reporting of "conversion rates" – the proportion of patients from each practice referred under a two week wait pathway who received a cancer diagnosis.
    ii. Whether a patient on a two week wait pathway was seen within two weeks. The Department of Health is considering reducing the number of cancer waiting time targets, and may replace the target of being seen within 14 days with receiving a diagnosis within 28 days. If this change occurs, we will assess that outcome instead. Additionally, we will explore the actual waiting time for these patients.
- Survival measures: 30-day; 1-year (these two can be identified from patient records of the cancer registry dataset). 5-year survival will also be analysed, but the main trial will report on 30 day and 1-year, with 5-year data being a subsidiary report.
- Adverse events (using data from the Diagnostic Imaging Dataset): These are expected to be few, and largely related to complications from hospital investigation such as colonoscopy. There is no mechanism for adverse events to be collected using routine data. We will, however, estimate any change in the expected number of adverse events from imaging investigations (colonoscopies, sigmoidoscopies, upper gastro-intestinal endoscopies, chest x-rays, abdominal ultrasounds, and abdominal CT scans) through investigating any change in the rate of these investigations in intervention practices relative to control practices (see data analysis section). Psychological adverse events of being labelled with 'possible cancer' are explored as a major aspect of the process evaluation. We will also report at the end of the study the number of 'false positives' – the number of individuals who were referred for investigations/tests and who did not receive a diagnosis of cancer. Like the process evaluation work, this will give an insight into the proportion of individuals potentially subjected to perceived unnecessary psychological distress as a result of GPs referrals following suspicion of possible cancer.

Data collection procedures

All primary and secondary outcome measures will be available from the cancer registry: applications for data release will be made to NCRAS. Public Health England (NCRAS) have, in principle, assigned us an in-house statistician to support the data collection process. We will be guided by NCRAS but anticipate requesting two data exports. Currently, there is approximately a 12 month time lag in availability of some of the outcome data we require. As a result, our first export will occur at the end of the trial data collection period. Our second export will occur 12 months after that. Data will not contain any personally identifiable information; we will be requesting and collecting depersonalised (pseudo-anonymised) data. The Public Health England Office for Data Release (ODR) guidelines indicate that no legal gateway (e.g., section 251 approval) will be necessary to obtain these data. For each export, data will be securely transferred in accordance with the registry's policies and placed into a database developed by Exeter CTU situated on secure computer servers. The CTU will ensure the appropriate security measures are in place to comply with ODR and other required regulatory policies.

Data analysis

All analyses will follow CONSORT guidelines for cluster-randomised and pragmatic trials. The full statistical analysis plan (SAP) will be written by the trial statistician for feedback from senior statisticians, the Chief Investigator and TMG. The SAP will then be reviewed by the TSC and their feedback incorporated. The final SAP will be approved by the TMG and TSC prior to the end of practice recruitment. The analyses will be based on all patients (as relevant) in practices recruited to the trial. As a pragmatic cluster-RCT, the eRATs will be available at all times to all GPs within practices randomised to the intervention arm. We cannot, however, ensure that all GPs within an intervention practice will utilise the eRATs consistently with regard to when they are used, and how they are used to inform patient management. GPs in the control practices will be asked not to acquire eRATs – we will monitor any acquisition that may occur via an interim and exit questionnaire – which will help us describe usual care. Analyses will take the form of mixed-effects models of a type appropriate for the outcome, and the intraclass correlation coefficient (ICC) reported for all primary and secondary outcomes.

The primary analysis, exploring the proportion of patients diagnosed with cancer who had an advanced stage at diagnosis, will take the form of a mixed-effects logistic regression with a random intercept for practice to accommodate the hierarchical nature of the data (i.e. random allocation by practice). This regression will include trial-arm as a practice-level effect, and will adjust for patient-level covariates known to be associated with stage (age, sex, quintile of the income domain from the Index of Multiple Deprivation (IMD), and cancer site)(40), and the practice-level minimisation variable (national tertile of age-sex standardised two-week wait referral ratio). We will further adjust the model at the practice-level for list size, clinical IT system used, and Care Quality Commission (CQC) overall rating, should these variables be associated with stage in preliminary analyses. The degree of change in the percentage of patients diagnosed at a late stage in intervention practices will be investigated by exploring the marginal distributions of trial arm on the risks predicted by these models.

For the secondary outcome of the stage at diagnosis of six cancers without eRATs, we will repeat the above model including data on the six non-eRAT cancers as well as the six eRAT cancers. This model will include all the variables described above, and additionally include an indicator variable for

whether the cancer site is included in the intervention and an interaction term between this variable and trial arm. From this model, we will obtain odds ratios (with 95% CIs) for i) the "spill over" effect of having the intervention on cancer sites not included in the intervention, and ii) for the relative effect of the intervention on stage for included cancer sites compared to those not included in the intervention.

Mixed-effects logistic regression models with a random intercept for practice will also be fitted for relevant secondary outcomes; whether cancer patients were diagnosed through each route to diagnosis of interest, and whether patients on a two week wait referral route were diagnosed with cancer (to assess the conversion rate) and were seen within two weeks (target success rate). These models will include trial arm as a practice-level effect, and will adjust at the patient-level for age, sex, and quintile of the IMD income domain, and at the practice-level for the minimisation variable (national tertile of age-sex standardised two-week wait referral ratio). These analyses will also adjust at the patient-level for cancer site (routes to diagnosis analyses) or for referral type (two-week wait analyses) as appropriate. The models will be further adjusted at the practice-level for list size, clinical IT system used, and CQC overall rating, should these covariates be shown to be associated with the outcome in preliminary analyses. The degree of change in intervention practices relative to control practices across these outcomes will be investigated by exploring the marginal distributions of trial arm on the risks predicted by these models.

Time-to-event secondary outcomes (length of waiting time, survival) will be analysed using mixed-effects parametric survival models with a random intercept for practice. These models will include trial-arm as a practice-level effect, and will adjust for the same patient-level factors as described above (waiting times adjusted for referral pathway rather than cancer site as above), and the practice-level minimisation variable (national tertile of age-sex standardised two week wait referral ratio). The models will be further adjusted at the practice-level for list size, clinical IT system used, and CQC overall rating, should these covariates be shown to be associated with the outcome in preliminary analyses. An appropriate distribution to model the baseline hazard will be utilised, as determined by a comparison of the Akaike Information Criteria under different distributions.(41)

For rate outcomes (number of 2-week wait referrals, cancers, and imaging investigations), we will analyse the rates per 100,000 registered patients per year by age-sex strata using mixed-effects Poisson regression models including a random intercept for practice. These models will include trial-arm as a predictor, and will adjust for the age and sex of the strata, and at the practice-level for the minimisation variable (two week wait referral ratio) and deprivation (quintile of Index of Multiple Deprivation overall score). Should the following covariates be found to be associated with the outcome, the models will be further adjusted at the practice-level for list size, clinical IT system used, CQC overall rating, and for the age and sex case-mix of practices. Case-mix will be incorporated by including variables representing proportions of practice populations in different age-sex strata (5-year age groups by sex, excluding one age group-sex stratum that can be determined once all others are known, and thus adds no information).

All the above analyses will combine data for the six eRAT cancers for each model. For outcomes related to two week wait referrals, data will be combined for all referral pathways relevant to the six eRAT cancers. To investigate whether the eRATs produce a "spill-over" effect, whereby diagnostic

activity is increased for other cancers, we will repeat all analyses using data for the six non-eRAT cancers combined for each model. Investigation of a spill-over effect for two week wait referral outcomes will use data for all referral pathways combined.

Additional sensitivity analyses will be conducted for the primary outcome in order to explore the modifying effect of practice-level characteristics, using interaction terms. Although the trial has not been powered to detect low-moderate subgroup differences, large interaction effects that differ with respect to the direction of effect across subgroups, are of interest. The potential impact of missing staging data on the primary outcome will also be explored through use of multiple imputation methods.

Managing practice splits and mergers in analyses

Although we will exclude practices that report imminent restructuring during recruitment, we recognize that given the long duration with which practices will be participating in the trial, there may be some changes in practice size which may result from unforeseen mergers or separations or which may arise due to a practice closures or expansion without formal merging. Where mergers and separations are concerned, this could mean, for example, that some of our practices who were in the control arm may merge with an intervention practice. Similarly, a non-trial practice may become part of a trial practice (intervention or control). Changes in practice size have implications on the denominator – the number of patients that each practice is likely to be contributing to our sample – and is a particular issue for three of our secondary outcome measures that are based on rates (cancer diagnosis rate, two week wait referral rate, and adverse event rate). Importantly, however, this issue is not a problem for our primary outcome of staging.

For the purposes of this study, splits and mergers will all be identified according to practice identifier codes (one letter followed by five digits). For the purposes of this trial a practice is an entity defined by its practice code. We will define a split and mergers as follows: Split – Where a population of patients registered to a single practice with a single practice code become registered with 2 or more individual practices with different practice codes. The practice codes of the new practices may be new codes (i.e. did not exist prior to the split) or one may inherit the original practice code (although this is not a requirement). Note that the change in registration of patients must occur to a substantial number of patients and not at their request. Merger – Where a population of patients registered to one or more practices with different practice codes become registered at a single individual practices with a single practice code. The practice code of the new practices may be a new code (i.e. did not exist prior to the split) or it may inherit one of the original practice codes (although this is not a requirement). Note that the change in registration of patients must occur to a substantial number of patients and not at their request. A federation is not a “merger” in these terms.

We will exclude practices known to be planning an imminent change. However, excluding those who do change during the trial may unnecessarily reduce our power. Therefore, we will try and accommodate ‘changers’. Table 2 outlines our approach. The assumption is that the change takes place at time T. Any practice which splits goes from X to Y and Z, and mergers are Z plus Y becoming X. Intervention practices are I, and comparison practices C.

Practices size fluctuations will be monitored in real time. Practice size data are freely and publicly available from NHS digital and are updated on a monthly basis. Each month during the two year data collection period, the trial statistician will download the practice size data and inspect size for all of the practices in the trial (the statistician will remain blinded to outcome allocation). If the practice size differs by more than 10% the statistician will alert the trial manager who will contact the research champion in the relevant practice to explore the reasons for this practice size change. Reasons (e.g., mergers, separations) will be recorded.

Table 2: managing changes in practice size – mergers and separations

<table>
<tr><th>Split or merger</th><th>X pre change</th><th>Y pre change</th><th>Z pre change</th><th>X post change</th><th>Y post</th><th>Z post</th></tr>
<tr><td rowspan="2">Split</td><td>I</td><td></td><td></td><td></td><td>I</td><td>I</td></tr>
<tr><td>C</td><td></td><td></td><td></td><td>C</td><td>C</td></tr>
<tr><td colspan="7">We will allow the daughter practices to withdraw from the trial if they desire, which would mean we lose Y or Z (or both). If daughter practices decide to withdraw we will include data up to time T plus 2 months to allow for average diagnostic time to cancer.</td></tr>
<tr><td rowspan="5">Merger</td><td></td><td>I</td><td>I</td><td>I</td><td></td><td></td></tr>
<tr><td></td><td>I</td><td>C</td><td>I</td><td colspan="2" rowspan="2">There is likely to be wash over under these conditions, so the merged practice will be considered as I</td></tr>
<tr><td></td><td>I</td><td>Non-trial</td><td>I</td></tr>
<tr><td></td><td>C</td><td>Non-trial</td><td>C</td><td></td><td></td></tr>
<tr><td></td><td>C</td><td>C</td><td>C</td><td colspan="2"></td></tr>
</table>

We will manage changes in practice size at the data analysis stage of the trial. Where changes in list size of more than 10% within a month are seen, data for that practice will not be included in the analysis of rate outcomes from one month prior to the drop. There are two exception to this; 1) splits where all the daughter practices remain in the trial and we continue to treat them as a single practice for rate analyses, 2) mergers where merged practices are in the same arm of the trial and we will analyse them as a single practice from the start for rate analyses.

Nested Studies

Health Economics

Scope of Health Economics

We will estimate the cost and cost-effectiveness of the eRATs versus usual diagnostic practice using the primary perspective of the NHS and Personal Social Services (i.e. third-party payer). We will estimate the cost-effectiveness of the ERICA intervention based upon the primary outcome (the proportion of the combined six cancers diagnosed during 2-year follow-up that were at Stage 1/2 (early – cure likely) at diagnosis versus Stage 3/4, clustered by GP practice) and secondary outcome (30 day and one-year survival; 5-year survival will be a subsidiary report) for the six cancer sites that are the focus of the main statistical analysis.

For three of these cancer sites we will also estimate the cost per quality-adjusted life-years (QALY) over the longer term. The three cancer sites have been chosen *a priori* to represent the impact of ERICA on cancers with: a) a short diagnostic interval diagnostic interval (i.e. colorectal cancer, median diagnostic interval 31 to ≤60 days), b) medium diagnostic interval (i.e. bladder, median diagnostic

interval 61 to ≤91 days) c) long diagnostic intervals (i.e. lung, median diagnostic interval 91 to ≤120 days).(42) The framework for estimating the cost per quality-adjusted life-years (QALY) over the long term for the ERICA intervention will be based on the evidence synthesis and the development and subsequent use of decision analytic models to predict the future costs and benefits associated with an expected between-group difference in the ERICA RCT stage of diagnosis in the three cancer sites. The decision analytic models will combine data from the within-trial analysis of ERICA intervention on costs and benefits, with longer estimates derived from the evidence synthesis of the costs and benefits of stage of diagnosis and disease progression to estimate the cost per QALY over the longer term.

Method

Intervention costings- The resources used for training and delivering the ERICA intervention (preparation, delivery, travel time) will be collected from the research champions and the trial manager; nationally applicable unit costs will be applied (see process evaluation section for how we will collect data from the research champions). The results from this trial-based analysis will be presented in a disaggregated form, by the main cost drivers.

Health related quality of life and resource use- To investigate whether the eRATs intervention was associated with a change in health-related quality of life using the EQ5D-5L, we plan to sample patients in the intervention arm who had a consultation where an eRAT alert occurred, and also patients in the control arm who had a consultation where an eRAT alert would have occurred. We will strategically target practices in both trial arms who have either high, medium, or low two week wait referral rates. Practices located in the South/South West of England will be approached if possible. The eRATs have a reporting mechanism that captures who the eRAT(s) were triggered on. We will ask intervention practices to switch this mechanism on for a 2-week period. We will ask practices in the control arm to run a pre-prepared search to identify patients whose consultation would have triggered an eRAT alert. Intervention practices may also be asked to complete this search if the reporting mechanism fails. It is anticipated that 15-20 patients per practice over a 2-week period will have a consultation with an eRAT alert. All patients who have an eRAT alert will be invited to complete the EQ5D-5L questionnaire, as will equivalent patients in the control arm. We anticipate that 40% of patients will accept, and of these there will be 20% who do not respond. Using a conservative figure of 15 patients per practice, we anticipate a cluster size of 5 patients responding to the questionnaire. Using an MCID of 0.1 for the EQ5D-5L (43) and a standard deviation of 0.23(44), with an ICC of 0.03 (45), we calculated the sample size required to detect a between group difference with 90% power and alpha of 0.05. We used a range of values for the coefficient of variation (CV) of cluster size: 0, 0.5 and 0.7. With a CV of 0.7 we would require 28 clusters (140 participants) per arm.

Via the GP practice, the research team will send out: a letter to invite patients to take part in the health economics nested study, a patient information sheet, a consent form, a blank contact details sheet also requesting patients date of birth (to allow easy identification in the GP practice clinical system), and a pre-paid envelope to return the completed forms. Patients will be asked if they will give permission:

- To a review of their medical records, or
- To a review of their medical records and agree to complete a health economics questionnaire at baseline and 3 months

Participants will be asked to send their completed consent form and contact details sheet directly to the research team in the pre-paid envelope. Participants who agree to both the medical records review and completion of the questionnaires will be sent a baseline quality of life questionnaire to complete at home, a letter thanking them for agreeing to participate, and a pre-paid envelope for returning the questionnaire. We will send the questionnaire as a hard copy, through the post, or electronically via email, depending on the participant's preference. This baseline questionnaire will be sent to the participant within two weeks of receiving their completed consent form. For those who return the baseline questionnaire, we will send the follow-up questionnaire 3 months after the baseline questionnaire was sent. The follow up questionnaire will contain questions on resource use and the follow up quality of life questions.

The health-related quality of life questionnaire (EQ-5D 5L) explores the impact of the diagnostic phase on quality of life. Nationally applicable unit costs will be used for all community health and social care contacts (46) and secondary care services, tests and investigations will be costed using the National Schedule of Reference Costs 2016-2017 (47).

A member of the research team, with the necessary letters of access/research passport will visit the practice to complete the medical records review for all participants who have given permission. Participant's records will be reviewed only from the date in which the eRAT was triggered (or would have been triggered in control practices), for 60 days after the index date. To minimise response burden the medical records will identify the majority of service usage including recording the use of primary care services (nurse and GP contacts), intermediate care referrals and tests and secondary care and other unscheduled primary or community care (out-of-hours services and walk-in centres) and A&E appointments. The resource use questionnaire will collect scans/tests that are not well captured by the medical records (based on data collection forms from DIRUM (www.dirum.org).

Stage of diagnosis - Data on the effectiveness of interventions at a practice level on stage of diagnosis 1-2 versus 3-4 will be from the National Cancer Registration and analysis service (http://www.ncras.nhs.uk/, Public Health England).

Analytical Methods

Within-Trial Analysis

The within-trial analyses will estimate the costs and benefits of the ERICA intervention over the duration of the trial compared to usual diagnostic practice. The within trial analysis will assess the impact of the ERICA intervention on each of the six cancer sites separately to address the question of whether cancers with short medium or long diagnostic intervals are more likely affected by the intervention.

For each of the six cancer sites we will calculate the between-group differences within the control and intervention practices in the proportion of patients diagnosed with cancer who had a late stage at diagnosis (Stage 3/4) and their costs. A regression model will be used to adjust for systematic differences between intervention and control arms that have not been accounted for by randomisation. The regression model will also be used to isolate the impact of the intervention on

outcomes and costs. The regression analysis will take the form of a mixed-effects logistic regression with a random intercept for practice to accommodate the hierarchical nature of the data (i.e. random allocation by practice). This regression will adjust for patient-level covariates (age, sex, deprivation, and cancer site) and practice-level minimisation variables and covariates available for all practices (list size) shown to differ in descriptive analyses. Sensitivity analyses will also adjust for practices national tertile of age-sex standardised two week wait referral ratio.

The same mixed-effects logistic regression model structure described above will be fitted for the one year survival data and the costs within the control and intervention practices for each of the six cancer sites separately.

Decision Analytic Model

Data from the within-trial analysis will be combined with predictions of the longer term costs and benefits using decision-analytic models to predict the future costs and benefits associated with the expected between-group difference in the ERICA RCT primary outcome measure, for the cancer sites that are the focus of this analysis: bladder/oesophago-gastric, colorectal and lung.

The decision-analytic models will examine the question of the longer term effectiveness and cost-effectiveness of the ERICA intervention versus usual care following good practice modelling guidance (48, 49). The model development process will be informed by a systematic review of the cost effectiveness models used to extrapolate stage of diagnosis outcomes and guided by the need to extrapolate from effectiveness data derived from the ERICA trial (at 3 month follow-up) over a longer-term and policy-relevant time horizon. That is, the modelling aims to predict the expected impact of a change in stage of diagnosis, and any resulting change in the distribution of cancer stage at diagnosis (intervention vs. control) over time, building on the published literature in this area,(50, 51) and using stage at diagnosis health events of primary importance (when there is robust evidence of the relationship between incidence of events and stage of diagnosis, applicable to a general population analysis). The decision analytic models will not need to separately model the diagnostic phase, and we will take the trial's primary outcomes, stage at diagnosis (Stage 1-4 separately and not summed into Stage 1-2 and Stage 3-4), to model the longer term effects on survival, QALYs and secondary care costs.

Scenario analysis will be used to examine the impact on the results of multiple parameters changing simultaneously (based on *a priori* judgement about the combination of parameters to include).(52) Probabilistic sensitivity analysis will be used to explore the proportion of results that are considered cost-effective in relation to a given cost-effectiveness threshold and these results will be illustrated graphically using a cost-effectiveness acceptability curve.(53)

The study will follow the CHEERs guidelines for reporting cost-effectiveness studies and models,(54) and will discount both costs and outcomes at 3.5% as recommended by the National Institute of Health and Care Excellence.(55)

We will run sensitivity analyses to consider alternative assumptions about the missing data mechanisms.(56)

Service Evaluation

We will draw upon published systematic reviews of Quality of Life measures, that are based on public preferences and measured in patients (as required by NICE guidelines (57) and that have been used for economic evaluation modelling studies.(58)

Service Delivery Modelling

Background and rationale

Cancer diagnosis has become one of the principal areas of focus and concern for the NHS in England.(3) For some time, NHS performance in both early diagnosis, delays in referral, and associated survival rates has been poor relative to our national aspirations and when compared with other first world countries.

In this context, many of the issues of concern are centred on key aspects of service delivery. How the NHS organises its services is often pivotal in determining the cost, feasibility, and effectiveness. For instance, factors such as workforce availability, prioritisation, service location, scale, and resources are fundamental to the performance of the NHS in delivering effective cancer services.

This component of the ERICA project will investigate the key factors central to the organisation of NHS diagnostic services for cancer referrals. We will use a range of methods, both quantitative and qualitative, to analyse service delivery alternatives. Specifically, we will aim to build an economic model to assess the likely implications of different scenarios.

Implementation of the eRAT diagnostic tool at primary care level is likely to impact directly on the follow-on pathway for cancer diagnosis (for example in terms of the volume and case mix of referred patients for diagnosis). Our model will therefore provide an assessment of the likely effect of this impact in terms of costs and performance, and highlight any changes in organisation that might be implied by the introduction of the eRAT tool.

This research will run in parallel with the substantive work conducted for the controlled trial of eRAT implementation within ERICA. It will also liaise closely with the detailed and standard analysis of cost-effectiveness for disease progression (which is inherently abstracted from the service delivery aspects of care) in order to provide an added dimension to the cost-effectiveness outputs from the ERICA study as a whole.

Objectives

To build and populate a model of the cancer diagnostic pathway for England, in order to provide an assessment of the costs and effectiveness of different scenarios for service delivery. In particular, we will investigate the potential aspects relative to implementation of eRATs based on the study data collected from the ERICA trial. In addition, qualitative research with NHS staff in secondary care will be used to assess key areas central to successful implementation and sustainability.

Methods

A wide range of methods will be essential to fulfil the objectives of the work outlined here. Early work will include a literature search and survey of current systems for diagnostics in cancer. We will therefore conduct a systematic review of the related literature in the field and carry out a survey of current service delivery organisation across a range of settings. This work will aim to identify the key

factors bearing on the organisation of services such a regional variation, metropolitan versus rural context, and population case mix differences.

Phase two work will aim to build a model in order to capture the key elements of service delivery for diagnostic services for cancer. This will explore a range of modelling approaches and test which is most suited to specific needs. For example, discrete event simulation, Systems Dynamics, geographic analysis, and Markov modelling will all be tested in terms of their relevance and appropriateness to specific requirements. In this context it is highly likely that different modelling tools will be relevant to the diverse needs of the study, so no single approach will be dominant.

Phase three of the study will focus on the service delivery implications for the introduction of the eRAT diagnostic tool in primary care looking particularly at the potential knock-on effects in other areas of service.

In addition to our modelling work, we aim to use qualitative methods, such as problem structuring methods, soft systems mapping, and semi-structured interviews to provide an assessment of some key elements of implementation. Using our established contacts, we will aim to complete up to 40 semi-structured interviews with NHS staff involved across the range of relevant roles with the delivery of diagnostic services. This will aim to provide an assessment of key elements of implementation and inform the recommendation for service delivery as part of the outputs. Staff will be given the option of a face-to-face (if safe to do so) or telephone interview.

Data

A wide range of data will be used to complete this component of the work. We will aim to integrate sources from across routinely collected datasets such as those listed below to construct our models: NHS activity data, Waiting time data, Reference cost data, Diagnostic Imaging Data (DIDs), Hospital Episode Statistics (HES), Workforce reference data, GP and hospital referral data, QOF data, Population data (e.g. ONS). In addition, we will aim to incorporate the primary data derived from the main ERICA study in order to model and assess the pathway impact from the use of eRATs. We will also use the outputs from the standard economic analysis as an input for the cost effectiveness of the service delivery modelling. Output from the qualitative research will also provide important data for informing the outputs of this work, for example in feeding into the recommendations and conclusions of the study.

Process Evaluation

Scope of process evaluation

The process evaluation work aims to identify and investigate the contextual factors that impact upon the effectiveness of the eRATs with a particular focus on intervention fidelity and GP engagement. The impact of the eRATs on the patients' experience of their GP consultation and their experiences of subsequent care will also be explored. Underpinned by the COM-B framework for understanding behaviour change (59). This framework will outline the interactive nature of how the GP's capability (IT skill for using the eRATs), opportunity (eRAT prompts), and motivation (to do the training and use all the eRAT features) might influence their behaviour – i.e., ongoing use of the eRATs, symptom checker, coding of symptoms and changes to referral letters). We will use a mixed-methods approach to explore how the intervention was delivered (including fidelity and dose - if the eRATs were being

used as intended and their degree of use across intervention practices and over time) and GP engagement with and acceptability of using the eRATs (GP's experiences of the eRATs).(60) For delivery, we will be particularly interested in fidelity of function. (61) GPs will be given clear training videos on how to use the eRATs and we will explore the extent to which GPs engaged with training as well as how they subsequently engaged with the software, and the GP's experiences of how it impacted on the GP-patient relationship in order to evaluate how they responded to the intervention.

Methods

Intervention fidelity and GP engagement (intervention arm only): Prior to the start of the intervention GPs will require a minimum level of training in how to use the eRATs. Although the software is designed to be intuitive, a clinical system specific walkthrough for the two main functions of the eRATs (prompt and symptom checker) and FAQs will be available via separate videos on a trial-linked webpage. The research champion will be required to sign-in to the web-page video hub to watch these videos and should disseminate the video content to all GPs in the practice (by showing the videos during a practice meeting or providing a demonstration themselves). After watching the videos, the research champion will be offered a short on-line quiz testing their understanding of how to use the eRATs. Their anonymised quiz responses will be electronically and securely sent to the research team. Once practices have started the data collection phase, we will invite up to 10 research champions to interview to discuss in depth their experiences of the set-up and training procedures and to explore whether their GPs have the capability, opportunity and motivation to use the eRATs. We will purposively sample research champions based on whether they are from a practice with a high, middle or low two week wait referral rate, their gender, and their level of experience in practice (10+ years vs. less than 10 years in practice).

Detailed eRAT usage can be captured for all IT systems. Usage will be captured in two ways – i) via a central log and ii) via local 'at practice' reports. For i), usage logs will be routinely and automatically sent from the practice to the Informatica 'digital warehouse' and will contain anonymised, practice-level data for each eRAT including reports of: how many times the prompt was shown, how many times the symptom checker was used, the number of times the symptoms were changed during use of the symptom checker, the length of time the symptom checker was open for, and whether clinical guidance was accessed from the eRAT. These centrally reported logs will be available on a monthly basis throughout the course of the trial and will be securely sent from Informatica to the research team who will add the data to the trial database.

Usage will also be examined via reports run locally at each practice. These reports include individual patient level data outlining which eRAT was triggered, the patient's risk score on the eRAT, when the symptom checker was opened and closed, patient's age and sex, and a list of possible eRAT symptoms and whether they were changed. These reports contain depersonalised (pseudo-anonymised) data.As it is possible to potentially identify the patient via the practice ID number we will ask practices to make a copy of the report, add in a new patient study ID variable (e.g., p1, p2, p3, etc) and save it to the practice computer. We will then ask them to send a copy to the trial tram with the original practice ID number removed. They will also send the file with a predetermined practice ID number. These measures should ensure the data is anonymised. The local at practice reports will be securely and electronically transferred to a secure Exeter CTU computer.

For identifying GPs to interview we will use maximum variation purposive sampling (sampling on practice two week wait referral rate (high vs. medium vs. low); gender, length of time in practice (10+years vs. < 10 years), and working status (part time vs full time)) and expect to interview up to 18 GPs from intervention practices to ask them about their experience of the eRATs including the training provided. We will invite GPs to interview after the intervention has been running for at least 3 months. Written information will be provided about the interview study and written consent will be taken prior to the interview, and will be verbally confirmed before the interview commences. Interviews will be audio-recorded and carried out by telephone, face-to-face (only if it is safe to do so), or over the internet (e.g., Zoom or MS Teams) depending on the GPs preference, by members of the research team using a pre-defined topic guide that focuses on their training and capability to use eRATs, their opportunity to use the eRATS over the study period and their motivation to continue using the system. If a face-to-face interview is chosen (and safe to perform), interviews will take place in a private room at the practice. The researcher will comply with the lone worker policy, ensuring that have a 'buddy' within the research team monitoring their activities and whereabouts. The interviews may raise sensitive issues such as workload and GP overburden or burnout and the interview study information sheet will provide appropriate sources for accessing confidential support. GPs will be reminded that they have the right to not answer any question, stop the interview or withdraw from the interview study.

GP coding behaviour: It is possible that the eRATs will impact GP coding behaviour - GP coding behaviour for cancer specific symptoms may increase; this would cause a minor increase in triggering of eRATs. We will capture the impact of eRATs on coding rates. We will purposively sample 12 intervention practices and 12 control practices in the South/South West of England based on two week wait referral rate (i.e., 4 low, 4 moderate, 4 high referring practices). In the first instance we will invite practices who are participating in the nested study to support this work. If insufficient numbers agree, we will approach other practices who are not participating in the nested studies. We will explore the rate of coding of the most frequent symptom for each eRAT cancer in the study that underpins that particular cancer (e.g. cough, abdominal pain, haematuria)(16, 18-20) for a month in the first three months of entry into ERICA, and for the same calendar month a year and two years later (as some symptoms have seasonal variation). This will be performed retrospectively, by the search code being given to the research champion, who will arrange for the search to be conducted in the practice. The results of the search will be emailed to the research team.

Patient experience of care: We will adopt a phased, targeted recruitment strategy with an aim to purposively sample up to (based on two week rate referral rate (low vs. medium vs. high); gender, age (40-60 vs. 60+)) 16 patients from each trial arm (n= 32 in total). We will approach five practices at a time (and expect to recruit around 5-10 practices from each trial arm to reach the target number of participants), to ensure that we can interview participants in a timely manner.

The in-practice eRAT reports are the mechanism by which we will be able to identify individuals to invite to participate in the activities associated with both the process evaluation and health economics evaluation nested studies. The local (at practice) reporting mechanism will allow the research team to identify individuals for whom the eRATs were used and thus who are potentially eligible to participate in a semi-structured interview. We will run searches in the control practices to identify patients for

whom an eRAT would have fired should they have been in operation. Purposive sampling will take place – practices will hold the master eRAT report containing both the patients practice ID number and the new patient study ID. The research team will let the practice know the patient study IDs for those whom an invitation letter will be sent.

Via the GP practice, the research team will send out a letter and information booklet to the identified patients to invite participation in an interview to discuss their experience of care. We will adopt a longitudinal case study design (62) – patients' care pathways will differ, some will receive referrals into secondary care for investigations and tests, while some will be on a 'watch and wait' plan, revisiting their GP at an agreed interval. Some patients will have tests for cancer and the test will indicate that there is no cancer (false positives) whereas some patients will be diagnosed with cancer. So that we can fully capture all patient groups at different stages of their care, individuals will be invited for repeat interviews at regular intervals (i.e., at least one month apart and no more than 3 interviews within 12 months).

We aim to perform the first interview within one month of the consultation in which an eRAT was triggered (or would have been triggered, for control participants). Written information about the interview study will have been provided and written informed consent will be taken prior to all interviews, and will be verbally confirmed before the interview commences. Interviews will be audio-recorded and carried out by members of the research team using pre-defined topic guides. The initial interview will be conducted face-to-face at the participant's home or via video conferencing software such as MS Teams at a time convenient for the participant, with any subsequent interview conducted either face-to-face, over the phone, or via video conference software, depending upon the participant's preference. We will monitor the progression of the Covid-19 pandemic and fully adhere to government advice around social distancing and travel. We will not put the research team or participants at risk and will primarily conduct interviews online. If it is safe to conduct face-to-face interviews, the researcher will comply with the lone worker policy, ensuring that have a 'buddy' within the research team monitoring their activities, whereabouts and expected completion time. The interviews may raise anxiety or concerns related to uncertainty about diagnosis during the referral and investigation period or the watch and wait period; or psychological distress associated with a cancer diagnosis or a false-positive result. The interview study information sheet will provide appropriate sources for accessing confidential support and patients will be reminded that they have the right to not answer any question, stop the interview or withdraw from the interview study.

A note on practice recruitment to the nested studies: We expect to recruit up to 76 practices across the nested studies (56 in the health economics nested study and up to 20 in the process evaluation) practices across the nested studies (38 practices per trial arm). Practices will only be asked to help with either the health economic nested study or the process evaluation nested study – not both.

Analysis

For the quantitative results the individual data sources will be summarised descriptively, including a summary of data completeness. For the qualitative data we will adopt a framework approach (63) which allows the inclusion of key concepts and ideas identified from the literature, alongside themes emerging from the data. The framework approach produces a structured output matrix, with cells of data organised by practice and by code (a descriptive label applied to a section of transcript).

At least two researchers will work on the analysis. Interviews will be audio recorded, transcribed and anonymised. Data familiarisation will be achieved through the listening to and reading of interview recordings and transcripts. Transcripts will be imported into the qualitative data analysis software package NVivo 11 (QSR International) to facilitate data management, sharing and development of a coding framework. A proportion of the interview transcripts will be coded by each researcher. The 'constant comparative method' (64) will be utilised: each incident in the data will be compared with other incidents for similarities and differences and any 'negative cases', where a case does not fit the pattern or cannot be explained by the emerging analysis, will be explored and recorded. Following this initial coding, a PPI meeting (one for the GP interviews and one for the patient interviews) will be held to discuss the emerging themes from the interviews, and to gain alternative perspectives from the PPI group on those themes. Following the PPI meeting, the analytical framework will be developed, incorporating researcher and PPI perspectives on the results, with a final set of themes and codes being agreed upon.

The analytical framework will be applied to all interview transcripts; one researcher will index all transcripts, with a second researcher indexing a proportion, to check the reliability of the indexing and to ensure that the themes of the framework are being interpreted consistently. Any differences in interpretation will be discussed between the two researchers. Following the indexing process, data will be charted into the structured output matrix, which will summarise the data on each theme from all transcripts. A subsequent meeting of the PPI group will be held once all of the results from the process evaluation have been gathered to gain a users' perspective of the global findings.

The final step in the process evaluation analysis will be to integrate results from the various mixed method data sources using a triangulation protocol(65) to give a more complete picture once individual data sources have been individually analysed. We plan to create a summary matrix, known as a convergence coding matrix, which summarises the findings from each data source after assessing whether the findings are in agreement, partial agreement or no agreement, or whether the data source is silent for the finding under consideration i.e. when a theme or finding arises from one data set but not another.

Foreseen difficulties

1. *Practice Recruitment*: This is a very large trial, albeit one which requires very little active participation (in that once the software is activated there is minimal additional work for GPs). Furthermore, data collection is done without practice input. Recruitment may nonetheless be difficult. This concern is mitigated via using the CRN and targeting practices within the research incentive scheme. Providing remote access to recruitment, FAQ videos, a trial helpline and website should extend our reach across England and facilitate recruitment.

2. *Development of* eRATs: As a result of the changes to the NHS buying catalogue framework and recognising that developments were needed to improve software integration, Informatica Systems

Ltd have created a new cloud-based version of the eRATs. This is a complete rebuild of their infrastructure and the eRATs within tight timelines. At time of writing, development of the Informatica system is on target for delivery in Q4 2021. A slippage would impact our trial delivery timelines. The new cloud-based version of eRATs has significant advantages over their predecessors – which requires less NHS IT supplier support for integration and can largely be managed remotely by the software developers.

3. *Patient level recruitment for the nested studies*: Individual patient recruitment may be difficult. Patients will be identified via the reports generated from the practices' eRAT log files. These log files will be 'switched on' for a limited period of time owing to their potentially heavy processing demands which may impact the practice computer system. We do not know *a priori* how many patients the eRAT prompts will trigger for during this period. If it is very few, we may have a very limited sample to invite to interview, and to request access to medical records. We may need to ask practices to turn on the log files for longer, or we may need to increase our sample of practices to run the nested studies in. If the reporting function does not work, we will ask practices to run practice database searches that would identify patients for who the eRATs would have fired (as we will be doing in the control arm of practices to identify patients).

4. *Contamination in the control arm:* It is possible that the Department of Health or some CCGs or LHBs decide that all practices under their jurisdiction should have access to eRATs. Similarly, Macmillan (or another cancer charity) may want to strategically promote the use of the eRATs during the duration of the trial. We will aim to maximise the visibility of the trial amongst cancer charities and communicate the importance of trial conditions – testing the effectiveness of the eRATs before there is any promotion of their uptake. Macmillan and Cancer Research UK are key partners and are supportive of the trial.

We will not be able to stop CCGs providing access to eRATs. Under such circumstances practices in the control arm of the study could have access to eRATs and use them if they so desired. We will strongly discourage control practices from using eRATs, outlining our request in the practice agreement, and will monitor usage via an 'interim questionnaire' and an end of trial 'exit questionnaire'.

In late 2020 the Department of Health and Cancer Alliances have introduced policy encouraging GPs to use cancer tools to aid early diagnosis. Some of these tools include electronic risk tools. We have clarified our inclusion/exclusion criteria to indicate that GPs are eligible to use complementary risk tools – however any risk tools that automatically alert GPs to the risk of cancer. (e.g. QCancer) would make the practice unsuitable for participation in ERICA and they would need to withdraw.

5. *The Covid-19 pandemic:* Trial recruitment was paused in March 2020 and restarted in October 2020. The delay has impacted timelines and finances. However, the Furlough scheme and budgeted financial contingencies have ensured that the trial can be delivered within budget. There still remain uncertainties around the pandemic. It could further negatively impact the trial if 1) there is a further national lockdown that impact GPs resources to deliver care and participate in the trial. We see this

as a small risk given that substantive work has already taken place within the NHS to support GP remote working. 2) Many GPs started delivering the vaccine from Dec 2020. This may impact on resource to also support research activities. Given that there is no data collection required within practice we also see this as low risk to study continuity. However, it is more likely to impact on a practice's capacity to sign up to/ and set-up the trial and may impact recruitment slightly.

Patient and Public Involvement

Our Patient and Public Involvement (PPI) group, including cancer survivors, have been consulted widely during the development of this study. The PPI group have reviewed and commented on the protocol and supported the development of all patient-facing materials including information sheets and study lay summaries. One experienced PPI representative sits on the Trial Management Group (TMG), and another will join the Trial Steering Committee (TSC). A total of seven people have joined our PPI group for this study and will contribute by reviewing study materials and documentation, commenting upon and proof reading reports and contributing to dissemination activities. This group will be supported in their work by Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC) PPI team, for example by attending workshops on critical appraisal skills. All PPI representatives will be recompensed for their time given to the study.

Study timeline

The study timeline was impacted by the COVID-19 pandemic. In line with guidance from HRA, the trial sponsor and requests from General Practice colleagues, trial recruitment was paused in March 2020. It restarted in October 2020. The broad timetable for the research can be seen in Figure 1: Ethics and governance approvals will take place in months 1-4 (preparatory work has begun prior to the start of the trial trial): Practice recruitment, randomisation and training of intervention practices will happen during months 8-36: Data collection will take place across months 39-62. Data availability from the English registry currently runs about 9 months year behind real time activity. As a result, exports capturing 1 year and 2 years of data collection will respectively be received in month 51 and 75. Analysis of the primary and secondary outcomes (and linkages with the process evaluation and health economics evaluation studies) will take place between months -74-81, and the study write-up will be performed between months 75and 84 (though in reality some components of the trial - e.g., literature reviews and design - will be written up earlier than this). Dissemination activities for the main trial findings will be performed between months 81-84. The Health economics arm will run in between months 40-78, the service delivery modelling arm between months 40-78-, and the process evaluation nested arm will run between months 40-78 -.

Figure 1: Gantt chart showing key study activities – COVID-19 adjusted

Year: 2019	**Month**	1	2	3	4	5	6	7	8	9	10	11	12
		Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation													
Health Economics Evaluation													
Service Delivery Modelling													
Main Trial Data Analysis													
Write up													
Dissemination													

Year: 2020	**Month**	13	14	15	16	17	18	19	20	21	22	23	24
		Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training				Trial Recruitment Paused Due to COVID-19									
Data Collection													
NCRAS Data Export													
Process Evaluation													
Health Economics Evaluation													
Service Delivery Modelling													
Main data analysis													
Write up													
Dissemination													

Year: 2021	**Month**	25	26	27	28	29	30	31	32	33	34	35	36
		Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation													
Health Economics Evaluation													
Service Delivery Modelling													
Main data analysis													
Write up													
Dissemination													

Year: 2022	**Month**	37	38	39	40	41	42	43	44	45	46	47	48
		Jan-22	Feb-22	Mar-22	Apr-22	May-22	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation													
Health Economics Evaluation													
Service Delivery Modelling													
Main data analysis													
Write up													
Dissemination													

Year: 2023	**Month**	49	50	51	52	53	54	55	56	57	58	59	60
		Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	Oct-23	Nov-23	Dec-23
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation													
Health Economics Evaluation													
Service Delivery Modelling													
Main data analysis													
Write up													
Dissemination													

Year: 2024	**Month**	61	62	63	64	65	66	67	68	69	70	71	72
		Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24	Nov-24	Dec-24
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation (PE)													
Health Economics Evaluation (HEE)													
Service Delivery Modelling													
Data analysis (incl PE & HEE)													
Write up													
Dissemination													

Year: 2025	**Month**	73	74	75	76	77	78	79	80	81	82	83	84
		Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25
Activity Summary													
Ethics and Governance Approvals													
Practice Recruitment, Randomisation & Training													
Data Collection													
NCRAS Data Export													
Process Evaluation (PE)													
Health Economics Evaluation (HEE)													
Service Delivery Modelling													
Data analysis (incl PE & HEE)													
Write up													
Dissemination													

Governance and ethical considerations

Drafts of the trial protocol have been reviewed by the Southwest Research Design Service and the CRN. The trial is registered with ISRCTN: (trial no: ISRCTN22560297). This is a University of Exeter-sponsored research study, working in collaboration with Macmillan, and the English CRNs.

Ethics approval

We will be applying for Health Research Authority REC and HRA approval, with subsequent capacity and capability approvals. The study will be conducted in accordance with the principles of the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines (66) and the UK Policy Framework for Health and Social Care.(67) Any amendments to the trial documents will be approved by the sponsor before submission to the HRA. The University of Exeter will cover its legal liability for injury or illness caused to a participant of the trial caused by the University or University members of staff's negligence.

It is unclear whether access to the suite of eRATs will increase investigations and referrals. This is one possibility. However, another possibility is that the number of referrals will not necessarily increase but the quality of referrals will – the eRATs may increase the number of appropriate referrals while simultaneously reducing inappropriate referrals. Referral and conversion rates will be evaluated as part of the study. These will be for both eRAT-specific cancers and for the practice as a whole. As an example, if eRATs facilitated 'better' referrals without an increase in total referrals, then the conversion rate would rise.

As a result of being referred for tests or investigations there is a risk of an adverse incident. If referral rates do increase as a result of access to eRATs, there is an increased risk of an AE to patients of practices allocated to the intervention. We are not routinely tracking individuals throughout the trial and there is no mechanism for monitoring any AEs as a result of referral.

Psychological distress may be a consequence of referral. Individuals for whom cancer is diagnosed at an early stage may be relieved by the diagnosis and see the psychological distress as justifiable. Individuals for whom a referral does not lead to a diagnosis of cancer (false positives) may have undergone unnecessary psychological distress. Our process evaluation work will help us to understand the extent of this and its potential impact on the individuals' life.

During interviews, patients may report being distressed – either as a result of research activity or as a result of their health, and events in their private lives. Should such a situation arise, the researchers will implement the trial risk protocol and manage the participant in accordance with this policy. Participants will be reminded that they have the right to not answer any question, stop the interview or withdraw from the interview study. Under high-risk situations (e.g., where there is perceived immediate risk to a participant's health), the study team may be required to break confidentiality, to inform appropriate authorities who will need to provide essential care services. We will also signpost participants to sources of support. This information will be outlined in the Participant Information Sheet. Participants will be informed of possible benefits and known risks of participation in the

interviews by means of a Patient Information Sheet and through discussion with the research team. Written consent will be obtained immediately prior to the interview study.

There are minimal risks to researchers as most interviews will take place in the GP practices or by telephone/online; however, if a home visit is undertaken to interview patient participants the researcher will follow the lone worker policy: researchers will make sure that their whereabouts, contact telephone number and estimated time of return are known to their colleagues and/or manager. Researchers will also have the opportunity to debrief with a senior colleague on the research team should they need any support after conducting an interview; this debrief may be in person or by telephone.

Data management

Cancer registry data (NCRAS) will be managed and prepared by the registry themselves and securely, electronically transferred to the study team. There will be no patient identifiable data within these datasets. Data from NCRAS will be stored on the Secure Data Resource Hub at Exeter University (which meets requirements for secure storage of sensitive data) and linked to existing practice data held within the CTU's Redcap database. The data will be stored and retained in accordance with registry policies.

Informatica Systems Ltd have developed a separate agreement ('Data processing deed') for intervention practices which will be used between the GP practices and Informatica Systems Ltd. The deed was necessary because the development of Skyline has impacted on the processing arrangements for the eRATs software that is used. The ERICA research study will still use the Organisation Information Document which outlines the research teams data processing requirements, to be signed between the practice and Sponsor.

All study data will be kept for 10 years (unless data registry policy requires otherwise) under secure conditions on University of Exeter secure servers. Data will also be subject to standard secure storage and usage policies. Data will be collected and retained in accordance with the UKGDPR 2018, and the Data Protection Act 2018,(68) and managed in accordance with the trial-specific standard operating procedure for data management.

In the recruitment of NHS staff and patients for interviews or permission for access to medical notes, participant details will be passed between NHS services and the research team by telephone, post or secure email transfer (e.g., encrypted word document or NHS to NHS email account) following permission from participants. All participants agreeing to interview and/or medical notes review, and all GPs agreeing to interview will be allocated a unique study ID, and the information linking their ID to their personal details will be kept securely at the University of Exeter. All other participant-related paper records will be anonymised and stored separately from the personal information. The electronic database for the trial will be stored on the secure servers of the University of Exeter with password-controlled access provided for the research team by ExeCTU. Single data entry with extensive in-built validity checks will be used to reduce the risk of transcription errors. The study database will include prompts for missing data, and warnings to alert staff when values are entered that are outside of the

expected range, or if the type of value entered is incorrect (for example, a numeric value entered rather than text).

Audio recordings will be digitised, encrypted and stored on the University's secure server. Audio recordings will be retained until after anonymised transcripts have been finalised and analysed. At this stage they will be securely and permanently deleted. Access to personal data will be restricted to the research team. Names and participant details will not be passed to any third parties and no named individuals will be included in the write up of the results. All participants (patients, NHS staff) will be asked for their consent for the study team to retain interview transcripts for the purposes of future research by those involved directly in the study team or to be used for educational purposes.

We will not share cancer registry data with anybody outside the ERICA research team. Anonymised interview transcripts may be made available to third parties providing they have the requisite independent ethical approval to hold the data. Requests from third parties need to be put to the Chief Investigator in writing and must be made within five years of the end of the trial.

Note re timelines, the impact of COVID and of Skyline on randomisation

The original dates for the trial were approximately 2 years earlier. A tranche of practices was recruited in 2019, and randomised. They have been unable to receive the intervention as Skyline was being developed. Furthermore COVID-19 blocked trial participation even if the software had been installed. With Skyline being installed in the fourth quarter of 2021, the decision has to be made as to when the practices 'entered' the trial. Usually this is around the time of randomisation. In this case that would mean intervention practices would be contributing intervention time, but without having the intervention. Thus, all practices are deemed to enter on Jan 1st 2022, with some intervention practices having had the intervention installed a few weeks before that date.

Dissemination and impact activities

Trial progress will be reported to our PPI group at meetings and through quarterly newsletters. At the end of the study we will seek input from our PPI group to help disseminate a lay summary of the findings. We envisage a number of key papers arising from this pilot trial. A trial publication policy will be developed which outlines the strategic plan for dissemination. The results of the trial will be reported first to study collaborators, the TSC, and the funder. The main report will be drafted by the study team and circulated to all collaborators, The TMG and the TSC for comment. Key outputs from the trial will be presentations at national and international conferences, seminars, PPI events and dissemination through internationally recognised peer reviewed journal publications (including open access web sources), newsletters and media releases.

Finance

The trial is funded by The Dennis and Mireille Gillings Foundation, The University of Exeter, and Cancer Research UK.

Amendment history

This table will be updated when amendments have been requested and approvals granted.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2	04.06.2019	Raff Calitri & Luke Mounce	1. Confirmation of CE marking for the Informatica version of the eRATs 2. Substitution of Microtest clinical software system with EMIS clinical software systems. 3. Explication of inclusion criteria: practice must have two week wait referral rate data available on public registry. 4. Removal of mention for section 251 from CAG. A new process a data anonymisation has been introduced to obviate the need for CAG. 5. Further specificity of analytic models including minor clarifications of terminology to align protocol with our statistical analysis plan
2	n/a	n/a	n/a	We submitted a notice of a non-substantial amendment request permission to add all the local Clinical Research Networks as research sites. No amendment to the protocol was necessary
3	3	09.10.2019	Raff Calitri	1. Addition of Dr Jamie Murdoch (independent process evaluation and qualitative expert) to the TSC. 2. Collect an eRAT report from ALL intervention practices rather than just those taking part in the nested studies. 3. Adjust the study timeline to reflect latter recruitment start and consequences of this. 4. Amendment to insurance statement following new advice from University Insurance Office.
4	4	TBC	Raff Calitri, Luke Mounce & Hannah Baber	1.Change in trial staff – a new Trial manager 2. Outline an update to our statistical analytical approach for managing the impact of Covid-19 on cancer diagnosis and trial delivery. 3.Outline of a new cloud-based version of eRATs which replaces the old Audit+ version. 4. To be included in the trial, practices must host either EMIS or SystmOne clinical systems. We will no longer seek to include Vision practices due to the eRATs software

				not being available in a version suitable for this system. 5. Clarification of inclusion criteria recognising a DoH and Cancer Alliance recommendation for GPs to be using cancer risk tools. 6. Clarification that Informatica Systems Ltd have performed the necessary conformity assessment (UKCA) which has been registered with the MHRA (Application reference: 2021082601213536). 7.Updated risks to acknowledge ongoing Covid-19 impact 8. Updated Timeline following trial pause for Covid-19 9. Update to the Process Evaluation data collection to allow for online data collection (e.g., Zoom/ MS Teams)given Covid-19 restrictions 10. Updated process evaluation methods to include online data collection by the trial team for patient and GP participant interviews (e.g. via MS Teams) due to ongoing COVID-19 restrictions. Clarification that there are no longer training videos for each specific GP IT system; there is one overall video for the Skyline cloud-based eRATs software. There is also no longer a need for in-person visits to practices to support installation of and training on the software, which can now be delivered remotely. 11. Minor edit added regarding recruitment communications being sent by email rather than by letter. 12. Minor edit regarding the process for alerting practices to their allocation (i.e. the 'research team' will communicate practices' allocation) 13. Removal of the requirement for the research champion to complete a questionnaire regarding the extent to which training was undertaken among GPs in the practice 14. Removal of practice's 'local' eRATs reports potentially slowing down computer efficiency; the Skyline cloud-based software is not expected to hinder a practice's IT system processing power.

Amendments to the trial will be decided by the Chief Investigator and checked by the Sponsor prior to submission to the HRA REC and/or the Health Research Authority Amendments team to seek approval. Local sites will be notified of any amendments as approved.

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