Study Title:

CASNET2: Evaluation of an e-safety netting cancer template in primary care: a pragmatic stepped-wedge RCT

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There are no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	**Evaluation of an e-safety netting cancer template in primary care: a pragmatic stepped-wedge RCT**	
Study Design	Pragmatic Stepped Wedge RCT, with qualitative process evaluation and identification of improvements	
Unit of randomisation	General practice	
Unit of analysis	Patients	
Study Practices	70 - 82 practices contributing data to the RCGP Research Surveillance and Research Centre (RSC) Network.	
Study Patients	Adult patients (>18y) registered in participating practices consulting in primary care with low-risk symptoms not eligible for referral through the two week cancer referral pathway.	
Planned Sample Size	70 - 82 practices	
Planned Study Period	18 months	
	Objectives	**Outcome Measures**
Primary	To compare the primary care interval for cancer during periods of time when the E-safety netting toolkit (E-SN toolkit) is inactive with periods when the E-SN toolkit is active	Primary care interval for cancer diagnoses (time between first recorded symptom of cancer and referral to secondary cancer care)
Secondary	To compare the frequency of diagnostic outcomes during periods of time when the E-safety netting toolkit (E-SN toolkit) is inactive with periods when the E-SN toolkit is active	• Proportion of cancers diagnosed after emergency presentation • Recorded new diagnoses in those who have a template activated (by cancer site and stage, non-cancer) • Total time to diagnosis (from 1st recorded symptom to definitive diagnosis) – all cancer diagnoses and all diagnoses with template activation

	To compare consultation outcomes during periods of time when the E-SN toolkit is inactive with periods when the E-SN toolkit is active	• Number of GP consultations/patient between first record of symptom and cancer referral • Rates of patients completing direct access cancer investigations • Rates of patients referred (2 week wait; urgent; routine) • Timing of template activation within the primary care interval (from first symptom to referral)
	To quantify practice-level variation in E-SN toolkit uptake and describe the clinical situations for which the E-SN toolkit is activated	• Template activation rate amongst consulting patients ○ (Total and Stratified by individual GP) • Proportion of diary entries that were completed; • Reason for template activation (based on 20 high level READ codes); • Symptoms leading to direct access to investigations; • Recorded vague symptoms in the template • Demographic details of patients with activated templates • GP type completing templates (e.g. partner, locum, trainee) • Diagnostic codes in patients with activated templates

2. ABBREVIATIONS

CI	Chief Investigator
CFIR	Consolidated Framework for Implementation Research
CRN	Clinical Research Network
CTRG	Clinical Trials & Research Governance, University of Oxford
EHR	Electronic Healthcare Records

EMIS	Egerton Medical Information System (one of the most commonly used electronic health records systems).
EOI forms	Expression of Interest forms
E-SN Toolkit	Electronic Safety Netting Toolkit
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
ICF	Informed Consent Form
ICPC-2	International Classification of Primary Care v2
IRAS	Integrated Research Application System
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PIL	Participant/ Practice Information Leaflet
PLO	Practice Liaison Officer
R&D	NHS Trust Research & Development Department
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SW-CRCT	Stepped Wedge Cluster Randomised Controlled Trial

There are no sources in the current document.

3. BACKGROUND AND RATIONALE

Safety-netting is regarded as “best practice” in cancer diagnosis in primary care (1). It aims to ensure patients do not drop through the healthcare net but are followed-up until symptoms are explained (2) or resolve. Our research highlights an absence of evidence on how best to safety-net, especially in patients with non-specific cancer symptoms (1). Expert consensus, international survey data and interviews with GPs and patients show that effective patient communication, shared decision making and improved clinical systems are needed to ensure that tests and referrals are followed-up and recurrent consultations are identified in patients with unexplained symptoms (3-5). To achieve this, significant improvements in Electronic Health Record (EHR) utilisation are required, by integrating information and communication technology with clinical care (6-8).

In the NHS, fail-safes do not exist to ensure tests are conducted, returned and reconciled (9). Confusion exists about which staff member is responsible for test communication (10). Patients can be unaware of their responsibility to follow up investigations and referrals, assuming “no news is good news,” and taking no action if they do not feel better or develop new symptoms (11, 12). The

success of a systems-based approach to safety-netting is jeopardised by inadequate administrative processes and marked variation in approaches to follow-up (13). EHR based interventions show promise: trials in the United States (US) of electronic prompts increased the proportion of patients with cancer symptoms who receive follow-up (8, 14-16). However, despite reporting enthusiasm for new initiatives, GPs do not always engage with new information technology, and this driven in part by social and technical factors, such as pop-up fatigue and information overload (12, 13, 17-20) and being under-resourced.

A new electronic safety-netting toolkit (E-SN toolkit) has been developed through consultation with GPs. Though the technology is not new, as it uses functionalities within one of the major clinical systems in England - Egerton Medical Information System (EMIS) Web, it is a new way of working. The toolkit is designed to replace existing verbal or paper methods by utilising administrative staff for tracking and follow-up. The E-SN toolkit provides practices with a rigorous, robust, traceable and auditable pro-active approach to tracking patients. It allows clinical data to be entered using templates, and diary entries to be generated (time reminders to check an action has been completed). Reminders are created to ensure test requests, referrals, and non-specific but concerning symptoms are followed-up. Outstanding actions appear as Alert Flags to identify incomplete diary entries. Outstanding follow-up actions can be collated. The E-SN toolkit was embedded within EMIS Web in an inactive format in May 2018, which means that practices have access to it if they proactively turn it on.

This project has 3 broad aims:

1) To evaluate the effectiveness of an embedded electronic safety-netting toolkit (E-SN toolkit) for patients with possible symptoms of cancer.
2) To understand the barriers and facilitators to the use of the E-Safety netting toolkit (E-SN toolkit) in primary care.
3) To identify and prioritise features to be included in future electronic safety-netting systems.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of these outcome measures**
Primary Objective To compare the primary care interval for cancer during periods of time when the E-safety netting toolkit (E-SN toolkit) is inactive with periods when the E-SN toolkit is active	Primary care interval for cancer diagnoses (time between first recorded symptom of cancer and referral to secondary cancer care)	12 month period prior to the start of the trial (for first recorded symptom) During all inactive phases and active

		phases (for referral)
Secondary Objectives		
To compare the frequency of diagnostic outcomes during periods of time when the E-safety netting toolkit (E-SN toolkit) is inactive with periods when the E-SN toolkit is active	• Proportion of cancers diagnosed after emergency presentation • Recorded new diagnoses in those who have a template activated (by cancer site and stage, non-cancer) • Total time to diagnosis (from 1st recorded symptom to definitive diagnosis) – all cancer diagnoses and all diagnoses with template activation	12 month period prior to the start of the trial (for first recorded symptom) During active phases (for template-related variables) During all inactive phases and active phases (for other variables)
To compare consultation outcomes during periods of time when the E-SN toolkit is inactive with periods when the E-SN toolkit is active	• Number of GP consultations/patient between first record of symptom and cancer referral • Rates of patients completing direct access cancer investigations • Rates of patients referred (2 week wait; urgent; routine) • Timing of template activation within the primary care interval (from first symptom to referral)	12 month period prior to the start of the trial (for first recorded symptom) During active phases (for template-related variables) During all inactive phases and active phases (for other variables)
To quantify practice-level variation in E-SN toolkit uptake and describe the clinical situations for which the E-SN toolkit is activated	• Template activation rate amongst consulting patients ○ (Total and Stratified by individual GP) • Proportion of diary entries that were completed; • Reason for template activation (based on 20 high level READ codes);	During all active phases

	• Symptoms leading to direct access to investigations; • Recorded vague symptoms in the template • Demographic details of patients with activated templates • GP type completing templates (e.g. partner, locum, trainee) • Diagnostic codes in patients with activated templates	

5. STUDY DESIGN

This is a stepped wedge cluster-randomised controlled trial (SW-CRCT), in which the intervention (E-SN toolkit) will be introduced to all participating practices in phased stages. The unit of randomisation will be clusters, defined as general practices. The unit of analysis will be individual patient data level.

Practices will contribute data for the 24 month period before the stepped-wedge introduction of the E-SN toolkit (cancers detected in 12 months prior to start, plus the preceding 12 months to calculate primary care interval). All practices will get the opportunity to use the E-SN toolkit, but some will be delayed in activation. Practices will be randomised in blocks of 10 to the timing of activation of the E-SN toolkit and will cross-over in these blocks to the activated phase every two months. Therefore practices will have contributed between 2 months and 12 months of E-SN toolkit-activated time (Figure 1).

Figure 1. Stepped wedge design with 12 months pre-randomisation period

	Pre-randomisation period (months)						Post-randomisation cross-over period (months)					
Practices*	-12	-10	-8	-6	-4	-2	0-2	2-4	4-6	6-8	8-10	10-12
1-10												
11-20												
21-30												
31-40												
41-50												

51-60												

*Practices will be randomly allocated to the group and date of cross-over

Blue cells represent inactive E-SN toolkit period
Purple cells represent active E-SN toolkit period

Clinicians and practice staff will not be blinded to activation status. Consulting patients will be unaware of any changes in the availability of the E-SN toolkit.

The anticipated length of the study is 18 months. This consists of 3 months recruitment, followed by a 12 month period during which time the intervention will be introduced, and 3 months for analysis.

6. PARTICIPANT IDENTIFICATION

6.1. Participating practices

We will recruit 70 - 82 GP practices that contribute data to the RCGP Research and Surveillance Centre (RSC) Network (21, 22) and use the EHR system EMIS. RCGP RSC includes general practices in England. The target number of practices is 60, but we will recruit up to 72 to account for drop-out during the period. The additional 10 practices are to account for 10 practices who were recruited and initiated with the intervention in March 2020. It was then necessary to pause the study and stop new practices being initiated with the intervention, due to the COVID19 pandemic. Since the intervention cannot be withdrawn and re-implemented, an additional 10 practices are needed to allow for the full stepped wedge design.

6.2. Inclusion Criteria: practices

- Practice is actively contributing data to the RCGP RSC.
- Utilises EMIS EHR system
- Data available for the previous 24 months

6.3. Exclusion Criteria: practices

- Practices that express an interest, but are not fully set up to start downloading data.
- Any practice already deploying the E-SN toolkit

6.4. Study Patients

Adult patients (>18y) registered in participating practices consulting in primary care. No direct involvement will be needed from consulting patients and we will not be seeking individual patient consent (see section 7.2). Outcome data will be extracted from the EHR by the Structured Query Language (SQL) developer and provided in a pseudonymised form to the analysis team.

Patients will be informed about the study via posters (privacy notices) displayed in their practices' waiting rooms. These notices will include information on how data would be used, patients' rights to opt-out if they do not wish their data to be shared and how they could do that.

6.5. Inclusion Criteria: patients

- Male or female, aged 18 years or above.

6.6. Exclusion Criteria: patients

- Patients who have opted out of data sharing.

7. STUDY PROCEDURES

7.1. Recruitment

Potential practices will be identified from the RCGP RSC network of practices and details of the study will circulated to all RCGP RSC EMIS practices before and during the recruitment period. Expressions of Interest (EOI) will be obtained from all interested practices. Practices will also be approached directly by the RCGP RSC Practice Liaison Officers (PLOs). All practices will be recruited at the start of the study so that randomisation in blocks of 10 can be achieved and the schedule for switching from inactive to active phase can be generated.

General practices will receive reimbursement of up to £500 per practice for participation in the 12 month stepped-wedge randomised intervention study through this grant.

7.2. Informed Consent

Practices that are randomised to take part in the study will be provided with a welcome pack, which includes: (1) Practice Information Leaflet; (2) Practice poster; (3) Copy of the protocol; (4) Copy of ethical approval documentation and (5) Instructions of how to complete the study activities. These

documents will provide detailed information about the exact nature of the study; study requirements; the implications and constraints of the protocol; and any risks involved in taking part. Site agreements will be in place with each practice and it will be clearly stated that the practice is free to withdraw from the study at any time for any reason, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

No direct or active involvement will be required from consulting patients and we will not be seeking individual patient consent. The rationale for obtaining agreement at the cluster (practice) level is that the activation of the Toolkit will be through the EMIS software system and health care practitioners are the intended recipient of the intervention. (23, 24)

Patients who have opted not to share their information for disease surveillance will be respected by RCGP RSC and by the research team. The research team will not extract records of patients who have registered opt-out codes in the GP information system.

Outcome data will be extracted from the EHR by the SQL developer and provided in a pseudonymised form to the analysis team.

7.3. Randomisation

The eligible practices will be ranked according to their list size from smallest to the largest. These will then be stratified into 10 strata (by list size) such that each strata contains the same number of practices. This is based on the allocation of 10 practices per step.

7.4. Random allocation and blinding

A statistician (Rafael Perera, Nuffield Department of Primary Care Health Sciences, University of Oxford) who is independent to the intervention development and implementation will produce a stratified randomisation schedule so that within each strata, practices are randomly allocated to each of the 6 steps, with some replacement practices. The random sequence will be generated using R software. The allocation will be undertaken for all practices at the same time.

Given the practice change nature of the intervention, clinicians and practice managers will be aware when their practice has switched to the intervention period. Consulting patients providing outcome data will not be informed of the experimental nature of the E-SN Toolkit activation and therefore will be blind to the stage of study occurring in the practice they attended. Study personnel involved in extracting outcome data will be blind to the allocated order of the delivery of the intervention across the practices. All data management of extracted data to calculate the outcome measures will be conducted blinded to the timing of switching to intervention. Similar methods have been used in other implementation SW-CRTs. (25)

7.5. The intervention and training

The E-SN toolkit is based on a series of templates to track cancer events like referrals, direct access tests and monitoring of low risk through read codes attached to diary entries. These events would be routinely looked for through automated searches once they expire and actioned by the admin

lead as appropriate. If an event was complete i.e. CT scan results done in 2 weeks and result back - then the diary entry is closed, resolving the episode. The E-SN toolkit has extra features such as pop up alerts to remind any user there is an open diary entry and also allows the E-SN toolkit to pop up automatically if a Read code is typed within a template.

Further details and demonstration video are available from:
https://www.uclh.nhs.uk/OurServices/ServiceA-Z/Cancer/NCV/MICa/Pages/Primarycareimprovement.aspx

All practices will receive training in the use of the E-SN toolkit prior to their switching date.

Practices will be asked to search for open diary entries every week during the intervention period, and to save these to an Excel spreadsheet. The central study research team will use these spreadsheets to track which diary entries are closed during the course of the intervention. Spreadsheets will be provided by practices to the research team on a monthly basis during the intervention period. Spreadsheets will be pseudonymised by the RCGP RSC team before providing them to the researchers, so that each diary entry can be linked to the equivalent entry in the electronic health record download.

Practices will all be encouraged to adhere to the schedule for switching and will receive part-payment for study initiation and then full payment when they adhere to the activation schedule.

7.6. Data extraction: demographics and outcome measures

Data extractions from all participating practices will correspond to two major time points: at the start of the introduction to the stepped wedge implementation of the E-SN toolkit, and at the end of the stepped wedge period (12 months later). At these two time points, consultation data from the participating practices will be obtained for the previous 24 months. It may be necessary or desirable to obtain interim downloads to ensure data integrity. No data will be extracted until appropriate agreements are in place between Oxford University and the RCGP RSC.

Information to be downloaded will include: demographic information of age, sex, dates of GP and Nurse consultations; coded consultation data for symptoms, diagnoses, tests ordered, and referrals made within the consultation records. Where a definitive diagnosis has been made (for cancer and non-cancer conditions), the clinical features recorded in the year prior to diagnosis will be captured. These actions will be achieved by extraction of the electronic health record rather than by hand searching notes.

These data will be utilised to derive the stated outcome measures. Although no personal identifying information will be downloaded, we will be extracting several items from the clinical record. However, we have taken care to minimise the number of data items/variables that would be extracted. Furthermore, we are only requesting information pertaining to age rather than date of birth, and despite obtaining individual level data we believe that aggregation of this information would still not enable identification of an individual.

7.7. Discontinuation/Withdrawal of Participants from Study

Each practice has the right to withdraw from the study at any time. Data from withdrawn practices will be included in analyses up to the point of withdrawal, unless they indicate that they wish to withdraw previously collected data from analysis.

7.8. Definition of End of Study

The end of study is the date of the last data download. The study team will notify the main REC that the study has ended and will provide them with a summary of the clinical trial report within 12 months of the end of study.

8. SAMPLE SIZE

Size of effect: Practice lists sizes within the RCGP RSC are approximately 10,000. In England diagnosis rate of new cancer was 523/100,000 per year (2014/15) (28). Therefore we could expect 53 new cancers per year per practice. Therefore, in each 2 month step there would be 8 - 9 cancers per cluster.

The median primary care interval between first presentation and specialist referral (29, 30) is 5 days, interquartile range of 0-27 (31). Some cancers present with clear red flag symptoms leading to immediate specialist referral. Presentations of vague symptoms such as weight loss are less likely to be immediately referred and may benefit from using the safety-netting template. This symptom is associated with several cancers such as prostate, colorectal, lung, gastro-oesophageal, and pancreatic (32). The median primary care interval for lung cancer is 14 days (interquartile range 2-45) (31). Using the *steppedwedge, detectable difference incomplete(1)* command in Stata 14 showed that with the design in Figure 1 and 60 practices we would be able to detect a difference of 2 days with 80% power.

Currently approximately 19% of cancers are diagnosed following an emergency presentation(33). With 9 cancers per step per cluster we would be powered to detect a difference of 5%.

Under another scenario of considering primary care intervals towards the 90th centile of 60 days, with 60 practices, entering the stepped wedge design in 6 steps we would be able to detect a minimal difference of 13 days. However, if we consider that these patients with longer delays are in the 90th centile, then instead of expected cancers per cluster per step of 9 – there would be around 1. This would allow us to detect a minimal difference of between 9 and 39 days dependent on the assumption of the distribution of the primary care delays.

Several scenarios are shown in the table below, all based on 60 practices, entering in 6 blocks, with a 12 month pre-intervention period. In summary our main analysis will focus on all cancers, but we can conduct pre-specified subgroup analyses restricting to cancers that typically have longer delays.

Assumptions	All cancers (based on lung cancer)	All cancers	All cancers	All cancers	Restricting to only 90th centile delays	Restricting to only 90th centile delays
Median (days)	14	14	60	60	60	60

Range (days)	0-60	0 – 100	0 - 365	0 - 100	14 - 100	14 - 365
N of cancers per step per cluster	9	9	9	9	1	1
Minimum detectable difference (days)	2	5	13	4	9	39
notes		Allowing greater range		Lower upper value for Primary Care Interval	Minimum set to median of all cancers	Min set to median of all cancers, but increased upper range

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the patient's GP the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures.

As patients remain under their GP's care throughout the study, and serious adverse events such as death and hospitalisation unrelated to the study are expected in this patient group, no formal monitoring of SAEs will be carried out.

10. STATISTICS AND ANALYSIS

10.1. The Number of Participants

We will approach general practices with the aim of randomising 60-72 practices. Average list sizes for the practices in the RCGP RSC are approximately 10,000. Therefore the coverage of this SW-CRCT would be about 600, 000 people. Utilising national statistics from England (new diagnosis rate of 523/100,000 per year (2014/15)) (28), just over 3,000 people to be diagnosed with cancer in a one year period. An additional 10 practices are needed to allow for the 10 practices in who the intervention was started in March 2020 before the study was paused due to COVID19.

10.2. Definition of Outcome Measures

10.2.1 Primary care interval for cancer diagnoses

In line with published research and guidelines on diagnostic intervals, we will search the patient record for all patients with a cancer diagnosis for the year prior to diagnosis: one year is a trade-off between misattributing unrelated symptoms occurring more than a year before and missing symptoms of relevance by restricting to a shorter period (29, 34). Within our team, and through collaboration with the wider primary care (cancer) research community, we hold a comprehensive library of Read codes that map onto the International Classification of Primary Care v2 (ICPC-2) classification and the symptoms included in the 2015 National Institute for Health and Care Excellence (NICE) guidance. These repositories allow us to carefully identify clinical features related to cancer from the primary care literature as a well as casting a wider net to catch symptoms in patients not diagnosed with cancer.

The primary care interval is defined as the number of days between 1st recorded symptoms of cancer (within the year prior to diagnosis) and subsequent referral for secondary cancer care.

10.2.2 Proportion of cancers diagnosed after an emergency presentation

Where a cancer has been diagnosed we will aim to elicit the route to diagnosis (emergency presentation or otherwise). We recognise that routine recording of the route to cancer diagnosis in primary care records is likely to be underutilised, although the RCGP RSC network practices have dedicated staff time to ensure that secondary care outcomes as returned to primary care are coded and therefore this data is more likely to be recorded. However, we will also develop algorithms to identify emergency presentations of cancer (where a diagnosis of cancer is made prior to a referral), including following an attendance at A&E or an inpatient episode (35). Where there is uncertainty regarding the route of diagnosis, the PLO team within the RCGP RSC network will contact the practice in an attempt to augment the data.

10.2.3 Recorded new diagnoses in instances of E-SN toolkit activation

We will not pre-specify which non-cancer diagnoses are included but will identify coded entries for all alternative diagnoses where the E-SN toolkit has been activated.

10.2.4 Total time to diagnosis

1st recorded symptom of cancer (within the previous year) to definitive diagnosis for all cancers diagnosed, and for all patients with an activated template

10.2.5 Number of primary care consultations between 1st recorded symptom and referral

We will extract information regarding the number of primary care consultations between the 1st recorded symptoms (within the year prior to diagnosis) and subsequent referral, per patient.

10.2.6 Rates of patients completing direct access cancer investigations

The numerator will be the number of patients undergoing direct access cancer investigations (according to those specified in referral guidelines NG12 (36, 37)) in each period divided by the person years of observation for that period.

10.2.7 Referral rates, by urgency route (2 week wait, urgent, routine)

For all patients referred for specialist opinion to a secondary care cancer specialist, information will be ascertained about the route of referral (two-week wait, urgent, routine).

10.2.8 Timing of template activation within the primary care interval

The number of days between 1st recorded symptoms (within the year prior to diagnosis) and template activation and the number of days between template activation and subsequent referral.

10.2.9 Template activation rate amongst consulting patients

The number of patients with an activated template divided by the number of patients consulting, in each time period.

10.2.10 Proportion of diary entries that were completed

The number of diary entries that were completed divided by the number of diary entries that were opened.

10.2.11 Reason for template activation (based on 20 high level READ codes)

The coded reasons for activating the template.

10.2.12 Symptoms leading to direct access to investigations

10.2.13 Recorded vague symptoms in the template

All symptoms recorded within the template.

10.2.14 Demographic details of patients with activated templates

Age and sex of patients that had a template activated during the course of the trial.

10.2.15 GP type completing templates (e.g. partner, locum, trainee)

Descriptive data on the type of GP that first activated the template

10.2.16 Diagnostic codes in patients with activated templates

Diagnoses recorded after the activation of template.

10.3. Analysis of Outcome Measures

Specifically, amongst consulting patients we will calculate the rate of direct access cancer investigation and rates of referrals via 2 week wait, urgent and routine pathways and number of consultations between first recorded symptom (see above) and referral (primary outcomes), and the template activation rate (process measure). In patients with a diagnosis of cancer we will calculate the primary outcomes of primary care interval, proportion diagnosed after emergency presentation and the recorded diagnosis.

Regarding the analysis of the stepped-wedge design and the effect of correlation of observations within clusters, will model the association using a fixed effect for the intervention condition of the cluster at each time step, a fixed effect for time and other covariates (which will help to deal with missing data), and then include a random effect for practice and a random effect for patient to account for correlation of the observations from the same centre and from the same participant.

Analyses will include all participants. Practices that withdraw their agreement to participate will be included in analyses up to the point of withdrawal, unless they indicate that they wish to withdraw previously collected data from analysis.

10.3.1 Planned subgroups

Where applicable, subgroups will be:

Patients in whom an E-SN toolkit entry was completed

Patients diagnosed with cancer

10.3.2 Planned sensitivity analysis

We will undertake a sensitivity analysis excluding these patients (who started the diagnostic journey before the introduction of the E-SN toolkit) to estimate the effect once the E-SN toolkit is universally available.

10.3.3 Data display and reporting

We will combine or suppress any cells with small numbers (under 5) of observations to prevent any potential identification during the reporting of the results.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Recording and Record Keeping

The principal data source for the this study are pseudonymised routinely collected care data extracted from general practices of the Royal College of General Practice (RCGP), Research and Surveillance Centre (RSC) network.

The Research Team has no roles in updating these clinical data recorded by clinicians as part of their consultation and care. The Research Team, however, maintains an auditable trail for all the stages of data processing to ensure the quality of data are not compromised by the processing. For example, the Research Group's Senior SQL Developer checks the prevalence of certain conditions and outliers revealed by the data is consistent with those reported in the literature. The Research Group's standard operating procedures for data extraction and data processing and for data access and sharing for staff of the Research Group can be accessed from https://clininf.eu/index.php/information-governance/).

The RCGP Research and Surveillance Centre (RSC), is a network of over 500 general practices providing pseudonymised, coded data on a weekly basis for infectious disease surveillance. All GP practices in the UK use a computerised medical system to maintain patient medical records. Data are entered into a patient's computerised medical system as coded data or free text. Coded data, pseudonymised at source, are extracted twice weekly from RCGP RSC general practice systems by Apollo, part of Wellbeing Software. The RCGP RSC extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the Electronic Health Record (EHR) system.(38)

Data is extracted twice weekly from information systems of the RCGP RSC general practices by Apollo, part of Wellbeing Software (https://www.wellbeingsoftware.com/solutions/product/apollo/) on RCGP's behalf within formal data sharing and service level agreements. Data are pseudonymised by Apollo using a non-reversible 'hash' algorithm as close to source as possible. Patients who declined to share their data are excluded from the extraction process.

Data are held on dedicated secure servers at the RCGP data and analytics hub in the Clinical Informatics and Health Outcomes Research Group, University of Surrey (Figure 1). Over the coming year, the RCGP RSC secure network and database will move to The University of Oxford.

The Research Group's secure network is sited behind a firewall within the University of Surrey's network, all in-bounded connections are blocked, but outbounded connections are allowed. Only staff members or associated members of the Research Group approved by the Head of Department can access the data from secure workstations or secure laptops with encrypted drive. The use of personal equipment is not permitted and cannot be connected to the Surrey Secure Network. All staff members of the Research Group working within the team base work from secure workstations or secure laptops with encrypted drive within the Research Group's secure network. On transfer to The University of Oxford, the same safeguards will be employed.

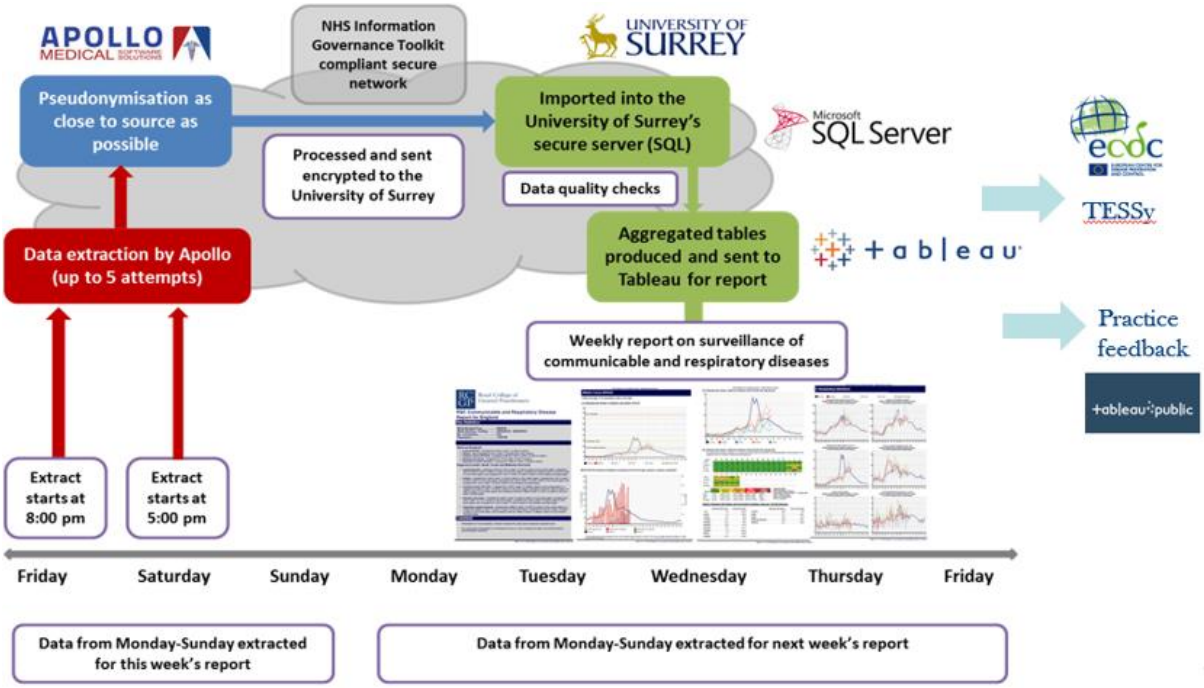

Figure 1: RCGP RSC Data Flow diagram showing data flow between RCGP RSC practices, PHE and Clinical Informatics and Health Outcomes Research Group, University of Surrey

These data extractions will be conducted in accordance with Good Clinical Practice, using the Research Group's standard operating procedures for data extraction, pseudonymisation, and transfer. The method and governance procedure has been developed by the University of Surrey, and are in alignment with University of Oxford SOPs.

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, practice information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the practices' patients anonymity is maintained. The practice patients will be identified only by an ID number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Although multiple items will be extracted from individual clinical records, we have taken care to minimise the number of data items/variables that would be extracted, and we are only requesting information pertaining to age rather than date of birth. We do not believe that the data being requested would be sufficient, even in aggregate, to identify an individual. Pseudonymisation by the RCGP RSC will ensure that it is not possible for research staff to link study data with data from other sources.

14. FINANCE AND INSURANCE

14.1. Funding

The study is being funded by Cancer Research UK, Early Diagnosis Advisory Group (EDAG). Further funding has been provided by the University of Oxford.

14.2. Development of a new Product/Process or the generation of Intellectual Property.

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

14.3. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR and will comply with NIHR publication policies. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.
Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

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17. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	**1.6**	**24 April 2020**	**Susannah Fleming**	**Increase in sample size by 10 practices to replace practices initiated before pause due to COVID-19** **Increase in study length to accommodate pause due to COVID-19** **Addition of funding from Oxford University to cover payments for 10 additional practices**

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.

18. Appendix B: List of additional documents

1. Practice information leaflet

2. Practice poster
3. Study activity completion instructions