Protocol for a randomised controlled phase III trial of a novel behavioural intervention for primary care teams to promote the earlier diagnosis of cancer (ThinkCancer!)

Study Title: ThinkCancer!: A pragmatic randomised controlled phase III trial of a novel behavioural intervention for primary care teams to promote earlier cancer diagnosis with embedded process and economic evaluation

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Ethics Ref:

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I, the undersigned, hereby approve this clinical trial protocol:

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LAY SUMMARY

Cancer diagnosis can be delayed in primary care. Our goal is to help general practices recognise *possible cancers* earlier which will lead to better outcomes for patients.

We have developed a unique educational and behavioural package called 'ThinkCancer!'. This involves a workshop consisting of three sessions for all staff in a practice team. We have tested 'ThinkCancer!' in a small pilot study in Wales, which showed that it can work well in primary care. We learnt important lessons about how the workshop should be delivered, and the best ways to collect information from practices.

Our aim now is to undertake a larger trial with 76 practices to test *how* well ThinkCancer! works and whether it is cost effective for the NHS. We will assess the effect of ThinkCancer! by measuring the time between a patient first contacting their general practice with a potential cancer symptom and their referral to hospital. A reduction in this time is known to be linked with earlier stage of cancer at diagnosis, needing less treatment, and costing the NHS less overall.

We have worked closely with patients throughout the development of ThinkCancer! and will form a Patient Advisory Group of four to six patients who will help ensure that patient views are fully represented as we interpret the results.

STUDY SUMMARY

Study Title	ThinkCancer!: A pragmatic randomised controlled phase III trial of a novel behavioural intervention for primary care teams to promote earlier cancer diagnosis with embedded process and economic evaluation
Protocol Version	Version 0.91
Internal ref. no. (or short title)	ThinkCancer! Phase III RCT
IRAS Project ID	316593
Trial Registration	'ThinkCancer!' ISRCTN submitted 27/01/2021 **43125**
Study Design	Randomised controlled pragmatic phase III trial
Study setting	Primary care
Study Participants	General practices and patients
Planned Size of Sample	76 general medical practices
Planned Study Period	46 months: 01/12/2022 - 31/08/2026
Planned Recruitment Period	9 months: 01/03/2023 – 30/11/2023
Research Objectives	**Primary:** to assess the effectiveness and cost-effectiveness of the ThinkCancer! intervention for general practice teams compared with usual care

	Secondary: ▪ To assess adherence to NICE NG12 guidelines by measuring the guideline interval. ▪ To understand the factors that contribute to longer Primary Care Intervals for patients diagnosed with cancer. ▪ To explore patient and carer experiences of urgent referral. ▪ To study mechanisms and contextual factors driving implementation of the intervention. ▪ To determine the acceptability of the intervention among practice teams. ▪ To establish whether the ThinkCancer intervention results in increased safety netting.
Intervention(s)	Behavioural and educational series of workshops delivered to general practice teams
Comparator	Usual care

We are not aware of any conflicts of interest affecting this trial

CONTENTS

ABBREVIATIONS

2WW	Two Week Wait
AE	Adverse Event
BCW	Behaviour Change Wheel
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CPD	Continuing Professional Development
CSNC	Cancer Safety Netting Champion
CSNP	Cancer Safety Netting Plan
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HCRW	Health and Care Research Wales
HRA	Health Research Authority
MRC	Medical Research Council
NIHR	National Institute for Health Research
NWORTH	North Wales Organisation for Randomisation Trials in Health
PCI	Primary Care Interval
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
R&D	Research and Development
RISP	Research Information Sheet for Practices
REC	Research Ethics Committee
SAE	Serious Adverse Event
SEA	Significant Event Audit
SOP	Standard Operating Procedures
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
USC	Urgent Suspected Cancer
WICKED	Wales Interventions and Cancer Knowledge about Early Diagnosis
WP	Work Package

1. INTRODUCTION

1.1 Background

Early diagnosis of cancer is key to improving outcomes and ultimately survival. This is a policy priority, with potential benefit for both patients and NHS treatment costs. The United Kingdom's (UK) five-year relative cancer survival is below the European average (CRUK, 2017), and mortality remains higher than in other high-income countries (Arnold et al., 2019). Despite some improvement in survival rates (ONS, 2019), the gap remains significant (Arnold et al., 2019).

Treatment delays significantly impact mortality (Hanna et al., 2020). Almost 50% of avoidable delays in the UK happen in primary care (Swann et al., 2020). Furthermore, 19% of new cancer diagnoses are made in accident and emergency (A&E) departments, often due to missed opportunities for earlier diagnosis in primary care (Swann, McPhail, Witt, et al., 2018). Cancer referral guidelines are often unclear (Evans et al., 2018; Tompson et al., 2019) and General Practitioners (GPs) vary greatly in their safety netting strategies (Evans et al., 2018). Diagnostic error and delayed referral are avoidable harms which can be mitigated by good communication among practice staff and a supportive administrative system (Avery et al., 2021; Makeham et al., 2016). The avoidable costs of late cancer diagnosis are striking. There is potential for annual savings of nearly £210m; and improved survival for 52,000 patients (CRUK, 2014). Societal productivity losses amount to £141.4 million, which includes £3.2 million associated with premature mortality, short-term and long-term work absence (Parsekar et al., 2021). The economic and social impact of cancer patients across Britain is £7.6 billion (Hilhorst & Lockey, 2020). Regardless of cancer type, early diagnosis is an optimal outcome for a better quality of life and cost-saving to the NHS.

Over 70% of cancers present in primary care (Swann, McPhail, Witt, et al., 2018), so general practice is the ideal setting for behaviour change, quality improvement, and education. The literature suggests complex interventions focusing on primary care may lead to a reduction in emergency presentations (Mitchell et al., 2015) and tailored multidimensional educational interventions could potentially reduce delays in the pathway and improve referral practices (Baskerville et al., 2012; Blank et al., 2014; Mansell et al., 2011; Schichtel et al., 2013).

'ThinkCancer!' is a theoretically driven, novel, complex behavioural intervention, aimed at reducing primary care cancer diagnostic delays, with the aim of improving stage shift in cancer diagnosis and therefore survival. All practice staff are targeted in a whole team approach, culminating in the development of a bespoke practice safety netting plan. Both Wales and the North West of England could benefit from this intervention. Wales has poorer survival outcomes within the UK (Coleman et al., 2011), with later stage diagnosis (CRUK, 2018; Wales Cancer Network, 2016), and lower referral rates (Nicholson et al., 2016); this is associated with higher mortality (Møller et al., 2015; Round et al., 2020). The North West region in England has seen significant increases in cancer incidence over the years (Arık et al., 2020), and currently has one of the highest incidence rates in England (ONS, 2019). Both Wales and North West England suffer health inequalities and therefore experience a higher burden of cancer incidence and lower cancer survival (CRUK, 2020; NWCR, 2021b, 2021a). ThinkCancer!, enables the general practice to develop a bespoke safety netting plan, therefore allowing specific regional variation and inequalities to be addressed.

1.2 Rationale and previous work

ThinkCancer! has been rigorously developed and tested in a feasibility randomised trial in Wales. The feasibility study revealed that a whole-practice workshop to expedite cancer diagnosis in primary care is timely and very

much appreciated by general practices across Wales; a full trial is needed to see whether ThinkCancer! can really achieve earlier cancer diagnosis and whether it is cost-effective.

As far as we are aware, this trial will be unique. One Australian trial addressing primary care differed substantially (addressing only one item of six in our programme theory) (Emery et al., 2017), and the ongoing CASNeT trial concentrates mainly on safety netting (Fleming et al., 2020a). There are currently no interventions aimed at the whole practice.

1.2.1 Development of ThinkCancer!

ThinkCancer! forms part of the Wales Interventions and Cancer Knowledge about Early Diagnosis (WICKED) Programme (Fig. 1), which aimed to improve quality and consistency of primary care approaches to improve the timely diagnosis of cancer. Work packages (WP) 1 & 2 focused on understanding the status quo in relation to early diagnosis, and resulted in identification of the target behaviour, *GPs thinking of and acting on clinical presentations that could be cancer*. This target behaviour was broadened to include the entire practice team as part of the iterative intervention development. The intervention was developed in WP3 using the Behaviour Change Wheel (BCW) (Michie et al., 2014). This culminated in the all-Wales ThinkCancer! randomised feasibility study (WP4) in 2020. The feasibility study in turn informed WP5, which encompassed the planning phase of this proposed Phase III trial.

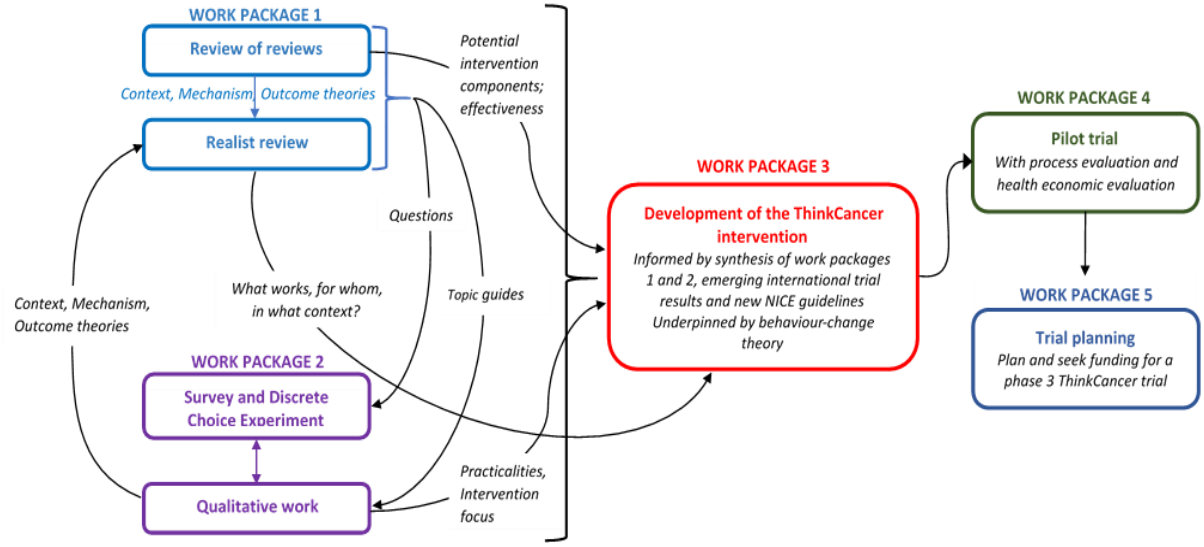

Figure 1: Overview of the WICKED Programme

1.2.2 Feasibility trial

The feasibility trial was rolled out throughout Wales in 2020, and all general practices in all seven health boards were invited to participate. The ThinkCancer! feasibility study was delivered successfully; progression criteria largely indicated a phase III trial is feasible and acceptable. The whole-practice workshop series was clearly timely and much appreciated by general practices. The recruitment target was achieved; retention was slightly below target due to general practices' time pressures during the pandemic. Intervention fidelity was demonstrated, and routine data collection proved feasible. Remote delivery proved to be highly advantageous, allowing more practices to participate, and multiple workshops to be delivered across practices, eliminating the need for travel.

The progression criteria results highlighted several methodological issues which have been addressed in this phase III trial and adaptations have been made. These have been further informed by PPI input, context changes in primary care (e.g. the re-start of group Continuing Professional Development (CPD) training), and comments following a peer review process.

2. OBJECTIVES AND OUTCOME MEASURES

The primary objectives of this pragmatic cluster randomised trial are to assess the effectiveness and cost-effectiveness of the ThinkCancer! intervention for general practice teams compared with usual care. Secondary objectives relate to the patient experiences and context.

The primary outcome measures are the primary care interval (PCI) - the time between the date of first consultation in primary care and the date of referral (Weller et al., 2012) - and cost-effectiveness. Reduced PCI and increased USC referrals have been shown to lead to more cancers being diagnosed at an earlier stage (known as stage shift) (Fleming et al., 2020b; Swann, McPhail, Shand, et al., 2018) and improvements in survival in association and modelling studies (Hanna et al., 2020; Hiom, 2015) . It is currently not possible to calculate the effect that PCI shift would have on stage shift - this trial will generate that information by collecting additional information on stage of cancer diagnosis. For the purposes of the economic evaluation, the main measure of effectiveness will be the same as the clinical primary outcome i.e., we are interested in measuring the incremental cost in a one-day reduction in the PCI.

The outcome measures are described in further detail in table 1.

Table 1: Objectives and outcome measures table

Objectives	**Outcome Measures**	**Timepoints of Evaluation**
Primary		
To assess the **effectiveness** and **cost-effectiveness** of the ThinkCancer! intervention for general practice teams compared with usual care	*Primary outcome measures*	
	Primary care interval (PCI - time between first presentation of potential cancer to primary care and referral to secondary care) data	Collected retrospectively by GP research staff or trained nurses, using a Case Report form, for the period 14 to 26 months post-randomisation.
	Cost-effectiveness in terms of incremental cost per day reduction in PCI and budget impact	Collected via health economics data collection sheets/diaries after each GP-educator training event and practice workshop.
	Secondary outcome measures	
	Conversion rate	Collected retrospectively via a Case Report Form sent to the practice, to be completed by the practice manager or allocated staff member for the following intervals: • The 12 months prior to randomisation

		• 2 to 14 months post randomisation
	USC/2WW referral rate	Collected retrospectively via a Case Report Form sent to the practice, to be completed by the practice manager or allocated staff member for the following intervals: • The 12 months prior to randomisation • 2 to 14 months post randomisation
	Detection rate	Collected retrospectively via a Case Report Form sent to the practice, to be completed by the practice manager or allocated staff member for the following intervals: • The 12 months prior to randomisation • 14 to 26-months post-randomisation
	Cancer stage at diagnosis	Collected retrospectively by GP research staff or trained nurses using a Case Report Form for the following intervals: • 14 to 26 months post-randomisation Data will initially be collected in plain text format and subsequently converted to categorical data by GP research staff or trained nurses.
Secondary		
To assess **adherence** to NICE NG12 guidelines (NICE, 2015)	Guideline interval – the time between patient first meeting any criterion within the NICE NG12 guidelines for referral to diagnosis (Price et al., 2021)	Collected retrospectively by GP research staff or trained nurses using a Case Report form for the period 14 to 26 months post-randomisation.
To understand the **factors that contribute** to longer Primary Care Intervals for	Qualitative measures plus subgroup analysis	Case note review data collected in summarised form by GP research staff or trained nurses for the period 14 to 26 months post-randomisation.

patients diagnosed with cancer		
To explore **patient and carer experiences** of urgent referral	Qualitative measures collected via qualitative interviews with patients and carers	Stakeholder interviews will take place between 3 and 6 months. Interviews with patients and carers will take place from month 10
To establish what **mechanisms and contextual factors** drive implementation of the intervention	Practice characteristics and demographics	Collected at baseline via the practice questionnaire, and at 12 months
	Reach – the proportion of staff members within the practice that attended any of the workshops or had the workshop materials disseminated to them	Collected during and after the workshops via workshop registration lists, the NoMAD survey and feedback forms.
	Recruitment – number of practices randomised	Collected throughout the study period via trial recruitment log
	Dose – defined as the number of workshop sessions delivered to each practice	Collected throughout the workshop delivery period via workshop completion lists
To determine the **acceptability** of the intervention among practice teams	Adherence to practice safety netting plan	Collected through the NoMAD questionnaire, which will be sent to participating practices 2 months post-workshop
	Acceptability	Feedback forms completed by participating staff members immediately following the workshop sessions
	Nomination of a safety netting champion	NoMAD and workshop notes
To establish whether the ThinkCancer intervention results in **increased safety netting**	Safety netting as evidenced by NoMAD questionnaire responses	Collected through the NoMAD questionnaire, which will be sent to participating practices 2 months post-workshop
	Cancer-related DATIX information	Practice manager to provide cancer-related DATIX information for 2 to 14 months post-randomisation period

In addition to the analysis of the clinical outcome measures as stated above, a secondary analysis of the primary care interval to explore whether ThinkCancer leads to a reduction in the **longest** PCIs. A secondary analysis will also be performed on the cancer stage at diagnosis data to determine whether ThinkCancer! leads to cancers being diagnosed at an earlier stage.

3. METHODS

3.1 Study design

This protocol describes a Phase III multicentre, pragmatic randomised controlled trial with embedded economic evaluation and process evaluation. General practices will be randomised with an allocation ratio of 1:1 intervention:control, and clinical data collected for the specified pre and post intervention period will be compared. The study will be 46 months in duration, with recruitment over a 9-month period.

The economic evaluation will investigate the resources society, through the NHS, is willing to spend to reduce the duration of the PCI, as a proxy for morbidity and quality of life. Therefore, the economic evaluation will be about system change. Whilst we are taking a predominantly NHS focus, where possible we will record any wider societal costs and benefits of earlier cancer diagnosis in primary care (Laudicella et al., 2016). The economic evaluation will run alongside the trial, starting with the refinement of the Health Economics Analysis Plan (HEAP) in order to cost the intervention. This will be followed by the economic modelling component of the study, which will involve combining data from the trial itself with parameter values drawn from the literature, and a subsequent sensitivity analysis.

A mixed methods process evaluation will run along the phase III randomised controlled trial and will aim to identify and explain the mechanisms and processes that enabled or acted as barriers to the implementation of the 'Think Cancer' intervention. More specifically, it will examine recruitment of practices, the reach to the practice team, intervention dose and fidelity, acceptability, unintended consequences and contextual factors. There will be a focus on underserved groups. Key stakeholders such as policy makers, PPI contributors, patients, carers and prior cancer safety netting champions will be identified at study outset to participate in qualitative interviews. Following this a purposive sample of patients will be included.

A case note review will be carried out to explore the factors which contribute to longer Primary Care Intervals for patients diagnosed with cancer. A purposeful sample of patients with longer PCI intervals will be selected for inclusion in a qualitative analysis drawing on methods described by van Erp et al. (2019) and Avery et al. (2021).

A nested internal pilot will be conducted using RAG (red, amber, green) criteria to ensure the trial's success by monitoring recruitment and intervention uptake 3 months into the study.

This study has been designed in accordance with the latest Medical Research Council (MRC) framework for evaluating complex interventions (Skivington et al., 2021). A schedule of procedures can be found in appendix 8.2.

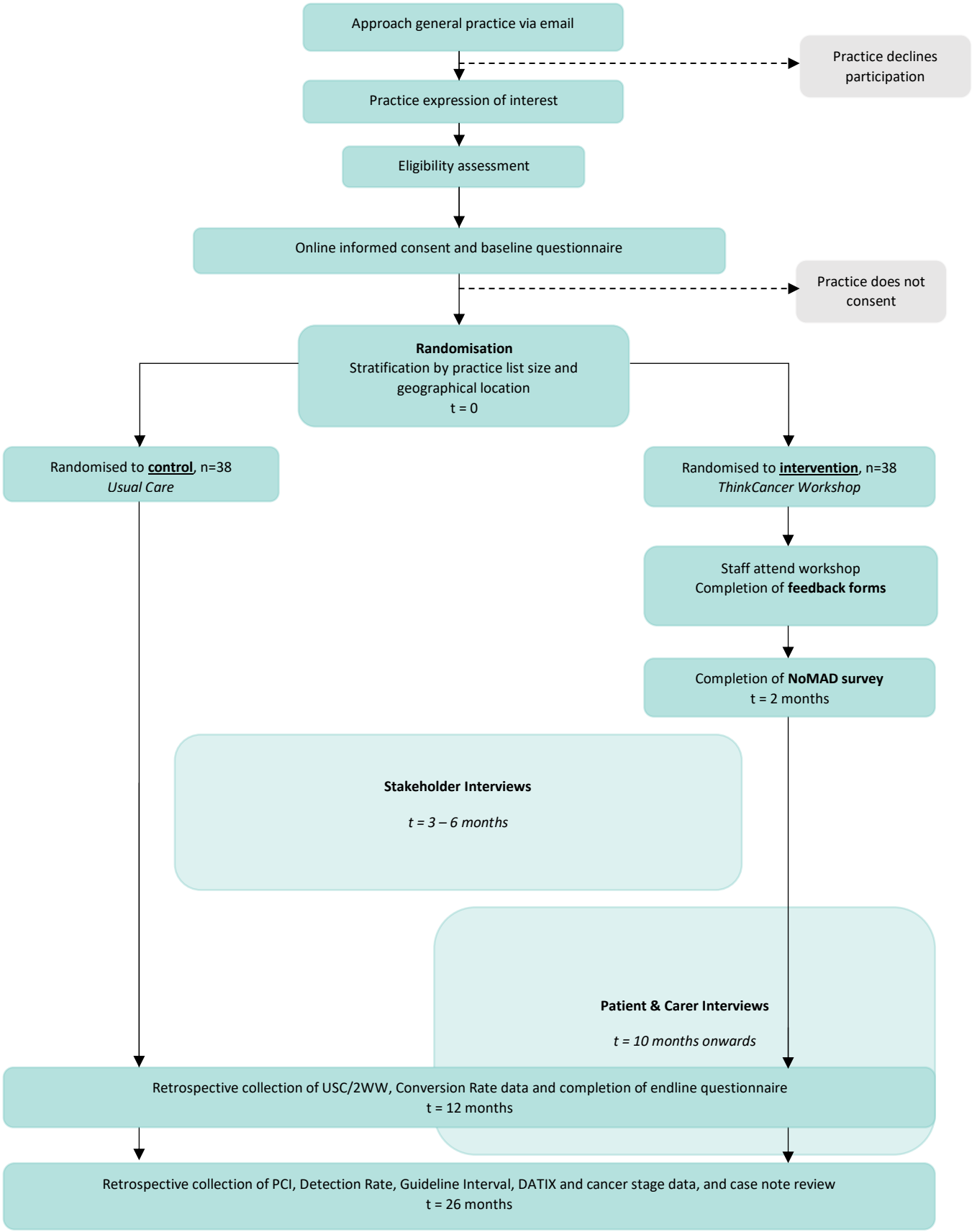

Figure 1: Participant flow diagram

3.2 Study setting

The setting for this study is primary care and the unit of allocation is the general medical practice. The intervention will be delivered online to individual general practices in Wales and the North West region of England and will incorporate a whole team approach. Depending on the ease of recruitment, the study may expand to the South West region of England if necessary.

3.3 Intervention

ThinkCancer! is a whole practice-based behavioural change complex intervention that aims to raise awareness and increase knowledge around current cancer diagnosis guidance. The intervention is delivered remotely as an educational and quality improvement workshop, via three distinct workshops. The first two workshops are educational sessions, one for all clinical staff (the 'early diagnosis' session) and one for non-clinical but patient-facing staff (the 'cancer aware' session), allowing exposure to the intervention for all members of practice staff who interact with patients or their carers/advocates in any way. The third session (the 'safety netting session') involves the final components of the intervention, the co-production of a bespoke Cancer Safety Netting Plan (CSNP) and appointment of a Cancer Safety Netting Champion (CSNC).

3.3.1 Early diagnosis session

The early diagnosis session is delivered as a live online teaching seminar to a cluster of practice teams (with an evergreen recorded version to enable wider reach of the intervention to those unable to attend any live sessions), lasting around **45** minutes and focusing on increasing knowledge and awareness around early diagnosis and safety netting. Content is regularly reviewed and updated in response to changing policy and guidance. This component of the workshop is supported by RedWhale GP Update in design and monitoring of content, along with the production of the intervention handbook. Learning outcomes are focussed on NICE NG12 Suspected Cancer: recognition and referral guidelines (NICE, 2015), hot topics exploring the harder to recognise cancer presentations and consultation-level safety netting. This session will also see the introduction of the ThinkCancer! Handbook, which contains a summary of the seminar content for future reference, resources regarding early diagnosis and safety netting and summary tables of the NICE NG12 referral guidance (NICE, 2015).

3.3.2 Cancer aware session

The cancer aware session is a less formal, convenor-led discussion around cancer red flag symptoms that non-clinical staff may encounter, delivered as a brief educational intervention and discussion, online, lasting around **20-25** minutes. This workshop is delivered remotely to individual practice teams or to groups of practices. A scenario and matching task based on the Be Clear on Cancer campaign (NHS, 2019) is used to drive discussion around experiences of patient presentations with potential cancer symptoms. The secondary aim of this session is to gauge and explore issues and norms around raising concerns within the practice team.

3.3.3 Safety netting session

This session is attended by a combination of clinical and administrative staff who will be involved in the design and implementation of a new Cancer Safety Netting Plan (CSNP). The CSNP will evolve from discussions built on three components, learning from the earlier educational parts of the workshop, evaluation of the current practice safety netting systems reported in the practice questionnaire and the attendee's personal reflections of cancer diagnosis and safety netting. This session is also delivered online to the practice team and may also be delivered to a cluster of practices at the same time, in order to facilitate shared learning and cross pollination of ideas. Following this discussion, a summary document highlighting potential new action points is

sent back to the practice for them to take forward and develop. Success in developing and implementing a new practice plan may be increased by the appointment of a champion to drive change and therefore the appointment of a CSNC is explored during this part of the workshop (Shaw et al., 2012).

3.3.4 Intervention delivery

Participant practices will be assigned post randomisation into a two month intervention delivery window, with the onus on the participants to engage with intervention workshop opportunities within the specified period. Recordings of the workshops will be made available for those unable to attend. Figure 2 demonstrates how the intervention can be delivered to a large group of participants and meet trial power requirements, including over 40 general practice teams and potentially well over 400 clinicians at a time.

Members of the research team will deliver the intervention; the GP Educator will oversee the workshop, supported by up to two researchers. Practices receiving the intervention will be sent all of the workshop materials, including the handbook via post in advance of their workshop dates. Practices randomised to the control group will also receive the pre-recorded videos at the end of the study period if they wish, along with the intervention materials.

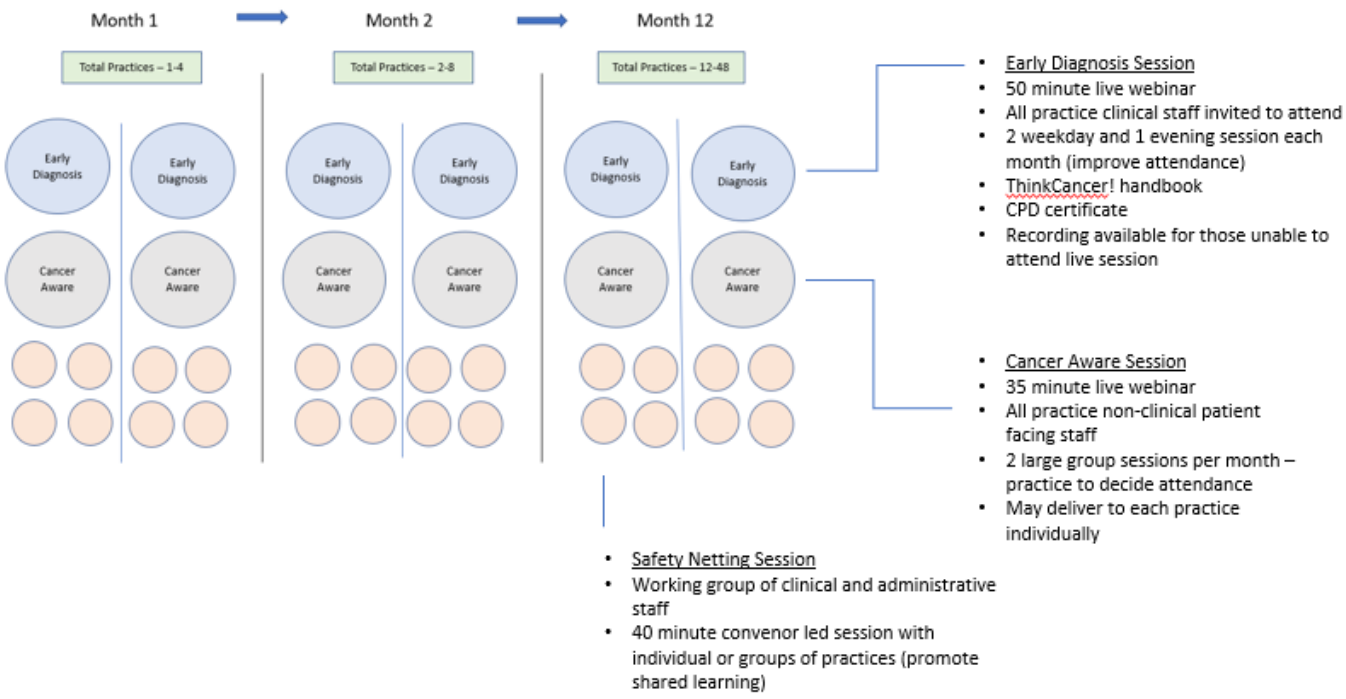

Figure 2: the ThinkCancer! delivery schematic

3.4 Sample size

The sample size is based on the PCI which is defined as the time from first consultation in primary care to date of referral (Coxon et al., 2018). The number of general practices required for a phase III trial is 76, randomised at 1:1 intervention:control. For this sample size calculation, the PCI is viewed as a measurement of time, rather than a continuous variable, which means that linear models are not appropriate to analyze PCI data since they require data to be normally distributed. For these reasons the most appropriate method for analyzing PCI data

is to use time to event models. These will assess whether there is a difference in the median PCI between the control and intervention groups.

The sample size calculation is based on a median PCI of five days for the control group and four days for the intervention group. A difference of one day in the median PCI may initially appear small, however, the median represents the value in the middle of the distribution, therefore reducing the median PCI by one day will require reducing the number of long PCIs in the distribution and increasing the number of shorter PCIs. A median of one day less means that the smallest 50% of PCIs would be four days or less, instead of five days or less. In order to illustrate this point, example distributions with a median of five days and a median of four days are presented in Figure 3.

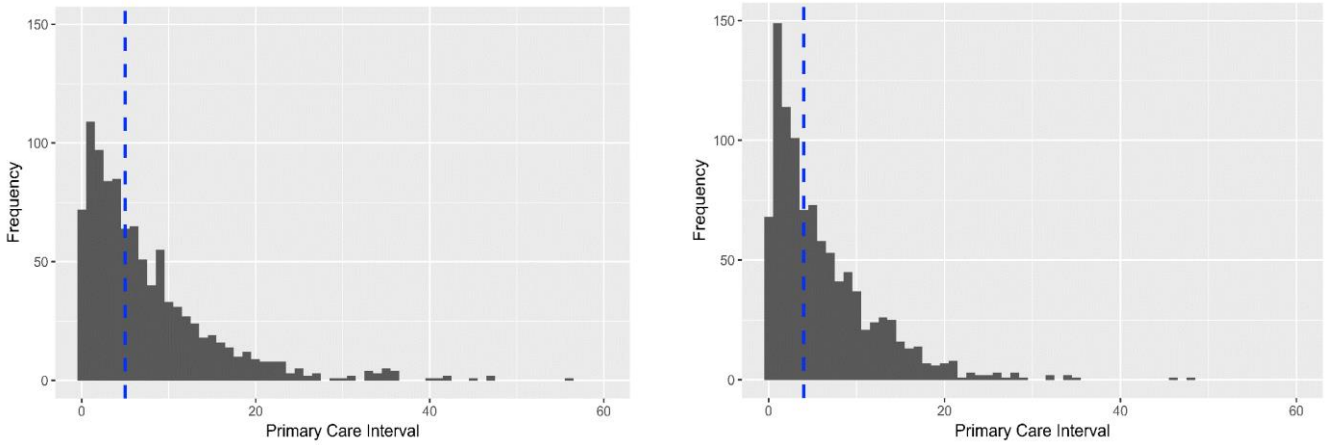

Figure 3: An example distribution of PCI data with a median of five days on the left and a median of four days on the right (median shown by blue line)

3.4.1 Qualitative sampling

3.4.1.1 Stakeholder interviews

Stakeholders including the CNSCs and practice staff will be identified via previous feasibility work. Patient and carer stakeholders will be identified via the Patient Advisory Group (PAG). We will use PI contacts and snowball sampling to identify key policy makers in each area. Up to 20 stakeholders will be invited to a qualitative interview.

3.4.1.2 Patient and carer interviews

A sample of patients will be identified via their GP across participating practices. In each area a purposive sample of 12 patients who had an urgent referral for potential cancer symptoms will be invited for a qualitative interview. In each area eight of these patients will have received a cancer diagnosis, and four will have received a non-cancer diagnosis. Up to 24 patients will be sampled for interview. Purposive sampling will ensure a range of age, gender and socio-demographic factors. From each area six patients interviewed will be asked to nominate a relative, carer or person close to them for interview. Up to 12 carer interviews will be conducted.

3.4.1.3 Case Note Review

Case notes with primary care intervals exceeding the 75th and 90th centile for a given cancer type, will be flagged during the PCI data collection process. A purposeful sample of up to 60 cases, reflecting a breadth of cancer types, will be selected for inclusion.

3.5 Recruitment and eligibility

3.5.1 Recruitment

General practices will primarily be recruited from Wales, topped up with practices from North West of England. We will recruit 8-10 practices from each of the seven Health Boards in Wales, and 8-10 from North West England; this conservative estimate is informed by feasibility study recruitment. Wales and North West England have similar regional demography; with higher deprivation and cancer rates compared with other UK areas (NWCR, 2021b, 2021a). If recruitment is challenging, we propose to extend the study into South West England. Networks and contacts established through the feasibility study will be maintained in order to maximise recruitment across Wales, and regional Clinical Research Network (CRN) teams will assist in recruiting the practices across all of the centres.

All practices within the study sites will be approached and invited to participate, with recruitment centres set up in the different recruitment areas. A targeted online recruitment campaign (social media, flyers, study website) followed by direct email invitation to each individual practice is proposed to optimize recruitment. The email recipient (most likely the practice manager) will be asked to consult with their team and then indicate their interest in participating in the study by responding to the email. They will also need to advise of their availability for potential workshop dates, if possible, within the same email response. If no response to the initial email is received, a reminder email will be sent followed by a telephone call.

Practices that take part in the study will be reimbursed a total of £250 once follow up measures have been completed. Control practices will also have access to a pre-recorded version of the workshop and materials once they have completed all the required data collection.

3.5.2 Qualitative recruitment

3.5.2.1 Stakeholders

Stakeholders including the CNSCs, and practice staff will be identified via previous feasibility work. Patient and carer stakeholders will be identified via the Patient Advisory Group (PAG). Once identified, they will be sent an invitation via email with a Stakeholder Participant Information Sheet (PIS) and response details; if interested in taking part they can contact the researcher, after which an interview will be arranged at a time and place convenient for the participant.

3.5.2.2 Patients and carers

Patients will be recruited via their GP and will be eligible if they have received an urgent referral for potential cancer symptoms within the last 12 months. Patients will be given an invitation pack containing an invitation letter, Patient PIS and response details. Those who wish to take part can contact the researcher and interviews will be arranged at a convenient time and location. Carers will be recruited via nomination from patients and will also receive an invitation pack containing an invitation letter, Carer PIS and response details.

3.5.3 Eligibility to participate

3.5.3.1 Inclusion

General medical practices in Wales, and North West England will be eligible to participate in this trial. If recruitment numbers are not reached, recruitment may expand to include practices in South West England. In cases where multiple 'satellite' practices are considered separate but have a crossover of staff, the practices will still be able to take part but for the purpose of the study, will be considered as one single practice.

Although there may be a risk of contamination, staff working on a short-term basis term (e.g. medical students, trainees, etc.) within participating practices will not be excluded from participation in workshops. The philosophy behind the workshop encourages inclusivity of the entire practice team, and the safety netting plan developed together with the practice at the end of the workshop is encouraged to plan for the eventuality of staff leaving and joining the practice team in terms of ensuring the safety netting plan is sustainable.

3.5.3.2 Exclusion

Practices in Wales that participated in the ThinkCancer! feasibility trial will be excluded from this full definitive trial, along with practices where any of the study GP Educators are based. Practices that don't have access to the required IT equipment, including a microphone, speakers and camera, will be excluded.

3.6 Consent

3.6.1 Participating practice teams

Practices that have expressed an interest to participate will be sent the initial study documentation, including a Research Information Sheet for Practices (RISP). They will also be sent a link to the baseline practice questionnaire, which will include a built-in consent form. Practice managers will be the point of contact for the duration of the study and will need to indicate that they have read the study information and agree with consent statements on behalf of the practice.

Practices randomised to the intervention will also receive Participant Information Sheets (PIS) and participant consent forms, which are to be distributed to all members of staff within the practice. These will also be accessible online. Informed written consent will be obtained from all participating members of staff prior to the workshop; time will be given at the start of the workshop to allow for consent forms to be completed. Staff can complete either the paper forms or they can complete an online form via a link provided via a QR code on the presentation slides at the start of the workshop. The consent form will cover consent to the use of anonymised data recorded on paper or electronically during the workshops, as well as data collected via workshop feedback forms. Participants will be able to provide the team with their contact details should they be happy to be contacted regarding workshop feedback forms and NoMAD forms.

Approval from a Confidentiality Advisory Group (CAG) will be sought to access the patient notes via the practice team.

3.6.2 Qualitative interviews

Written consent will be obtained from participants at the time of the interview.

3.7 Withdrawal

During the course of the study, practices, individual staff members within participating practices and interview participants will be free to withdraw from the trial at any time, and their right to refuse participation will be respected throughout the trial period.

If individuals within the practice team wish to withdraw, they will be allowed to do so but we will seek to understand their reasons where possible.

Participants may also withdraw their consent, which means that they wish to withdraw from the study completely. In this case, participants can withdraw from the study but permit data already collected via feedback forms, the NoMAD survey or workshop recordings (in the case of practice staff), and data collected

via interviews (in the case of patient, carer and stakeholder participants) to be retained for use in the study analysis. No further data will be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study at any time if they consider it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Clinical decision

Withdrawals will be recorded.

3.8 Randomisation and blinding

3.8.1 Randomisation

The general practice will be the unit of randomisation, with an allocation ratio of 1:1 intervention:control. Randomisation will be achieved online, through the remote randomisation centre at the North Wales Organisation for Randomisation Trials in Health (NWORTH) at Bangor University. The randomisation system will use a dynamic adaptive allocation algorithm. Practices will be stratified by practice list size and geographical area.

Practice List Size

The proposal for practice list size is above and below the median practice list size, which is around 8,000 patients. The stratification variable categories would therefore be:

1. Less than or equal to 8,000 patients;
2. More than 8,000 patients.

Geographical location

The stratification by location is based on the recruitment strategy for the trial. The strategy is to recruit from each health board in Wales, and also the North West of England. The stratification variable categories would be:

1. Each of the seven health boards in Wales, as for the feasibility, which creates seven categories:
    - Aneurin Bevan University Health Board
    - Betsi Cadwaladr University Health Board
    - Cardiff & Vale University Health Board
    - Cwm Taf University Health Board
    - Hywel Dda University Health Board
    - Powys Teaching Health Board
    - Swansea Bay University Health Board
2. The North West of England as an eighth category, supplemented by the South West of England, depending on recruitment success.

3.8.2 Blinding

It will not be possible to blind the GP practice staff or the staff from the trial team. The statisticians and health economists will be blinded until the blinded analysis has been completed.

3.9 Data collection

3.9.1 Clinical outcome measures

Clinical data collection will be achieved through a combination of routinely collected data, practice collected data, and independent clinical researcher collected data. Guideline interval, PCI and cancer stage at diagnosis are fields of clinical data which will need to be collected manually by accessing individual patient records. This data will be collected retrospectively, following the close of the follow-up data collection window, by independent clinical researchers (who will be either physicians or research nurses).

PCI is slightly subjective, in the sense that different clinicians may review patient notes and identify different symptoms and dates as first presentation of cancer, which is then used to calculate the PCI. In order to reduce the impact of this, a sample of PCI data from each clinical researcher will be selected to be reviewed by a second clinical researcher. In the case of difference of opinion there will be a request for both individuals to discuss and come to a consensus decision. In the event that this is a frequent occurrence there will be a request for more PCI data to be reviewed by two clinical researchers.

In terms of the guideline interval, data will be collected using a form that will include the red flags for each cancer pathway to see if the referral was within the guideline and timeframe, or the referral was triggered by a "non-red flag red flag" for that cancer (Macmillan, 2022; NICE, 2015).

Conversion rate, detection rate and USC referral rate data will be collected retrospectively for 12-month baseline and 12-month follow-up data collection windows, using data routinely collated by the practices themselves. The baseline data collection window will extend to 12 months prior to randomisation. The follow-up data collection windows will commence two-months post-randomisation for conversion rate and USC referral rate data, whilst detection rate data collection will begin at 14 months post-randomisation, in line with PCI and Guideline Interval data.

All clinical data will be collected using case report forms and entered into MACRO, the electronic data capture system.

All data collection forms and participant facing documents will also be made available in Welsh if requested.

3.9.1.1 Case note review

Case notes will be screened during the PCI data collection process and a purposeful sample of patients with long PCI selected for inclusion in the case note review. The precise duration of the PCI thresholds employed will be based upon previously published PCI data (Neil, 2014) enabling an estimate of the 75th and 90th centiles to be made and the case note data to be extracted in parallel to PCI data collection. Clinical data from the time of the primary care interval will be summarised and extracted from the patient's case notes in an anonymised form for further analysis at a later stage.

3.9.2 Practice questionnaire

The baseline practice questionnaire will be available online via SurveyMonkey™ to both intervention and control practices and is to be filled out by the Practice Manager or other designated person, ideally in collaboration with the practice team. The questionnaire will consist of closed questions and some open, free-text questions, and will be used to collect data for each individual practice on the practice characteristics and current systems, and existing practice systems relating to cancer diagnosis and safety netting. The baseline data may be used to inform some workshop planning - i.e. workshop content and delivery may be tailored to some extent to suit individual

practice needs and circumstances. The baseline questionnaire will be completed by all practices prior to randomisation; baseline measures will include the following:

- Demographic information and practice characteristics (practice size, whether research active, number of clinical and non-clinical staff members, whether a teaching practice, etc.)
- Practice culture (e.g. team structure, diversity of team member roles, team decision-making processes)
- Practice knowledge with regards to safety netting
- Current safety netting systems in place, if any, including:
    - What systems are in place
    - How widely, within the practice, they are used
    - How safety netting issues are communicated:
        - Between clinicians
        - To the wider practice team
        - To patients
    - How safety netting is recorded

Practices will need to complete the baseline questionnaire (with attached consent form) in order to enrol on the study. This will be emphasised in the information packages sent out to practices when they are invited to take part. A reminder email will be sent to practices if the questionnaire is not completed within the two weeks of the questionnaire being sent to the practices, followed by telephone calls to the practice manager.

The practice questionnaire will be administered again at 12 months.

3.9.3 Process evaluation

Recruitment rates, retention rates and questionnaire completion numbers will be recorded throughout the trial. Spreadsheet systems will be put in place to record practice responses and to track their progress in the trial (e.g. number of practices approached, whether they have responded to the initial invitation, whether they have agreed to be randomised, etc.). Separate spreadsheets will also record data relating to the workshop itself, such as participant attendance numbers.

3.9.3.1 Feedback forms

All staff participating in the workshop will be asked to complete a feedback form upon completion of the workshop. Responses will be requested using a combination of Yes/No choices, Likert scales and free-text comments. The forms will be used to assess acceptability, learning outcomes, usefulness and impact on future practice.

3.9.3.2 NoMAD survey

Survey data will be collected from all participants in intervention practices using the NoMAD tool four to six months after the workshop has taken place (Finch et al., 2015) to assess implementation of the cancer safety netting plan and activity of the safety netting champion.

3.9.3.3 Interviews

Qualitative data will be firstly collected via interviews with key stakeholders to establish context and gather background knowledge and experiences. Following recruitment of practices, patient and carer/relative perspectives regarding experiences of urgent referral will be gathered via in-depth qualitative interviews. Patient and carer interviews will last approximately one hour. All interviews will be conducted by a qualitative researcher, recorded and anonymised.

Due to the sensitive nature of the topic, there is a chance that the participant may experience distress during the interview. If the researcher becomes aware that the participant may be experiencing distress, they will pause the interview until the participant is ready to carry on or they may decide to stop the interview. The researcher will signpost participants to additional support if required.

3.9.4 Economic evaluation

This will investigate what resources society, through the NHS, is willing to spend to reduce the median primary care interval by 1 day, as a proxy for morbidity and quality of life. Therefore, the economic evaluation will be about system change.

We will collect data on the direct medical costs of delivering the ThinkCancer! intervention through the use of data collection sheets completed by the intervention deliverers. Micro-costing of the ThinkCancer! intervention will include intervention deliverers' time, materials, printing, publication, online materials, postage costs of delivering materials to the practices i.e. Red Whale Handbook, and intervention deliverer' travel costs (for face-to-face delivery). In addition, time spent training the intervention delivery trainers will also be logged so that it can be costed. We will cost live seminars/webinars including materials, professional staff time to reflect the co-production nature of CPD and to reflect on the opportunity cost of CPD in terms of time not spent on direct patient care activities, and mixed-format delivery – potential costs of a face-to-face/online delivery format across Wales and England in future following the COVID-19 pandemic. To incorporate opportunity cost in our analysis we will include a question in the feedback forms asking practice employees for information about what they would have been doing during the time taken to participate in the ThinkCancer! training programme and any subsequent change in practice.

An economic evaluation using a decision analytical model will be developed to model the patient transition and distribution across various cancer health states. The simulated model will be designed to reflect the time-to-event outcome. Data from the ThinkCancer! programme and micro-costing data will be structured into the model; all parameters, assumptions, and the model itself will be tested vigorously for variability and uncertainty using the CHEERS (Husereau et al., 2022) and the Assessment of the Validation Status of Health-Economic Decision Model (AdVISHE) (Vemer et al., 2016).

3.10 Internal pilot

Although progression criteria would usually not be required in a phase III trial, a nested internal pilot will be conducted using RAG (red, amber, green) criteria to ensure the success of the trial. After three months of recruiting, we will assess the following:

1. Number of practices randomised (green ≥ 80%; amber 50-79%; red <50%)
2. Number of practices allocated to the intervention arm that have booked their intervention (green 64%; Amber 40-63%; red <40%)

The results of this internal pilot will be discussed with the funder and the trial steering committee, to form strategies for addressing any amber or red results as necessary for progression of the trial. If this internal pilot shows that recruitment is below the target there will be consideration of recruiting more GP practices from the North West of England than was initially planned, as well as recruiting GP practices from the South West of England as an additional recruitment site.

3.11 Data analysis

3.11.1 Statistical procedures

Descriptive statistics will summarise data overall and per group. The adapted NoMAD will be reported descriptively, there will be no analysis of the data.

Primary analysis will be conducted on an intention to treat (ITT) basis, blinded to treatment allocation. PCI data and guideline interval data will be analysed using time to event models, adjusting for allocated group and stratification variables. Other secondary outcomes will be analysed using analysis of covariance (ANCOVA) models or fractional response regression models, adjusting for baseline scores, allocated group and stratification variables.

Secondary analysis of PCI and guideline interval data will repeat the time to event analysis on the 75th and 90th percentiles of data, corresponding to the longest 25% and 10% respectively, in order to further explore the impact of the intervention on those with the longest PCIs and guideline intervals.

There will also be a logistic regression analysis of cancer stage at diagnosis, which will provide additional information as to whether cancers are diagnosed at an earlier stage or not, and the factors that may influence this.

Sensitivity analysis will also be conducted. This sensitivity analysis will only include the GP practices from the intervention group who attended the workshops within two months of randomisation, as well as the GP practices from the control group.

For these analyses other covariates and factors may be included in the models, these will be defined a priori. All estimates of effect will be presented together with 95% confidence intervals. The aim is to minimise missing data; however, predictors of missingness will be investigated using regression models and any predictors found will be considered for inclusion in the models. Multiple imputation will be employed to address missing scores where appropriate. A full statistical analysis plan will be written and agreed before completion of the data collection. The independent committees will have an opportunity to comment on the analysis plan. If any deviations from the planned statistical analysis are required these will be fully documented and justified in the final analysis report.

3.11.2 Qualitative analysis

Qualitative interviews will be audio recorded and fully transcribed. Data will be analysed thematically using the Framework method (Richie & Lewis, 2003). Framework is a five stage matrix based system comprising immersion in the data, the development of a coding index, coding of the data, synthesis of the data into thematic charts and a final stage of interpretation (Richie and Lewis, 2003). Framework facilitates a teamwork approach and allows for multiple members of the team to be involved in interpretation. Interpretation workshops will be conducted to include members of the research team and the PPI contributors.

Anonymous data extracted from patient case notes will also be analysed thematically using Framework methodology.

The NoMAD survey data will be assessed with descriptive statistics.

Health economics

This will be conducted according to the Health Economics Analysis Plan (HEAP). We will use decision analytical modelling from an NHS perspective, drawing costs and transition probabilities from the ThinkCancer! trial data;

and undertake a micro-costing of the intervention from an NHS perspective, informed by the feasibility trial. A recent study explored the costs of initiatives to promote rapid diagnosis of cancer in a hospital setting in Spain using a micro-costing approach (Montori-Palacín et al., 2020). We will undertake a micro-costing of the ThinkCancer! intervention from an NHS perspective informed by pilot costing undertaken in the ThinkCancer! feasibility study (Anthony et al., 2022). We will conduct a base case analysis in line with the NICE reference case (NICE, 2013). This economic evaluation alongside the trial of the ThinkCancer! intervention is about system change rather than a single health technology or treatment. In this sense it is difficult to think about comparing the ICER for ThinkCancer! with any meaningful payer threshold as we do in terms of the NICE cost per QALY payer threshold of £20,000 to £30,000. There is no threshold for willingness to pay for a day reduced in time-to-event (diagnosis of cancer). Essentially, we are needing to think about what resources society, through the NHS, is willing to spend to reduce the length of the primary care interval by one day as an intermediate or proxy outcome for the potential benefits to life expectancy and quality of life as well as reduced health service use at a population level that we know can come about through earlier diagnosis of cancer.

3.11.2.1 Cost-effectiveness analysis

We will investigate the cost-effectiveness affordability curve (CEAFC) which captures both dimensions of the joint distribution of incremental costs and effects on the cost-effectiveness plane (Pedram Sendi & Briggs, 2001). The CEAFC will analyse the budget impact of ThinkCancer, as it can be used to estimate the joint probability that the programme is both affordable and cost-effective. A cost-effectiveness risk-aversion curve (CERAC) will also be studied by incorporating different levels of risk-aversion into the analysis, these can be used to inform decision-makers who are risk-averse (Pedram Sendi & Briggs, 2001).

3.11.2.2 Sensitivity analysis and subgroup analysis

We will conduct sensitivity analysis to vary the costs of inputs (e.g., the cost of face-to-face versus online delivery, the costs of different types of staff delivering the intervention other than research staff from a university setting).

Possible subgroup analyses will be considered for e.g. different types of cancers, practice size/patient population, ethnic mix of practices, GP age and gender, access to rapid diagnostic centres or other service improvement initiatives etc.

4. TRIAL MANAGEMENT AND GOVERNANCE

4.1 Data Monitoring

A monitoring plan will be prepared prior to recruitment detailing the monitoring strategy for the trial. The plan will include requirements for day-to-day centralised monitoring, and any requirements identified in the risk assessment. The CRF will be considered the source data and should be consistent and verifiable with the data recorded in the electronic data capture system. Information regarding how the data will be collected, sorted and transferred will be included in the Data Management Plan. We will adhere to the joint BCUHB/Bangor Univeristy Standard Operating Procedures (SOPs). Data held at NWORTH will be subject to NWORTH SOPs, for all data management, statistical and regulatory matters.

4.1.1 Operational group

The operational group will meet weekly and will be responsible for the overall conduct, supervision and progress of the study. They consist of the immediate research team, supported by a wider group of experts and

PPI representatives. A Trial Management Group (TMG) will meet monthly and will be responsible for the day-to-day management of the trial. The TMG will comprise the co-PIs, the Trial Manager, the trial statistician, the qualitative lead, the trial health economist and the members of the operational group.

4.1.2 Trial governance

A Trial Steering Committee (TSC) led by Professor David Weller will provide independent oversight for the study, ensuring it is conducted according to the standards set out by the HRA Research Governance Framework (HRA, 2017) and the Guidelines for Good Clinical Practice (GCP). Meetings are expected to be biannual and the Sponsor and Funder will be updated following each meeting. The TSC will have an independent chairperson and at least three independent members including Patient and Public Involvement (PPI) representation, trial co-applicants, statisticians, health economist(s) and GPs.

In addition to the TSC, a Data Monitoring and Ethics Committee (DMEC) will also be set up to monitor the trial, provide the TSC with advice on trial conduct and to ensure patient safety is maintained at the highest level.

4.2 Data Management

A detailed data management plan will be written by NWORTH staff. This plan will include the definition of the data quality checks that will be performed on the data throughout the life course of the trial. These will include source data validation, random data checks and timelines for data entry.

4.2.1 Data Protection and participant confidentiality

All investigators, trial site and research staff will comply with the requirements and regulations of the EU General Data Protection Regulation 2018 (GDPR) regarding the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles. All research staff involved will have up to date GCP training. Research data will be retained as per the Sponsor's research data management policy. Bangor University is the data custodian.

4.2.2 Data archiving

As per the Sponsor's research data management policy, research data and records will be archived along with the data management policy of the Sponsor.

In line with legal requirements, trial documents will be archived centrally at a secure facility with appropriate environmental controls and adequate protection from fire, flood and unauthorized access. Archived material will be stored in tamper- proof archive boxes that are clearly labelled. Electronic archiving will be provided by the Sponsor for post-project deposit and retention of data.

Destruction of essential documents will require authorisation from the Sponsor.

4.3 End of study

The end of study will be the point at which all the study data has been entered and queries resolved.

5. SAFETY REPORTING

5.1 Definitions of adverse events

A serious adverse event (SAE) 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.

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.

5.2 Reporting procedures for adverse events

A risk assessment has found this trial to be of minimal risk. Non-serious adverse events will not be collected. However, Serious Adverse Events (SAEs) will be reported to the REC that gave favourable opinion of the study for any event occurring unexpectedly (the type of event is not listed in this protocol as an expected occurrence) that could be related ("resulting from administration of any of the research procedures") to the intervention, as decided by the Chief Investigator (CI) and in line with current ICH-GCP guidelines (EMA, 2016). Reports of related and unexpected SAEs will be submitted within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form.

6. ETHICS

6.1 Research ethics approval

Full ethical approvals and agreements will be sought from the HRA and Health and Care Research Wales (HCRW), the Bangor University School of Health Sciences Ethics Committee, REC and the relevant NHS/HSC R&D office.

R&D approval from all participating Health Boards and England Regions will be sought.

Before the recruitment process starts, the CI will ensure all required approvals are in place. Any relevant correspondence with the regulatory bodies will be retained in the Trial Master File (TMF).

6.2 Amendments

It is the Sponsor's responsibility to make a decision on whether an amendment is substantial or non-substantial. Both minor and substantial amendments will be processed as per HRA guidance (HRA, 2017). HRA and HCRW approval must be received before the amendment may be implemented. All amendments need to be shared with NHS R&D departments of participating sites who have 35 days to raise any objections. If no objections have been raised after this time, the amendment can be implemented.

6.3 Protocol compliance

Protocol deviations and violations will be documented on the relevant forms and reported to both the CI and Sponsor immediately. The Bangor University/BCUHB SOP R01 'Reporting of Deviations and breaches of protocol or GCP' will detail the reporting procedure for trial related deviations, to include identification of the deviation, details of initial corrective actions and assessment of impact on trial participants. The trial manager will be responsible for setting up such a reporting procedure.

6.4 Declaration of interests

There are currently no competing interests.

6.5 Indemnity

1. Arrangements for insurance and/or indemnity to meet the potential legal liability of the Sponsor for harm to participants arising from the management of the research:
   This is the Sponsor's responsibility, and is provided for under the Sponsor's Public Liability cover for any negligent acts or omissions of the Sponsor or its staff involved with the management of the research.

2. Arrangement for insurance/indemnity to meet the potential legal liability of the Sponsor or employer(s) for harm to participants arising from the design of the research:
   This is the Sponsor's responsibility, and is provided for under the Sponsor's Professional Indemnity cover for any negligent acts or omissions of the Sponsor or its staff involved with the design of the research.

3. Arrangements for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research:
   This is the responsibility of each participating site and evidence of those sites' indemnity covers should be provided. On sites that are not covered by the NHS Indemnity Scheme (e.g. GP surgeries in primary care), investigators/collaborators will need to ensure that their activity on the study is covered under the own professional indemnity.

Documents provided by the Sponsor's insurers to present evidence of the relevant cover will be made available upon request.

6.6 Access to the final dataset

Access to the final dataset will be in accordance with governance policies, GCP guidelines and local arrangements. The trial statisticians will have full access to the dataset. The CIs and trial manager will have access to the full dataset after the analysis has been completed. The TSC will have access to the full dataset as required.

6.7 Dissemination policy

On completion of the study a final report will be prepared for Cancer Research Wales and North West Cancer.

Findings may be disseminated through various media, including the programme web pages, social media, open-access peer-reviewed publications, national and international conferences, and through an end-of-programme Symposium for key stakeholders. Findings will also be disseminated to participating practice teams. Authorship will be determined according to the ThinkCancer! Publication Plan and Policy authorship guidelines.

6.8 Peer review

The WICKED programme has been peer reviewed on behalf of the funding body, Cancer Research Wales and North West Cancer Research. Members of the TSC will provide some peer review throughout the trial period.

6.9 Patient and public involvement

Patient and public involvement (PPI) has been a central tenet throughout the WICKED programme and in this next phase of ThinkCancer!, we will continue to engage with a range of PPI representatives in order to maximise the relevance and impact of the study for people's lives in Wales, North West England and beyond. To achieve this, we intend to incorporate a range of different approaches.

This study has two PPI representative co-applicants, one of which (JR) has been actively involved since the very beginning of the WICKED programme and in the development of this trial, and is currently a member of the Trial

Management Group (TMG). A second PPI member (LG) has also been recruited from the PRIME Centre Wales SUPER Group and has been invited to join the Trial Management Group. Both PPI members will contribute to the development of this protocol and will advise throughout all stages of the trial.

In addition, JR leads our Patient Advisory Group (PAG) for additional PPI input at key project points. The PAG will have four to six members, with three expressions of interest having been already received. The PPI co-applicants and the PAG will work with the operational team to design study materials, especially patient facing documents such as the Patient Information Sheet (PIS) and Informed Consent Forms (ICF), and topic guides for the qualitative work. Members of the PAG will be consulted on qualitative data analysis and invited to interpretation workshops. The PAG members will have the opportunity to contribute to dissemination as co-authors of publications and conference presentations. We will also have PPI members on the Trial Steering Committee (TSC). We will comply with the NIHR UK Standards for Public Involvement and follow good practice including training, induction and joint development of role descriptions. We will use the GRIPP2 tool to evaluate and learn from PPI (Staniszewska et al., 2017). PPI contributors will be reimbursed for their time, travel and subsistence following the new (April 22) H&CRW rate of £25ph.

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8. APPENDICES

8.1 Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

8.2 Appendix 2 – SPIRIT Schedule of Procedures

	STUDY PERIOD								
	Pre-allocation	Allocation	Intervention Period	2 months	3 months	6 months	10 months	12 months	26 months
TIMEPOINT	$-t_1$	0	t_1	f_1	f_2	f_3	f_4	f_5	f_6
ENROLMENT:									
Eligibility screen	X								
Invitation email	X								
Practice information and consent	X								
Baseline questionnaire									
Randomisation		X							
INTERVENTION:									
Control group: usual practice		●	●					●	●
Intervention group: ThinkCancer! Workshop		●	●	●	●	●	●	●	●
ASSESSMENTS:									
Staff feedback forms			X						
Workshop delivery staff logs			X						
Collection of health economics data			X						
NoMAD survey				X					

Qualitative Interviews (stakeholders)					●	—	●		
Qualitative interviews (patients & carers)							●	—	●
Endline questionnaire								X	
Collection of clinical outcome measures: **2WW, CR**								X	
Cancer-related DATIX data								X	
Case note review									X
Collection of clinical outcome measures: **DR, PCI, cancer stage, GI**									X

Adapted version of a table from Chan et al. (2013)

8.3 Appendix 3 – SPIRIT Checklist

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT/CONSORT 2013 Checklist

Section/item	Item No.	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	i
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	iv
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	i
Funding	4	Sources and types of financial, material, and other support	i
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	
	5b	Name and contact information for the trial sponsor	i
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	i

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached separately
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.