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The IRCO Trial: a factorial cluster-randomised controlled trial of a complex intervention to reduce time to diagnosis in rural cancer patients in Western Australia: study protocol.



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4 **The IRCO Trial: a factorial cluster-randomised controlled**
5 **trial of a complex intervention to reduce time to diagnosis in**
6 **rural cancer patients in Western Australia: study protocol.**
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Abstract

Introduction

While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia. Internationally a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis. Approaches to reducing time to diagnosis of symptomatic cancer include public symptom awareness campaigns and interventions in primary care to improve early cancer detection. This paper reports the protocol of a factorial cluster-randomised trial of community and General Practice (GP) level interventions to reduce the time to diagnosis of cancer in rural Western Australia (WA).

Methods and analysis

The Community Intervention is a symptom awareness campaign tailored for rural Australians delivered through a community engagement model. The GP intervention includes a resource card with symptom risk assessment charts and local referral pathways implemented through multiple academic detailing visits and case studies. Participants are eligible if recently diagnosed with breast, colorectal, lung or prostate cancer who reside in specific regions of rural WA with a planned sample size of 1,350. The primary outcome is the Total Diagnostic Interval, defined as the duration from first symptom (or date of cancer screening test) to cancer diagnosis. Secondary outcomes include cancer stage, healthcare utilisation, disease-free status, survival at two and five years and cost-effectiveness.

Ethics and dissemination

Ethics approval has been granted by the University of Western Australia and from all relevant hospital recruitment sites in Western Australia. Results of this trial will be reported in peer-reviewed publications and in conference presentations.

Registration details

Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12610000872033

Strengths and Limitations of this study

- This is the first RCT to test the implementation of cancer risk tools based on the Hamilton CAPER studies. It is also novel in that it will measure the effect of separate and combined community and GP interventions on time to cancer diagnosis.
- Longer term follow-up will assess the impact on survival.
- The community control area was matched as closely as possible within the constraints of the population distribution in different regions of Western Australia.

Background

Rural Australians are more likely to die within 5 years of a cancer diagnosis than people from metropolitan areas.(1) While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia.(2) Similar disparities in cancer outcomes across certain patient groups have been described worldwide.(3) As part of the International Cancer Benchmarking Partnership, a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis.(4)

Previous studies have shown that patients living in rural Australia are less likely to receive curative or reconstructive surgery, radiotherapy or anti-cancer drug treatment.(5-8) Policy initiatives have focused, therefore, on reducing disparities in access to treatment.(9) Access to treatment is an important determinant of outcome, but later presentation and stage at diagnosis have also been observed in rural cancer patients.(10, 11) International research suggests that the time taken to appraise symptoms and seek help (so-called 'patient delay') and management in primary care are also key determinants of cancer outcomes.(12) Time to diagnosis is associated with poorer survival for several common cancers.(13, 14)

One of the approaches to reducing later presentation to healthcare has been community symptom awareness campaigns. These have formed a major component of the UK National Awareness and Early Diagnosis Initiative(NAEDI) as part of the policy to improve cancer outcomes.(15) A systematic review of cancer symptom awareness campaigns published in 2009 found insufficient evidence about their effect on presentation to healthcare.(16) Since then further studies have begun to show potential effects on presentation and cancer diagnoses.(17)

A second approach has aimed at improving early recognition of patients in primary care with symptoms suggestive of cancer. A major challenge for general practitioners (GPs) is that the symptoms of many cancers are common in the community and overlap with prevalent benign conditions. GPs need to assess the risk, or diagnostic probability, of an underlying

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3 cancer and determine whether further investigation is justified. Until recently, there was
4 little epidemiological evidence demonstrating how well symptoms predict risk of an
5 underlying cancer from primary care populations.(18) Analysis of data in case-control
6 studies using large UK general practice databases, notably the CAPER (Cancer Prediction in
7 Exeter) studies(19-22) and QCancer research(23, 24), has led to significant advances in our
8 understanding of the epidemiology of cancer symptoms in primary care.
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15 The CAPER studies have quantified the risk of individual and paired symptoms, signs and
16 primary care investigations for a number of cancers including colorectal, lung and prostate.
17 These have been evaluated as risk assessment tools (RATs) in paper versions(25) and are
18 currently undergoing evaluation as computerised decision support tools embedded in the
19 electronic medical records of English general practices.(26) Various interventions including
20 audit and feedback, educational visits, guidelines and decision support have been tested in
21 general practice to improve cancer diagnosis.(27) None of the 22 trials included in a
22 systematic review of interventions to support cancer diagnosis in primary care examined
23 effects on diagnostic delay, although audit and feedback was shown to improve clinical
24 management.(28)
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35 Conducting research in the field of 'diagnostic delay' in cancer has many methodological
36 challenges. The Aarhus Statement discusses these and provides consensus guidelines on
37 appropriate definitions and the conduct and reporting of such research.(29) One
38 recommendation is the application of theoretical models such as The Model of Pathways to
39 Treatment (30, 31) (Figure 1). This model proposes four key intervals:
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- 43 1. The **Appraisal Interval**. The nature of a person's symptoms is one of the most important
44 factors determining the duration of the Appraisal Interval. Misattribution of symptoms
45 either to a previous benign or concurrent condition or non-recognition of the
46 seriousness of symptoms contribute to longer Appraisal Intervals.
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- 50 2. The **Help-Seeking Interval**. Various factors may contribute to this interval including
51 patient factors such as competing events (e.g. holidays), and emotional ones such as
52 fear. This includes fear of the consultation and examination, or of the diagnosis and
53 treatment. Access to primary care and sanctioning help-seeking by family or friends, so
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3 that patients do not perceive themselves as wasting the doctor's time, are also
4 important factors.(32)

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7 3. The **Diagnostic Interval**. Depending on the healthcare setting this may involve a series
8 of healthcare visits, referrals and investigations and often represents a complex process.
9 System factors including the role of primary care as a gatekeeper and access to
10 investigations and specialist care are key factors determining this interval.
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12 4. **The Pre-Treatment Interval**. The time from formal cancer diagnosis to initiation of
13 treatment is also strongly influenced by several healthcare system factors such as access
14 to staging investigations and specialised treatments.
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21 **Figure 1: Model of Pathways to Treatment** (30, 31)

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24 Our research on rural cancer outcomes is applying the well-established Medical Research
25 Council (MRC) methodological framework for the design and evaluation of complex
26 interventions.(33, 34) Our initial exploratory mixed-methods study aimed to explore the
27 context of rural cancer diagnosis in WA and inform the development of our complex
28 intervention. In summary, in-depth interviews with 66 people recently diagnosed with
29 breast, lung, prostate or colorectal cancer from regional WA found longer duration of
30 symptom appraisal for colorectal cancer compared with other cancers. Participants defined
31 core characteristics of rural Australians as optimism, stoicism and machismo. These
32 features, as well as poorer access to health care, contributed to later presentation of
33 cancer.(18) In addition, there were significant overall differences between cancers in terms
34 of time from presentation in general practice to referral, from GP referral to specialist
35 appointment, and from specialist appointment to cancer diagnosis. These differences were
36 due to the nature of presenting symptoms, access to diagnostic tests and multiple visits to
37 specialists. Breast cancer was diagnosed more quickly because its symptoms are more
38 specific and well recognised by the community, and due to better access to diagnostic tests
39 and specialist one-stop clinics.(35)
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54 These findings contributed to the development of the interventions and design of the
55 Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled
56 trial of community-based and general practice-based interventions which aims to reduce
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3 the time to diagnosis in rural patients presenting with prostate, breast, colorectal or lung
4 cancer in Western Australia.
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9 10 **Methods and Trial Design**

11 *Design and setting*

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13 This 2x2 factorial cluster randomised controlled trial is set in Western Australia, the largest
14 Australian state geographically, with a population of 2.29 million (approximately 10% of the
15 Australian population). Two thirds of the WA population live in metropolitan Perth and the
16 remainder are widely geographically dispersed. Two Trial Areas were matched for
17 population size, demographics including age and Aboriginality, and similar cancer incidence ,
18 based on the most recent available data (from 2006) when the trial was planned (Figure 2
19 presents more recent data on population size from 2010). Trial Area A comprises the
20 Wheatbelt (155,256 km²), Goldfields (770,488 km²) and Great Southern (39,007 km²)
21 regions, and Trial Area B includes the Peel/South West (29,646 km²) and MidWest
22 (470,000km²) regions.(36)
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33 **Figure 2: Map of Western Australia depicting the regional boundaries of Trial Area A,**
34 **receiving the community intervention, and Trial Area B, acting as the community**
35 **control.**
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40 **Randomisation**

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42 Trial Area A has been allocated to receive the community symptom awareness campaign
43 intervention and Trial Area B acts as the community campaign control region. In both Trial
44 Areas general practices have been randomised to receive the education intervention or
45 control, stratified by practice size (<=1 GP; 2 to 4 GPs; 5+ GPs). GPs who worked at more
46 than one practice have been identified, and their practices have been treated as one
47 practice for the purpose of randomisation to avoid contamination (Figure 3).
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54 **Figure 3: The 2x2 factorial cluster randomised controlled trial design.(37)**
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3 Practices have been randomly assigned to intervention or control arm using a cluster
4 version of Zelen's method of post-randomised consent: intervention practices have been
5 invited to receive the educational package while control practices receive no information
6 about the trial.(38) This enables non-intervention practices to act as true controls by
7 minimising the Hawthorne effect in a situation where placebo and double blind
8 experimental conditions are impossible to achieve. The Hawthorne effect occurs when the
9 researchers' procedures and communications act as interventions in themselves that
10 change behaviours, such as if the control cluster were to adopt the practices or policies
11 promoted to the intervention cluster. This would destroy the trial's ability to identify a
12 benefit of the intervention, if one exists. Furthermore, it allows a pragmatic delivery of the
13 intervention and measure of its uptake in routine practice. Intervention practices which
14 decline the invitation to receive the educational package will be analysed on an intention-
15 to-treat basis. Randomisation has been performed by the trial statistician. As the number of
16 working GPs in a given practice varies, the randomisation has taken into account practice
17 size. Each practice has been categorized into: one GP in the practice, 2-4 GPs or five or
18 more GPs. A random sample proportional to the size of the practice has been used
19 employing 'samplepps' macro in Stata.
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37 ***Patient recruitment and inclusion criteria***

38 From 1 March 2012, four months after the interventions commenced, all patients meeting
39 the following criteria are being invited to contribute their data for the trial:
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- 42 • Adults aged over 18 years;
- 43 • Diagnosed with breast, lung, colorectal or prostate cancer between 1 January 2012
44 and the recruitment end date of 31 March 2014; and
- 45 • Resident of Trial Areas A or B at the time of diagnosis.
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50 ***Recruitment Strategy***

51 Eligible participants are identified via:
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3 1. The WA Cancer Registry (WACR). A letter and participant information sheet is mailed
4 from the WACR directly to newly diagnosed cancer patients. After three-weeks non
5 responders are followed up by the research team via phone or mail.
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8 2. Cancer Council Western Australia's (CCWA) residential lodges. We approach eligible
9 patients while staying at CCWA charitable accommodation during their cancer treatment in
10 Perth. A large proportion of rural cancer patients, especially those receiving radiotherapy or
11 chemotherapy, reside in one of the lodges for several weeks during their treatment. Eligible
12 patients receive the same participant information sheet as part of their Lodge Welcome
13 Pack by the lodge receptionists and are followed up by the research team.
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20 ***Study Interventions***

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22 The Trial includes interventions at two levels: a community symptom awareness campaign
23 ('the community intervention'); and a GP educational package incorporating symptom risk
24 assessment charts and referral guidance which is implemented through multiple academic
25 detailing visits and case studies ('the GP intervention'). Both interventions are being
26 delivered between 1 November 2011 to 31 December 2013.
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32 *The Community Intervention*

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34 We modified existing resources developed for The Cancer Research UK 'Spot Cancer Early'
35 and the UK National Health Service '3 week cough' campaigns to incorporate the findings of
36 our exploratory mixed-methods study (18,(35), and to make them relevant to a rural
37 Australian community.
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41 Materials have been further modified following three community forums held in the major
42 towns of the campaign target regions. Feedback was obtained about the campaign logo,
43 design, choice of images, locally acceptable language, and contact details. The campaign is
44 named the Find Cancer Early campaign and the materials explicitly use the Cancer Council
45 WA branding, recognising the strong community support and credibility of this organisation.
46
47 Community members wanted the campaign to focus on the positives associated with early
48 detection and the use of simple, non-medical terms when describing symptoms. A
49 campaign message development meeting was then held between the project team, social
50 marketing experts and health professionals to develop a framework for the campaign and
51 message hierarchy.
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5 The target of the campaign is men and women over the age of 40; it aims to raise awareness
6 of the symptoms of bowel, lung, prostate and breast cancer, and to help people overcome
7 the barriers to seeking medical help. The primary campaign item is a plain-language
8 symptom checklist (Figure 4). Other materials include: newspaper adverts based on
9 campaign materials; radio adverts for each of the 4 cancers; tumour-specific postcards
10 featuring regional images and quotations about relevant symptoms (Figure 4); generic
11 postcards providing strategies to overcome barriers to seeking help (Figure 4); a DVD
12 outlining tumour specific symptoms featuring health professionals and regional community
13 members; an Indigenous version of the symptom checklist; a website; and posters and
14 banners.
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24 **Figure 4: Examples of Find Cancer Early resources – General Symptom Checklist, Prostate**
25 **postcard and Tell your doctor postcard.**
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30 Five project officers, with a combined full time equivalent of 3.0, are delivering the
31 campaign across the three regions of WA in Trial Area A. They use a community
32 engagement approach building partnerships to deliver and disseminate the campaign
33 messages with presentations, displays and campaign resource distribution. Paid advertising
34 and articles in regional newspapers and radio supplement this dissemination strategy.
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42 *The GP Intervention*

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44 A GP education resource card, 'The Rural Cancer Initiative: a Guide for General
45 Practitioners', has been developed with input from rural GPs and health professional
46 advisors. The novel aspect of this intervention is the implementation of the CAPER risk
47 assessment charts for colorectal,(21) lung(20) and prostate(22) cancer. The resource card
48 contains the clinical implications of these risk charts including diagnostic assessment. In
49 addition the resource card summarises the National Breast and Ovarian Cancer Centre
50 guidelines for investigating new breast symptoms (39) and local referral guidelines and
51 hospital contacts, including recommendations about access to cancer multidisciplinary
52 teams.(40)
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5 The GP resource card is being implemented through a series of four academic detailing
6 practice visits, supplemented by a series of question-and-answer case studies for
7 completion between visits designed to reinforce key messages.(41) The practice visits
8 present specific components of the resource card and facilitate discussion within the
9 practice around recently diagnosed cancer patients. GPs are eligible for Royal Australian
10 College of General Practitioners and Australian College of Rural and Remote Medicine
11 professional development points on completion of the case studies and attendance at
12 practice visits.
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20 **Outcomes and Measures**

21 **Primary Outcome**

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25 The primary outcome is the Total Diagnostic Interval, defined as the time from first
26 symptom to diagnosis. We will report our time intervals according to the principles outlined
27 in the 'Aarhus Statement' on the conduct and reporting of research on cancer diagnosis,(29)
28 and will use the *Model of Pathways to Treatment* as our theoretical framework.(30, 31)
29 The date of first symptom is defined as '*the time-point when first bodily change(s) and/or*
30 *symptom(s) is noticed*'. For screen-detected cases we use the date of attendance for the
31 screening test as the initial date in the patient pathway. Date of diagnosis is based on
32 pathological diagnosis as reported to the WA Cancer Registry. We will divide the Total
33 Diagnostic Interval further to include time from first presentation in general practice to
34 referral (GP Interval), date of referral to first attendance at specialist (Specialist Access
35 Interval), and time from first attendance at the specialist to date of diagnosis (Specialist
36 Interval).(42) The GP Interval includes the time taken to order and respond to investigations
37 available directly in primary care. For patient-reported dates we will apply published mid-
38 point rules to estimate the actual date where uncertainty exists.(12) Where necessary, a
39 clinical consensus group will review the data to confirm the date of first symptom and first
40 presentation to healthcare.
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53 *Measurement tools*

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55 The following instruments will be used to obtain information about symptoms and key dates
56 to calculate the Total Diagnostic Interval:
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1. SYMPTOM Questionnaire

This self-administered questionnaire was developed from the C-SIM(43) measure and has been applied in the UK SYMPTOM study.(44) It includes items specific to each tumour site to capture details of symptoms, their date of onset and time taken to seek help.

2. GP record audit tool

This tumour-specific proforma is mailed to the participant's GP to obtain key information on: the date, type and duration of presenting symptoms within the last 12 months, referral information including referral date, and date of first appointment with specialist.

Date of cancer diagnosis is obtained from the WA Cancer Registry.

Secondary outcomes

1. Process Measures of Intervention Delivery

a. Campaign Dose

Process evaluation is conducted in each intervention town to collect data on the amount of media exposure achieved, number of campaign resources distributed, number of partnerships established, and number of presentations, events and other activities carried out by campaign staff to promote the campaign messages. Information is collected via monthly reports by the campaign project officers.

b. Media Exposure

Media exposure is measured by number and square centimetre coverage of paid press advertisements and unpaid press articles. The value of unpaid media is estimated by calculating the square centimetre space and calculating the cost to purchase that space.

c. GP Monitoring

The campaign project officers document number of visits conducted, GP attendance at each visit, and number of case studies completed.

d. Costs of intervention delivery

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3 Cost data of delivering the interventions are being collected prospectively (see Health
4 Economic Evaluation below).
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9 **2. Impact Measures of Intervention**

10 Campaign awareness is being measured at 18 months into the campaign intervention by a
11 computer assisted telephone interview survey. The survey is being conducted on a random
12 sample of adults over 40 years old from the campaign regions and control regions stratified
13 by sex and age, and regions within Trial Area A. Questions measure exposure to the
14 campaign, including unprompted and prompted awareness of campaign elements (i.e.
15 radio, print and campaign brand and logos). Respondents reporting any exposure to the
16 campaign are asked additional questions about comprehension and perceived effectiveness.
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27 **3. Measures of Clinical Outcomes**

28 We will use the WA datasets (45) to provide linked hospital morbidity and administrative,
29 cancer diagnostic and mortality data in order to examine trends across time on clinical
30 outcomes at the level of the community and individual. We will obtain these data in three
31 tranches:
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- 36 a. Cohort of patients diagnosed in 2002-2010 to provide a baseline understanding of
37 the patterns of care and survival;
- 38 b. Cohort of patients diagnosed in 2011-2013 with all linked data after at least two
39 years of follow-up to evaluate short-term clinical effects of the interventions on
40 cancer stage, health care utilisation and disease free status;
- 41 c. Cohort of patients diagnosed in 2011-2013 with all linked data after at least five
42 years of follow-up to evaluate medium-term clinical effects and survival.
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49 **Analysis**

50 The cluster randomised design provides protection against contamination across trial groups
51 when trial patients are managed within the same setting.(46) The primary analysis will
52 compare the Total Diagnostic Intervals and its sub-components between trial groups.
53 Simple analyses such as t-tests or more complex regression analyses will be undertaken.
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3 Time data are invariably skewed and bounded by the absence of negative times. We will
4 apply a log transformation prior to conducting general linear modelling to compare intervals
5 accounting for exposure to the community and GP interventions within the model,
6 accounting for clustering effects at the practice level. Where appropriate, comparisons of
7 arithmetic or geometric means will be performed. The aim of statistical modelling is to
8 identify the main factors that explain variation in the outcome e.g. patient and practice
9 characteristics. The primary aim is to adjust for the effect of covariates before the effect of
10 the intervention is tested as well as 'intervention × phase' interaction with pre- and post-
11 measurements comparison. We will conduct a series of sensitivity analyses to account for:

- 12 a. symptoms reported with a duration of greater than two years which will be excluded
13 from the primary analysis.
- 14 b. vague first symptoms such as fatigue and 'feeling different'.

15 Using cancer registry, hospital morbidity and death data we will compare patterns of
16 hospitalisation and treatment, pseudo-staging at diagnosis using established methods
17 where full staging data are not available(45, 47-50), disease-free intervals and survival in
18 people diagnosed with breast, lung, colorectal or prostate cancer resident in Trial Area A
19 with those in Area B and those resident elsewhere in non-metropolitan and metropolitan
20 WA. The comparisons will relate to patients diagnosed with one of the four target cancers
21 in the six years prior to the interventions (2005-2010) and during the two years of
22 intervention (late 2011 – late 2013). This will enable the effects of the community-level
23 intervention to be evaluated as a spatial contrast. The same analyses will be conducted
24 after five-years of follow-up. These analyses will entail all cancer patients in WA during the
25 specific time periods to assess the effects of the community intervention. In addition, we
26 will conduct analyses of all consented trial participants to measure the effects of exposure
27 to the GP intervention and combined effect of community and GP interventions on clinical
28 outcomes at two and five years.

29 All analyses will be conducted by trial statisticians blinded to participant allocation.

4. *Health economic evaluation*

A health economic evaluation from a health system perspective will be undertaken to determine whether the resources committed to the trial between the four intervention arms represent a worthwhile investment in terms of the measured outcomes. This will include a cost-analysis of each intervention and a cost-effectiveness analysis which will compare costs with related outcomes. Cost components include : campaign intervention costs (e.g. staffing, travel, campaign resources, media, events, in-kind support); GP intervention costs (e.g. staffing, travel, education program, resources); additional staff costs; non-intended costs of non-cancer diagnoses (hospital utilisation); in-kind personnel contributions from project partners. Resource units and cost per unit will be applied to calculate total cost.

Outcome data will be matched to cost data. In the first instance, cost per change in TDI will be calculated for each of the four arms of the trial. Longer term cost-effectiveness will also be calculated to estimate net cost per life year gained for each intervention. The TDI will provide a surrogate outcome for longer term outcomes using modelling techniques. Once longer term follow-up data are available, cost-effectiveness ratios will be calculated.

Sample Size

The original sample size required for 80% power and $\alpha=0.05$ to detect a halving of long-delay risk of 30% to 15% was 840 participants. This sample size calculation accounted for the design effects from hierarchical correlations and an intra-class correlation coefficient of 0.09 based on similar trial designs.(51)

Recruitment was planned to continue until four months after completion of intervention delivery to allow inclusion of a cohort of newly diagnosed cancer patients who were exposed to the interventions (i.e 31 March 2014). We have achieved approximately a 50% accrual rate into the trial which was much higher than our original estimates. Our final estimated recruitment is 1,359 participants. Based on the distributions of TDIs) from our previous research, (18,(35) this sample will provide 80% power to detect a 10% difference in TDI between intervention groups for all four cancers combined, and a 20% difference in TDI

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3 for breast, colorectal and prostate cancer separately, but not lung cancer as this would
4 require a sample of 2,600 participants.
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9 **Ethical Considerations**

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11 The trial obtained primary ethics approval from The University of Western Australia's
12 Human Research Ethics Committee (RA/4/1/4527). Additional approval was gained through
13 the Department of Health of Western Australia's ethics committee, as well as reciprocal
14 approvals with relevant metropolitan and regional hospitals.
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20
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23 Cancer Council Western Australia, the WA Cancer and Palliative Care Network, and the
24 Department of Health Western Australia.
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32 **Dissemination**

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34 This is the first randomised controlled trial to test the individual and combined effects of a
35 community awareness campaign and GP intervention on time to cancer diagnosis. We plan
36 to publish the main trial outcomes in a single paper and anticipate publishing additional
37 papers exploring the data in more detail and relating to the implementation of this complex
38 intervention. We will present the findings at national and international conferences from
39 late 2014.
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48 **Authors contributions**

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50 JDE, CDJH, CS, KA, AN, FMW, MB conceptualised and designed the study. All authors
51 assisted with the development of the protocol, study design and refinement of study
52 materials. All authors will contribute to implementation of the protocol and acquisition of
53 data. JDE, VG and CDJH led the writing of the protocol. All authors have been involved in
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3 drafting and critical evaluation of the manuscript. All authors have read and approved the
4 final version.
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8 *Conflicts of interest*

9
10 None declared
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12

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14
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18 *Council WA Lodges, participants, GPs and Hospital specialists, Cancer Research UK, AH*
19 *Crawford Treatment Society, Department of Health WA, WA Cancer and Palliative Care*
20 *Network, WA Country Health Service, National Health and Medical Research Council, Cancer*
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24 *Steve Pratt, David Preen, Babu Simon, Craig Sinclair, Hayley Staples, Simon Towler, Clare*
25 *Willix.*
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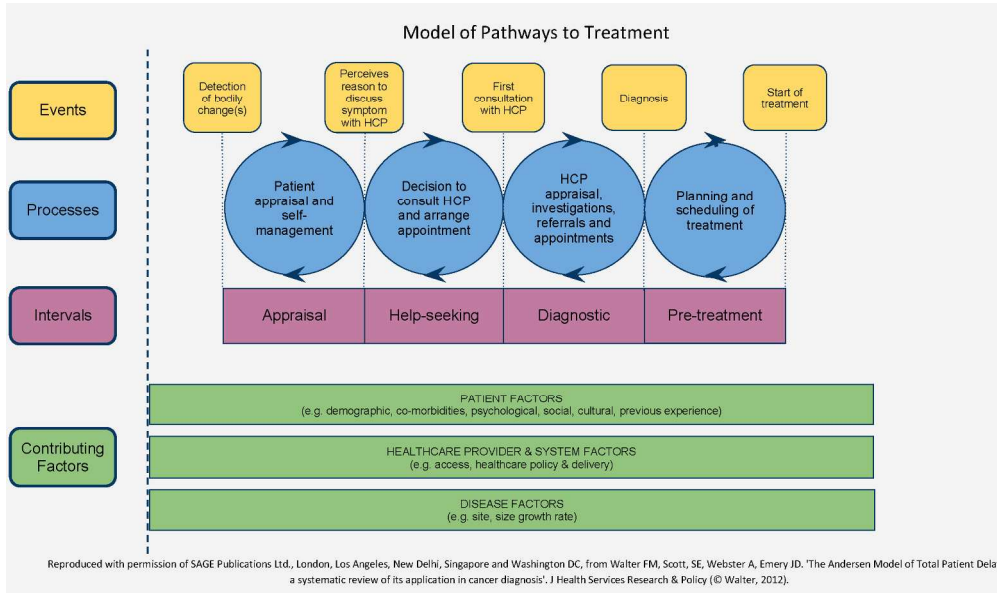
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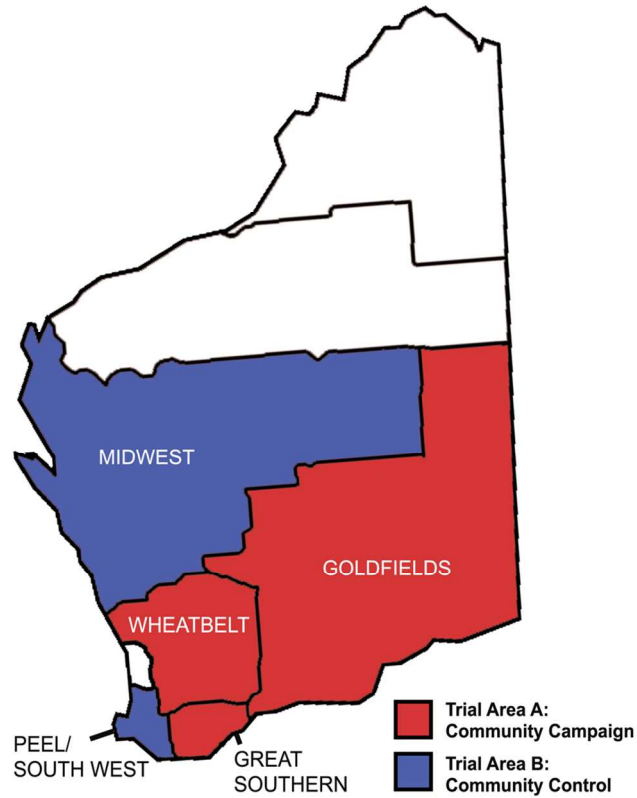
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Model of Pathways to Treatment (30, 31)
320x188mm (200 x 200 DPI)

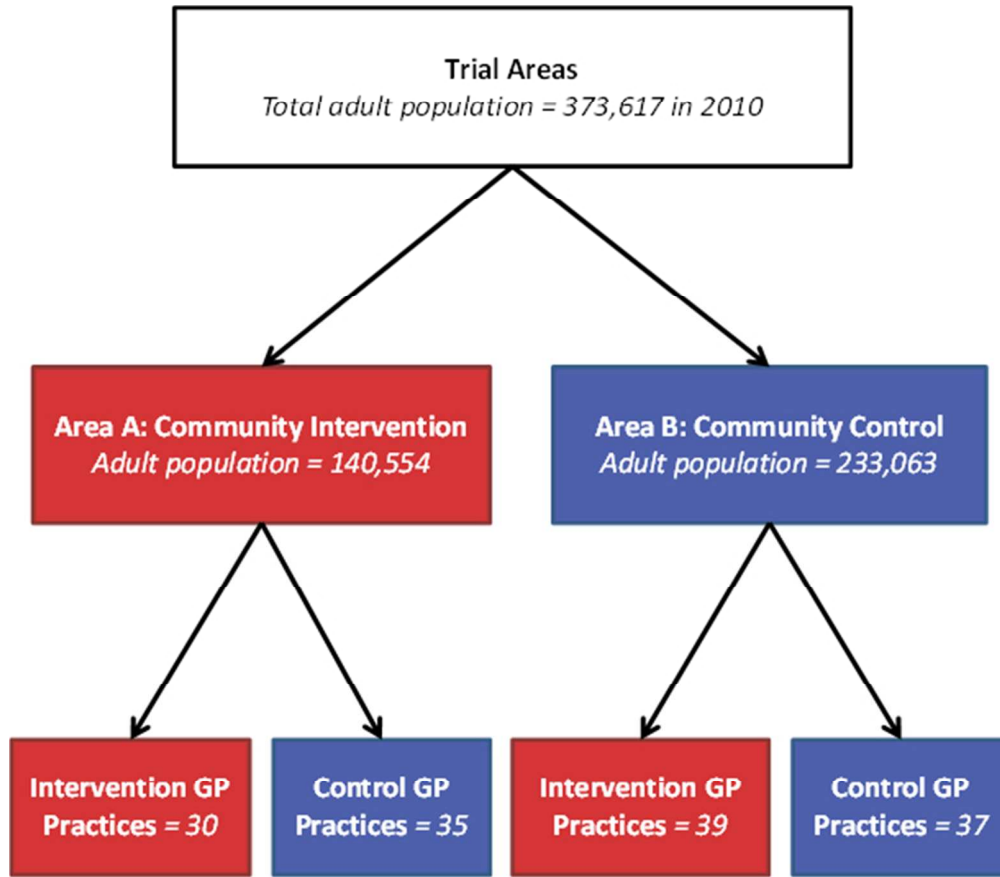
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Map of Western Australia depicting the regional boundaries of Trial Area A, receiving the community intervention, and Trial Area B, acting as the community control.

104x147mm (300 x 300 DPI)



The 2x2 factorial cluster randomised controlled trial design.(37)
215x188mm (72 x 72 DPI)

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General Symptom Checklist

Are you over 40?
Have you had any of these...

... for more than 4 weeks?

- Blood in your poo
- Problems peeing
- Looser poo
- Unexplained weight loss
- An unusual pain, lump or swelling anywhere in your body
- Becoming more short of breath
- A persistent cough

... once off?

- Coughing up blood
- Blood in your pee

**If you have...
Tell your doctor**

The earlier cancer is found, the greater the chance of successful treatment.

Find Cancer Early
Cancer Council Helpline 13 11 20
Cancer Council

For more information visit: www.findcancerearly.com.au

Prostate Symptom Postcard (Front and Back)

Front: "How's the ute? How's the Mrs? How's the waterworks?"
If your peeing is causing you problems, tell your doctor.

Back: Tell your doctor if you have any of these symptoms:

- If you ever find blood in your pee
- Waking frequently at night to pee
- Sudden or urgent need to pee
- Difficulty starting or stopping peeing
- Slow flow
- Pain when you pee
- Unexplained weight loss

These symptoms might be due to prostate cancer and the earlier it's found, the greater the chance of successful treatment.

For more information visit: www.findcancerearly.com.au

Tell your doctor Postcard (Front and Back)

Front: Your doctor is never too busy to see you.
Tell your doctor about any changes with your body, no matter how small or how often they occur.

Back: Tell your doctor - if you notice any of the possible symptoms of cancer.

Lots of questions and concerns may pass through your mind when you decide to see your doctor.

Excuse	Fact
<input checked="" type="checkbox"/> The doctor is always too busy, it's too hard to get an appointment.	<input checked="" type="checkbox"/> Phoning early in the morning can help.
<input checked="" type="checkbox"/> When I get to the doctor's my mind goes blank.	<input checked="" type="checkbox"/> Writing a list jogs your memory.
<input checked="" type="checkbox"/> I'm worried about what might happen when I see the doctor.	<input checked="" type="checkbox"/> The doctor might examine you, reassure you, and/or arrange tests or refer you.

For more useful tips visit: www.findcancerearly.com.au

Examples of Find Cancer Early resources – General Symptom Checklist, Prostate postcard and Tell your doctor postcard.
209x147mm (300 x 300 DPI)

Review only

BMJ Open

The Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled trial of a complex intervention to reduce time to diagnosis in rural cancer patients in Western Australia: study protocol.



Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-006156.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Aug-2014
Complete List of Authors:	Emery, Jon; University of Melbourne, General Practice and Primary Care Academic Centre Gray, Victoria; The University of Western Australia, School of Population Health Walter, Fiona; University of Cambridge, Dept of Public Health and Primary Care Cheetham, Shelley; The University of Western Australia, School of Primary, Aboriginal and Rural Health Care Croager, Emma; Cancer Council Western Australia, Education and Research; Curtin University, Centre for Behavioural Research and Cancer Control Slevin, Terry; Cancer Council WA, Education and Research Saunders, Christobel; The University of Western Australia, School of Surgery Threlfall, Timothy; The Department of Health of Western Australia, Western Australian Cancer Registry Auret, Kirsten; The University of Western Australia, Rural Clinical School of Western Australia Nowak, Anna; Sir Charles Gairdner Hospital, Department of Medical Oncology Geelhoed, Elizabeth; The University of Western Australia, School of Population Health Bulsara, Max; University of Notre Dame, Biostatistics Holman, Darcy; The University of Western Australia, School of Population Health
Primary Subject Heading:	Health services research
Secondary Subject Heading:	General practice / Family practice, Oncology, Public health, Research methods
Keywords:	Epidemiology < ONCOLOGY, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL EDUCATION & TRAINING, PRIMARY CARE, PUBLIC HEALTH

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Manuscripts

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4 **The Improving Rural Cancer Outcomes (IRCO) Trial: a**
5 **factorial cluster-randomised controlled trial of a complex**
6 **intervention to reduce time to diagnosis in rural cancer**
7 **patients in Western Australia: study protocol.**
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15 Jon D Emery, Victoria Gray, Fiona M Walter, Shelley Cheetham, Emma J Croager, Terry
16 Slevin, Christobel Saunders, Tim Threlfall, Kirsten Auret, Anna K Nowak, Elizabeth Geelhoed,
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Abstract

Introduction

While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia. Internationally a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis. Approaches to reducing time to diagnosis of symptomatic cancer include public symptom awareness campaigns and interventions in primary care to improve early cancer detection. This paper reports the protocol of a factorial cluster-randomised trial of community and General Practice (GP) level interventions to reduce the time to diagnosis of cancer in rural Western Australia (WA).

Methods and analysis

The Community Intervention is a symptom awareness campaign tailored for rural Australians delivered through a community engagement model. The GP intervention includes a resource card with symptom risk assessment charts and local referral pathways implemented through multiple academic detailing visits and case studies. Participants are eligible if recently diagnosed with breast, colorectal, lung or prostate cancer who reside in specific regions of rural WA with a planned sample size of 1,350. The primary outcome is the Total Diagnostic Interval, defined as the duration from first symptom (or date of cancer screening test) to cancer diagnosis. Secondary outcomes include cancer stage, healthcare utilisation, disease-free status, survival at two and five years and cost-effectiveness.

Ethics and dissemination

Ethics approval has been granted by the University of Western Australia and from all relevant hospital recruitment sites in Western Australia. Results of this trial will be reported in peer-reviewed publications and in conference presentations.

Registration details

Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12610000872033

Strengths and limitations

- This is the first large scale RCT to test the implementation of cancer risk tools based on the Hamilton CAPER studies. It is also novel in that it will measure the effect of separate and combined community and GP interventions on time to cancer diagnosis.
- Longer term follow-up will assess the impact on survival.
- The community control area was matched as closely as possible within the constraints of the population distribution in different regions of Western Australia.

Background

Rural Australians are more likely to die within 5 years of a cancer diagnosis than people from metropolitan areas.(1) While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia.(2) Similar disparities in cancer outcomes across certain patient groups have been described worldwide.(3) As part of the International Cancer Benchmarking Partnership, a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis.(4)

Previous studies have shown that patients living in rural Australia are less likely to receive curative or reconstructive surgery, radiotherapy or anti-cancer drug treatment.(5-8) Policy initiatives have focused, therefore, on reducing disparities in access to treatment.(9) Access to treatment is an important determinant of outcome, but later presentation and stage at diagnosis have also been observed in rural cancer patients.(10, 11) International research suggests that the time taken to appraise symptoms and seek help (so-called 'patient delay') and management in primary care are also key determinants of cancer outcomes.(12) Time to diagnosis is associated with poorer survival for several common cancers.(13, 14)

One of the approaches to reducing later presentation to healthcare has been community symptom awareness campaigns. These have formed a major component of the UK National Awareness and Early Diagnosis Initiative(NAEDI) as part of the policy to improve cancer outcomes.(15) A systematic review of cancer symptom awareness campaigns published in

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3 2009 found insufficient evidence about their effect on presentation to healthcare.(16) Since
4 then further studies have begun to show potential effects on presentation and cancer
5 diagnoses.(17)
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10 A second approach has aimed at improving early recognition of patients in primary care with
11 symptoms suggestive of cancer. A major challenge for general practitioners (GPs) is that the
12 symptoms of many cancers are common in the community and overlap with prevalent
13 benign conditions. GPs need to assess the risk, or diagnostic probability, of an underlying
14 cancer and determine whether further investigation is justified. Until recently, there was
15 little epidemiological evidence demonstrating how well symptoms predict risk of an
16 underlying cancer from primary care populations.(18) Analysis of data in case-control
17 studies using large UK general practice databases, notably the CAPER (Cancer Prediction in
18 Exeter) studies(19-22) and Qcancer research(23, 24), has led to significant advances in our
19 understanding of the epidemiology of cancer symptoms in primary care.
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29 The CAPER studies have quantified the risk of individual and paired symptoms, signs and
30 primary care investigations for a number of cancers including colorectal, lung and prostate.
31 These have been evaluated as risk assessment tools (RATs) in paper versions(25) and are
32 currently undergoing evaluation as computerised decision support tools embedded in the
33 electronic medical records of English general practices.(26) Various interventions including
34 audit and feedback, educational visits, guidelines and decision support have been tested in
35 general practice to improve cancer diagnosis.(27) None of the 22 trials included in a
36 systematic review of interventions to support cancer diagnosis in primary care examined
37 effects on diagnostic delay, although audit and feedback was shown to improve clinical
38 management.(28)
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49 Conducting research in the field of 'diagnostic delay' in cancer has many methodological
50 challenges. The Aarhus Statement discusses these and provides consensus guidelines on
51 appropriate definitions and the conduct and reporting of such research.(29) One
52 recommendation is the application of theoretical models such as The Model of Pathways to
53 Treatment (30, 31) (Figure 1). This model proposes four key intervals:
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3 1. The **Appraisal Interval**. The nature of a person's symptoms is one of the most important
4 factors determining the duration of the Appraisal Interval. Misattribution of symptoms
5 either to a previous benign or concurrent condition or non-recognition of the
6 seriousness of symptoms contribute to longer Appraisal Intervals.
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10 2. The **Help-Seeking Interval**. Various factors may contribute to this interval including
11 patient factors such as competing events (e.g. holidays), and emotional ones such as
12 fear. This includes fear of the consultation and examination, or of the diagnosis and
13 treatment. Access to primary care and sanctioning help-seeking by family or friends, so
14 that patients do not perceive themselves as wasting the doctor's time, are also
15 important factors.(32)
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- 18 3. The **Diagnostic Interval**. Depending on the healthcare setting this may involve a series
19 of healthcare visits, referrals and investigations and often represents a complex process.
20 System factors including the role of primary care as a gatekeeper and access to
21 investigations and specialist care are key factors determining this interval.
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- 24 4. **The Pre-Treatment Interval**. The time from formal cancer diagnosis to initiation of
25 treatment is also strongly influenced by several healthcare system factors such as access
26 to staging investigations and specialised treatments.
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35 Our research on rural cancer outcomes is applying the well-established Medical Research
36 Council (MRC) methodological framework for the design and evaluation of complex
37 interventions.(33, 34) Our initial exploratory mixed-methods study aimed to explore the
38 context of rural cancer diagnosis in WA and inform the development of our complex
39 intervention. In summary, in-depth interviews with 66 people recently diagnosed with
40 breast, lung, prostate or colorectal cancer from regional WA found longer duration of
41 symptom appraisal for colorectal cancer compared with other cancers. Participants defined
42 core characteristics of rural Australians as optimism, stoicism and machismo. These
43 features, as well as poorer access to health care, contributed to later presentation of
44 cancer.(18) In addition, there were significant overall differences between cancers in terms
45 of time from presentation in general practice to referral, from GP referral to specialist
46 appointment, and from specialist appointment to cancer diagnosis. These differences were
47 due to the nature of presenting symptoms, access to diagnostic tests and multiple visits to
48 specialists. Breast cancer was diagnosed more quickly because its symptoms are more
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3 specific and well recognised by the community, and due to better access to diagnostic tests
4 and specialist one-stop clinics.(35)
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8 These findings contributed to the development of the interventions and design of the
9 Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled
10 trial of community-based and general practice-based interventions which aims to reduce
11 the time to diagnosis in rural patients presenting with prostate, breast, colorectal or lung
12 cancer in Western Australia.
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17 18 19 20 **Methods and Trial Design**

21 ***Design and setting***

22 This 2x2 factorial cluster randomised controlled trial is set in Western Australia, the largest
23 Australian state geographically, with a population of 2.29 million (approximately 10% of the
24 Australian population). Two thirds of the WA population live in metropolitan Perth and the
25 remainder are widely geographically dispersed. Two Trial Areas were matched for
26 population size, demographics including age and Aboriginality, and similar cancer incidence ,
27 based on the most recent available data (from 2006) when the trial was planned (Figure 2
28 presents more recent data on population size from 2010). Trial Area A comprises the
29 Wheatbelt (155,256 km²), Goldfields (770,488 km²) and Great Southern (39,007 km²)
30 regions, and Trial Area B includes the Peel/South West (29,646 km²) and MidWest
31 (470,000km²) regions.(36)
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44 **Randomisation**

45 Trial Area A has been allocated to receive the community symptom awareness campaign
46 intervention and Trial Area B acts as the community campaign control region. In both Trial
47 Areas general practices have been randomised to receive the education intervention or
48 control, stratified by practice size (<=1 GP; 2 to 4 GPs; 5+ GPs). GPs who worked at more
49 than one practice have been identified, and their practices have been treated as one
50 practice for the purpose of randomisation to avoid contamination (Figure 3).
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3 Practices have been randomly assigned to intervention or control arm using a cluster
4 version of Zelen's method of post-randomised consent: intervention practices have been
5 invited to receive the educational package while control practices receive no information
6 about the trial.⁽³⁷⁾ This enables non-intervention practices to act as true controls by
7 minimising the Hawthorne effect in a situation where placebo and double blind
8 experimental conditions are impossible to achieve. The Hawthorne effect occurs when the
9 researchers' procedures and communications act as interventions in themselves that
10 change behaviours, such as if the control cluster were to adopt the practices or policies
11 promoted to the intervention cluster. This would destroy the trial's ability to identify a
12 benefit of the intervention, if one exists. Furthermore, it allows a pragmatic delivery of the
13 intervention and measure of its uptake in routine practice. Intervention practices which
14 decline the invitation to receive the educational package will be analysed on an intention-
15 to-treat basis. Randomisation has been performed by the trial statistician. As the number of
16 working GPs in a given practice varies, the randomisation has taken into account practice
17 size. Each practice has been categorized into: one GP in the practice, 2-4 GPs or five or
18 more GPs. A random sample proportional to the size of the practice has been used
19 employing 'samplepps' macro in Stata.
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Patient recruitment and inclusion criteria

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38 From 1 March 2012, four months after the interventions commenced, all patients meeting
39 the following criteria are being invited to contribute their data for the trial:
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- 42 • Adults aged over 18 years;
- 43 • Diagnosed with breast, lung, colorectal or prostate cancer between 1 January 2012
44 and the recruitment end date of 31 March 2014; and
- 45 • Resident of Trial Areas A or B at the time of diagnosis.
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Recruitment Strategy

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51 Eligible participants are identified via:
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3 1. The WA Cancer Registry (WACR). A letter and participant information sheet is mailed
4 from the WACR directly to newly diagnosed cancer patients. After three-weeks non
5 responders are followed up by the research team via phone or mail.
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8 2. Cancer Council Western Australia's (CCWA) residential lodges. We approach eligible
9 patients while staying at CCWA charitable accommodation during their cancer treatment in
10 Perth. A large proportion of rural cancer patients, especially those receiving radiotherapy or
11 chemotherapy, reside in one of the lodges for several weeks during their treatment. Eligible
12 patients receive the same participant information sheet as part of their Lodge Welcome
13 Pack by the lodge receptionists and are followed up by the research team.
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16 Participants are invited to sign a consent form, which includes agreement to access their
17 medical records, and return it with their completed SYMPTOM questionnaire.
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23 ***Study Interventions***

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25 The Trial includes interventions at two levels: a community symptom awareness campaign
26 ('the community intervention'); and a GP educational package incorporating symptom risk
27 assessment charts and referral guidance which is implemented through multiple academic
28 detailing visits and case studies ('the GP intervention'). Both interventions are being
29 delivered between 1 November 2011 to 31 December 2013.
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36 *The Community Intervention*

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38 We modified existing resources developed for The Cancer Research UK 'Spot Cancer Early'
39 and the UK National Health Service '3 week cough' campaigns to incorporate the findings of
40 our exploratory mixed-methods study (18,(35), and to make them relevant to a rural
41 Australian community.
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45 Materials have been further modified following three community forums held in the major
46 towns of the campaign target regions. Feedback was obtained about the campaign logo,
47 design, choice of images, locally acceptable language, and contact details. The campaign is
48 named the Find Cancer Early campaign and the materials explicitly use the Cancer Council
49 WA branding, recognising the strong community support and credibility of this organisation.
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Community members wanted the campaign to focus on the positives associated with early
detection and the use of simple, non-medical terms when describing symptoms. A
campaign message development meeting was then held between the project team, social

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3 marketing experts and health professionals to develop a framework for the campaign and
4 message hierarchy.
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8 The target of the campaign is men and women over the age of 40; it aims to raise
9 awareness of the symptoms of bowel, lung, prostate and breast cancer, and to help people
10 overcome the barriers to seeking medical help. The primary campaign item is a plain-
11 language symptom checklist (Figure 4). Other materials include: newspaper adverts based
12 on campaign materials; radio adverts for each of the 4 cancers; tumour-specific postcards
13 featuring regional images and quotations about relevant symptoms (Figure 4); generic
14 postcards providing strategies to overcome barriers to seeking help (Figure 4); a DVD
15 outlining tumour specific symptoms featuring health professionals and regional community
16 members; an Indigenous version of the symptom checklist; a website; and posters and
17 banners.
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28 Five project officers, with a combined full time equivalent of 3.0, are delivering the
29 campaign across the three regions of WA in Trial Area A. They use a community
30 engagement approach building partnerships to deliver and disseminate the campaign
31 messages with presentations, displays and campaign resource distribution. Paid advertising
32 and articles in regional newspapers and radio supplement this dissemination strategy.
33 Television is not being used to avoid contamination in the control area.
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39 40 *The GP Intervention*

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42 A GP education resource card, 'The Rural Cancer Initiative: a Guide for General
43 Practitioners', has been developed with input from rural GPs and health professional
44 advisors. The novel aspect of this intervention is the implementation of the CAPER risk
45 assessment charts for colorectal,(21) lung(20) and prostate(22) cancer. The resource card
46 contains the clinical implications of these risk charts including diagnostic assessment. In
47 addition the resource card summarises the National Breast and Ovarian Cancer Centre
48 guidelines for investigating new breast symptoms (38) and local referral guidelines and
49 hospital contacts, including recommendations about access to cancer multidisciplinary
50 teams.(39)
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3 The GP resource card is being implemented through a series of four academic detailing
4 practice visits, supplemented by a series of question-and-answer case studies for
5 completion between visits designed to reinforce key messages.(40) The practice visits
6 present specific components of the resource card and facilitate discussion within the
7 practice around recently diagnosed cancer patients. GPs are eligible for Royal Australian
8 College of General Practitioners and Australian College of Rural and Remote Medicine
9 professional development points on completion of the case studies and attendance at
10 practice visits.
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17 18 **Outcomes and Measures**

19 20 **Primary Outcome**

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22 The primary outcome is the Total Diagnostic Interval, defined as the time from first
23 symptom to diagnosis. We will report our time intervals according to the principles outlined
24 in the 'Aarhus Statement' on the conduct and reporting of research on cancer diagnosis,(29)
25 and will use the *Model of Pathways to Treatment* as our theoretical framework.(30, 31)
26 The date of first symptom is defined as '*the time-point when first bodily change(s) and/or*
27 *symptom(s) is noticed*'. For screen-detected cases we use the date of attendance for the
28 screening test as the initial date in the patient pathway. Date of diagnosis is based on
29 pathological diagnosis as reported to the WA Cancer Registry. We will divide the Total
30 Diagnostic Interval further to include time from first presentation in general practice to
31 referral (GP Interval), date of referral to first attendance at specialist (Specialist Access
32 Interval), and time from first attendance at the specialist to date of diagnosis (Specialist
33 Interval).(41) The GP Interval includes the time taken to order and respond to investigations
34 available directly in primary care. For patient-reported dates we will apply published mid-
35 point rules to estimate the actual date where uncertainty exists.(12) Where necessary, a
36 clinical consensus group will review the data to confirm the date of first symptom and first
37 presentation to healthcare.
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51 *Measurement tools*

52 The following instruments will be used to obtain information about symptoms and key dates
53 to calculate the Total Diagnostic Interval:
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1. SYMPTOM Questionnaire

This self-administered questionnaire was developed from the C-SIM(42) measure and has been applied in the UK SYMPTOM study.(43) It includes items specific to each tumour site to capture details of symptoms, their date of onset and time taken to seek help.

2. GP record audit tool

This tumour-specific proforma is mailed to the participant's GP to obtain key information on: the date, type and duration of presenting symptoms within the last 12 months, referral information including referral date, and date of first appointment with specialist.

Date of cancer diagnosis is obtained from the WA Cancer Registry.

Secondary outcomes

1. Process Measures of Intervention Delivery

a. Campaign Dose

Process evaluation is conducted in each intervention town to collect data on the amount of media exposure achieved, number of campaign resources distributed, number of partnerships established, and number of presentations, events and other activities carried out by campaign staff to promote the campaign messages. Information is collected via monthly reports by the campaign project officers.

b. Media Exposure

Media exposure is measured by number and square centimetre coverage of paid press advertisements and unpaid press articles. The value of unpaid media is estimated by calculating the square centimetre space and calculating the cost to purchase that space.

c. GP Monitoring

The campaign project officers document number of visits conducted, GP attendance at each visit, and number of case studies completed.

d. Costs of intervention delivery

Cost data of delivering the interventions are being collected prospectively (see Health Economic Evaluation below).

2. Impact Measures of Intervention

Campaign awareness is being measured at 18 months into the campaign intervention by a computer assisted telephone interview survey. The survey is being conducted on a random sample of adults over 40 years old from the campaign regions and control regions stratified by sex and age, and regions within Trial Area A. Questions measure exposure to the campaign, including unprompted and prompted awareness of campaign elements (i.e. radio, print and campaign brand and logos). Respondents reporting any exposure to the campaign are asked additional questions about comprehension and perceived effectiveness.

3. Measures of Clinical Outcomes

We will use the WA datasets (44) to provide linked hospital morbidity and administrative, cancer diagnostic and mortality data in order to examine trends across time on clinical outcomes at the level of the community and individual. We will obtain these data in three tranches:

- a. Cohort of patients diagnosed in 2002-2010 to provide a baseline understanding of the patterns of care and survival;
- b. Cohort of patients diagnosed in 2011-2013 with all linked data after at least two years of follow-up to evaluate short-term clinical effects of the interventions on cancer stage, health care utilisation and disease free status;
- c. Cohort of patients diagnosed in 2011-2013 with all linked data after at least five years of follow-up to evaluate medium-term clinical effects and survival.

Analysis

The cluster randomised design provides protection against contamination across trial groups when trial patients are managed within the same setting.(45) The primary analysis will compare the Total Diagnostic Intervals and its sub-components between trial groups. Simple analyses such as *t*-tests or more complex regression analyses will be undertaken. Time data are invariably skewed and bounded by the absence of negative times. We will apply a log transformation prior to conducting general linear modelling to compare intervals

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3 accounting for exposure to the community and GP interventions within the model,
4 accounting for clustering effects at the practice level. Where appropriate, comparisons of
5 arithmetic or geometric means will be performed. The aim of statistical modelling is to
6 identify the main factors that explain variation in the outcome e.g. patient and practice
7 characteristics. The primary aim is to adjust for the effect of covariates before the effect of
8 the intervention is tested as well as 'intervention × phase' interaction with pre- and post-
9 measurements comparison. We will conduct a series of sensitivity analyses to account for:

- 15 a. symptoms reported with a duration of greater than two years which will be excluded
16 from the primary analysis.
- 17 b. vague first symptoms such as fatigue and 'feeling different'.

20 Using cancer registry, hospital morbidity and death data we will compare patterns of
21 hospitalisation and treatment, pseudo-staging at diagnosis using established methods
22 where full staging data are not available(44, 46-49), disease-free intervals and survival in
23 people diagnosed with breast, lung, colorectal or prostate cancer resident in Trial Area A
24 with those in Area B and those resident elsewhere in non-metropolitan and metropolitan
25 WA. The comparisons will relate to patients diagnosed with one of the four target cancers
26 in the six years prior to the interventions (2005-2010) and during the two years of
27 intervention (late 2011 – late 2013). This will enable the effects of the community-level
28 intervention to be evaluated as a spatial contrast. The same analyses will be conducted
29 after five-years of follow-up. These analyses will entail all cancer patients in WA during the
30 specific time periods to assess the effects of the community intervention. In addition, we
31 will conduct analyses of all participants who have given their consent to measure the effects
32 of exposure to the GP intervention and combined effect of community and GP interventions
33 on clinical outcomes at two and five years.

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44 All analyses will be conducted by trial statisticians blinded to participant allocation.

51 **4. Health economic evaluation**

52 A health economic evaluation from a health system perspective will be undertaken to
53 determine whether the resources committed to the trial between the four intervention
54 arms represent a worthwhile investment in terms of the measured outcomes. This will
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3 include a cost-analysis of each intervention and a cost-effectiveness analysis which will
4 compare costs with related outcomes. Cost components include : campaign intervention
5 costs (e.g. staffing, travel, campaign resources, media, events, in-kind support); GP
6 intervention costs (e.g. staffing, travel, education program, resources); additional
7 staff costs; non-intended costs of non-cancer diagnoses (hospital utilisation); in-kind
8 personnel contributions from project partners. Resource units and cost per unit will be
9 applied to calculate total cost.
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17 Outcome data will be matched to cost data. In the first instance, cost per change in TDI will
18 be calculated for each of the four arms of the trial. Longer term cost-effectiveness will also
19 be calculated to estimate net cost per life year gained for each intervention. The TDI will
20 provide a surrogate outcome for longer term outcomes using modelling techniques. Once
21 longer term follow-up data are available, cost-effectiveness ratios will be calculated.
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28 **Sample Size**

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31 The original sample size required for 80% power and $\alpha=0.05$ to detect a halving of long-
32 delay risk of 30% to 15% was 840 participants. This sample size calculation accounted for
33 the design effects from hierarchical correlations and an intra-class correlation coefficient of
34 0.09 based on similar trial designs.(50)
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40 Recruitment was planned to continue until four months after completion of intervention
41 delivery to allow inclusion of a cohort of newly diagnosed cancer patients who were
42 exposed to the interventions (i.e 31 March 2014). We have achieved approximately a 50%
43 accrual rate into the trial which was much higher than our original estimates. Our final
44 estimated recruitment is 1,359 participants. Based on the distributions of TDIs) from our
45 previous research, (18,(35) this sample will provide 80% power to detect a 10% difference in
46 TDI between intervention groups for all four cancers combined, and a 20% difference in TDI
47 for breast, colorectal and prostate cancer separately, but not lung cancer as this would
48 require a sample of 2,600 participants.
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Ethical Considerations

The trial obtained primary ethics approval from The University of Western Australia's Human Research Ethics Committee (HREC) (RA/4/1/4527). Additional approval was gained through the Department of Health of Western Australia's ethics committee, as well as reciprocal approvals with relevant metropolitan and regional hospitals. There is no formal Data Monitoring Committee for this trial as it was felt unnecessary for this type of intervention. Data management procedures are reported in the HREC submission.

Funding

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Dissemination

This is the first randomised controlled trial to test the individual and combined effects of a community awareness campaign and GP intervention on time to cancer diagnosis. We plan to publish the main trial outcomes in a single paper and anticipate publishing additional papers exploring the data in more detail and relating to the implementation of this complex intervention. We will present the findings at national and international conferences from late 2014.

Authors contributions

JDE, CDJH, CS, KA, AN, FMW, MB conceptualised and designed the study. All authors assisted with the development of the protocol, study design and refinement of study materials. All authors will contribute to implementation of the protocol and acquisition of data. JDE, VG and CDJH led the writing of the protocol. All authors have been involved in drafting and critical evaluation of the manuscript. All authors have read and approved the final version.

Conflicts of interest

None declared

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Protocol version 3. 27 June 2014.

FIGURE LEGENDS

Figure 1. Model of Pathways to Treatment

Figure 2. Map of Western Australia depicting the regional boundaries of Trial Area A, receiving the community intervention, and Trial Area B, acting as the community control.

Figure 3. The 2x2 factorial cluster randomised controlled trial design.(37)

Figure 4. Examples of Find Cancer Early resources – General Symptom Checklist, Prostate postcard and Tell your doctor postcard.

For peer review only

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The Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled trial of a complex intervention to reduce time to diagnosis in rural cancer patients in Western Australia: study protocol.

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Abstract

Introduction

While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia. Internationally a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis. Approaches to reducing time to diagnosis of symptomatic cancer include public symptom awareness campaigns and interventions in primary care to improve early cancer detection. This paper reports the protocol of a factorial cluster-randomised trial of community and General Practice (GP) level interventions to reduce the time to diagnosis of cancer in rural Western Australia (WA).

Methods and analysis

The Community Intervention is a symptom awareness campaign tailored for rural Australians delivered through a community engagement model. The GP intervention includes a resource card with symptom risk assessment charts and local referral pathways implemented through multiple academic detailing visits and case studies. Participants are eligible if recently diagnosed with breast, colorectal, lung or prostate cancer who reside in specific regions of rural WA with a planned sample size of 1,350. The primary outcome is the Total Diagnostic Interval, defined as the duration from first symptom (or date of cancer screening test) to cancer diagnosis. Secondary outcomes include cancer stage, healthcare utilisation, disease-free status, survival at two and five years and cost-effectiveness.

Ethics and dissemination

Ethics approval has been granted by the University of Western Australia and from all relevant hospital recruitment sites in Western Australia. Results of this trial will be reported in peer-reviewed publications and in conference presentations.

Registration details

Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12610000872033

Background

Rural Australians are more likely to die within 5 years of a cancer diagnosis than people from metropolitan areas.(1) While overall survival for most common cancers in Australia is improving, the rural-urban differential has been widening, with significant excess deaths due to lung, colorectal, breast and prostate cancer in regional Australia.(2) Similar disparities in cancer outcomes across certain patient groups have been described worldwide.(3) As part of the International Cancer Benchmarking Partnership, a major focus on understanding variations in cancer outcomes has been later presentation to healthcare and later diagnosis.(4)

Previous studies have shown that patients living in rural Australia are less likely to receive curative or reconstructive surgery, radiotherapy or anti-cancer drug treatment.(5-8) Policy initiatives have focused, therefore, on reducing disparities in access to treatment.(9) Access to treatment is an important determinant of outcome, but later presentation and stage at diagnosis have also been observed in rural cancer patients.(10, 11) International research suggests that the time taken to appraise symptoms and seek help (so-called 'patient delay') and management in primary care are also key determinants of cancer outcomes.(12) Time to diagnosis is associated with poorer survival for several common cancers.(13, 14)

One of the approaches to reducing later presentation to healthcare has been community symptom awareness campaigns. These have formed a major component of the UK National Awareness and Early Diagnosis Initiative(NAEDI) as part of the policy to improve cancer outcomes.(15) A systematic review of cancer symptom awareness campaigns published in 2009 found insufficient evidence about their effect on presentation to healthcare.(16) Since then further studies have begun to show potential effects on presentation and cancer diagnoses.(17)

A second approach has aimed at improving early recognition of patients in primary care with symptoms suggestive of cancer. A major challenge for general practitioners (GPs) is that the symptoms of many cancers are common in the community and overlap with prevalent benign conditions. GPs need to assess the risk, or diagnostic probability, of an underlying

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3 cancer and determine whether further investigation is justified. Until recently, there was
4 little epidemiological evidence demonstrating how well symptoms predict risk of an
5 underlying cancer from primary care populations.(18) Analysis of data in case-control
6 studies using large UK general practice databases, notably the CAPER (Cancer Prediction in
7 Exeter) studies(19-22) and QCancer research(23, 24), has led to significant advances in our
8 understanding of the epidemiology of cancer symptoms in primary care.
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15 The CAPER studies have quantified the risk of individual and paired symptoms, signs and
16 primary care investigations for a number of cancers including colorectal, lung and prostate.
17 These have been evaluated as risk assessment tools (RATs) in paper versions(25) and are
18 currently undergoing evaluation as computerised decision support tools embedded in the
19 electronic medical records of English general practices.(26) Various interventions including
20 audit and feedback, educational visits, guidelines and decision support have been tested in
21 general practice to improve cancer diagnosis.(27) None of the 22 trials included in a
22 systematic review of interventions to support cancer diagnosis in primary care examined
23 effects on diagnostic delay, although audit and feedback was shown to improve clinical
24 management.(28)
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35 Conducting research in the field of 'diagnostic delay' in cancer has many methodological
36 challenges. The Aarhus Statement discusses these and provides consensus guidelines on
37 appropriate definitions and the conduct and reporting of such research.(29) One
38 recommendation is the application of theoretical models such as The Model of Pathways to
39 Treatment (30, 31) (Figure 1). This model proposes four key intervals:
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- 43 1. The **Appraisal Interval**. The nature of a person's symptoms is one of the most important
44 factors determining the duration of the Appraisal Interval. Misattribution of symptoms
45 either to a previous benign or concurrent condition or non-recognition of the
46 seriousness of symptoms contribute to longer Appraisal Intervals.
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- 50 2. The **Help-Seeking Interval**. Various factors may contribute to this interval including
51 patient factors such as competing events (e.g. holidays), and emotional ones such as
52 fear. This includes fear of the consultation and examination, or of the diagnosis and
53 treatment. Access to primary care and sanctioning help-seeking by family or friends, so
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3 that patients do not perceive themselves as wasting the doctor's time, are also
4 important factors.(32)

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7 3. The **Diagnostic Interval**. Depending on the healthcare setting this may involve a series
8 of healthcare visits, referrals and investigations and often represents a complex process.
9 System factors including the role of primary care as a gatekeeper and access to
10 investigations and specialist care are key factors determining this interval.
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12 4. **The Pre-Treatment Interval**. The time from formal cancer diagnosis to initiation of
13 treatment is also strongly influenced by several healthcare system factors such as access
14 to staging investigations and specialised treatments.
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21 Our research on rural cancer outcomes is applying the well-established Medical Research
22 Council (MRC) methodological framework for the design and evaluation of complex
23 interventions.(33, 34) Our initial exploratory mixed-methods study aimed to explore the
24 context of rural cancer diagnosis in WA and inform the development of our complex
25 intervention. In summary, in-depth interviews with 66 people recently diagnosed with
26 breast, lung, prostate or colorectal cancer from regional WA found longer duration of
27 symptom appraisal for colorectal cancer compared with other cancers. Participants defined
28 core characteristics of rural Australians as optimism, stoicism and machismo. These
29 features, as well as poorer access to health care, contributed to later presentation of
30 cancer.(18) In addition, there were significant overall differences between cancers in terms
31 of time from presentation in general practice to referral, from GP referral to specialist
32 appointment, and from specialist appointment to cancer diagnosis. These differences were
33 due to the nature of presenting symptoms, access to diagnostic tests and multiple visits to
34 specialists. Breast cancer was diagnosed more quickly because its symptoms are more
35 specific and well recognised by the community, and due to better access to diagnostic tests
36 and specialist one-stop clinics.(35)
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51 These findings contributed to the development of the interventions and design of the
52 Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled
53 trial of community-based and general practice-based interventions which aims to reduce
54 the time to diagnosis in rural patients presenting with prostate, breast, colorectal or lung
55 cancer in Western Australia.
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Methods and Trial Design

Design and setting

This 2x2 factorial cluster randomised controlled trial is set in Western Australia, the largest Australian state geographically, with a population of 2.29 million (approximately 10% of the Australian population). Two thirds of the WA population live in metropolitan Perth and the remainder are widely geographically dispersed. Two Trial Areas were matched for population size, demographics including age and Aboriginality, and similar cancer incidence, based on the most recent available data (from 2006) when the trial was planned (Figure 2 presents more recent data on population size from 2010). Trial Area A comprises the Wheatbelt (155,256 km²), Goldfields (770,488 km²) and Great Southern (39,007 km²) regions, and Trial Area B includes the Peel/South West (29,646 km²) and MidWest (470,000km²) regions.(36)

Randomisation

Trial Area A has been allocated to receive the community symptom awareness campaign intervention and Trial Area B acts as the community campaign control region. In both Trial Areas general practices have been randomised to receive the education intervention or control, stratified by practice size (<=1 GP; 2 to 4 GPs; 5+ GPs). GPs who worked at more than one practice have been identified, and their practices have been treated as one practice for the purpose of randomisation to avoid contamination (Figure 3).

Practices have been randomly assigned to intervention or control arm using a cluster version of Zelen's method of post-randomised consent: intervention practices have been invited to receive the educational package while control practices receive no information about the trial.(37) This enables non-intervention practices to act as true controls by minimising the Hawthorne effect in a situation where placebo and double blind experimental conditions are impossible to achieve. The Hawthorne effect occurs when the researchers' procedures and communications act as interventions in themselves that change behaviours, such as if the control cluster were to adopt the practices or policies promoted to the intervention cluster. This would destroy the trial's ability to identify a

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3 benefit of the intervention, if one exists. Furthermore, it allows a pragmatic delivery of the
4 intervention and measure of its uptake in routine practice. Intervention practices which
5 decline the invitation to receive the educational package will be analysed on an intention-
6 to-treat basis. Randomisation has been performed by the trial statistician. As the number of
7 working GPs in a given practice varies, the randomisation has taken into account practice
8 size. Each practice has been categorized into: one GP in the practice, 2-4 GPs or five or
9 more GPs. A random sample proportional to the size of the practice has been used
10 employing 'samplepps' macro in Stata.
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21 ***Patient recruitment and inclusion criteria***

22 From 1 March 2012, four months after the interventions commenced, all patients meeting
23 the following criteria are being invited to contribute their data for the trial:
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- 26 • Adults aged over 18 years;
- 27 • Diagnosed with breast, lung, colorectal or prostate cancer between 1 January 2012
28 and the recruitment end date of 31 March 2014; and
- 29 • Resident of Trial Areas A or B at the time of diagnosis.
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36 ***Recruitment Strategy***

37 Eligible participants are identified via:

- 38 1. The WA Cancer Registry (WACR). A letter and participant information sheet is mailed
39 from the WACR directly to newly diagnosed cancer patients. After three-weeks non
40 responders are followed up by the research team via phone or mail.
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42
- 43 2. Cancer Council Western Australia's (CCWA) residential lodges. We approach eligible
44 patients while staying at CCWA charitable accommodation during their cancer treatment in
45 Perth. A large proportion of rural cancer patients, especially those receiving radiotherapy or
46 chemotherapy, reside in one of the lodges for several weeks during their treatment. Eligible
47 patients receive the same participant information sheet as part of their Lodge Welcome
48 Pack by the lodge receptionists and are followed up by the research team.
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53 Participants are invited to sign a consent form, which includes agreement to access their
54 medical records, and return it with their completed SYMPTOM questionnaire.
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Study Interventions

The Trial includes interventions at two levels: a community symptom awareness campaign ('the community intervention'); and a GP educational package incorporating symptom risk assessment charts and referral guidance which is implemented through multiple academic detailing visits and case studies ('the GP intervention'). Both interventions are being delivered between 1 November 2011 to 31 December 2013.

The Community Intervention

We modified existing resources developed for The Cancer Research UK 'Spot Cancer Early' and the UK National Health Service '3 week cough' campaigns to incorporate the findings of our exploratory mixed-methods study (18,(35), and to make them relevant to a rural Australian community.

Materials have been further modified following three community forums held in the major towns of the campaign target regions. Feedback was obtained about the campaign logo, design, choice of images, locally acceptable language, and contact details. The campaign is named the Find Cancer Early campaign and the materials explicitly use the Cancer Council WA branding, recognising the strong community support and credibility of this organisation. Community members wanted the campaign to focus on the positives associated with early detection and the use of simple, non-medical terms when describing symptoms. A campaign message development meeting was then held between the project team, social marketing experts and health professionals to develop a framework for the campaign and message hierarchy.

The target of the campaign is men and women over the age of 40; it aims to raise awareness of the symptoms of bowel, lung, prostate and breast cancer, and to help people overcome the barriers to seeking medical help. The primary campaign item is a plain-language symptom checklist (Figure 4). Other materials include: newspaper adverts based on campaign materials; radio adverts for each of the 4 cancers; tumour-specific postcards featuring regional images and quotations about relevant symptoms (Figure 4); generic postcards providing strategies to overcome barriers to seeking help (Figure 4); a DVD outlining tumour specific symptoms featuring health professionals and regional community

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3 members; an Indigenous version of the symptom checklist; a website; and posters and
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5 banners.
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9 Five project officers, with a combined full time equivalent of 3.0, are delivering the
10 campaign across the three regions of WA in Trial Area A. They use a community
11 engagement approach building partnerships to deliver and disseminate the campaign
12 messages with presentations, displays and campaign resource distribution. Paid advertising
13 and articles in regional newspapers and radio supplement this dissemination strategy.
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15 Television is not being used to avoid contamination in the control area.
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20 21 *The GP Intervention*

22 A GP education resource card, 'The Rural Cancer Initiative: a Guide for General
23 Practitioners', has been developed with input from rural GPs and health professional
24 advisors. The novel aspect of this intervention is the implementation of the CAPER risk
25 assessment charts for colorectal,(21) lung(20) and prostate(22) cancer. The resource card
26 contains the clinical implications of these risk charts including diagnostic assessment. In
27 addition the resource card summarises the National Breast and Ovarian Cancer Centre
28 guidelines for investigating new breast symptoms (38) and local referral guidelines and
29 hospital contacts, including recommendations about access to cancer multidisciplinary
30 teams.(39)
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40 The GP resource card is being implemented through a series of four academic detailing
41 practice visits, supplemented by a series of question-and-answer case studies for
42 completion between visits designed to reinforce key messages.(40) The practice visits
43 present specific components of the resource card and facilitate discussion within the
44 practice around recently diagnosed cancer patients. GPs are eligible for Royal Australian
45 College of General Practitioners and Australian College of Rural and Remote Medicine
46 professional development points on completion of the case studies and attendance at
47 practice visits.
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Outcomes and Measures

Primary Outcome

The primary outcome is the Total Diagnostic Interval, defined as the time from first symptom to diagnosis. We will report our time intervals according to the principles outlined in the 'Aarhus Statement' on the conduct and reporting of research on cancer diagnosis,(29) and will use the *Model of Pathways to Treatment* as our theoretical framework.(30, 31) The date of first symptom is defined as '*the time-point when first bodily change(s) and/or symptom(s) is noticed*'. For screen-detected cases we use the date of attendance for the screening test as the initial date in the patient pathway. Date of diagnosis is based on pathological diagnosis as reported to the WA Cancer Registry. We will divide the Total Diagnostic Interval further to include time from first presentation in general practice to referral (GP Interval), date of referral to first attendance at specialist (Specialist Access Interval), and time from first attendance at the specialist to date of diagnosis (Specialist Interval).(41) The GP Interval includes the time taken to order and respond to investigations available directly in primary care. For patient-reported dates we will apply published mid-point rules to estimate the actual date where uncertainty exists.(12) Where necessary, a clinical consensus group will review the data to confirm the date of first symptom and first presentation to healthcare.

Measurement tools

The following instruments will be used to obtain information about symptoms and key dates to calculate the Total Diagnostic Interval:

1. *SYMPTOM Questionnaire*

This self-administered questionnaire was developed from the C-SIM(42) measure and has been applied in the UK SYMPTOM study.(43) It includes items specific to each tumour site to capture details of symptoms, their date of onset and time taken to seek help.

2. *GP record audit tool*

This tumour-specific proforma is mailed to the participant's GP to obtain key information on: the date, type and duration of presenting symptoms within the last 12 months, referral information including referral date, and date of first appointment with specialist.

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3 Date of cancer diagnosis is obtained from the WA Cancer Registry.
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5 **Secondary outcomes**

8 **1. Process Measures of Intervention Delivery**

10 *a. Campaign Dose*

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12 Process evaluation is conducted in each intervention town to collect data on the amount of
13 media exposure achieved, number of campaign resources distributed, number of
14 partnerships established, and number of presentations, events and other activities carried
15 out by campaign staff to promote the campaign messages. Information is collected via
16 monthly reports by the campaign project officers.
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22 *b. Media Exposure*

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24 Media exposure is measured by number and square centimetre coverage of paid press
25 advertisements and unpaid press articles. The value of unpaid media is estimated by
26 calculating the square centimetre space and calculating the cost to purchase that space.
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31 *c. GP Monitoring*

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33 The campaign project officers document number of visits conducted, GP attendance at each
34 visit, and number of case studies completed.
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38 *d. Costs of intervention delivery*

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40 Cost data of delivering the interventions are being collected prospectively (see Health
41 Economic Evaluation below).
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46 **2. Impact Measures of Intervention**

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48 Campaign awareness is being measured at 18 months into the campaign intervention by a
49 computer assisted telephone interview survey. The survey is being conducted on a random
50 sample of adults over 40 years old from the campaign regions and control regions stratified
51 by sex and age, and regions within Trial Area A. Questions measure exposure to the
52 campaign, including unprompted and prompted awareness of campaign elements (i.e.
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3 radio, print and campaign brand and logos). Respondents reporting any exposure to the
4 campaign are asked additional questions about comprehension and perceived effectiveness.
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9 **3. Measures of Clinical Outcomes**

10 We will use the WA datasets (44) to provide linked hospital morbidity and administrative,
11 cancer diagnostic and mortality data in order to examine trends across time on clinical
12 outcomes at the level of the community and individual. We will obtain these data in three
13 tranches:
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- 18 a. Cohort of patients diagnosed in 2002-2010 to provide a baseline understanding of
19 the patterns of care and survival;
- 20 b. Cohort of patients diagnosed in 2011-2013 with all linked data after at least two
21 years of follow-up to evaluate short-term clinical effects of the interventions on
22 cancer stage, health care utilisation and disease free status;
- 23 c. Cohort of patients diagnosed in 2011-2013 with all linked data after at least five
24 years of follow-up to evaluate medium-term clinical effects and survival.
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32 **Analysis**

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34 The cluster randomised design provides protection against contamination across trial groups
35 when trial patients are managed within the same setting.⁽⁴⁵⁾ The primary analysis will
36 compare the Total Diagnostic Intervals and its sub-components between trial groups.
37 Simple analyses such as *t*-tests or more complex regression analyses will be undertaken.
38 Time data are invariably skewed and bounded by the absence of negative times. We will
39 apply a log transformation prior to conducting general linear modelling to compare intervals
40 accounting for exposure to the community and GP interventions within the model,
41 accounting for clustering effects at the practice level. Where appropriate, comparisons of
42 arithmetic or geometric means will be performed. The aim of statistical modelling is to
43 identify the main factors that explain variation in the outcome e.g. patient and practice
44 characteristics. The primary aim is to adjust for the effect of covariates before the effect of
45 the intervention is tested as well as 'intervention × phase' interaction with pre- and post-
46 measurements comparison. We will conduct a series of sensitivity analyses to account for:
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- a. symptoms reported with a duration of greater than two years which will be excluded from the primary analysis.
- b. vague first symptoms such as fatigue and 'feeling different'.

Using cancer registry, hospital morbidity and death data we will compare patterns of hospitalisation and treatment, pseudo-staging at diagnosis using established methods where full staging data are not available(44, 46-49), disease-free intervals and survival in people diagnosed with breast, lung, colorectal or prostate cancer resident in Trial Area A with those in Area B and those resident elsewhere in non-metropolitan and metropolitan WA. The comparisons will relate to patients diagnosed with one of the four target cancers in the six years prior to the interventions (2005-2010) and during the two years of intervention (late 2011 – late 2013). This will enable the effects of the community-level intervention to be evaluated as a spatial contrast. The same analyses will be conducted after five-years of follow-up. These analyses will entail all cancer patients in WA during the specific time periods to assess the effects of the community intervention. In addition, we will conduct analyses of all ~~consented trial~~ participants who have given their consent to measure the effects of exposure to the GP intervention and combined effect of community and GP interventions on clinical outcomes at two and five years.

All analyses will be conducted by trial statisticians blinded to participant allocation.

4. Health economic evaluation

A health economic evaluation from a health system perspective will be undertaken to determine whether the resources committed to the trial between the four intervention arms represent a worthwhile investment in terms of the measured outcomes. This will include a cost-analysis of each intervention and a cost-effectiveness analysis which will compare costs with related outcomes. Cost components include : campaign intervention costs (e.g. staffing, travel, campaign resources, media, events, in-kind support); GP intervention costs (e.g. staffing, travel, education program, resources); additional staff costs; non-intended costs of non-cancer diagnoses (hospital utilisation); in-kind personnel contributions from project partners. Resource units and cost per unit will be applied to calculate total cost.

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5 Outcome data will be matched to cost data. In the first instance, cost per change in TDI will
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7 be calculated for each of the four arms of the trial. Longer term cost-effectiveness will also
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9 be calculated to estimate net cost per life year gained for each intervention. The TDI will
10 provide a surrogate outcome for longer term outcomes using modelling techniques. Once
11
12 longer term follow-up data are available, cost-effectiveness ratios will be calculated.
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14 15 16 **Sample Size**

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18 The original sample size required for 80% power and $\alpha=0.05$ to detect a halving of long-
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20 delay risk of 30% to 15% was 840 participants. This sample size calculation accounted for
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22 the design effects from hierarchical correlations and an intra-class correlation coefficient of
23
24 0.09 based on similar trial designs.(50)
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27 Recruitment was planned to continue until four months after completion of intervention
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29 delivery to allow inclusion of a cohort of newly diagnosed cancer patients who were
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31 exposed to the interventions (i.e 31 March 2014). We have achieved approximately a 50%
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33 accrual rate into the trial which was much higher than our original estimates. Our final
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35 estimated recruitment is 1,359 participants. Based on the distributions of TDIs) from our
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37 previous research, (18,(35) this sample will provide 80% power to detect a 10% difference in
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39 TDI between intervention groups for all four cancers combined, and a 20% difference in TDI
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41 for breast, colorectal and prostate cancer separately, but not lung cancer as this would
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43 require a sample of 2,600 participants.
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46 **Ethical Considerations**

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48 The trial obtained primary ethics approval from The University of Western Australia's
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50 Human Research Ethics Committee ([HREC](#)) (RA/4/1/4527). Additional approval was gained
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52 through the Department of Health of Western Australia's ethics committee, as well as
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54 reciprocal approvals with relevant metropolitan and regional hospitals. There is no formal
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56 Data Monitoring Committee for this trial as it was felt unnecessary for this type of
57
58 intervention. Data management procedures are reported in the HREC submission.
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Dissemination

This is the first randomised controlled trial to test the individual and combined effects of a community awareness campaign and GP intervention on time to cancer diagnosis. We plan to publish the main trial outcomes in a single paper and anticipate publishing additional papers exploring the data in more detail and relating to the implementation of this complex intervention. We will present the findings at national and international conferences from late 2014.

Authors contributions

JDE, CDJH, CS, KA, AN, FMW, MB conceptualised and designed the study. All authors assisted with the development of the protocol, study design and refinement of study materials. All authors will contribute to implementation of the protocol and acquisition of data. JDE, VG and CDJH led the writing of the protocol. All authors have been involved in drafting and critical evaluation of the manuscript. All authors have read and approved the final version.

Conflicts of interest

None declared

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11 Willix.

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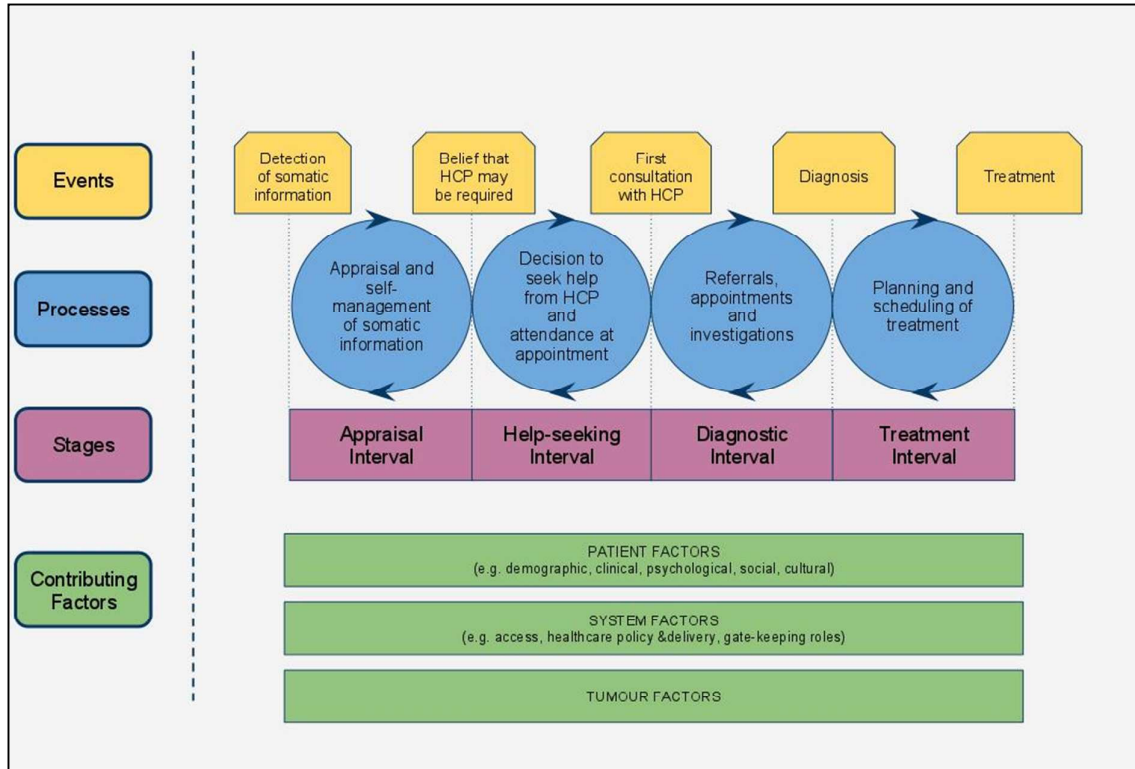
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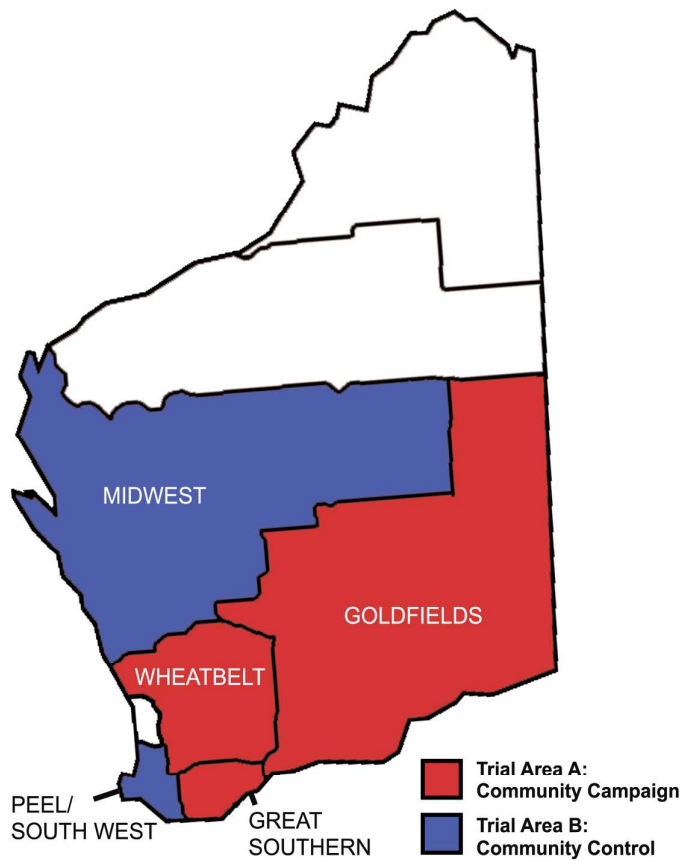
Tables and Figures

Figure 1: Model of Pathways to Treatment (30, 31)



Review only

Figure 2: Map of Western Australia depicting the regional boundaries of Trial Area A, receiving the community intervention, and Trial Area B, acting as the community control.



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Figure 3: The 2x2 factorial cluster randomised controlled trial design.(51)

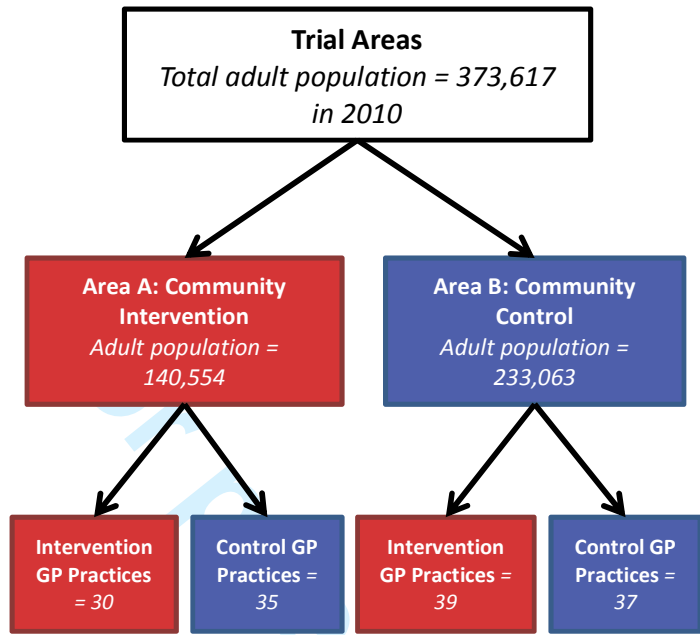


Figure 4: Examples of Find Cancer Early resources – General Symptom Checklist, Prostate postcard and Tell your doctor postcard.

General Symptom Checklist



Are you over 40?
Have you had any of these...

... for more than 4 weeks?

- Blood in your poo
- Problems peeing
- Looser poo
- Unexplained weight loss
- An unusual pain, lump or swelling anywhere in your body
- Becoming more short of breath
- A persistent cough

... once off?

- Coughing up blood
- Blood in your pee

**If you have...
Tell your doctor**

The earlier cancer is found, the greater the chance of successful treatment.

Find Cancer Early
Cancer Council Helpline 13 11 20
Cancer Council

For more information visit: www.findcancerearly.com.au

Prostate Symptom Postcard (Front and Back)



**"How's the ute?
How's the Mrs?
How's the waterworks?"**

If your peeing is causing you problems, tell your doctor.

Turn over to find out more information



Tell your doctor if you have any of these symptoms:

- If you ever find blood in your pee
- Waking frequently at night to pee
- Sudden or urgent need to pee
- Difficulty starting or stopping peeing
- Slow flow
- Pain when you pee
- Unexplained weight loss

These symptoms might be due to prostate cancer and the earlier it's found, the greater the chance of successful treatment.

For more information visit: www.findcancerearly.com.au

Tell your doctor Postcard (Front and Back)



Your doctor is never too busy to see you

Tell your doctor about any changes with your body, no matter how unimportant you think they are.

Turn over for advice about visiting your doctor



Tell your doctor – if you notice any of the possible symptoms of cancer

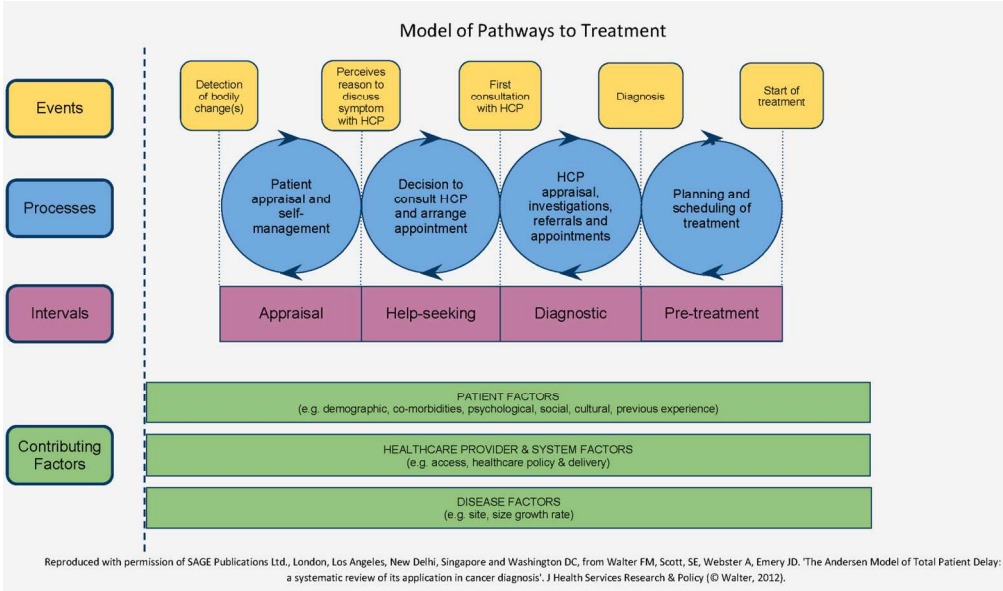
Lots of questions and concerns may pass through your mind when you decide to see your doctor:

<p>Excuse</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> The doctor is always too busy. It's too hard to get an appointment <input checked="" type="checkbox"/> When I get to the doctors my mind goes blank <input checked="" type="checkbox"/> I'm worried about what might happen when I see the doctor 	<p>Fact</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Phoning early in the morning can help <input checked="" type="checkbox"/> Writing a list jogs your memory <input checked="" type="checkbox"/> The doctor might examine you, reassure you, order some tests or refer you
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For more useful tips visit: www.findcancerearly.com.au

Review only

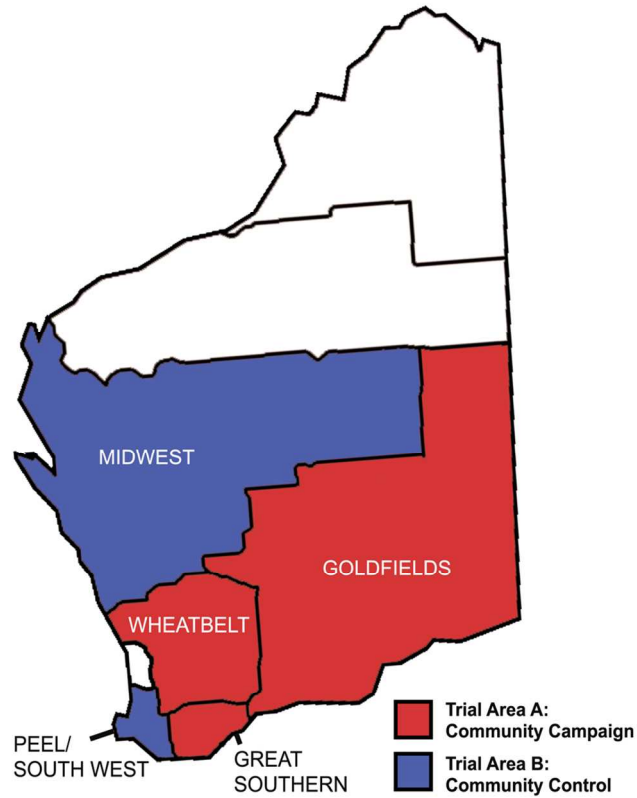
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Model of Pathways to Treatment (30, 31)
152x90mm (300 x 300 DPI)

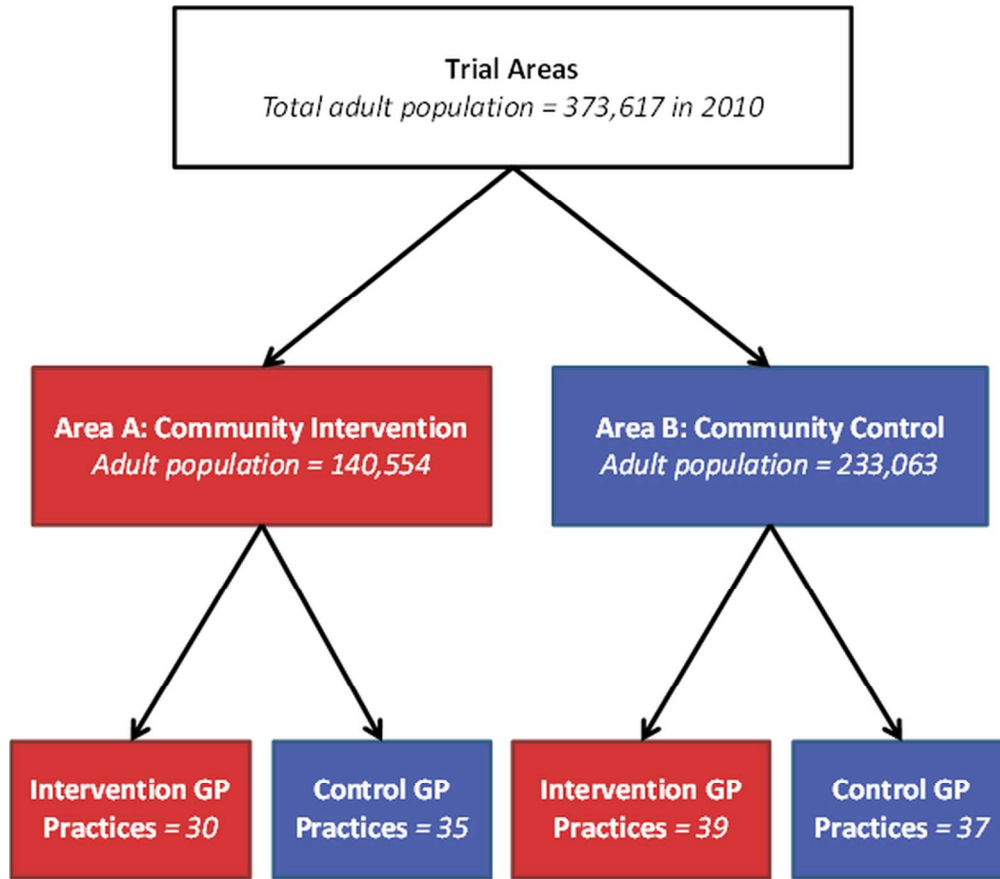
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Map of Western Australia depicting the regional boundaries of Trial Area A, receiving the community intervention, and Trial Area B, acting as the community control.

104x147mm (300 x 300 DPI)



The 2x2 factorial cluster randomised controlled trial design.(37)
103x90mm (300 x 300 DPI)

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General Symptom Checklist

Are you over 40?
Have you had any of these...

... for more than 4 weeks?

- Blood in your poo
- Problems peeing
- Looser poo
- Unexplained weight loss
- An unusual pain, lump or swelling anywhere in your body
- Becoming more short of breath
- A persistent cough

... once off?

- Coughing up blood
- Blood in your pee

**If you have...
Tell your doctor**

The earlier cancer is found, the greater the chance of successful treatment.

Cancer Council
Helpline
13 11 20

For more information visit:
www.findcancerearly.com.au

Prostate Symptom Postcard (Front and Back)

**"How's the ute?
How's the Mrs?
How's the waterworks?"**

If your peeing is causing you problems, tell your doctor.

Turn over to find out more information

Tell your doctor if you have any of these symptoms:

- If you ever find blood in your pee
- Waking frequently at night to pee
- Sudden or urgent need to pee
- Difficulty starting or stopping peeing
- Slow flow
- Pain when you pee
- Unexplained weight loss

These symptoms might be due to prostate cancer and the earlier it's found, the greater the chance of successful treatment.

For more information visit: www.findcancerearly.com.au

Helpline
13 11 20

Tell your doctor Postcard (Front and Back)

Your doctor is never too busy to see you

Tell your doctor about any changes with your body, no matter how small or how often they occur.

Turn over for advice about visiting your doctor

Tell your doctor - if you notice any of the possible symptoms of cancer

Lots of questions and concerns may pass through your mind when you decide to see your doctor.

<p>Excuse</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> The doctor is always too busy, it's too hard to get an appointment. <input checked="" type="checkbox"/> When I get to the doctor's my mind goes blank. <input checked="" type="checkbox"/> I'm worried about what might happen when I see the doctor. 	<p>Fact!</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Phoning early in the morning can help. <input checked="" type="checkbox"/> Writing a list jogs your memory. <input checked="" type="checkbox"/> The doctor might examine you, reassure you, and/or arrange tests or refer you.
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For more useful tips visit: www.findcancerearly.com.au

Helpline
13 11 20

Examples of Find Cancer Early resources – General Symptom Checklist, Prostate postcard and Tell your doctor postcard.
209x147mm (300 x 300 DPI)

Review only

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Yes
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Yes
	2b	All items from the World Health Organization Trial Registration Data Set Yes
	3	Date and version identifier Yes
Protocol version	3	Date and version identifier Yes
Funding	4	Sources and types of financial, material, and other support Yes
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Yes
	5b	Name and contact information for the trial sponsor Yes
	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 Yes
	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) Yes
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 Yes
	6b	Explanation for choice of comparators Yes
Objectives	7	Specific objectives or hypotheses Yes
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) Yes

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 Yes
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) Yes
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Yes
	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) N/A
	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 Yes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. Yes
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 Yes
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Yes

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 Yes
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned Yes
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7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions Yes
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how Yes
13			
14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial N/A
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19 **Methods: Data collection, management, and analysis**

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21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol Yes
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28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols N/A
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33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol. Yes
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38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol Yes
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) Yes
44			
45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation) Yes
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50 **Methods: Monitoring**

51			
52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed Yes
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1		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 N/A
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6	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 N/A
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A
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Ethics and dissemination

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17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Yes
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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) NA
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24			
25	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Yes
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28		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
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31	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 Yes
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Yes
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39	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 N/A
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43	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
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46	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 Yes
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52		31b	Authorship eligibility guidelines and any intended use of professional writers Yes
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55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code N/A
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates N/A
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.