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Solving unknown primary cancer with earlier diagnosis - the SUPER-ED trial: study protocol for a stepped-wedge cluster randomised controlled trial to support earlier diagnosis for people presenting with malignancy of undefined primary origin

Anna Ugalde[1*], Richard W. Tothill[2,3,4], Stephen Quinn[5], Hui-Li Wong[2,3], Owen Prall[2], Catherine Mitchell[2,3], Nilmini Wickramasinghe[5,6], Clare Fedele[7], Natalie Richards[2], Elizabeth Todio[2,5], Cindy Bryant[5], Louisa G. Collins[8,9], Sarah McLean[2], Hyun Soo Ko[3,10,11], Tim Akhurst[2], Christopher Steer[12], Bo Gao[13,14], Mark Wong[14], Chloe Georgiou[15], Narayan Karanth[16], Anna Kuchel[17], Louise Nott[18], Shamsudheen Padinharakam[19], Mark Shackleton[20,21], Ian M. Collins[1,22], Madhu Singh[23], Rachel Wong[24], Zee Wan Wong[25], Alexis Butler[2], Tharani Sivakumaran[2,3], Penelope Schofield[3,5,26†] and Linda Mileshkin[2,3†]

Abstract

Background People with malignancy of undefined primary origin (MUO) have a poor prognosis and may undergo a protracted diagnostic workup causing patient distress and high cancer related costs. Not having a primary diagnosis limits timely site-specific treatment and access to precision medicine. There is a need to improve the diagnostic process, and healthcare delivery and support for these patients. This trial aims to implement and evaluate an optimal model of care for people presenting with MUO to reduce time to diagnosis, improve patient experiences and reduce healthcare costs.

Methods/design This is a pragmatic stepped-wedge cluster randomised trial comparing a control phase of standard practice with an intervention phase. Patient inclusion criteria are: 1) age 18 years or older, 2) presenting with suspected metastatic malignancy without an obvious primary site on imaging, 3) clinically appropriate to undergo diagnostic work-up and 4) able to provide written or verbal consent. The intervention is a new model of care comprising four key components: standardised diagnostic workup, dedicated cancer care coordinators, virtual multidisciplinary meetings and a website resource for patients, carers and clinicians. The primary endpoint is the time to completion of minimum diagnostic workup. Secondary outcomes are whether the type of tumour is diagnosed, clinical trial participation, referral to palliative care, patient-reported physical, social and mental health, patient-reported

†Penelope Schofield and Linda Mileshkin Joint senior author.

*Correspondence:
Anna Ugalde
a.ugalde@deakin.edu.au
Full list of author information is available at the end of the article

understanding and uncertainty. Implementation outcomes include acceptability, feasibility, fidelity and adoption and health care use and costs. Intervention implementation will be supported using clinical leadership, education and reinforcement. Patients who consent to having their data collected will receive the model of care active at the site at the time of recruitment. Patients will complete a patient-reported outcomes questionnaire four months after study enrolment. A health economic analysis will be included. Across 15 hospitals, a total sample size of 240 is planned.

Discussion There is a lack of intervention research for people presenting with MUO. The stepped-wedge design seeks to mitigate the potential challenge of enrolling people with a poor prognosis and high symptom burden in trials. This research will generate important evidence with scalability for future research at trial completion.

Trial registration ACTRN12622001504707

Keywords Cancer, Support, Diagnosis, Care, Unknown primary cancer, Stepped-wedge cluster

Background

Malignancy of undefined primary origin (MUO) occurs when people present with a metastatic malignancy without an obvious primary site [1, 2]. MUO presentations can result in a diagnosis of cancer of unknown primary, a diagnosis which encompasses a diverse range of cancer types, whereby a metastatic lesion is identified but a primary tumour evades clinical detection [3]. Although cancer of unknown primary accounts for only 1.6% of all malignancies in Australia making it the fifteenth most common cancer diagnosis [4], it is the sixth most common cause of cancer death, with median survival well below one year [5]. Cancer of unknown primary is essentially a diagnosis of exclusion; it can only be made if a standardised diagnostic workup does not identify a primary tumour.

People with cancer of unknown primary have poor clinical outcomes [6, 7]. Limited diagnostic workup is common and not having a primary diagnosis limits timely site specific treatment and access to precision treatments [5]. The lack of standardised diagnostic workup can be due to deteriorating health, availability of diagnostic modalities or expert opinion [8]. Conversely, there may be a risk of over investigation leading to a prolonged diagnostic odyssey. People with cancer of unknown primary experience high levels of psychological distress and uncertainty and low understanding of their illness [9]. Compared to people with a known metastatic cancer, they are less likely to understand their cancer and test results, less likely to find written information helpful and have more uncertainty [10]. Indeed, research shows that low understanding leads to higher levels of uncertainty which in turn increases psychological distress [9]. Health service use in this group is high: although people with cancer of unknown primary receive less treatment than other cancer types, they have more primary care consultations, emergency department visits, hospitalisations and a higher risk of death within 30 days [11]. Compared to ovarian cancer, healthcare costs for cancer of unknown primary are nearly triple [12]. The structuring of cancer care according to tumour specific multidisciplinary teams means that cancer of unknown primary patients can feel they are not looked after by a specific clinical team [13]. There is a need to improve the diagnostic process, healthcare delivery, and support for this group given the burden of disease, often short prognosis and poorer cancer experiences.

Given the poor prognosis and delays to diagnosis, there is an opportunity to focus optimal delivery of care for patients with suspected undefined primary malignancies during the workup phase. The Optimal Care Pathways are developed in Australia to serve as frameworks for delivery of quality, consistent and evidence-based care for people affected by cancer [14]. They have been established for multiple cancer types and focus on the 1) prevention and early detection; 2) presentation, initial investigations and referral, 3) diagnosis, staging and treatment planning, 4) treatment, 5) care after initial treatment and recovery, 6) managing recurrent and progressive disease and 7) end-of-life care [14, 15]. While the optimal care pathways are nationally endorsed, clinician awareness may be low [16] and uptake is suboptimal [17].

An essential feature of high quality cancer care is care coordination, which can drive improvements in cancer screening, patient experience and quality care [18]. However, for people with MUO, consistent engagement with cancer care coordinators is less common as most care coordinators work in dedicated and common cancer groups such as breast or prostate cancer [19, 20]. Roles covered by cancer care coordinators includes assessing clinical and supportive care needs, providing information and education about cancer and coordinating clinical care [19]. Care coordination may be particularly important in MUO or cancer of unknown primary given the complexity of this patient group and the poorer understanding of their disease [9]. Similarly, multidisciplinary meetings are a component of best practice cancer care implemented across cancer services internationally, with a focus on involving a variety of professionals with a range of clinical expertise to make timely decisions

about patient care [21]. Yet this important component of cancer care is less well established for MUO or cancer of unknown primary patients despite a clear clinical need [13]. To date, trials for cancer of unknown primary have focused on drug trials or genomic studies, despite the known gap for delivering standardised, high quality cancer care.

Aims

This trial aims to implement and evaluate a new model of care for people with MUO to reduce time to diagnosis, improve patient experiences and reduce healthcare costs. The new model of care consists of a) standardised diagnostic workup, b) a national virtual multidisciplinary meeting of clinical experts in cancer of unknown primary, c) embedded and dedicated cancer care coordinators and d) an educational website providing information for patients, carers and clinicians.

The specific aims are to: 1) understand the impact of the model of care on patient diagnostic workup, patient experience and healthcare costs; and 2) evaluate the implementation of the model of care.

Hypotheses

We hypothesise that implementing the intervention at local health services will:

- reduce time from identification of metastatic disease on imaging to completion of minimum diagnostic workup;
- increase the proportion of patients who have a primary tumour type diagnosed;
- increase the likelihood of receiving active anti-cancer treatment;
- increase participation in clinical studies/trials;
- increase referrals to palliative care;
- reduce patient-reported poor diagnostic experiences, low understanding of diagnostic tests, uncertainty and psychological morbidity;
- reduce healthcare costs associated with diagnosis;
- demonstrate evidence of acceptability, feasibility, fidelity and adoption.

Methods

Design

SUPER-ED is a pragmatic stepped-wedge cluster randomised trial comparing a control phase of standard practice with an intervention phase. The stepped-wedge trial design features random and sequential clusters which cross from a control to intervention at staggered time points, with all clusters ending with exposure to the intervention [22]. This trial has a continuous recruitment with short exposure design as participants are exposed to the intervention with the outcomes measured after a follow up period [23]. This trial consists of a control phase for each site followed by a crossover point of one month before the intervention commences, where recruitment is paused and data are not collected, representing an incomplete design [23]. This allows for implementation of the new model of care and a washout period so control patients have minimal or no crossover with the intervention phase. The total recruitment period is 25 months, including four study periods corresponding to six months with a one-month changeover period between Control and Intervention when recruitment is paused, see Fig. 1: Randomisation schedule. This design has been selected as it presents a randomised evaluation of the intervention and all sites will complete the trial with the intervention implemented [24]. This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [25].

Setting and study population

SUPER-ED will be a nation-wide multisite trial. Sites have been identified through previous involvement in cancer of unknown primary studies. Recruitment is underway. Patient inclusion criteria are age 18 years or older, presenting with MUO (i.e. suspected metastatic malignancy without an obvious primary site on imaging), clinically appropriate to undergo diagnostic work-up as determined by the treating clinician and able to provide written or verbal consent. For participants with limited English proficiency a legally acceptable representative may be a witness such as a qualified interpreter.

Randomisation

The unit of randomisation is the hospital site. The participating sites will be randomised to one of three clusters as part of the stepped-wedge cluster design in blocks of three to ensure equal allocation to each arm by the blinded study statistician. Numbers corresponding to cluster allocation will be given to the project manager who will match to hospital site using a prespecified list. Each site will commence receiving the intervention at the time corresponding to their randomised cluster. Each period corresponds to 6 months, with a one-month changeover period between control and intervention, see Fig. 1.

Intervention

The intervention is a new model of care comprising four key components, see Fig. 2: Overview of the intervention.

<table>
<tr><th>Schedule</th><th>Months in Period</th><th>Sites in Cluster 1</th><th>Sites in Cluster 2</th><th>Sites in Cluster 3</th></tr>
<tr><td>Period 1
Month 0-6
all sites start in control</td><td>6m</td><td>Control (6m)</td><td rowspan="2">Control (12m)</td><td rowspan="3">Control (18m)</td></tr>
<tr><td>Period 2
Month 7-12
Crossover 1 for Cluster 1 in m7</td><td>6m</td><td>Crossover (1m)</td></tr>
<tr><td>Period 3
Month 13-18
Crossover 2 for Cluster 2 in m13</td><td>6m</td><td rowspan="2">Intervention (18m)</td><td>Crossover (1m)</td></tr>
<tr><td>Period 4
Month 19-25
Crossover 3 for Cluster 3 in m19</td><td>6m</td><td rowspan="2">Intervention (12m)</td><td>Crossover (1m)</td></tr>
<tr><td colspan="2"></td><td></td><td>Intervention (6m)</td></tr>
<tr><td colspan="2">Control
Standard of Care</td><td>6m</td><td>12m</td><td>18m</td></tr>
<tr><td colspan="2">Crossover
Recruitment Paused</td><td>1m</td><td>1m</td><td>1m</td></tr>
<tr><td colspan="2">Intervention
New Model of care</td><td>18m</td><td>12m</td><td>6m</td></tr>
<tr><td colspan="2">Total Recruitment
Active recruitment</td><td>25m
24m</td><td>25m
24m</td><td>25m
24m</td></tr>
</table>

Fig. 1 Randomisation schedule

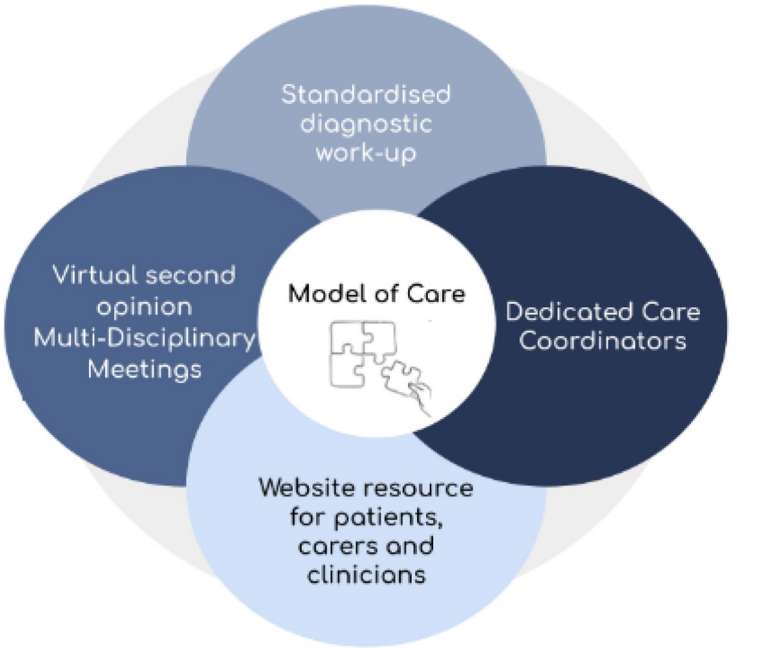

Fig. 2 Overview of the intervention

Standardised diagnostic work-up

A standardised diagnostic workup has been developed, based on the Australian Optimal Care Pathways [14] and the European Society for Medical Oncology Clinical Practice Guideline for diagnosis, treatment and follow-up for cancer of unknown primary [26]. Investigation of patients presenting with suspected metastatic cancer without an obvious primary site, or MUO, should be guided by the patient's clinical presentation.

Development by a multidisciplinary clinical team with relevant expertise, a guidance document describing the recommended approach to diagnostic workup based on the Australian cancer of unknown primary Optimal Care Pathway will be provided to participating sites. The minimum diagnostic workup encompasses:

a. a thorough medical history and physical examination;
b. routine blood tests;
c. contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis;
d. mammogram in female patients and a PSA in male patients;
e. an adequate tissue sample from one site of disease for histopathology and immunohistochemistry (IHC).

Additional investigations that may be performed include site- or subtype-directed investigations based on the specific presentation, fluorodeoxyglucose-positron emission tomography (FDG-PET), and molecular testing.

Dedicated care coordinators

The cancer care coordinator role is patient-facing and will encompass:

a. assessing patients' clinical and supportive care needs;
b. providing information and education about their cancer;
c. planning and coordinating clinical care (e.g. ordering tests, specialist appointments, clinic visits);
d. referring to other services (palliative care, social work, pastoral care etc.);
e. providing counselling;
f. delivering clinical care (depending on the background of the care coordinator);
g. working within the local oncology clinics and multidisciplinary meeting settings;
h. supporting access to the SUPER-ED website;
i. facilitating discussion of cases at the virtual multidisciplinary meeting.

Virtual multidisciplinary meetings

Multidisciplinary meetings are a feature of quality cancer care that can improve cancer management plans [27]. They can be challenging to operate in settings with rare cancer types owing to a reduced throughput of patients and virtual multidisciplinary meetings may serve as a solution [28]. This component of the intervention will bring together national experts to deliver higher quality care recommendations for people with cancer of unknown primary. A regular virtual multidisciplinary meeting will be coordinated, with representation from medical oncology, anatomical pathology, molecular pathology, diagnostic radiology and nuclear medicine. During the intervention phase, any patient participating in this trial from any site can be referred to the virtual multidisciplinary meeting. Microsoft Teams software will be utilised as has been adopted as consistent with guidelines [29] and as used in other virtual multidisciplinary meetings [30]. Clinicians from all participating sites will be invited to attend and the outcome of the multidisciplinary meeting discussion for each patient will be documented.

Website resource for patients, carers and clinicians

An interactive and dynamic web-based platform will be built utilising participatory research and user centric methods. Consumers, clinicians and health service managers will be involved in the development of the website. The purpose of the website will be to 'upskill' patients, carers and clinicians in the latest information and resources related to MUO and cancer of unknown primary. Specifically, it will provide information on current clinical studies or trials open for patient enrolment, filmed interviews with clinicians and scientists providing comprehensive information on diagnosis and treatment, filmed interviews with people with or affected by cancer of unknown primary, information on optimal treatments and Australia's Optimal Care Pathways, a 'Clinicians corner' which displays the most recent key publications in genomic, clinical and psychosocial cancer of unknown primary research and consultation help and support services for patients and carers. A prototype will be developed and pretested with consumers and clinicians or researchers. The website will be reviewed by consumers, clinicians and investigators prior to implementation. Further details on the development process will be published elsewhere.

Implementation of the intervention

Three key implementation strategies will be used to enhance implementation of the intervention across each site:

Leadership

A clinical leader within the service which manages people presenting with MUO will be invited to be the site champion. They will facilitate consultation with senior medical, nursing, facility management staff and primary care referrers and assist in identifying a nurse or other allied health clinician to take on the nurse coordinator role. The site champions and nurse coordinator will be part of a national steering committee. The steering committee will also include consumer representatives and all study investigators. Prior to commencement of the intervention period for each cluster, the research team will virtually meet with each site champion for sites within the cluster to adapt the new model of care to local circumstances and address local challenges. Clinical leadership is considered an important component of change in oncology services as described by key informants internationally [31]. A study explored the role of clinical champions on implementing guideline prescribing in community health settings. This study found that of the five sites that demonstrated significant increases in guideline prescribing, clinical champions with influence, credibility and capacity appeared to be a relevant factor; whereas of the seven health centres that did not show improvement, they lacked clinical champions [32].

Education

The site champions and national steering committee will oversee the development of process manuals for tailoring diagnostic workup and referring to the virtual multidisciplinary meeting. The site champions will facilitate local presentations at each site which will include an overview of the diagnostic experience of people with cancer of unknown primary and introduction to the model of care. Presentations will occur during departmental meetings to maximise staff attendance and minimise unavailability. Presentations will be conducted at the commencement of the intervention period and again six months later. Site champions will also have a role in ongoing teaching for new staff about the Model of Care. Education of staff is a critical component of implementing new models of care [33].

Reinforcement

Audit and feedback will be conducted across sites. This will involve healthcare providers receiving a summary of their clinical performance at specified time points following the collection of diagnostic audit data. Feedback will include: 1) the number of people presenting with MUO who receive a diagnosis and the length of time to diagnosis of cancer of unknown primary or a specific primary tumour type; 2) the number of cancer of unknown primary patients or patients with MUO presented at the virtual multidisciplinary meeting; 3) the number of patients who commence anti-cancer treatment; 4) the number of patients enrolled in clinical studies/trials 5) the number of patients referred to palliative care; and 6) the proportion of patients who have a likely primary tumour or favourable cancer of unknown primary subtype identified. Feedback on patient experience will also be provided: 1) data on patients' diagnostic experiences; and 2) de-identified case studies of the clinical outcomes for patients enrolled in clinical/research studies/trials. The research team will work with individual sites to determine the preferred format of providing audit and feedback data. Audit and feedback may be more effective when baseline performance is low, when feedback is provided both verbally and in writing, when feedback is delivered by a supervisor or colleague, when the process is performed more than once and when the feedback includes clear targets and an action plan [34]. For this trial, reinforcement will be operationalised at each site, considering the above design elements.

Procedures

As people with a MUO present to an oncology clinic, they will be approached to participate in the study. Involved clinicians in the medical oncology clinics at participating sites will initially approach eligible patients to determine their interest in the study. The clinician will introduce the study to potential participants. If interested, they will be referred to the Study Coordinator or Research Assistant who will provide them with the Participant Information Sheet and Consent Form. This may occur face-to-face, over the phone, remotely arranged by the coordinating centre, via telehealth or via REDCap™ electronic framework depending on the availability of both project staff and participant.

Patients will be asked to provide consent to complete questionnaires and have their data recorded as part of the study. Being a stepped-wedge trial, all people presenting with MUO that go through the clinic during the time of the control and the intervention phases will receive the current model of care that is currently active.

Patients will complete a patient-reported outcomes questionnaire four months after study enrolment, in a format they nominate, either online (via REDCap™), a mailed-out copy with a reply-paid envelope, or in a telephone interview with a trained research assistant. The questionnaire will take 15—20 min to complete. Participants with limited English proficiency are not

required to complete the questionnaire but can choose to participate. Clinical data for study endpoints, including the primary endpoint, will be collected at four months after patient consent via medical record audit. MBS and PBS data will be collected after the final recruit has exited the study.

Outcome measures

The primary outcome for this study is the time to completion of minimum diagnostic workup. Secondary endpoints encompass a suite of clinical and implementation outcomes; all outcomes and their definitions are provided in Table 1. Implementation outcomes are defined by relevant variables within Proctor et al.'s Implementation Outcomes Framework [35].

Sample size

Sample size calculation is based on a Type 1 error rate of 5% and a Type 2 error rate of 20%. Our unpublished data on 207 cases found that the mean (sd) time from identification of metastatic disease to diagnosis was 57.4 (49.1). The aim of this study is to reduce the time to diagnosis from 57.4 to 30 days. Assuming an ICC of 0.015, the total sample size of 240 (20 per cluster per period) gives 80% power to detect this difference. Approximately 15 sites are anticipated to be involved in the trial across three clusters (five sites per cluster).

Statistical analysis

Analyses will be conducted on an intention-to-treat basis and the trial conducted and reported according to CONSORT extension for stepped-wedge guidelines [39]. Missing data for the primary analysis will be recovered

Table 1 Primary, secondary and implementation endpoints and their definitions

Endpoint	Definition/Measures
PRIMARY ENDPOINTS	
Time to completion of minimum diagnostic workup	Number of days from the date of imaging that first detected metastasis, to the date of completion of minimum diagnostic workup
SECONDARY ENDPOINTS	
Primary tumour type diagnosed	Excluding patients who have a benign diagnosis, the proportion of patients who have a primary tumour type diagnosed after completion of the standardised diagnostic tests out of the total proportion of patients recruited who completed standardised diagnostic workup
Clinical trial participation rates	Proportion of patients recruited to any clinical trial out of the total proportion of patients recruited and who completed standardised diagnostic workup
Referral to Palliative Care	Proportion of patients with a cancer of unknown primary diagnosis referred to palliative care out of the total proportion of patients recruited and who completed a standardised diagnostic workup
Patient-reported physical, social and mental health	Patient-Reported Outcomes Measurement Information System (PROMIS) short forms measuring [36]: a) Emotional Distress – Anxiety b) Emotional Distress – Depression c) Fatigue d) Pain interference e) Pain intensity f) Sleep disturbance g) Physical function h) Satisfaction with social roles
Patient-reported uncertainty	Mishel Uncertainty in Illness Scale – Community Form (MUIS-C) [37]
Patient-reported understanding	Single items, drawn from the UK Cancer Patient Experience Survey [38] and adapted for Australia setting: understanding of their diagnosis, diagnostic tests and treatment, adequacy of communication, information and experiences with hospital staff and the health system
IMPLEMENTATION ENDPOINTS	
Acceptability of the model of care	Semi-structured clinician interviews
Feasibility of the model of care	• Number of patients who have contact with the care coordinator • Number of care coordinator interactions per patient • Number of cases discussed in virtual multidisciplinary meetings • Number of clinicians attending virtual multidisciplinary meetings • Number of patients provided with website details • Duration of diagnostic workup per patient
Fidelity to the model of care	• Number and types of diagnostic investigations per patient
Adoption of the model of care	Website analytics, including click information, pages visited, time spent on each page, information viewed and/or downloaded, videos viewed

using multiple imputation, redrawing 50 samples. For the primary endpoint analysis of days from date of first imaging that detected metastasis to completion of minimum workup, a random effects linear mixed model will be used, with days as the dependent variable and adjusting for group assignment and period. Site and cluster will be entered as a random effects and covariance matrices will be used to model the correlation of random effects and within-group effects over time to improve model fit. Specifically, we will explore model fit using Stata's residuals and covariance options. The final model reported will be the one with the lowest Akaike Information Criterion.

Sensitivity analyses will be conducted linear regression, with days as the dependent variable, time as the independent variable, clustering over site to account for correlated errors.

Health economic sub-study

The aims of the economic sub-study are 1) to assess differences in diagnosis-related costs between the intervention and control arms and 2) conduct a trial-based cost-utility analysis to assess if the intervention offers the health system value for money. A health system perspective will be used and incorporate costs to state-based hospitals, Medicare and private providers. All resources required to conduct the intervention (e.g., staff, training, materials, communications, etc.) will be monitored during the study. Medicare records (Australia's national health payment system for out-of-hospital services and therapies) will be extracted for healthcare consultations, services, medications and procedures in community care and private health services. Derived from the EORTC QLQ-C30, the QLU-C10D will be used to measure health utilities at study entry and 4-months follow-up and will be used to calculate Quality Adjusted Life Years (QALYs). The QLU-C10D is a cancer-specific health utility tool supported by an Australian algorithm and norms and has been validated in Australian patients with metastatic cancer [40].

For Aim 1 of the economic sub-study, generalised linear models will be employed to deal with skewed data and adjust for necessary covariates. For Aim 2 of the economic sub-study, incremental cost per QALY ratios or net monetary benefits will be generated for the intervention over current practice. Costs will be inflated where necessary using the health price index. Generalised linear models will be used to analyse non-parametric costs and QALYs. Bootstrapping using the bias-corrected approach [41] will be used to produce 95% confidence intervals around the incremental cost per QALY ratios. Cost-effectiveness acceptability curves will be generated, and relevant sensitivity analyses will also be performed to address uncertainty. Methods will be governed by international guidelines in trial-based economic evaluations and performed using STATA [42].

Study management

This is a consumer-led project whereby people with a lived experience of cancer of unknown primary informed the intervention and have input into all study phases. A Consumer Steering Committee has been formed with national representation from patients and carers affected by cancer of unknown primary; and chaired by a nurse who was a carer. This committee directs and reviews all aspects of the project. The trial has procedural oversight by a steering committee with representation from investigators, a consumer representative (chair of the consumer steering committee), clinicians and site leads and champions. Working parties are established to progress the development of the model of care, the website development and piloting and the implementation of the intervention across sites. The steering committee chair and working party chairs (as required) report back to the Consumer Steering Committee on progress or for direction. There is a weekly project management meeting.

The database for this project will be a current version of the secure web application REDCap (Research Electronic Data Capture system). REDCap will be used to create online versions of the patient information and consent form, the Medicare/PBS consent form, clinical data collection forms and patient questionnaire. This is a password-protected system and only authorised staff will have access. This database maintains a comprehensive audit trail; all actions are listed in a secure, time-stamped, retrievable log.

This protocol for this study has been approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee (number 22/141). This study is being conducted in compliance with the National Statement on Ethical Conduct in Human Research and relevant state and national legislation, regulations and guidelines. Governance applications will be lodged at all participating sites. Any significant changes to the conduct, objectives, design, or eligibility criteria of the study will require a formal protocol amendment. Any protocol amendment will be reviewed by the project steering committee with decisions and outcomes recorded in the minutes of those meeting.

Discussion

To our knowledge this is one of the first controlled studies on standardising diagnostic workup for people with MUO. To date, there is a striking lack of research for this patient group with poor clinical outcomes, high health service use and suboptimal patient experience. We are evaluating a complex intervention implementing a new

model of care with the aim to improve time to completion of minimum diagnostic workup, reduce health care costs and improve patient experiences with a stepped-wedge trial.

International data shows the implementation of cancer treatment pathways can improve patient outcomes. In Denmark, utilising a dataset of over 7000 people, implementation of national pathways was associated with improved one- and three-year survival and lower mortality across all cancers [43]. Similarly in Australia, utilising a registry of over 13,000 individuals, alignment with care pathways for people with colon cancer demonstrated lower disease stage at diagnosis, improved three-year survival and reduced likelihood of emergency surgery [44]. A systematic review has established that cancer pathways reduce cancer costs through the prevention of unnecessary care [43]. Given this evidence, there is a need to develop and implement diagnostic pathways to improve the cancer care and experience of people with cancer of unknown primary.

SUPER-ED will also investigate the implementation of the new model of care. Other trials have successfully evaluated implementation of a new model of care [45]. Development of the implementation strategies are informed by past systematic reviews which demonstrate an overreliance on teaching to change clinician behaviour [33]. In this trial, teaching of the new model of care is a component and is supported with clinical leadership and audit and feedback on adherence to the new model of care.

Another key element of this research is the study design. Stepped-wedge trials are a pragmatic design that allows for both implementation of a model of care and evaluation of intervention effect [22]. This approach avoids contamination at a practitioner or health service level [22]. A challenge of this approach is the management of the transition between control and intervention periods and some stepped-wedge trial designs incorporate an allowance for the time taken to embed the intervention [22]. For this trial, we propose a three-month crossover phase whereby recruitment is paused and this time allows for necessary implementation of the new model of care. Stepped-wedge trials are being adopted for several oncology studies currently underway, including a Dutch nationwide project implementing best practice in pancreatic cancer care with a multisite stepped-wedge cluster randomised controlled trial aiming to improve survival through the delivery of best practice treatments [46]; an Australian trial to embed smoking cessation interventions in hospitals for people with cancer [47]; and a trial from United States implementing a community-led regional patient navigation and registry system to reduce cancer disparities [48].

A challenge to this trial is the enrolment of people with poor prognoses and high symptom burden. The stepped-wedge trial design assists to mitigate some of this impact as participants receive either the control or intervention that is being delivered at the site at the time of enrolment into the trial [22]. Participants consent to medical and demographic data extracted and to be contacted at four months post enrolment to complete a survey on patient reported outcomes. This approach maximises recruitment and minimises patient burden. People with cancer of unknown primary who are eligible to participate are able to verbally consent.

A strength of this trial is that it is consumer-led, with consumers determining the aims of this research (reducing time to diagnosis and improving patient experience), assisting in the grant writing and providing guidance over all study phases. In particular, consumers advocated for the website component of the intervention to increase understanding and knowledge of cancer of unknown primary amongst patients, carers and clinicians and the inclusion of filming people affected by cancer of unknown primary discussing their lived-experiences. They also proposed incorporating a cancer of unknown primary care coordinator as critical to assist patients and carers navigate the diagnostic process.

Conclusions

The SUPER-ED trial is a stepped-wedge pragmatic randomised controlled trial being conducted at several health services to implement and evaluate a new model of care for people with MUO. This trial utilises a consumer-driven research strategy and focuses on the delivery and implementation of best practice cancer care. We aim to reduce the time to diagnosis in people with MUO and improve their experience of cancer, while reducing the costs associated with diagnosis. This research will establish a model of care and generate important evidence. Future work can include broader rollout and scalability at the completion of the trial.

Abbreviations

MUO	Malignancy of Undefined Primary Origin
CT	Computed Tomography
IHC	Histopathology and Immunohistochemistry
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
PROMIS	Patient-Reported Outcomes Measurement Information System
MUIS-C	Mishel Uncertainty in Illness Scale – Community Form

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Authors' contributions

PS, LM, AU, SQ, RT, HW, OP, CM, NW, CF contributed to study conceptualisation; PS, LM, AU, SQ, RT, HW, OP, CM, NW, CF, NR, ET, CB, LGG, SM, HK, TA, CS, BG, MW, CG, NK, AK, NL, SP, IMC, MS, MW, RW, ZWW, AB, TS have contributed to study preparation, CS, BG, MW, CG, NK, AK, LN, SP, MS, IC MS, RW, ZWW, will

contribute to and support recruitment, AU, LM, NR, ET, PS will manage the study. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from Peter MacCallum Cancer Centre Human Research Ethics Committee (number 22/141). All methods will be performed in accordance with relevant guidelines and regulations. Participants will provide informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Institute for Health Transformation, Faculty of Health, Deakin University, 221 Burwood Highway, Burwood, Geelong, Victoria 3125, Australia. [2]Peter MacCallum Cancer Centre, Parkville, Victoria, Australia. [3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia. [4]Department of Clinical Pathology and Centre for Cancer Research, University of Melbourne, Parkville, Victoria, Australia. [5]Swinburne University of Technology, Hawthorn, Victoria, Australia. [6]Latrobe University, Bundoora, Victoria, Australia. [7]CSL Innovation, Melbourne, Victoria, Australia. [8]QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [9]Viertel Cancer Research Centre, Cancer Council Queensland, Queensland, Australia. [10]Department of Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia. [11]Department of Diagnostic and interventional Radiology, University Hospital Bonn, Bonn, Germany. [12]Border Medical Oncology, Albury Wodonga Regional Cancer Centre, Albury, New South Wales, Australia. [13]University of Sydney, Sydney, New South Wales, Australia. [14]Department of Medical Oncology, Westmead Hospital, Sydney, New South Wales, Australia. [15]Department of Medical Oncology, Bendigo Health, Bendigo, Victoria, Australia. [16]Department of Medical Oncology, Royal Darwin Hospital, Darwin, Northern Territory, Australia. [17]University of Queensland, Brisbane, Queensland, Australia. [18]Department of Medical Oncology, Royal Hobart Hospital, Hobart, Tasmania, Australia. [19]Launceston General Hospital, Launceston, Tasmania, Australia. [20]Department of Oncology, Alfred Hospital, Melbourne, Victoria, Australia. [21]School of Translational Medicine, Monash University, Melbourne, Victoria, Australia. [22]Southwest Healthcare, Warrnambool, Victoria, Australia. [23]Barwon Health, Geelong, Victoria, Australia. [24]Eastern Health, Melbourne, Victoria, Australia. [25]Monash Health, Clayton, Victoria, Australia. [26]School of Computing, Engineering and Mathematical Sciences, La Trobe University, Melbourne, Australia.

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