Trials

STUDY PROTOCOL

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Implementation and evaluation of a navigation program for people with cancer in old age and their family caregivers: study protocol for the EU NAVIGATE International Pragmatic Randomized Controlled Trial

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Abstract

Background Cancer navigation programs aim to support, educate, and empower patients and families, addressing barriers to diagnostics, treatment, and care. Navigators engage with people to ensure timely access to services and resources. While promising for older people with cancer, these programs are scarce in Europe, and research on their effectiveness and implementation is limited. We describe the protocol of the EU NAVIGATE randomized controlled trial, aimed to evaluate (1) effectiveness and cost-effectiveness of NavCare-EU, an intervention that aims to support older people with cancer throughout their illness trajectory, spanning the continuum of supportive, palliative, and end-of-life care, and (2) the intervention's implementation processes and feasibility of its integration into different health care systems in Europe, contextual barriers and facilitators for effective and sustainable implementation, and mechanisms involved in reaching the outcomes.

Methods We will conduct a multisite pragmatic fast-track randomized controlled trial with embedded convergent mixed-method process evaluation in Belgium, Ireland, Italy, Netherlands, Poland, and Portugal. The study targets people with cancer and declining health, 70 years or older, and their close family caregivers. The trial compares the NavCare-EU intervention plus standard care with standard care alone. We will perform a baseline measurement prior to randomization and follow-up measurements at 12 weeks, 24 weeks, and 48 weeks in intervention and control group, and an additional measurement at 72 weeks in the control group. Primary outcomes, measured at 24 weeks are (1) the older person's global health status/quality of life, a 2-item subscale from EORTC-QLQ-C30 (revised) measuring health-related quality of life, (2) level of social support measured with Medical Outcomes Study Social Support

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Survey (MOS-SSS scale). The study will include at least 246 older persons with completed global health status/quality of life at 24 weeks.

Discussion The EU NAVIGATE trial will cross-nationally test the effectiveness and cost-effectiveness of a navigation intervention for older people with cancer and their family caregivers, and its implementation in different health care systems in Europe. As continuity and access to health, social, and community care is a priority for patients and caregivers, the trial is timely and critically needed.

Trial registration Clinicaltrials.gov: identifier NCT06110312 (2023/10/31).

Keywords Volunteers, Palliative care, Supportive care, Older persons, Navigation, Quality of life, Family caregivers, Public Health, Cancer

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Introduction

Background and rationale {6a}

Older people are at increased risk of developing cancer, with most new diagnoses and deaths occurring in individuals aged 70 and above, according to EU estimates from 2020 [1, 2]. Advances in cancer treatments have extended survivorship, leading to a larger population of older cancer patients managing the disease as a chronic condition until the end of life [3]. Evidence suggests that older people can experience unique challenges during their cancer trajectory compared to younger people, which may negatively impact their quality of life and wellbeing. Beyond medical concerns, emotional, social, and practical needs can be unmet among older people with cancer. Older people are also at particular risk of experiencing multiple issues that complicate their disease trajectory, such as poverty, social isolation, and limited support networks [4, 5]. Additionally, a lack of awareness about the available community health and social services is a risk factor to disparities in access to care and health outcomes among older adults and their families [6, 7].

Navigation programs hold promise to meet the needs of older people with cancer and their families across the illness trajectory. These interventions aim to support, educate, and empower patients, and sometimes their families, addressing barriers to cancer-related diagnostics, treatment, and care. A key component of these programs is the navigator; in existing navigation programs, navigators are volunteers, nurses, social workers, or community health workers. Navigators, sometimes known as patient navigators, patient advisors, coaches, case managers, or link workers [8] engage with people on an individual and personalized manner to facilitate a timely access to needed services and resources. While various navigation programs have been developed and tested [8, 9], particularly in the USA and Canada, few such services exist in Europe, and research on their effectiveness and implementation is extremely limited.

Evidence from the USA and Canada supports the feasibility and effectiveness of navigation in cancer care, particularly in the early stages, such as in increasing uptake of and adherence to cancer screenings, timely diagnosis, higher completion rates for cancer therapy, and higher rates of attending medical appointments [10, 11]. However, its effectiveness in supportive, palliative, or end-of-life care, especially for older populations with cancer [6], remains largely unknown [10]. One notable exception is Nav-CARE©, developed by Pesut & Duggleby in Canada [7, 12–14], a navigation program originally developed to support older persons with chronic illnesses and those with advanced cancer in rural areas. Nav-CARE© has demonstrated feasibility and received positive feedback from clients, indicating benefits such as social support, assistance with navigating healthcare systems, increased knowledge of available services, access to resources, and family respite [7]. These factors contribute to potential improvements in quality of life and wellbeing.

Despite the reported benefits of the Nav-CARE© program for older people with cancer and their family caregivers, further evidence is needed regarding its effectiveness and cost-effectiveness compared to standard cancer care. Additionally, understanding how the program functions within different healthcare systems and for various subgroups is essential. The EU NAVIGATE project, a Horizon Europe-funded project running from 2022 until 2027 aims to fill these evidence gaps. In the project's first year, we translated and adapted Nav-CARE© from the Canadian to the European context, resulting in a standardized European NavCare-EU program tailored to country and cultural-specific contexts [15]. To evaluate its effectiveness, cost-effectiveness, and implementation, we aim to conduct a pragmatic fast-track randomized controlled trial (RCT) across six EU countries.

Objectives {7}

The research objectives are:

(1) To compare the NavCare-EU intervention in addition to standard care with standard care alone, in terms of its effectiveness and cost-effectiveness for improving quality of life and level of social support in older persons with cancer living at home and for reducing caregiver burden in close family caregivers of older persons with cancer, and
(2) To evaluate the implementation processes of the NavCare-EU intervention and the feasibility of its integration into different health care systems and care regimens in Europe, the contextual barriers and facilitators for effective and sustainable implementation, and the mechanisms involved in reaching the outcomes in each country, as perceived by clients, family caregivers, and healthcare providers.

This article outlines the protocol of the EU NAVIGATE pragmatic fast-track RCT.

Trial design {8}

We will conduct an international six-country multisite pragmatic fast-track RCT with embedded convergent mixed-method process evaluation. The trial will compare the NavCare-EU intervention plus standard care with standard care alone. The trial has a superiority parallel-group design. RCTs range from pragmatic (effectiveness trials, asking "can this intervention work under usual conditions?") to explanatory (efficacy

trials, asking "can this intervention work under ideal conditions?" [16]. Pragmatic trials aim to inform a clinical or policy decision by providing evidence for real-world clinical practice adoption. Fast-track RCTs compare an intervention group to a control group until the primary endpoint (24 weeks in our study, see Fig. 2), after which the control group is also offered the intervention. We designed the trial following the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) guidance [17].

For the convergent mixed-method process evaluation, we will collect quantitative and qualitative data in each country to assess how the NavCare-EU intervention works in real-world contexts, aiming to maximize the feasibility of its implementation in different countries. The process evaluation will be guided by the UK Medical Research Council (MRC) guidance for process evaluations of complex interventions [18] with attention to context, implementation and mechanisms of change, integrating the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [19] and The Practical, Implementation, Sustainability (PRISM) model [20]. Using PRISM and RE-AIM allows us to assess multi-level contextual factors to plan, implement, evaluate, and disseminate the NavCare-EU intervention, improving the adoption and sustainable implementation of evidence-based interventions in various settings.

The trial is registered on clinicaltrials.gov: identifier NCT06110312.

The protocol structure is based on Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and a checklist was provided.

Methods: participants, interventions, and outcomes

Study setting {9}

The trial will be conducted in Belgium, Ireland, Italy, the Netherlands, Poland, and Portugal. The selection of countries was based on achieving good variation in healthcare systems characteristics and socio-cultural factors. Within each country, the intervention will be implemented in real practice (see Table 1).

Eligibility criteria {10}

The recruitment and eligibility criteria are formulated to include people who would typically use the program if it were implemented in current practice, following pragmatic trial principles. The eligibility criteria for the older person with cancer and declining health and for the family caregiver are detailed in Table 2.

Who will take informed consent? {26a}

Researchers will perform eligibility screening and obtain informed consent before inclusion in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable. No ancillary study is conducted, and no biological specimens are collected.

Intervention description {11a}

The NavCare-EU program

Nav-CARE© was developed and successfully tested in Canada by Pesut and Duggleby [7, 12–14, 21]. Nav-CARE© is a person- and family-centered navigation intervention, aimed at improving quality of life and wellbeing throughout a client's trajectory, via the involvement of a navigator. Navigators are volunteers or health care professionals who collaborate with older people, families, and communities to connect them with appropriate resources, information, and others to promote quality of life, support independence and facilitate community connections. A family centric, culturally sensitive, and palliative approach is used. Nav-CARE© was designed to enhance, not replace, professional health and social care in the region where it is implemented and to be responsive to the individual needs and wishes of the clients and their families. Nav-CARE© is a free program. The copyright concerns the need to acknowledge the original developers of the intervention and their expectation the program is implemented with a high level of quality and consistency.

Nav-CARE© was adapted to NavCare-EU within the EU NAVIGATE project, using user and stakeholder engagement following the Adapting interventions to new contexts (ADAPT) guidance [22]. This adaptation process is described in detail elsewhere [15]. The relevant procedures ensured that adaptations did not compromise the functional integrity of the program as a whole, i.e., the extent to which the core functions and processes of the original, evidence-based program are maintained. The program was visualized as a system-based logic model as recommended by the "Integrated assessment of complex health technologies" (INTEGRATE-HTA) guidance [23], addressing all elements of the Template for Intervention Description and Replication (TIDieR) checklist [24]. Figure 1 shows the intervention's core and discretionary components, how they are expected to work to impact older people's and family caregivers' outcomes and which contextual and personal characteristics can influence the implementation of the intervention and its outcomes. This logic model was used to guide the outcome and process evaluation.

Table 1 Overview of implementation settings, organizations, and type of navigators in the participating countries

Countries	Implementation setting	Implementation organization	Type of navigator
Belgium	East-Flanders (region Dender)	Palliative Care Network	Each implementation organization will engage volunteers
	West-Flanders (region Waregem)	Primary Care Network	
Ireland	Dublin	Hospital (cancer centre)	Volunteers from general population
Italy	Lombardy and the surrounding area (Milano metropolitan area and Hinterland, Monza and Brianza province) Milan	Local League against Cancer Fondazione IRCCS Istituto Nazionale dei Tumori	Volunteers from the local League against Cancer
Poland	Krakow and surrounding area	Municipal Social Care Centre	Social workers from the Municipal Social Care Centre in Kraków
Portugal	Coimbra	Portuguese League Against Cancer – Centre Regional Branch Portuguese Institute of Oncology of Coimbra Francisco Gentil	Volunteers from the Portuguese League Against Cancer – Centre Region Branch
Netherlands	Amsterdam	One organization for volunteer support and one hospice facility that offers a volunteer buddy program	Volunteers from the two participating organizations

Core components of the program (Fig. 1)

Navigators in NavCare-EU are selected, trained, and mentored volunteers (i.e., in Belgium, Ireland, Italy, the Netherlands, and Portugal) or professionals (i.e., social workers in Poland). They collaborate with older people with cancer and their caregivers throughout the continuum of supportive, palliative, and end-of-life care. Their main activities focus on connecting clients to social supports, both formal and informal, advocating for clients in meeting their quality-of-life goals, resourcing

Table 2 Inclusion and exclusion criteria for older people with cancer and close family caregivers

Inclusion criteria for older people with cancer
Have a cancer diagnosis (active cancer, meaning not being cancer free, of any stage and involving any treatment/care regimen, i.e., curative, life-extending, or palliative), AND
Aged 70 years or over[a], AND
Have declining or deteriorating health using the Clinical Frailty Scale[b], AND
Live at home (own home or home of the family caregiver) (or discharged home if recruited in hospital), AND
Live within the catchment area of the navigation program/service
Exclusion criteria for older people with cancer
The close family caregiver living with the person with cancer or providing care at least on a weekly basis, and identified as the primary family caregiver by the person with cancer, *if present*, does not agree to participate in the study (unless participation is explicitly requested by the patient), OR
Lives in a care or nursing home, or is incarcerated, OR
Currently receives care from a formally recognized community-based multidisciplinary or specialist palliative care team[c], OR
Is unable to provide informed consent or has difficulties understanding the information about the study, OR
Has a psychiatric condition (i.e., schizophrenia, bipolar disorder, or major depressive disorder) or has an active substance abuse disorder
Is not able to participate in data collection in the country's language
Inclusion criteria for close caregivers (if present)
Aged 18 years or over, AND
Lives with the older person with cancer OR provides care at least on a weekly basis, AND
Identified as primary caregiver by the older person with cancer
Exclusion criteria for close family caregivers (if present)
Is unable to provide informed consent or has difficulties understanding the information about the study, OR
Is not able to participate in data collection in the country's language

[a] Following EORTC reference point for older cancer patients

[b] The Clinical Frailty Scale (CFS) will be used to determine whether the patient has declining or deteriorating health. More specifically, declining or deteriorating health means at least 1 change in CFS score ending in score 4 in the last 6 months, OR everyone scoring 5 or higher

[c] i.e., services whose main task is to provide palliative care (e.g., in Flanders, multidisciplinary palliative home care team, admission to palliative care unit)

by identifying needs and negotiating access to meeting those needs, and engaging clients in what is most meaningful to them. Navigators have face-to-face and/or telephone or IT-supported contact with clients and carers, every 2 weeks on average or as needed. Navigators are matched to clients and caregivers by navigator coordinators who are also responsible for championing the program and for networking with and connecting to health and social care professionals and local initiatives in the community.

To support implementation in the six countries, country trainers are appointed, trained, mentored, and coached in each country by international trainers. This team consists of an international trainer and the original developers from Canada. The country trainers and the international trainers meet on a regular basis (monthly or as needed). Training is competency-based, combines online and face-to-face components, and uses a train-the-trainer approach. The international trainer will aid country trainers to implement the intervention in their specific healthcare contexts and address general and country-specific barriers and facilitators.

Discretionary components of the program are those features which are modifiable depending on the context and clients at hand and include adaptations to adhere to countries' existing laws and regulations, boundaries of navigator roles, provision of additional training if needed depending on the experience of new navigators, safety protocols, and reporting requirements as needed in each site.

Explanation for the choice of comparators {6b}

All older persons with cancer participating in the trial will receive what is standard care in each of the participating countries. We have described for each country the current organization of cancer care in terms of laws and regulations, and the current integration of palliative and end-of-life care within oncology regimens (See Supplementary Table 1).

Criteria for discontinuing or modifying allocated interventions {11b}

Participants will be informed that they may withdraw participation at any point in the study without negative consequence. Reasons for discontinuing the intervention will be documented by the researcher in REDCap (Research Electronic Data Capture), if participants wish to state them. REDCap is a software for building and managing questionnaires and facilitating electronic data collection and storage [25].

Strategies to improve adherence to interventions {11c}

Strategies to improve adherence will include regular feedback sessions with volunteers, allowing us to maintain oversight of the visits and address any deviations from the protocol promptly. We will also monitor

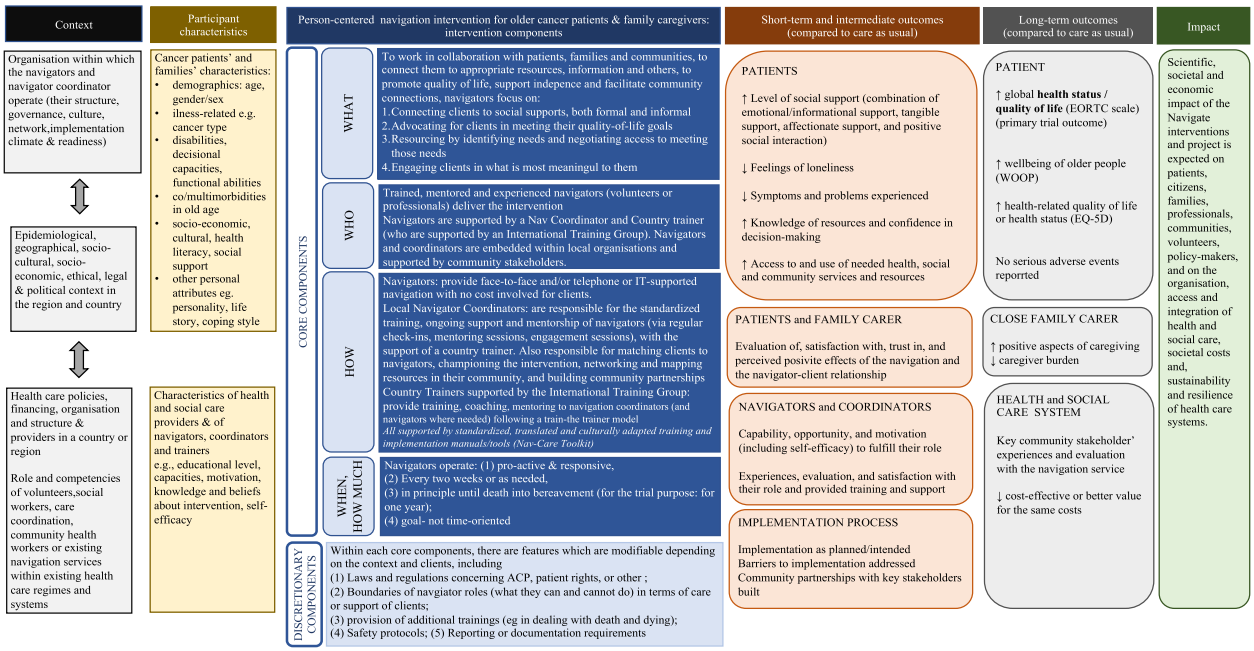

Fig. 1 Conceptual model with core components of the NavCare-EU program after adaptation from the Canadian NavCare

volunteer engagement closely to ensure adherence to the intervention. For monitoring adherence, volunteer diaries will be used to track the frequency and content of visits, providing a clear record of whether the intervention is being delivered as intended. This will allow us to assess both the consistency and quality of the visits throughout the trial.

Relevant concomitant care permitted or prohibited during the trial {11d}

There are no restrictions regarding concomitant care during the trial outside of the trial arms.

Provisions for post-trial care {30}

Participants in the trial are referred to services or community resources based on needs identified during intervention visits or after the trial. After the trial, implementation organizations may allow volunteers to continue supporting patients as part of normal practice, if both agree.

Outcomes {12}

All outcomes are assessedat baseline (T0), 12 weeks (T1), 24 weeks (T2), and 48 weeks (T3) for group 1, andat baseline (T0), 12 weeks (T1), 24 weeks (T2), 48 weeks (T3), and 72 weeks (T4) for group 2 (Fig. 2). We will use established and validated measures for all outcomes. All outcomes are continuous variables. Each outcome measure is aggregated as a summary score of multiple items.

Primary outcomes

The study has two co-primary outcomes; change from baseline at 24 weeks in [1] global health status/quality of life of the older person with cancer, assessed on a 2-item subscale from the EORTC Core Quality of Life questionnaire (EORTC-QLQ-C30 revised) measuring health-related quality of life [26], and (2) the level of social support measured with the Medical Outcomes Study Social Support Survey (MOS-SSS) [27] (see Table 3). Both primary outcomes will be reported by the older person with cancer.

The NavCare-EU intervention will be considered effective if the estimated effect on at least one of the outcomes is considered statistically significant ($p < 0.025$) and clinically relevant (≥ 10 points mean difference).

Secondary outcomes

The secondary outcome for the older person with cancer is change from baseline at 24 weeks in feelings of loneliness, measured with the 3-item-UCLA Revised Loneliness Scale [28]. A secondary outcome for the close family caregivers (if present) is change from baseline at 24 weeks in caregiver burden measured with the Zarit Burden Interview Short Form [29].

Tertiary or exploratory outcomes

As presented in Table 3, we will collect and analyze tertiary or exploratory outcomes for older people with cancer and their family caregivers. Measures for the cost-effectiveness evaluation of the intervention will also be collected.

Other socio-demographic and clinical measures

We will assess sociodemographic and clinical information of the older person with cancer and the family caregivers (Table 3).

Participant timeline {13} (Figs. 2 and 3)

Potentially eligible patients and their close family caregivers (if present) are identified and referred to the researcher by professionals and organizations, or by self-referral. For all patients (and family caregivers) who are potentially eligible, researchers will perform eligibility screening and ask the patients and family caregivers for informed consent before inclusion in the study. After inclusion, participants will take part in the baseline measurements. Immediately after the baseline measurement, participants are randomized to either group 1 or group 2. Group 1 will start with the navigation intervention as soon as possible and group 2 will start the navigation 24 weeks after randomization. Participants in both groups will have a follow-up measurement at 12 weeks, 24 weeks (primary outcome), and 48 weeks after randomization, and group 2 will have an additional follow-up measurement 72 weeks after randomization.

Sample size {14}

To achieve at least 80% power to detect a mean difference between groups of 10 points in patient's global health status/quality of life (considered the smallest clinically relevant difference in the mean score of EORTC QLQ-C30) [30] using an analysis of covariance (ANCOVA) adjusted for baseline global health status/quality of life, at the two-sided 2.5% significance level assuming a standard deviation of 25 points [30] and a correlation of 0.3 between baseline and 24 weeks, a total sample size of 220 clients is needed with a balanced design (allocation ratio 1:1). Taking into account the partially nested study design (there is a cluster effect of navigators in the intervention group), 115 patients in the control group and 131 patients in the intervention group (246 in total) is most efficient, assuming on average 1.5 patients per navigator in Belgium

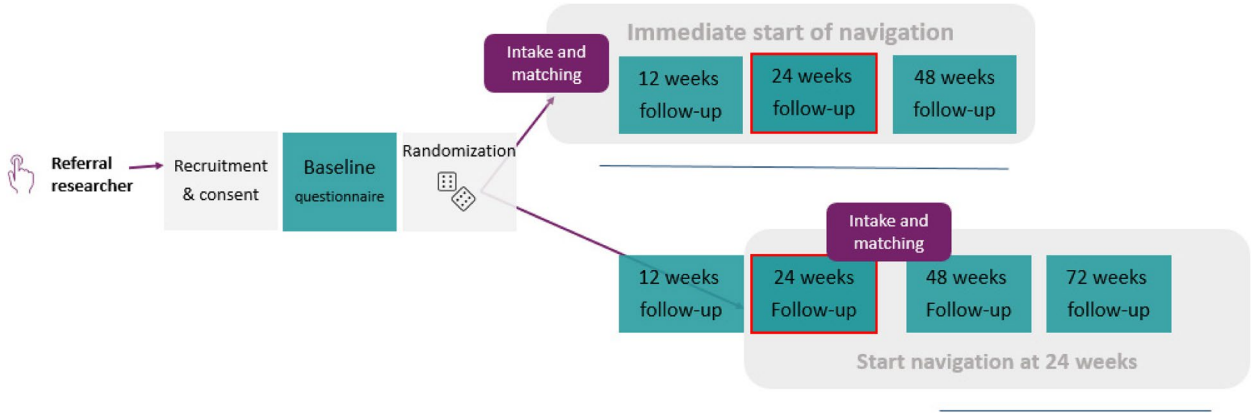

Fig. 2 Participant timeline

(Flanders), Ireland, Italy, the Netherlands, and Portugal (recruiting 5/6 of all patients), and 10 patients per navigator in Poland (recruiting 1/6 of all patients), and an intra-cluster correlation (ICC) of 0.10. An ICC of 0.1 was chosen as a conservative estimate as there is currently no empirical data to support an exact estimate of the ICC.

We will continue randomization until 246 patients have completed the primary endpoint at 24 weeks, with a predetermined maximum sample size set at 489 patients (229 subjects in the control group and 260 subjects in the intervention group). This maximum sample size will allow for a drop-out rate of 50% (17.5% due to mortality, 32.5% due to other reasons) [7, 12, 13]. The sample size calculation was performed using SAS software (version 9.4) and is based on the methods of Moerbeek and Wong [31].

Recruitment {15}

We will recruit participants from a range of settings where patients from the target population receive care/support, i.e., hospitals, community, or volunteer organizations. The recruitment strategies per country are aimed to achieve enrolment of the targeted sample size and to recruit a diverse sample, e.g., in terms of age, gender, cancer diagnoses, or cancer care regimen (curative or non-curative/no treatment).

Depending on the recruitment setting, potentially eligible older persons with cancer and their close family caregivers (if present) will be identified via different professionals and organizations following ethical and informed consent procedures. Referral can be done by health or social care professionals following in-person contact or by self-referral (in all countries except Ireland). All researchers will be trained to ensure all research procedures as outlined in the research protocol are followed.

Recruitment is expected to run over 12 months or until the targeted sample size is achieved.

Assignment of interventions: allocation

Sequence generation {16a}

Randomization will take place after all baseline measurements have been completed. We will randomize clients according to a 1:1.08 allocation ratio (Control: Intervention) allocation ratio in Belgium, Ireland, Italy, The Netherlands, and Portugal, and a 1:1.45 allocation ratio in Poland. These are the most efficient allocation ratio's given the partially nested design (see sample size calculation). We will use permuted block randomization with varying block sizes. Randomization will be stratified by country.

Concealment mechanism {16b}

Randomization lists will be uploaded in REDCap. Centralized randomization uses an automated system that assigns participants to trial groups based on a predefined randomization schedule.

Implementation {16c}

The researcher will randomize the participants using REDCap and inform them of their group assignment.

Assignment of interventions: Blinding

Who will be blinded {17a}

Due to the nature of the intervention which includes clients being visited by navigators, neither the older persons and their family caregivers nor the researchers can be blinded to allocation. Data will be collected via questionnaires and interviews with a researcher that is present for assistance and additional explanations. Those conducting the data analyses will remain blind as

Table 3 Constructs measured in the study and corresponding instruments*

Constructs	Measures	Items	Timing				
			T0 (baseline)	T1 (T0 + 12 weeks)	T2 (T0 + 24 weeks) Primary endpoint	T3 (T0 + 48 weeks)	T4 (T0 + 72 weeks; control group only)
Primary outcomes at 24 weeks							
Older person with cancer							
Global health status /quality of life	EORTC QLQ-C30 (version 3.0): global health/quality of life scale	2	✓	✓	✓	✓	✓
Levels of Social support	Medical Outcomes Study Social Support Survey	19	✓	✓	✓	✓	✓
Secondary outcomes at 24 weeks							
Older person with cancer							
Feelings of Loneliness	3-item-UCLA Revised Loneliness Scale.(6)	3	✓	✓	✓	✓	✓
Family caregiver							
Caregiver burden	Zarit Burden Interview Short Form	12	✓	✓	✓	✓	✓
Exploratory outcomes / potential mediators or moderators of intervention effects							
Older person with cancer							
Perceived health-related quality of life and symptoms or problems experienced (i.e., physical, role, emotional, cognitive, and social functioning as measured by the EORTC-QLQ-C30 for cancer patients	EORTC QLQ-C30 (v 3.0) emotional functioning scale and symptom scales	16	✓	✓	✓	✓	✓
Well-being of older people	WOOP	9	✓	✓	✓	✓	✓
Knowledge of resources and services and confidence in decision making	Items from Patient Engagement Survey Canada	9	✓	✓	✓	✓	✓
Health status	EQ-5D	5	✓	✓	✓	✓	✓
Health and social care services and resource use	Adapted Client Services Receipt Inventory*		✓	✓	✓	✓	✓
Family caregiver							
Health status	EQ-5D	5	✓	✓	✓	✓	✓
Positive Aspects of Caregiving	Positive Aspects of Caregiving (PAC)	9	✓	✓	✓	✓	✓
Independent variables and subgroup descriptors for patients and family caregivers (socio-demographics)							
Socio-demographic & clinical characteristics		Client: 17 Carer: 13	✓				

* Each outcome measure is a summary score of multiple items. Scores for global health / quality of life are computed if at least 50% of the items are valid [26]. Other summary scores are computed if at least 70% of the items are valid. In case of missing items, summary scores are the weighted sum of the observed items with weights inversely proportional to the number of valid items

STUDY PERIOD							
	Approach and referral to researcher	Eligibility screening and consent	Baseline assessment and randomization	Post randomization			
TIMEPOINT			T0	T1 (T0+12 weeks)	T2 (T0 + 24 weeks)	T3 (T0 + 48 weeks)	T4 (T0 +72 weeks; control group only)
ENROLLMENT:							
Approach of potential participants and referral to researcher	X						
Eligibility screening		X					
Informed consent			X				
Baseline assessment			X				
Randomization (after baseline assessment)			X				
INTERVENTIONS:							
NavCare-EU intervention immediate start (group 1)				→	→	→	
NavCare-EU intervention delayed start					→	→	→
(group 2)							
ASSESSMENTS older person with cancer:							
Global health status /quality of life			X	X	X	X	X
Levels of Social support			X	X	X	X	X
Feelings of Loneliness			X	X	X	X	X
Perceived health-related quality of life and symptoms or problems experienced			X	X	X	X	X
Well-being of older people			X	X	X	X	X
Knowledge of resources and services and confidence in decision making			X	X	X	X	X
Health status			X	X	X	X	X
Health and social care services and resource use			X	X	X	X	X
Socio-demographic & clinical characteristics			X				
ASSESSMENTS close family caregiver:							
Caregiver burden			X	X	X	X	X
Health status			X	X	X	X	X
Positive Aspects of Caregiving			X	X	X	X	X
Socio-demographic & clinical characteristics			X				

Fig. 3 SPIRIT figure of study enrollment, interventions, and assessments

to what trial arm participants were randomized to until data lock.

Procedure for unblinding if needed {17b}

Not applicable (see item 17a).

Data collection and management

Plans for assessment and collection of outcomes {18a}

For outcome evaluation

After obtaining informed consent from both the older person and their family caregiver (if present), the researcher will conduct baseline measurements. If the first contact was by phone, an appointment will be made to meet at the older person's preferred location. Following baseline measurements, the researcher will randomize the participants using REDCap and inform them of their group assignment. If assigned to the intervention group, they will be contacted by the navigator coordinator within a week. If assigned to the control group, they will be visited by the researcher after 12 weeks and contacted by the navigator coordinator after 24 weeks. The researcher will send the contact details and group allocation to the navigator coordinator after each enrollment.

Data for primary, secondary, and exploratory outcomes will be collected at baseline, and at weeks 12, 24, and 48 (and at 72 weeks for the control group). Data collection for the intervention group will stop at 48 weeks; for the control group, it will continue until 72 weeks. The researcher will try to collect data within 1 week of each scheduled time point, as outlined in Table 3.

Data will be collected through structured questionnaires during face-to-face visits at the participant's preferred location. Patient questionnaires will be administered by the researcher in a structured interview, while family caregivers will complete their questionnaires on paper, with researcher support if needed. If face-to-face contact is not possible, remote data collection (e.g., via video call) will be used. Each assessment will last approximately 60 min for patients and 30 min for family caregivers.

After completing the questionnaires, the researcher will enter the de-identified responses into REDCap, a secure, password-protected database.

For mixed-method process evaluation

This evaluation includes two phases:

– Development phase before intervention delivery, when the original Canadian Nav-CARE program

(Nav-CARE©) is adapted to the European context. A report per country will be written and potential barriers and facilitators will be mapped.
- Evaluation phase during and after intervention delivery using RE-AIM [19] and PRISM [20] to evaluate the quality and quantity of the delivered intervention and analyze the role of context.

To measure RE-AIM and PRISM constructs we will use several measures:

- Structured interview with organizations that implement the intervention to measure the organizational characteristics and organizational perspective of the intervention
- Short questionnaires filled in by navigator coordinators and navigators to measure their feelings of preparedness for being a navigator (coordinator),
- Diaries filled in by coordinators and trainers of their work during the intervention to measure the time they spent on the different tasks and the successes and challenges they experience.
- Short report for each client visit filled in by navigators to get insight in the delivery of the intervention.
- Qualitative (group)interviews with navigators and coordinators will be held in each country after the intervention period to get a better understanding of their experiences of performing their role and specific tasks as navigator (coordinator) and the successes and challenges they experienced.
- Group interviews with all country trainers will be held after the intervention period to measure their experiences, their experienced barriers and facilitators for the intervention and their recommendations to improve the intervention. Qualitative interviews with clients and care givers will be held in all countries at the end of the intervention, to measure their experiences with receiving support from a navigator.

Table 4 provides an overview of the measurements per group, the time and content of the measurements.

Plans to promote participant retention and complete follow-up {18b}

Dropout due to illness or death is expected in a population of older people with cancer and declining health. Our strategy has been to ensure that the duration from randomization to the measurement of the primary outcome is long enough to observe the intervention's effects, yet short enough to avoid significant attrition due to death. Participants may withdraw from the data collection or voluntarily stop intervention sessions at any time. In case participants only wish to withdraw from the intervention, they are invited to continue with data collection, and priority will be given to collection of primary outcomes.

Data management {19}

De-identified data will be collected via REDCap, in compliance with GDPR, and stored on a secure, password-protected external server with access restricted to authorized researchers. Only pseudonymized data will be accessible. Data cleaning will include removing duplicates, checking consistency, correcting labels, and ensuring variables are properly typed and leveled. Data management procedures are detailed in a data management plan approved by all partners involved in the RCT.

Confidentiality {27}

Personal information will be collected via REDCap and stored on a secure server with restricted access. Only pseudonymized data will be accessible to researchers, and data will be stored on encrypted, password-protected devices. Data will only be shared with third parties after signing a data-sharing agreement, ethical committee approval, and evaluation by the Data Protection Officer. Confidentiality will be ensured before, during, and after the trial through these security measures, including removal of personal identifiers from interview transcripts and storing consent forms in secure, restricted-access locations.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable, no samples collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

For outcome evaluation

All effectiveness outcomes are continuous variables that are expected to be (log)normally distributed. Hence, linear mixed models (LMMs) for a normal distribution with identity link will be fitted. The random effects part will include a random intercept for navigator and a random intercept for participant ID (patient ID / caregiver ID) nested within navigator for outcomes assessed in older persons with cancer / family caregivers respectively. The fixed effects include group (intervention vs usual care), time point (post-intervention measurement at 24 weeks vs. baseline), their interaction group x time,

Table 4 Process evaluation: overview measurements per group, time and content of measurement

Method	Target group	Time	Content
Structured interviews with topic list	Participating organizations (Manager + coordinator)	Before and after intervention	- Organizational perspective of the intervention and organizational characteristics - Barriers and facilitators that are assumed (before intervention) and experienced (after intervention)
Short questionnaires	All navigators, All navigator coordinators	Before and after intervention	- Feelings of preparedness for being a navigator (coordinator) referring to the 5 tasks of a navigator (coordinator) as educated in the NavCare-EU training - Successes and challenges that are foreseen (before intervention) and experienced (after intervention)
Diaries (pre structured)	All navigator coordinators All country trainers	During intervention	- Time spent on different tasks - Successes and challenges they experience in their role
Visit reports (pre structured)	All navigators	During intervention	- Time spent with client - Content of the visit - Actions taken as result of the visit - Successes and challenges they experienced
Qualitative (group) interviews with topic list	About 5 navigators per country All navigator coordinators All country trainers	After intervention	- Experiences in their role - preparedness for their role - Successes and challenges they experienced - Suggestion for improvements of the intervention (in general and in their country)
Qualitative interviews with topic list	About 5 clients and 5 care givers per country	After intervention	- Experiences with their navigator - Satisfaction with the NavCare-EU intervention - Suggestion for improvements of the intervention - Why they would (not) recommend a navigator to someone else

and country (stratification factor for randomization). The interaction effect will capture the mean difference between groups in change from baseline. The analysis of the primary outcome "social support" will further be adjusted for the older person's living situation (i.e., living alone vs not living alone). Estimated marginal means with corresponding confidence interval (CI) will be reported. For the subgroup analyses, formal interaction tests will be conducted to explore the extent to which the primary outcomes differ between subgroups. The LMMs will be fitted based on restricted maximum likelihood. The analysis includes all available information from subjects with missing outcome values and yields valid inferences under the assumption that missing outcome data are missing at random (MAR). If outcomes are truncated due to death, the observed value of the respective outcome prior to death will be used (while alive strategy).

All hypothesis testing will be two-sided. The two primary outcomes will be tested at the 2.5% significance level (Bonferroni correction for multiplicity). The CIs for the estimated mean differences in the primary outcomes will be 97.5% CIs. If superiority can be demonstrated on one of the primary outcomes, comparisons of secondary outcomes will be interpreted at the 5% significance level. All reported CIs for outcomes other than the primary will be 95% CIs.

Interim analyses {21b}

No interim analyses to stop for efficacy or futility are planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Pre-defined subgroup analyses

The pre-defined subgroups are based on (1) patient/caregiver characteristics known to affect health equity and equitable access to health care (age, gender, educational level, socio-economic status based on perceived financial hardship to meet daily needs, living situation, and level of needs at baseline (measured using EQ-5D questions on

mobility, self-care, and usual activities, and primary and secondary endpoints at baseline), older person's cancer type); (2) country characteristics (healthcare system type, navigator profile, i.e., paid worker vs. volunteer).

Sensitivity analyses

We will perform sensitivity analyses for the primary endpoints, regarding the assumption behind the missing data generating mechanism. Furthermore, we will handle the intercurrent event death in a different way by estimating the effect of the intervention within an unobservable subpopulation that would have survived under either arm (principal stratum strategy) [32].

For cost-effectiveness evaluation

We will analyze the cost-effectiveness of the interventions by calculating the change in healthcare costs and the change in quality of life and combining these changes in an incremental cost-effectiveness ratio. In primary analysis, quality of life will be measured using EQ-5D-5L and these data combined with survival and country-specific utility weights to derive quality-adjusted life years (QALYs). Formal cost data will be estimated by combining participant responses on frequency of healthcare utilization with country-specific unit costs. We will estimate the resources associated with the intervention through analysis of the diaries of coordinators and trainers, and navigator reports, augmented by discussion with each of these groups. Consistent with the primary analysis of trial outcomes, we will address missing data using mixed-effects models and conduct sensitivity analysis on the MAR assumption [33].

Follow-up analyses will incorporate data on the types and amounts of informal care provided to patients in the control group and the intervention group, to investigate if the amount or patterns of informal care change as a result of the intervention, and if these changes impact the cost-effectiveness results. We will compare cost-effectiveness results derived using EQ-5D-5L with results using global health status/quality of life measured using the EORTC-QLQ-C30. We will employ decision analytic modelling to estimate under uncertainty progression of disease, survival, and associated costs and outcomes beyond the 6-month period of observation, and so to provide an overall cost-effectiveness estimate from study entry to death.

For process evaluation

The structured interviews with the organizations will contain mostly qualitative data. The researchers of each country will collect the data in their own language and will enter the data in English in a database. This will be analyzed with thematic content analyses.

The surveys among navigators and coordinators will also be collected in the countries' own language and entered in English in a database. These data will be analyzed with descriptive statistics.

The (group) interviews with navigators, coordinators, clients, and caregivers will be performed in each country in their own language, using a topic list. The researchers per country will make a summary of the interviews based on a format with topics in English. In this way all interviews can be analyzed by the same person. A thematic analysis will be done on the summaries of all countries.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analysis populations

All analysis will be performed on the intent-to-treat (ITT) population, which consists of all patients randomized. The ITT approach may reflect the effects of NavCare-EU on the different endpoints in daily practice.

Statistical methods to handle missing data

Missing baseline characteristics Missing values in the descriptive analysis of the baseline characteristics will be reported as missing. Missing baseline covariate data is assumed to be missing completely at random.

Missing outcome data The LMM is fitted based on restricted maximum likelihood (REML). The analysis includes the available information from subjects with missing outcome values and yields valid inferences under the assumption that missing outcome data are missing at random (MAR). In our main analyses, we assume that missing outcome data can be related to the allocated intervention, baseline value of the outcome, and/or country, but that it is unrelated to other values. We will perform sensitivity analyses regarding the assumption behind the missing outcome data generating mechanism.

Pilot testing of the research procedures

We performed a small-scale pilot testing of the research procedures to maximize feasibility of the study and troubleshoot issues that arose during set up of the implementation. The pilot study was performed using five fictional cases of clients and family caregivers, carried out as role-plays by researchers and data collectors in each country.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

After completion of all analyses, data will be made available upon reasonable request and upon signing a unilateral data sharing agreement.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The project's trial coordination team from Vrije Universiteit Brussel oversees the trial design, conduct, data analysis, and reporting, and they meet every 2 weeks to closely monitor the trial and its conduct internationally. The trial coordination team works closely with the principal investigators in each country to ensure that the trial is conducted according to the trial protocol. Moreover, to ensure the smooth execution of the project and the trial, the team conducts regular meetings with (1) all researchers every 6 weeks and (2) the Supervisory Board of EU NAVIGATE every 6 months.

Composition of the data monitoring committee, its role and reporting structure {21a}

An Ethics Evaluator external to the project was appointed who will monitor the ethical aspects of the study, including data management and privacy concerns. This person will provide evaluation and advice on ethical, legal, data protection, and data management issues based on regular monitoring evaluations performed by independent trial monitors in the participating countries. Monitoring evaluations will be done shortly after the start of the trial, and at least at three follow-up occasions.

Adverse event reporting and harms {22}

The EU NAVIGATE study protocol and the NavCare-EU intervention are non-invasive and do not pose any known risk of injury, hence adverse effects are unlikely. Adverse events are defined as *every event in the study that takes a course that is significantly more unfavorable to study participants than foreseen in the normal course of the illness.*

Adverse events are categorized as:

(1) Anticipated or expected adverse events, which includes two categories (serious or not serious), and
(2) Unanticipated or unexpected adverse events, which includes two categories (serious or not serious).

Any adverse event that occurs will be documented in an adverse event reporting log kept by the Principal Investigators in the participating countries and will be reported yearly to the local ethics committee or otherwise following the local mechanisms for reporting these events.

Frequency and plans for auditing trial conduct {23}

Auditing will be independent from investigators and the sponsor and will be done by independent trial monitors in each country.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Important protocol amendments will be communicated to the ethics committees.

Dissemination plans {31a}

Results will be submitted for peer-reviewed publication.

Authorship eligibility guidelines and any intended use of professional writers {31b}

Authorship on scientific papers is limited to those who fulfil the ICMJE guidelines for authorship of scientific papers. The Supervisory Board of the project approves the content, authorship, and timing of submission for all publications.

Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code {31c}

After completion of all analyses, data will be made available upon reasonable request and upon signing a unilateral data sharing agreement.

Discussion

Advancements in cancer care alleviate the morbidity and mortality burden of the disease in Europe, but more patients who are older and with complex needs must engage with complex healthcare systems. Vulnerable or underserved groups face difficulties accessing essential health and social services, especially for supportive, palliative, and end-of-life care. Navigation programs, where trained individuals empower patients to navigate healthcare systems, offer promise in overcoming these barriers while providing companionship and support. We will evaluate the effectiveness and cost-effectiveness of a navigation program that aims to support older people with cancer throughout their illness trajectory, spanning the continuum of supportive, palliative, and end-of-life care.

The EU NAVIGATE trial is highly innovative as it will be the first cross-national RCT of a navigation program in a population of older people with cancer. Compared to the USA and Canada [10, 11, 34–36], only few such programs exist in Europe. Should the NavCare-EU intervention demonstrate effectiveness and cost-effectiveness, it could be the first evidence-based

patient- and family-centered navigation model of care for older people with cancer and their caregivers that can be used in different healthcare systems in Europe and that operates across disease stages and settings.

The trial will evaluate patient navigation under "real-world" conditions, as opposed to highly specialist sites or services. This will deliver important insights into barriers and opportunities for implementation in highly diverse health care contexts. The study will reveal which characteristics of health care systems facilitate or hinder the implementation and effectiveness and cost-effectiveness of the navigation program. This approach will give the best chances of delivering a navigation program that can be feasibly implemented, and that is accessible and scalable in Europe. The combination of established implementation science frameworks such as RE-AIM [19] and PRISM [20], and guidance by an implementation logic model, will aid to reveal implementation and context and how they impact outcomes. Another strength of the trial lies in its fast-track study design [37], which allows all eligible participants to receive the intervention while the RCT remains rigorously controlled. It can also help counter people's reluctance to be randomized to a control group that is not receiving an intervention, and it can be used with patients with longer or shorter (i.e., several weeks) survival periods [37].

The NavCare-EU program is innovative in several ways.

First, it works across the continuum of supportive, palliative, and end-of-life care, while most navigation programs in cancer focus only on the early phases of cancer screening and detection [10]. By building sustainable relationships with clients and family caregivers, navigators offer continuous support and companionship to clients and their families throughout the illness trajectory, including after death into bereavement, enhancing continuity of care [7].

Second, NavCare-EU focusses on the patient together with the caregiver, while most other navigation programs focus on the patient [34], or on the family caregiver alone [36].

Third, the program fits well within emerging public health approaches to palliative care [38]. By working closely with clients and families to navigate the complexities of the healthcare system and providing support, navigators promote a culture of care and compassion, contributing to creating a supportive environment where people feel valued, supported, and empowered throughout their illness journey [13].

Finally, the program holds potential to reduce access barriers to care services and resources, particularly to palliative care, by informing and guiding clients about available support options, professionals, and community resources. Navigators are trained to talk with persons about sensitive topics like palliative and end of life care, advance care planning, dying and grief, thus facilitating equitable access to services and resources as needed. The EU NAVIGATE trial aims to actively involve populations at risk of inequitable access to care and health inequities such as people with poor social support and those with low socioeconomic status, populations that have so far been highly underrepresented in cancer research on supportive, palliative, and end-of-life care interventions.

Conclusion

We are cross-nationally testing the effectiveness for improving quality of life and level of social support in older persons with cancer living at home and for reducing caregiver burden in close family caregivers of older persons with cancer, and cost-effectiveness of a patient- and family-centered navigation program for older people with cancer and their caregivers, and its implementation processes and the feasibility of its integration into different health care systems and care regimes in Europe. As continuity and access to health, social, and community care is an important priority for patients and caregivers, the NavCare-EU program and the trial are timely and critically needed. Focusing on a population of older people, who are often excluded from intervention studies and trials, is highly relevant given the rapid evolution towards growing numbers of people dying from cancer in older age.

Trial status

Recruitment of study participants began November 6th, 2023, and will be completed by December 31, 2024. Protocol version 2, July 2, 2024.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08633-5.

Supplementary Material 1.

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TS, LP, RM, FVC, CV, BP, WD, AND, AL, PM, BG, MFB, VR, KS, VK, IB, SDB, DF, SA, BS, HDC, KC, JG, AvdP, RHP, BOP, and LvdB contributed substantially to the conception and design of the study, and to the development of the study protocol. TS wrote the first draft of the manuscript of the study protocol. LP, RM, FVC, CV, BP, WD, AND, AL, PM, BG, MFB, VR, KS, VK, IB, SDB, DF, SA, BS, HDC, KC, JG, AvdP, RHP, BOP, and LVdB, commented on the first draft of the manuscript. TS, RM, and LvdB critically revised the manuscript after receiving comments from all authors. All authors read and approved the final manuscript for publications. All authors have sufficiently participated in this work to take public responsibility for appropriate portions of the content. TS was responsible for the final submission. TS and LvdB are the guarantors of the content.

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Data availability
After completion of all analyses, data will be made available upon reasonable request and upon signing a unilateral data sharing agreement.

Declarations

Ethics approval and consent to participate
Ethics approval from the relevant ethics committees were obtained in all participating countries. Belgium: Commissie Medische Ethiek, 09/08/2023; Ireland: SJH/TUH Joint Research Ethics Committee, 14/11/2023; Italy: Comitato Etico Territoriale Lombardia 4, Istituto Tumori, 31/07/2023; the Netherlands: METC Amsterdam UMC, 22/08/2023; Portugal: Ethics Committee of the Faculty of Medicine of the University of Coimbra and Ethics Committee of the Portuguese Institute of Oncology of Coimbra Francisco Gentil, 25/09/2023; Poland: Komisja Bioetyczna, Uniwersytetu Jagiellońskiego, 14/06/2023.
If all eligibility criteria are met, the researcher or research assistant will obtain informed consent from both the older person and the close family caregiver (if there is one). Patients and caregivers will be given the time to consider participation and will be assured that they are free to withdraw their participation without any effect on their care. Written consent will be obtained without any coercion of study participants. The research team will provide all participants with full disclosure about the nature and goal of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Hub. ES. 2020 Cancer incidence and mortality in EU-27 countries. 2020 [Available from: https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/2020-cancer-incidence-and-mortality-eu-27-countries-2020-07-22_en.
2. Cancer. WIAfRo. Global cancer burden growing, amidst mounting need for services. 2024 [Available from: https://www.iarc.who.int/news-events/global-cancer-burden-growing-amidst-mounting-need-for-services
3. Ramsey I, Eckert M, Hutchinson AD, Marker J, Corsini N. Core outcome sets in cancer and their approaches to identifying and selecting patient-reported outcome measures: a systematic review. J Patient Rep Outcomes. 2020;4(1):77.
4. Mohile SG, Dale W, Somerfield MR, Hurria A. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology Summary. J Oncol Pract. 2018;14(7):442–6.
5. Arastu A, Patel A, Mohile SG, Ciminelli J, Kaushik R, Wells M, et al. Assessment of Financial Toxicity Among Older Adults With Advanced Cancer. JAMA Netw Open. 2020;3(12): e2025810.
6. van Ee IB, Hagedoorn M, Slaets JP, Smits CH. Patient navigation and activation interventions for elderly patients with cancer: A systematic review. Eur J Cancer Care (Engl). 2017;26(2).
7. Pesut B, Duggleby W, Warner G, Bruce P, Ghosh S, Holroyd-Leduc J, et al. A mixed-method evaluation of a volunteer navigation intervention for older persons living with chronic illness (Nav-CARE): findings from a knowledge translation study. BMC Palliat Care. 2020;19(1):159.
8. Reid AE, Doucet S, Luke A, Azar R, Horsman AR. The impact of patient navigation: a scoping review protocol. JBI Database System Rev Implement Rep. 2019;17(6):1079–85.
9. Corbett CM, Somers TJ, Nunez CM, Majestic CM, Shelby RA, Worthy VC, et al. Evolution of a longitudinal, multidisciplinary, and scalable patient navigation matrix model. Cancer Med. 2020;9(9):3202–10.
10. Bernardo BM, Zhang X, Beverly Hery CM, Meadows RJ, Paskett ED. The efficacy and cost-effectiveness of patient navigation programs across the cancer continuum: A systematic review. Cancer. 2019;125(16):2747–61.
11. Roland KB, Milliken EL, Rohan EA, DeGroff A, White S, Melillo S, et al. Use of Community Health Workers and Patient Navigators to Improve Cancer Outcomes Among Patients Served by Federally Qualified Health Centers: A Systematic Literature Review. Health Equity. 2017;1(1):61–76.
12. Duggleby W, Pesut B, Warner G, Ruiz KJ, Nekolaichuk C, Ghosh S, et al. A Feasibility Study of a Volunteer Navigation Program in the Palliative Context. Am J Hosp Palliat Care. 2021;38(8):963–71.
13. Pesut B, Duggleby W, Warner G, Fassbender K, Antifeau E, Hooper B, et al. Volunteer navigation partnerships: Piloting a compassionate community approach to early palliative care. BMC Palliat Care. 2017;17(1):2.
14. Pesut B, Hooper B, Jacobsen M, Nielsen B, Falk M, BP OC. Nurse-led navigation to provide early palliative care in rural areas: a pilot study. BMC Palliat Care. 2017;16(1):37.
15. Van Campe F CK, Pivodic L, Gilissen J, Pesut B, Duggleby W, Smets T, Szczerbińska K, Gomes B, Davies AN, Ferraris D, Onwuteaka-Philipsen BD, Van den Block L. Adapting public health palliative care interventions across settings using ADAPT guidance: the example of EU NAVIGATE. Abstract presented at the EAPC 13th World Research Coungress, 16–18 th May. Barcelona. Spain: Pall Med; 2024.

16. Ford I, Norrie J. Pragmatic Trials. N Engl J Med. 2016;375(5):454–63.
17. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350: h2147.
18. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015;350: h1258.
19. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. Front Public Health. 2019;7:64.
20. McCreight MS, Rabin BA, Glasgow RE, Ayele RA, Leonard CA, Gilmartin HM, et al. Using the Practical, Robust Implementation and Sustainability Model (PRISM) to qualitatively assess multilevel contextual factors to help plan, implement, evaluate, and disseminate health services programs. Transl Behav Med. 2019;9(6):1002–11.
21. Warner G, Kervin, E., Pesut, B., Urquhart, R., Duggleby, W., & Hill, T. . How do inner and outer settings affect implementation of a community-based innovation for older adults with a serious illness: a qualitative study. . BMC Health Services Research. 2021;21.
22. Moore G, Campbell M, Copeland L, Craig P, Movsisyan A, Hoddinott P, et al. Adapting interventions to new contexts-the ADAPT guidance. BMJ. 2021;374: n1679.
23. WAHLSTER P, BRERETON, L., BURNS, J., HOFMANN, B., MOZYGEMBA, K., OORTWIJN, W., PFADENHAUER, L., POLUS, S., REHFUESS, E., SCHILLING, I., VAN HOORN, R., VAN DER WILT, G.J., BALTUSSEN, R., GERHARDUS, A. . Guidance on the integrated assessment of complex health technologies - The INTEGRATE-HTA Model 2016.
24. Network E. The TIDier (Template for Intervention Description and Replication) Checklist.
25. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95: 103208.
26. Life EQo. Core questionnaires [Available from: https://qol.eortc.org/questionnaires/core/.
27. Hays RDSC, Mazel RM. User's Manual for Medical Outcomes Study (MOS) Core Measures of health-related quality of life. Santa Monica, CA: RAND Corporation; 1995.
28. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies. Res Aging. 2004;26(6):655–72.
29. Gratao ACM, Brigola AG, Ottaviani AC, Luchesi BM, Souza EN, Rossetti ES, et al. Brief version of Zarit Burden Interview (ZBI) for burden assessment in older caregivers. Dement Neuropsychol. 2019;13(1):122–9.
30. EORTC Quality of Life Group (July 2008). EORTC-QLQ-C30 Reference Values. Brussels Belgium) https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf
31. Moerbeek M, Wong WK. Sample size formulae for trials comparing group and individual treatments in a multilevel model. Stat Med. 2008;27(15):2850–64.
32. Chiba Y, VanderWeele TJ. A simple method for principal strata effects when the outcome has been truncated due to death. Am J Epidemiol. 2011;173(7):745–51.
33. Achana F, Gallacher D, Oppong R, Kim S, Petrou S, Mason J, et al. Multivariate Generalized Linear Mixed-Effects Models for the Analysis of Clinical Trial-Based Cost-Effectiveness Data. Med Decis Making. 2021;41(6):667–84.
34. Urquhart R, Kendell C, Pfaff K, Stajduhar K, Patrick L, Dujela C, et al. How do navigation programs address the needs of those living in the community with advanced, life-limiting Illness? A realist evaluation of programs in Canada. BMC Palliat Care. 2023;22(1):179.
35. Rocque GB, Partridge EE, Pisu M, Martin MY, Demark-Wahnefried W, Acemgil A, et al. The Patient Care Connect Program: Transforming Health Care Through Lay Navigation. J Oncol Pract. 2016;12(6):e633–42.
36. Dionne-Odom JN, Azuero A, Taylor RA, Dosse C, Bechthold AC, Currie E, et al. A lay navigator-led, early palliative care intervention for African American and rural family caregivers of individuals with advanced cancer (Project Cornerstone): Results of a pilot randomized trial. Cancer. 2022;128(6):1321–30.
37. Higginson IJ, Booth S. The randomized fast-track trial in palliative care: role, utility and ethics in the evaluation of interventions in palliative care? Palliat Med. 2011;25(8):741–7.
38. J C. Serious illness, dying and grieving as public health issues. Public Health. 2021;198:59–61.

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