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NAVIGATE: improving survival in vulnerable patients with lung cancer through nurse navigation, symptom monitoring and exercise – study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction and aim Low socioeconomic position (SEP) has been shown to be strongly associated with impaired lung cancer survival. Barriers related to receiving recommended treatment among patients with lung cancer with low SEP may include adverse health behaviour and limited physical and psychosocial resources influencing the ability to react on high-risk symptoms and to navigate the healthcare system. To address the underlying factors that drive both decisions of treatment, adherence to treatment and follow-up in vulnerable patients with lung cancer, we developed the Navigate intervention. The aim of this randomised controlled trial is to investigate the effect of the intervention on survival (primary outcome), lung cancer treatment adherence, health-related quality of life and other psychosocial outcomes as well as health costs and process evaluation (secondary outcomes) in a study population of vulnerable patients with lung cancer.

Methods and analysis This two-armed multicentre randomised trial will recruit patients from five lung cancer clinics in Denmark identified as vulnerable according to a screening instrument with nine clinical and patient-reported vulnerability criteria developed for the study. We will enrol 518 vulnerable patients ≥18 years old diagnosed with non-small cell lung cancer at all stages with a performance status ≤2. Participants will be randomly allocated to either standard treatment and intervention or standard treatment alone. The Navigate intervention is based on principles from motivational interviewing and includes three components of nurse navigation, systematic monitoring of patient-reported outcomes (PROs) and physical exercise in a person-centred delivery model. Data will be collected at baseline and 3, 6, 12 months after randomisation using questionnaires, clinical data and physical function tests.

Ethics and dissemination Ethics Committee, Region Zealand (SJ-884/EMN-2020-37380) and the Data Protection Agency in Region Zealand (REG-080-2021) approved the trial. Participants will provide written informed consent. Results will be reported in peer-reviewed journals.

Trial registration number NCT05053997.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Navigate intervention is the first to target survival in vulnerable patients with lung cancer.
⇒ To optimise patient motivation, the Navigate intervention is based on principles from motivational interviewing specifically to engage, focus and set goals for small step changes.
⇒ Participants and health professionals cannot be blinded due to the nature of the intervention.
⇒ The multicentre randomised controlled trial design including patients with lung cancer in all regions of Denmark increases external validity and may facilitate the implementation of the intervention, if results are positive.

INTRODUCTION

Lung cancer continues to be the most commonly diagnosed malignancy in men and women and the leading cause of cancer death worldwide.[1] Although the overall 5-year survival rate for patients with lung cancer has increased during the last decade from 8% to beyond 15% due to advances in medical treatment,[2] the prognosis is still poor, especially for patients diagnosed with advanced disease.[3]

Patients with low socioeconomic position (SEP) have a higher lung cancer incidence and shorter survival after lung cancer compared with patients with high SEP.[4 5] Several studies have shown that patients with

lung cancer with low SEP are less likely to receive first-line treatment compared with patients with high SEP regardless of stage, histology and healthcare system.[6–11] Differences in received treatment, stage and comorbidity may explain a large proportion of the social inequality in lung cancer prognosis both among early stage and advanced stage patients.[8] Thus, in the current study we define vulnerability as social, behavioural and disease factors that may contribute to poor adherence to lung cancer treatment. To our knowledge, no studies have attempted to improve treatment adherence[12] nor access to rehabilitation and palliative care[13] among patients with lung cancer who are vulnerable in terms of social, behavioural and disease factors and at risk of non-adherence to treatment and follow-up. Studies on other cancer groups have, however, shown promising results from nurse navigation,[14–16] use of patient-reported outcomes (PROs)[17] and physical exercise[18 19] to address non-adherence to cancer treatment and follow-up.

Nurse navigation

Nurse navigation is the coordination of cancer care achieved through individualised support to ensure completion of recommended treatment and follow-up and is performed by nurses who have experience with treatment of patients with cancer and with the healthcare system.[20 21] Key components include offering psychosocial support, providing education for symptom management and referring to relevant healthcare or social services.[20 21] Nurses have the clinical expertise to match the complex clinical challenges that can emerge through multidisciplinary care from the time of diagnosis across phases of treatment, in particular for vulnerable cancer patients with multiple comorbidities.[22 23] We have shown a positive effect on distress, anxiety and depression among 50 psychologically vulnerable patients with breast cancer in a pilot randomised controlled trial (RCT) combining nurse navigation with PRO.[24] Two retrospective observational studies among patients with lung cancer have compared diagnostic and treatment outcomes before and after the implementation of nurse navigation and suggested improvement of timeliness in lung cancer care.[25 26] So far, only one RCT (N=108) has investigated the effect of a tailored supportive care intervention among the patients with inoperable lung cancer[27] with no support for significant improvements in unmet needs, psychological morbidity, distress, and health-related quality of life (HRQoL) among patients in the intervention group, but the study was small and did not focus particularly on timeliness of treatment nor investigated the effect on adherence. Nurse navigation in lung cancer care may have the potential to increase the proportion of vulnerable patients at all stages of lung cancer receiving treatment and shorten the time to delivery of treatment by improving supportive strategies and management of symptoms. Although being promising, evidence is thus still needed for the effect of nurse navigation on clinical outcomes among vulnerable patients with lung cancer.

Use of PRO in lung cancer care

In an attempt to optimise quality of cancer care and increase patient involvement, PROs have been found to improve patient–provider communication, symptom control, patient satisfaction and increased use of supportive care.[17] Basch *et al*[28] tested the effect of a web-based weekly PRO, with automated alerts to prompt clinicians for worsening of symptoms among 766 patients with metastatic cancer (25% patients with lung cancer). They found improvements in HRQoL, less frequent use of emergency rooms, longer treatment with chemotherapy, and more patients alive at 1 year (75% compared with 69% in the control group). A similar RCT by Denis *et al*[29] among patients with advanced lung cancer (N=133) tested weekly web-based PRO compared with routine follow-up with regular CT scans. The study reported that the median overall survival in the experimental arm was significantly improved (19 months compared with 12 months in the control arm)[29] potentially due to early detection of adverse events and recurrence and better performance status at recurrence.[29 30] Together these studies indicate that close monitoring and adequate clinical reactions to key alert symptoms may have the potential to improve treatment adherence,[28] the efficiency of follow-up[29] and overall survival.[28–31] However, the benefits of PROs have not yet been explored in vulnerable cancer patients.

Physical exercise in patients with lung cancer

A Cochrane review from 2019[32] including six RCTs (N=221 patients) found significant effects of >4 weeks exercise training at least once a week during treatment among the patients with advanced lung cancer on 6 min walk distance and HRQoL, but not on specific physical and psychological symptoms or survival. A recent Danish RCT (N=218 patients with advanced inoperable lung cancer) reported significant reductions in anxiety and depression, improvement in muscle strength (not in VO2 peak), and maintenance of social well-being among patients randomised to a 12 weeks, two times a week supervised cardio and strength training programme.[33]

Even though physical exercise has proven beneficial[32 33] and safe[34 35] among patients with lung cancer, keeping up adherence to exercise during oncology treatment is a challenge for most patients and may be especially difficult for socially vulnerable patients.[36] Activation of the patient's individual motivation and developing an environment of autonomy, competence and relatedness may be of key importance.[37] However, no previous studies have specifically targeted exercise training during treatment in vulnerable patients with lung cancer.

PROPOSED THEORETICAL FRAMEWORK

Vulnerability in patients with lung cancer may be driven by multiple factors including adverse health behaviour such as smoking and alcohol use, poor physical health, limited psychosocial resources, health literacy and transportation

barriers influencing the ability to adhere to recommended treatment, react to high-risk symptoms and advocate for oneself in the healthcare system.[38] Targeting the complex underlying factors that drive both decisions of treatment as well as adherence to treatment and follow-up are important to improve outcomes for vulnerable patients with lung cancer and intervention development should consider both *how to facilitate* changes as well as the *delivery mode* appropriate for the study population.[39]

Activating patient motivation may be especially important *to facilitate* change in patients who struggle with physical and emotional challenges of cancer treatment and survivorship.[40] Motivational interviewing (MI) has been applied in a number of settings including cancer populations to enhance patient motivation and promote behaviour change such as lifestyle improvements, psychosocial support and cancer-related symptom management.[40]

To optimise *delivery mode* for vulnerable lung cancer patients, a person-centred and flexible approach to each patient's needs and resources is essential,[41] for example, proactively providing resources to address transportation barriers, managing symptoms with a telephone-based nurse navigator and maintaining or increasing functional status by home-based exercise sessions supervised by physiotherapist by telephone.

Aims

We aim to examine the added effect of NAVIGATE—a novel intervention including nurse navigation in combination with PRO and physical exercise targeting vulnerable patients with lung cancer in addition to standard care with survival at 12 months after randomisation as primary outcome and adherence to lung cancer treatment, HRQoL and other psychosocial outcomes as well as health costs and process evaluation as secondary outcomes.

METHODS AND ANALYSIS

Setting and participants

The Navigate trial is a multicentre (five Danish hospitals: Zealand University Hospital, Odense University Hospital, Vejle Hospital, Sønderborg Hospital and Gødstrup Hospital) two-armed RCT testing the effect of an intervention including nurse navigation, systematic use of PROs and physical exercise and standard care compared with standard care alone among vulnerable patients with lung cancer. Recruitment started 1 March 2022 and is anticipated to end 1 March 2024 resulting in end of follow-up on 1 March 2025. The trial protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials[42] and the Template for Intervention Description and Replication.[43]

Eligibility criteria

Patients who fulfil the following criteria are eligible to participate: ≥18 years, diagnosed with non-small cell lung cancer (NSCLC) at all stages, performance status ≤2, eligible for cancer treatment, and vulnerable according to three or more vulnerability criteria from a screening instrument described below. Excluded are patients who are not able to read and understand Danish, with severe untreated psychiatric disorder or cognitive problems preventing informed consent. Each year, approximately 4000 patients are diagnosed with NSCLC at all stages in Denmark,[3] and based on data from pilot testing of the vulnerability screening instrument, we expect that approximately 60% will be screened vulnerable according to three or more criteria. Once included in the trial, there are no exclusions criteria and patients may remain in the study even if they wish to discontinue the exercise programme.

Vulnerability screening instrument

To our knowledge, there are no validated instruments to identify vulnerability in patients with lung cancer defined as being at risk for not adhering to lung cancer treatment. Thus, for the current study we developed an instrument inspired by geriatric assessment tools[44 45] and through involvement of patients and clinical experts (see the Patient and public involvement section). The screening instrument include nine clinical and patient-reported vulnerability criteria: (1) stage IIIB–IV (from medical journal), (2) comorbidity (somatic or psychiatric) with impact on treatment or comorbidity resulting in hospitalisation within last 3 years (from medical journal), (3) age >80 years (from medical journal), (4) performance status =2 (from medical journal), (5) activities of daily living (three patient-reported items regarding difficulties with personal hygiene, taking a walk and climbing stairs), (6) social support (three patient-reported items regarding emotional support as well as support with practicalities at home and transportation), (7) health literacy (three patient-reported items regarding difficulties in understanding healthcare information, instructions from healthcare professionals and filling in forms), (8) transportation related barriers for treatment (three patient-reported items regarding difficulties in reaching the hospital due to lack of transportation, long distance to the hospital or limited energy) or (9) alcohol abuse (three patient-reported items regarding alcohol consumption).

Inclusion procedure and study group allocation

During a 1.5-year period (prolonged if necessary to reach target population), consecutive newly diagnosed (<1 week) patients with lung cancer will be screened for eligibility, invited to participate and randomised by project nurses from clinical trial units at the participating departments. Participants who provide informed consent (online supplemental file B) will be randomised (1:1) to standard treatment plus the intervention (intervention group) or standard treatment alone (control group) as we are interested in evaluating the effect of the intervention compared with what is already offered in the healthcare system. The computer-based randomisation

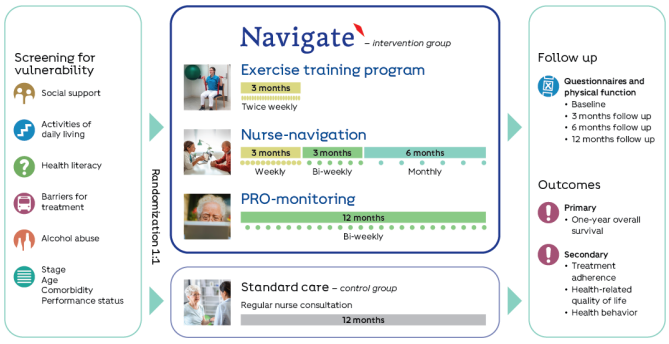

Figure 1 Study flow and intervention components. Source: iStockphoto.com/StefaNikolic/Rawpixel/SDI Productions.

will ensure a balanced number of random assignments to the two groups in blocks of randomly varying sizes of four or six patients stratified according to study site, performance status and disease stage at diagnosis. No blinding is possible due to behavioural intervention.

INTERVENTION PROGRAMME

Based complex intervention guidelines,[46] review of the literature and feedback from clinical experts and patients, we have developed a patient-centred and flexible intervention programme including nurse navigation, systematic use of PROs and physical exercise (figure 1).

Nurse navigation

The manualised nurse navigation programme is based on techniques from MI[40] to:

- Identify patients with high-risk symptoms or worsening in symptoms in order to optimise symptom management.
- Motivate and support patients in making decisions concerning treatment in order to increase treatment initiation and adherence through frequent contact and follow-up.
- Motivate and support patients in health behaviour changes such as increased physical activity, smoking cessation, healthy diet, alcohol moderation by initiating self-management strategies and referral to existing rehabilitation services.

Individual nurse navigation sessions will be performed by 1–2 trained nurses at each department. The nurse navigation manual includes techniques building on MI processes and describes in detail the structure of the first and last sessions as well as an overall format for the sessions in between. A general structure for all sessions include uncovering what is most important for the individual patient, cocreating an agenda and setting goals. Focus is on key MI processes including: engaging, focusing, evoking and planning, and they rely on five central MI communication techniques; asking open questions, affirming the patient, reflective listening, summarising and giving information or advice. The nurse navigation manual includes a total of 16 dialogue tools. To assess and build motivation for change, three MI-based dialogue tools are included to uncover different aspects important for change such as importance, confidence and readiness, to codevelop an overview of potential benefits and harms and to set goals. Moreover, the manual includes four dialogue tools regarding the potential benefits of changing behaviour for example, smoking, alcohol, diet and physical exercise and five dialogue tools supporting value clarification and emotion regulation. The first nurse navigation session will if possible take place at the hospital to enhance a confident relationship. Face-to-face or telephone (by patient's preference) sessions are then offered weekly during the training programme, bi-weekly after training and while still receiving treatment, and monthly after end of treatment throughout the 1-year intervention. Moreover, the nurse navigator guides patients in self-management strategies according to PROs. Adherence to nurse navigation will be considered sufficient if patients participate in at least 75% of the planned in-person or telephone-based sessions.

PRO screening

The aim of collecting PROs is to systematically monitor symptoms and initiate appropriate actions in terms of medical treatment or self-management strategies. PRO screening for symptoms will be collected from diagnosis and up to 1 year bi-weekly through an electronic platform or alternatively through telephone interviews with the nurse-navigator, as per patient preference. Patients will report 12 physical symptoms adapted from the European Organisation for Research and Treatment of Cancer (EORTC).[28 29] An algorithm has been developed describing recommended actions by the nurse-navigator according to each elevated symptom, for example, appointment with oncologist or self-management of symptom. Adherence to PROs will be considered sufficient if participants report at least 75% PROs.

Physical exercise

The aim of the manualised exercise programme is to prevent decline of physical function and enhance level of physical activity to improve eligibility for cancer treatment as well as treatment adherence. The programme will include 24 exercise sessions (two times a week) over 3 months targeting muscle strength, endurance and cardiorespiratory fitness and encouragement to follow the physical activity guidelines for adults with chronic conditions.[47] The sessions can be individual or in smaller groups and will be supervised by 1–4 trained physiotherapists at each department. The exercise manual describe the programme structure, format and progression and the first exercise session will take place at the hospital to ensure the necessary skills to self-manage the programme at home. Participants are encouraged to participate in sessions at the hospital when possible, and any home-based sessions are supported by a video-based exercise guide and telephone supervision by the physiotherapists. Intensity level of the aerobic exercises will be guided using Borg's rating of perceived exertion scale 6–20

(Borg scale).[48] The exercise programme will consist of the following exercise elements with optional stretching exercises:

- Warm up (5 min) on a stationary bike, as walking or other mode equivalent to this with intensity level 11–13 on Borg scale.
- Aerobic exercise (15 min) on a stationary bike, as walking or other mode equivalent to this with intensity level 14–15 on Borg scale.
- Muscle strength/muscle endurance exercises performed in a sitting position with elastic bands in different strengths (25 min with 3 sets of 15 repetitions). Pull to chest, sit to stand, shoulder press and abdominal crunch.

Progression (encouragement to obtain an intensity level >14 on the Borg scale) in the aerobic exercises will take place at the end of week 5 if possible. Progression in the muscle strength and endurance exercises will be done continuously when patients are able to perform >15 repetitions in the last set by using elastic bands with greater resistance. Adherence to exercise will be reported by the physiotherapists or patients using exercise diaries and will be considered sufficient if patients participate in at least 75% supervised or home-based exercise sessions.

STANDARD CARE

Patients randomised to the intervention group and the control group will receive standard treatment and care by a nurse and a physician, who sees the patient at treatment schedules and during follow-up, that is, every 3 months for the first year after diagnosis. In some cases, shorter intervals are offered, for example, if the patient has a poor performance status. At the first treatment schedule, the patient's physical, mental and social problems related to the lung cancer diagnosis and treatment are assessed as well as patient-reported needs of support related to diet, smoking, alcohol and exercise using a standardised questionnaire. The patient's response is used to assess any side effects or rehabilitation needs as well as to refer to relevant rehabilitation services. The nurse will continue to assess potential side effects or psychological or social issues during treatment and follow-up and if needed refer patients to a dietitian or social worker. The treating physician refers to a specialist palliative care team if needed.

Patient and public involvement

Patients were involved in both the development of the vulnerability screening instrument and the intervention content and procedures.

The vulnerability screening instrument was first discussed at a *workshop* including clinical experts in lung cancer and a patient organisation representative. The draft-screening instrument was then discussed against existing geriatric assessment tools screening for increased risk for treatment complications, prediction of symptom burden and survival among older patients with lung cancer[49–51] as well as *expert interviews* with seven lung cancer experts and *patient interviews* with 10 patients with lung cancer in terms of completeness, relevance, comprehension, format and setting. Finally, we pilot tested the vulnerability screening procedure in *feasibility questionnaires* among 20 patients and found that 65% patients (N=13) had three or more criteria and would be considered vulnerable.

To ensure clinical and patient relevance, the study design and procedures including barriers to trial recruitment and data collection as well as the intervention components, were discussed at the *workshop* as well as through the *patient interviews*. Overall, patients found the intervention components highly relevant, but expressed concerns about transportation barriers. This resulted in replacement of in-person meetings at the hospital with flexible telephone-based nurse navigation and home-based exercise sessions. Finally, we will evaluate the study and intervention procedures as well as adherence goals within an ongoing *feasibility intervention study* including 15 patients with lung cancer at Zealand University Hospital, which may result in further adjustments. Any important modifications will be added at ClinicalTrials.gov. We will inform study participants about the study results through email or letter, as per patient preference.

DATA COLLECTION

Data from both groups on the primary outcome survival and treatment factors (table 1) will be obtained from the Lung Cancer Clinical Database and individual medical records.

Both groups will fill out questionnaires (table 1) at baseline prior to randomisation as soon as possible and within 1.5 months after diagnosis (T_0), and 3 months (T_1), 6 months (T_2) and 12 months (T_3) after diagnosis (figure 1). Scales such as EORTC[52 53] and European Quality of life Questionnaire-5 Dimensions-5 Levels[54] will be scored according to published manuals. Considering that participating patients are vulnerable with limited resources, we will proactively support patients in responding to questionnaires electronically, on paper or via telephone. If participants do not fill in the questionnaires at prespecified times, they will receive a reminder by email or telephone. Objective measures of physical function and activity (6 min walk test,[55] 30 s chair stand test[56] and a hand grip strength dynamometer test[57 58] will be assessed at T_0, T_1 and T_3. We will allow assessment of physical function postrandomisation at T_0 to ensure prompt enrolment into the study. Data will be confidently and safely stored at Region Zealand and the Danish Cancer Society Research Center using the electronic platform REDCAP.[59]

In order to perform cost-effectiveness analyses, use of health services including all outpatient visits to any healthcare clinic will be retrieved from the Danish National Patient Registry and medical records while information on disability and productivity loss (sick leave, disability pension and retirement pension) will be obtained from

Table 1 Data from medical journals, the lung cancer clinical database and electronic questionnaires

Variables	Data
Medical journal, the lung cancer clinical database and the Civil Registration System	
Lung cancer treatment adherence	Date of skipped lung cancer treatments or delays if any, and dose administered
Lung cancer diagnosis	Histology, stage and performance status
Standard treatment initiated	Surgery, chemotherapy, radiotherapy, immunotherapy and medical treatment of side-effects
Vital status	Date of death or date last registered in live
Municipality rehabilitation	Referral status
Follow-up adherence	Date of non-response, if any
Comorbidities and medical treatment	Date of diagnosis of comorbidities and medical treatment for comorbidities, if any
Patient-reported factors related to vulnerability	Activities of daily living, social support, health literacy, barriers for treatment and alcohol abuse
Questionnaire	
Demographics (baseline only)	Age, gender, partner, education, job
HRQoL	EORTC QLQ-C30+lung QLQ-LC13+5Q-5D-5L
Health behaviour	Alcohol, smoking and physical activity measured by single-item questions
Self-activation/self-efficacy	Measured by single items from PAM and HEIQ
Rehabilitation services	Measured by a single item question

EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; HEIQ, Health Education Impact Questionnaire; Lung QLQ-LC13, Quality-of-life Questionnaire Lung Cancer 13; PAM, Patient Activation Measure; 5Q-5D-5L, European Quality of life Questionnaire-5 Dimensions-5 Levels.

the Integrated Database for Labour Market Research.[60] The cost-analyses will also include nurse navigator sessions and supervised physiotherapy as outpatient visits to estimate the cost of the intervention.

INTERVENTION FIDELITY

To enhance *fidelity prior to the study*, all nurse-navigators will enrol in a 5-day training course focusing on social inequality in lung cancer, lung cancer treatment, symptoms of recurrence, physical and psychological late effects, research methodology, health behaviour and MI including training the techniques included in the manual. Physiotherapists will attend a 1-day training course focusing on the effects of exercise among patients with lung cancer, the exercise manual and the physical tests. To enhance *fidelity during the study*, nurses and physiotherapists will receive monthly supervision regarding techniques and study procedures. To *evaluate fidelity*, nurse navigators will use a checklist to document use of tools from the nurse-navigator manual, use of PROs and the number and length of patient sessions and physiotherapists will use exercise diaries to document use of the exercise programme. In addition, nurse navigator sessions will on patient consent be audio-recorded to assess implementation fidelity (app. 10% of sessions) to MI spirit and techniques using the Motivational Interviewing Treatment Integrity Code.[61] Finally, to evaluate mechanisms of intervention impact, observations by a research assistant of nurse and excise sessions (N=10) as well as qualitative interviews with participants (N=10) and focus group interviews with nurse navigators (N=5) and physiotherapists (N=5) concerning intervention facilitators and barriers.

POWER CONSIDERATIONS

The power calculation is based on a presumed improvement in 1-year survival of 13% corresponding to half of the effect in the study by Denis *et al*.[29] Assuming that patients in the control group have a 50% 1-year overall survival and the intervention group have 63% 1-year overall survival and a 15% withdrawal probability, then we have 80% power to detect a significant difference using a log-rank test with a total of 518 patients that is, 259 per group. Assuming that 60% (N=865) will be considered vulnerable with three or more vulnerability criteria (based on numbers from the pilot testing of the screening instrument (N=20)), and a conservative 50% participation rate, a total of 1730 patients will be invited.

STATISTICAL ANALYSES

Descriptive statistics will be used to estimate the frequencies, means and SD of the baseline patient, clinical and treatment characteristics including any adverse events. Analyses will be based on intention-to-treat with primary analyses testing the effect of the intervention on overall 1-year survival defined as time from randomisation to death with censoring at withdrawal or end of follow-up.

Overall survival in the two groups will be estimated by the Kaplan-Meier method and compared by the log-rank test. In the primary analysis, Cox proportional hazards model will be used to estimate the HR and 95% CIs for time to death in the intervention group versus the control group adjusted for the stratification factors in the randomisation (study site, performance score and disease stage at diagnosis).

In secondary analyses, we will test the effect of the intervention on overall survival at 3 and 6 months from randomisation using the same survival model as described for the primary analysis. Moreover, the longitudinal measurements of lung cancer treatment adherence, symptom burden, HRQoL, health behaviour, self-efficacy, self-activation and use of rehabilitation services at 3, 6 and 12 months from randomisation will be compared between the two groups using methods that take into account informative censoring due to withdrawal and truncation by death as described by previous studies.[62 63] Analyses will be adjusted for the randomisation stratification factors. If there is a substantial amount of missing data due to non-response, missing data techniques will be employed. Cost-effectiveness of the intervention versus standard care will be assessed at 12 months follow-up with the ratio of the net healthcare costs to net quality-adjusted life years between the two groups.

In sensitivity analyses for the primary and secondary outcomes, we will adjust for potential imbalances in variables such as age, stage and gender at baseline. To identify subgroups of patients who may especially benefit from the intervention we will examine effect modification according to for example, gender, age and specific vulnerability criteria both in the survival model and in the longitudinal models. Adherence to the intervention (≥75% vs <75%) will be explored in the intervention group by estimating the proportion of adherence. We will further explore the potential of full adherence to the intervention by the use of methods for causal inference.[64]

ETHICS, DISSEMINATION OF RESULTS AND PERSPECTIVES OF THE TRIAL

Ethical considerations

The study has been approved by and follows the requirements from The National Committee on Health Research Ethics (Ref no SJ 884, EMN-2020-37380). Participation will be voluntary, and patients will receive written and verbal information about the study and sign written informed consent before study participation. Participants will have the right to withdraw from the study at any time without giving any reason and with no consequences for continued treatment. Participants will not be restricted from any activities or treatments outside the study.

We cannot rule out that weekly collection of physical and psychological symptoms during treatment may lead to increased risk for uncertainty and anxiety.[65] All participants in the study are instructed to report if they experience any side effects, risks or harms associated with study participation. There are no known circumstances that may lead to termination of this study or that participants will be excluded from study participation.

Dissemination of study results

All papers related to the study will be published in accordance to the Consolidated Standards of Reporting Trials statement[66] in relevant peer-review journals. The study results will be presented at international conferences and at the website of the Danish Research Center for Equality in Cancer, COMPAS (www.compas.dk). Moreover, we will communicate the results to broader groups in the society in a video format at social media platforms.

DISCUSSION

This protocol describes the first RCT aimed to improve survival after lung cancer by targeting vulnerable patients with lung cancer. The underlying factors that drive social inequality in lung cancer prognosis are multifactorial and calls for a complex intervention with a person-centred and flexible approach for reaching this study population. The overarching challenges related to the study include recruitment of patients and attrition during the exercise programme. We plan to address these challenges by applying a high degree of patient involvement in the development phase and by assigning the recruitment of patients to trained research nurses from clinical research units at each participating department. To increase adherence to the exercise programme patients may use home-based sessions with telephone-based supervision by physiotherapists. Moreover, due to the nature of the intervention, participants and health professionals cannot be blinded, which may introduce measurement bias of the self-reported secondary outcomes. It was not possible to include patients who are unable to read or speak Danish, as we were not able to ensure adequate translation services in the intervention and the study procedures. As non-Danish speaking patients may represent some of the most vulnerable patients, this is expected to limited generalisability of our results to this group. Finally, the applied cut-off for the vulnerability screening instrument for identifying patients at risk for not completing treatment before trial initiation was established in a feasibility study and further psychometric evaluation is planned.

Results from the Navigate trial hold great potential for improving supportive care to vulnerable lung cancer patients with fragile social support, low health literacy and complex needs. The primary success criteria is that patients in the intervention group experience clinically relevant improvements in survival and symptoms. The ultimate success criteria will be implementation of the intervention at lung cancer clinics in Denmark, if results support it. By applying a high degree of patient involvement in the development phase and evaluating the intervention in a national multicentre setting, we hope to optimise the potential for implementation. Still, implementation at a national level would require an

implementation plan, training of nurses based on the Navigate manual as well as training of physiotherapists to perform the exercise programme.

The Navigate trial has the potential to make an international contribution to clinical practice by providing clinicians with a new comprehensive model of care targeting vulnerable patients with lung cancer. We believe this model of care may also be relevant for other vulnerable patients with cancer and chronic diseases. With the Navigate intervention, we hope to take the first important steps towards reducing inequality in our healthcare system by giving vulnerable patients with lung cancer a greater possibility to achieve the same treatment outcomes as the more resourceful patients.

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