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Strengthening interprofessional collaboration for patients with non-oncological palliative care needs – development and evaluation of a new concept: study protocol of the multicentre KOPAL cluster randomised controlled trial

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Strengthening interprofessional collaboration for patients with non-oncological palliative care needs – development and evaluation of a new concept: study protocol of the multicentre KOPAL cluster randomised controlled trial

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ABSTRACT

Introduction

Progressive chronic, non-malignant diseases (CNMD) like congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and dementia are of growing relevance in primary care. Most of these patients suffer from severe symptoms, reduced quality of life and increased numbers of hospitalisations. Outpatient palliative care, can help to reduce hospitalisation rate by up to 50%. Due to the complex medical conditions and prognostic uncertainty of the course of CNMD early interprofessional care planning among GPs who provide general palliative care and specialist palliative home care (SPHC) teams seems inevitable. The KOPAL study will test the effectiveness of a SPHC nurse-patient consultation followed by an interprofessional telephone case conference.

Methods and analysis

The multicentre two-arm cluster randomised controlled trial KOPAL is located in Northern Germany and aims to recruit 616 patients in 56 GP practices. Randomisation will take place on GP practice level immediately after inclusion (intervention group/control group). Allocation concealment is carried out upon confirmation of participation. Patients diagnosed with CHF (NYHA classification 3-4), COPD (GOLD stage classification 3-4, group D), or dementia GDS stage 4 or above. Primary outcome is a reduced hospital admission within 48 weeks after baseline, secondary outcomes include symptom burden, palliative care needs, and quality of life. The primary analysis will follow the intention-to-treat (ITT) principle. Intervention will be evaluated after the observation period using qualitative methods.

Ethics and dissemination

The responsible ethics committees of the cooperating centres approved the study. All steps of data collection, quality assurance and data analysis will continuously be monitored. The concept of KOPAL could serve as a blueprint for other regions and meet the challenges of geographical equity in end-of-life care. Further, the results could be implemented in the curricula for education and training of medical students, physicians, nurses, or other professions.

Trial registration number UTN U1111-1245-3448.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- KOPAL investigates a low-threshold and easy-to-use new medical concept to strengthen interprofessional collaboration amongst GPs and SPHC teams aiming at a reduced hospitalisation.
- KOPAL aims at the early detection of patients’ palliative care needs to improve generalist palliative care provided by GPs.
- The mixed-methods design including multi-perspective evaluation allows insights into acceptance, practicability, beneficial aspects and barriers of the KOPAL-intervention.
- KOPAL focusses on non-cancer patients who are still underrepresented in palliative care although they suffer from severe symptoms in an advanced stage of their diseases.
- As KOPAL is cluster-randomised study the risk of selection bias cannot be ruled out, but will be minimized by the standardised patient-screening.
INTRODUCTION

Congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and dementia are among the most common chronic, non-malignant diseases (CNMD) and causes of death in Europe and worldwide. (1–4) Due to demographic change these diseases will be of growing relevance. The course of CNMD is progressive, characterised by ‘long-term limitations with intermittent serious episodes’ (5) and, with increasing age, by higher hospitalisation rate when crises occur. These phases of crisis and wellbeing make the course of the diseases difficult to predict. (5,6) In 2015, the overall hospitalisation rate in Germany for CHF was 20.6%, 11.7% for COPD, and 24-44% of patients with advanced dementia were hospitalised at least once during the end stage of the disease. (7) Hospitalisation may not only be traumatic for patients but also a major cost factor within health expenditure in Germany. (7–10) While most patients wish to be cared for at home, about 46% die in hospitals. (11–13) Studies showed that inpatient as well as outpatient palliative care programs helped to reduce the hospitalisation rate by up to 50%. (14–19) At the same time research points to an increased unmet demand of specialised palliative care among patients with final stage CNMD (20), yet 80-90% of medical end-of-life care for CNMD patients is provided by general practitioners (GP). (21) During the course of the illness patients are increasingly afflicted with physical and mental impairments, experience a loss of autonomy, change in their social role and reduced quality of life wherefore palliative care focuses on four dimensions of life following WHO definition of palliative care: physical, mental, social, and spiritual. (22)

Due to the complex medical conditions and prognostic uncertainty of the course of CNMD early interprofessional care planning among GPs who provide general palliative care and specialist palliative home care (SPHC) teams seems inevitable. Forming an early collaboration with SPHC teams would allow to form a treatment plan based on the patients’ individual disease and burden management including multiple care providers (e.g. PC nurses, physiotherapists, music therapists, pastors) and volunteers. The complex medical conditions of CNMD patients demand interprofessional collaboration, since evidence points to the necessity of such collaboration. (23,24) An Australian pilot study showed first evidence for the beneficial use of case conferences for CNMD patients with primary care and specialist public sector-based professionals. (25) Mitchell et al. reported a reduction in emergency department visits, number of hospital admissions, and length of stay. Further national and international studies refer to the wish for intensified collaboration among GPs and SPHC providers. (21,26–29)
In Germany, GPs and SPHC providers need to consolidate their collaboration and broaden their interconnectedness. Coordination of medical services from different care suppliers is restricted due to the heterogeneous structural conditions in SPHC across the federal states in Germany. Therefore, the KOPAL-study aims to develop and implement a structured palliative care nurse home visit followed by an interprofessional telephone case conference. KOPAL further aims at enhancing the collaboration between GPs and SPHC teams and enabling an early interprofessional care planning for patients with CHF, COPD, and dementia in an advanced stage and thereby improving health care for this special group of patients. We hypothesise a reduction in hospitalisation within 48 weeks (primary outcome) as well as a decrease in symptom burden, use of medication, and increase in quality of life of these patients and collaboration among the medical providers (secondary outcomes).

METHODS AND ANALYSIS

Study design and study setting

The KOPAL study is a multi-centre, two-arm, cluster randomised controlled trial (CRT) with usual care in the control arm. The study is carried out in the cooperation of Departments of Primary Care, Palliative Care, Health Economics and Statistics of four Universities in Hamburg, Hanover, Goettingen, and Oldenburg located in two federal states of northern Germany. The latter ensures to cover different medical service structures of the SPHC teams.

The study will be conducted in three steps: 1) Development of the KOPAL conversation GUIDE, 2) intervention and quantitative investigation, 3) Evaluation: 3a) health economic analyses and 3b) qualitative evaluation of the KOPAL-intervention.

Step 1: Development of the KOPAL conversation GUIDE

The KOPAL conversation GUIDE for the SPHC nurses’ conversation with the patients will be developed based on the British ‘PEPSI COLA aide memoire’ (used with permission from the National GSF Centre in End of Life Care). (30) The PEPSI COLA aide memoire is a holistic common assessment of supportive and palliative care needs for adults with cancer. It aims to detect needs in the following areas of life during the interview: physical, emotional, personal, social support, information/communication, control/autonomy, out of hours/emergency, living with your illness and after care. For KOPAL, the PEPSI COLA framework will be adapted to the German health care system with a focus on patients with CHF, COPD and dementia in an advanced stage. The prefinal KOPAL conversation GUIDE will be discussed and revised in
three workshops with patients of the target group and/or their relatives, with health care providers (e.g. palliative care providers, GPs), and with scientific experts and representatives, i.e. the advisory board (see figure 1).

Insert figure 1 about here

Step 2: Quantitative investigation of the KOPAL-intervention

The second step will investigate the effectiveness of the KOPAL-intervention at five time points (baseline, after 6, 12, 24 and 48 weeks). Data collection will take place in the broader region of Hamburg and Lower Saxony.

Recruitment and eligibility

In Germany, SPHC teams provide care in a defined local region. All SPHC teams of Hamburg and Lower Saxony will be assigned to a study centre and invited to participate in written form, successively. SPHC teams are eligible for participation if the participating nurses and doctors have a specialised qualification in palliative care. Once a SPHC team will have agreed to take part all GPs within the respective regions will be invited to participate. Inclusion criteria for GPs are: specialisation in primary care or internal medicine, focus on primary care medicine, and a computer-based documentation software which allows to filter for patients according to their diagnosis and last visit in the last quarter. GPs who work as a palliative care specialist in a SPHC team will be excluded.

After written consent is given by the practice, patients will be screened by the GP according to inclusion criteria: confirmed diagnosis of CHF with NYHA classification 3-4, COPD with GOLD stage classification 3-4, group D, or dementia with stage 4 or above in the Global Deterioration Scale. Additionally, participants must have had at least one consultation with the GP during the last quarter, and the ability to give oral/written consent. If possible, participants with dementia will be informed and will sign the consent form. If unable to consent, a legal representative will sign on behalf of the participant. Exclusion criteria for participants are a current cancer diagnosis, current SPHC support, lack of proficiency in German language, or residence in a care home.

Eligible patients will be invited in written form by their GP. Patients or their legal representatives willing to participate can contact the research team of the responsible study centre by sending in the included contact form. After having received the contact form, the
research team contacts the patient or the legal representative and arranges a personal meeting at the patient’s home. At this meeting detailed study information will be given in written and oral form. Participation is voluntary. Patients/legal representative’s give their informed consent in written form.

**Randomisation and blinding**

Block-Randomisation will take place on practice level immediately after inclusion. Allocation concealment is carried out upon confirmation of participation. Randomisation will be performed by the local research teams using a web-based program provided by the clinical trials unit Goettingen. Since the intervention includes a face-to-face conversation, blinding is not possible for participating patients, providers and researchers, who are involved in data collection. Allocation concealment is ensured when practices confirm their participation.

**Intervention**

The KOPAL-intervention is a low-threshold and easy-to-use medical concept to strengthen the interprofessional collaboration amongst GPs and SPHC teams. It consists of a) one home visit of approx. 60 minutes by a SPHC nurse to assess the participant’s current life and health situation using the KOPAL conversation GUIDE, b) a brief consultation between SPHC nurse and SPHC physician regarding the patient’s situation, and c) the interprofessional telephone case conference of approx. 30 minutes between the GP, SPHC nurse, and SPHC physician to discuss the patient’s current health and care situation as well as possible PC needs and next steps of treatment and care. A scientific researcher will be present to protocol the telephone case conference. To evaluate the results from the SPHC’s home visit and telephone case conference, the SPHC nurse will forward the completed KOPAL conversation GUIDE form to the research team. A maximum of 14 days is scheduled between the SPHC home visit and the telephone case conference. Baseline will be assessed one day before the SPHC home visit.

Participants of the control group will receive care as usual. Possible prescription of SPHC during the course of the study does not lead to exclusion, but will be documented.

**SPHC training**

To improve intervention protocol adherence, SPHC nurses will be provided with a full online training course on background information of the KOPAL study, the use of the KOPAL conversation GUIDE, and data security before starting the intervention. Additionally, SPHC
teams will be provided with a detailed description of their role within the KOPAL study and an intervention checklist.

**Primary and secondary outcome measures**

Primary outcome is the reduction of hospital admissions within 48 weeks after baseline, as documented by participant. In case of missing or invalid data, hospital admissions according to discharge report will be collected from the GP.

As for secondary outcomes symptom burden and palliative care needs will be measured with the *Integrated Patient Outcome Scale* (IPOS). (31) The *Brief Pain Inventory* (BPI) (32) will be used to measure pain and impairment due to pain. To observe pain in non-communicative participants with dementia the *Pain Assessment in Advanced Dementia Scale* (PAINAD, German version *Beurteilung von Schmerzen bei Demenz, BESD*) (33) will be used. Quality of life will be assessed using *EQ-5D-5L*. (34) The *Questionnaire for Health-Related Resource Use in an Elderly Population* (FIMA) (35) will be used to measure health care utilisation including use of medication, involved health care providers, and use of health care services.

Diagnosis of hospital admission, hospitalisation, and discharge as well as the number of days in intensive or palliative care unit, the reason for admission (scheduled or emergency), and collaboration among the medical providers serve as additional secondary outcomes (see table 1).

Participants will receive the ‘KOPAL patient diary’ including visualisation aides for scales used during the interviews (t0-t4) which allows participants to record hospital admissions as well as consultations with doctors and therapists. This diary will help participants in remembering events since the last interview.

**Additional measures**

To describe the sample and to gain knowledge about selected aspects of patients, participants will further be asked about the use of SPHC services, thoughts on dying and preferred place of death, living will and healthcare proxy, sociodemographic questions. In case of drop-out or death of the participants, GPs will provide date, place, and cause of death. Demographic data on GPs specialisation, number of years of experience, and changes in their medical service due to the Coronavirus disease pandemic will be assessed.

Numbers of completed interviews, home visits, case conferences and GP participant interviews will be recorded. In case of drop-out, information on hospital admissions and
diagnosis during the last follow-up and time of drop-out will be gathered from the participant’s GP.

**Data collection**

Data will be collected at baseline and four follow-up time points (after 6, 12, 24, and 48 weeks) by members of the research team, who undergo a prior training. For participants in the control group the follow-up date refers to baseline while for participants in the intervention group it refers to the date of the telephone case conference. All parameters (except sociodemographic data) will be collected at each time point. Baseline will be assessed as face-to-face interview to establish a relationship with persons of this vulnerable group. Data at follow-up will be collected by telephone. GPs data will be assessed via telephone at baseline and at follow-up 48 weeks after baseline or at the time of drop-out/death of the participant. The electronic data capture system and database (secuTrial®) will be used in this study and was configured by the department for biostatistics and data management of the University Medical Center Goettingen. For instruments and timing see table 1.

**Table 1 KOPAL measurements**

| Instruments used in KOPAL                  | Time of measurement |
|-------------------------------------------|---------------------|
| **Participants**                          | **t0** | **t1** | **t2** | **t3** | **t4** |
| Hospital admissions                       | x      | x      | x      | x      | x*     |
| Medication                                | x      | x      | x      | x      | x      |
| BPI – Brief Pain Inventory                | x      | x      | x      | x      | x      |
| IPOS – Integrated Palliative Care Outcome Scale Patient/Staff | x      | x      | x      | x      | x      |
| BESD – Beurteilung von Schmerzen bei Demenz | x      | x      | x      | x      | x      |
| Healthcare proxy                          | x      | x      | x      | x      | x      |
| Thoughts on preferred place of death      | x      | x      | x      | x      | x      |
| EQ-5D-5L – Health-related quality of life | x      | x      | x      | x      | x      |
| FIMA - use of medical and non-medical services in old age | x      | x      | x      | x      | x      |
| Sociodemographic data                     | x      | x      | x      | x      | x      |
| **General practitioners – participant related questionnaire** |         |         |         |         |         |
| ICD-10 diagnosis                          | x      | x      |         |         |         |
| Date of last consultation                  | x      | x      |         |         |         |
| Hospital admissions                       | x      | x      |         |         |         |
| Prescriptions for palliative care         | x      | x      |         |         |         |
Sample size and power

Participants with the above-mentioned diseases and severity levels are usually admitted to hospital several times a year; we expect an average of about two admissions per participant per year. A 30% reduction is relevant and realistic. (15,16) Under these assumptions, a case number of 93 participants per group gives a statistical power of 90% for a test comparing two Poisson rates to the usual bilateral significance level of 5%. The distribution of hospital admissions per participant shows some extra-Poisson variation, i.e. the variance is greater than the mean (19). We correct the overdispersion by multiplying the number of cases by the corresponding factor of 2. (36) We also correct for 20% dropout of participants. This results in a total case number of 465 participants. The cluster randomisation and the expected cluster size of 11 participants per practice, which are based on the assumptions of population-related values for palliative care needs for the selected chronic diseases (cf. (37)), feasibility of the intervention at GP level, and assumed intra-cluster correlation (ICC) of 0.032 (38), result in a design effect of 1.32 (39).

This results in a rounded total case number of 616 participants (56 practices with 11 participants each, 28 practices per group). Practices, which drop out, will be replaced. The aim is to recruit 7 GP practices with 11 participants each in all four study centres per condition (intervention and control). Since literature on annual hospitalisation rates varies and the assumptions on extra-Poisson variation, ICC and dropout are subject to a certain degree of uncertainty, we will conduct a sample size review after recruitment of the first 300 participants, and adjust case number planning accordingly. (40)

Statistical analysis

The primary analysis will follow the intention-to-treat (ITT) principle. The effect of the KOPAL-intervention on the number of hospital admissions will be analysed using a generalised linear
model with logarithmic link function as well as fixed effects for the intervention and important prognostic factors at practice and participant-level (e.g. size of the practice, underlying disease of the participant), and random effects for the practices and the participants. The data of all recruited participants will be included in the analysis regardless of the time of drop out or death; the logarithmic follow-up times will be included in the model as offset. The intervention effect will be reported as an incidence ratio with a 95% confidence interval and p-value testing the null hypothesis of the incidence ratio being equal to 1. If mortality within the 48-weeks period is higher than expected, death will be modelled as a competing event. Further secondary effects will be examined by linear regression analyses in a multi-level model. Binary outcomes will be modelled by logistic regression with mixed effects. Furthermore, GP factors and specific symptom complexes of the participant can be considered as possible confounders. Participant subgroups will be formed based on diagnoses, symptom burden, socioeconomics, etc. and included in the analyses on an exploratory basis. Missing data will be dealt with using multiple imputation methods. The statistical evaluations are further detailed in a statistical analysis plan.

Step 3 Evaluation

Step 3a: Health economic analysis

Health economic analysis will include the evaluation of health care utilisation, costs and cost-effectiveness. Health care utilization will be assessed using the FIMA questionnaire, which was adapted to the diseases focused in KOPAL and the palliative care setting. Subsequently, health care utilization will be monetarily valued by standardised unit costs from the societal and payer’s perspective in Germany. (41) Besides descriptive analysis, cost determinants will be evaluated using regression models, which will account for the skewness of costs distributions. For cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) will be calculated. The effectiveness will be measured by quality-adjusted life years (QALYs) based on the EQ-5D-5L index. (42) Finally, uncertainty in the ICER will be evaluated by cost-effectiveness acceptability curves based on the net-benefit regression approach. (43)

Step 3b: Qualitative evaluation of the KOPAL-intervention

With regard to the implementation of the KOPAL-intervention qualitative evaluation will assess acceptance and feasibility considering different perspectives: health providers, patients/proxys, and relatives/associates.
Health providers: After follow-up four, all 28 GPs of the intervention group, and all involved members of the SPHC teams will be interviewed individually by trained members of the research team. Narrative interview techniques will be used in order to allow individual accentuation of relevancies. (44) The focus will be on: acceptance, practicability, beneficial aspects and barriers of the KOPAL-intervention, as well as interprofessional communication and consequences on participants care previous to the KOPAL-intervention according to each perspective. Interviews will be audio recorded, transcribed verbatim and analysed with a Grounded Theory approach (45) using abductive reasoning (46) in order to transfer the practical experiences into a databased theory on interprofessional collaboration in the area of primary and palliative care.

Additionally, all telephone case conferences will be observed by a researcher using an observation protocol (non-participating observation (40)). Matters of interest are: course of actions, constellation of interactions, proportion of speech, main focus, omissions, and conclusions. According to Grounded Theory, observation protocols will enrich the analysis of interviews with GPs and SPHC teams.

Participants/proxies and relatives/associates: Semi-structured interviews (40,47) will be conducted with 16 to 22 participants (or proxies respectively) of the intervention group. Two semi-structured focus groups including 5-8 participants each (40) with relatives (or associates respectively) of KOPAL participants on their perception and experiences of the (effects of the) KOPAL-intervention, e.g., relevant changes in daily life and care. Audio recordings of the interviews and focus groups will be transcribed verbatim and analysed with a qualitative content analysis approach. (48)

Findings from the qualitative evaluation will give insights into strengths and limitations of interprofessional collaboration amongst GPs, SPHC nurses and SHPC physicians at the intersection of primary and specialised palliative home care. Considering the needs of participants and their relatives will provide the basis for identifying structural or professional collaboration barriers.

**Monitoring**

All aspects of study design and data collection have been discussed in advance with the advisory board of the KOPAL study. The advisory board, which is independent from the investigator and the sponsor, will supervise the study process at least once a year. The department for biostatistics and data management of the University Medical Center
Goettingen will continuously monitor all steps of data collection, quality assurance and data analysis and will conduct a blinded interim analysis to proof the statistical power. They will oversee the intra-study data sharing process. The main risks of the study are possible negative events for the patients due to talking about their life situation. In case of negative events occurring during data collection the monitoring and safety board will be informed. If the board decides that these events are to be seen in connection with study participation or trial conditions the trial will be stopped. All participating patients receive usual care. In case of early withdrawal, the GP will be informed about the end of further patient related data collection and usual care will continue.

**Patient and Public involvement statement**

Participants affected by COPD and CHF, patient representatives for participants with dementia, and professional caregivers (nurses and physicians) will be involved in the development of the KOPAL conversation GUIDE. Their experiences and opinions will be discussed in three workshops and considered in the final version of the guide. Professional caregivers and patient representatives are members of the advisory board. The general public will not be actively involved.

**ETHICS AND DISSEMINATION**

KOPAL has been approved by the local ethics committee of the Medical Association Hamburg, Germany (no. PV7090) as well as the ethics committees of the University Medical Centre Goettingen, Germany (no. 34/1/20Ü), the Hannover Medical School (no. 8815 BO K 2019), and the University of Oldenburg (no. 2019-145). The trial is registered on the International Clinical Trials Registry Platform (registration number UTN U1111-1245-3448; 17-Nov-2021, version 05). Important protocol modifications will be submitted to the ethical boards as well as they will be communicated to the funder, the trial registry and to participating GPs, SPHC teams and patients.

Study participants will be informed about the study details by members of the respective research team. All participants (including those affected with dementia) will give written informed consent. Additionally for participants with dementia, a legal representative will have to give informed consent on participant’s behalf. Participants and legal representatives have the right to withdraw from the study at any point during the study without giving reasons, or any negative effect on patient care. In this case, the GP will be informed about
withdrawal and no further data will be collected. All study and patient-related information will be stored securely at the study sites.

The KOPAL study will develop and test an intervention of a lowthreshold contributing to strengthen interprofessional collaboration in palliative care and cross-sectoral care. The intervention will be tested in two German federal states. In case of effectiveness, the concept of the KOPAL study could serve a blueprint for other regions and meet the challenges of geographical equity in end-of-life care.

Independent from results, the findings of our study will be disseminated in peer-reviewed, international, and national journals, and national and international conferences targeting medical professions involved in the care of patients with advanced chronic conditions such as COPD, CHF and dementia. Regarding education and training of medical students, physicians, nurses or other professions the results could be implemented in the respective curricula.

**DISCUSSION**

Improvement in palliative primary health care (PHC) is urgently needed in European countries. (49) Not only is palliative care underprovided in general, this applies in particular for patients with other conditions than cancer. (50–52) In Germany, palliative care is structurally separated into two coverage areas, primary (general) and specialised palliative care. While the need for SPHC for non-oncological patients is accepted, it is still mostly provided to patients suffering from cancer for historical reasons. The integration of a concept to strengthen the early collaboration of primary and outpatient specialised palliative care providers in general and the interprofessional collaboration in particular could be a relevant step to consider more strongly the palliative care needs of non-cancer patients in primary care. The multicentre KOPAL RCT aims to develop and test an intervention including a home visit by a SPHC nurse using the KOPAL conversation GUIDE followed by an interprofessional telephone case conference.

Unfortunately, the scheduled start of recruitment and data collection coincided with the increase of the COVID-19 pandemic in Germany which had a negative impact on the study progress. The SPHC teams were faced with a strong increase of SPHC prescriptions. Movable hospitalisations were stopped to keep hospital beds for COVID-19 patients which were often forwarded to SPHC to compensate for homecare needs. During the following months, also GPs reported increase of workload caused by insufficient information, lack of personal protective equipment, the need to restructure practice procedures, and insufficient individual...
and structural pandemic preparedness. The fact of the fast worldwide spread and the absence of medication and vaccine led to high additional workload and financial worries. Since the progression of the COVID-19 pandemic was difficult to predict, the KOPAL study group, in consultation with the funder, decided to close recruitment at the scheduled time and to recalculate the study power.

Therefore, the sample size reduced from a planned of 616 participants to 191 participants, resulting in 51 practices with approximately 4 participants each. With the same ICC as in the original planning, the design effect was therefore reduced to 1.096 (down from 1.32). Then, using the same methodology as in the original sample size calculation, a total sample size of 191 participants would be sufficient to prove a significant difference between intervention and control group with 80% power (down from 90%), assuming a likewise clinically relevant reduction in hospitalisations of 40% (up from 30%). Significance level, dropout rate and assumptions on overdispersion were kept as planned originally.

To gain information about possible confounding factors of the pandemic on the effectiveness of the KOPAL-intervention, additional health related questions regarding the COVID-19 pandemic will be collected at baseline with GPs and patients.

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Scientific experts and representatives (physicians, nurses, researcher and patient representatives) serve as advisory board and counsel the KOPAL study group once a year.

Author contributions
GM, TM, NP, FS, JD, MZ, TA, SB, CM, MF, EH, RvdB, IS, HHK, SSt, NSch, FN, TF, MS contributed substantially to the conception of the study. MS (principal investigator), GM (coprincipal investigator), MF, EH, RvdB, IS, HHK, SSt, NSch, FN and TF are the applicants of the trial. GM coordinates the trial. TF and TA are the trial statisticians and contributed to the statistical analysis aspect of the protocol. GM, NP, MZ and FS contributed substantially to the qualitative method of the protocol. GM and TM coordinated ethics approval and wrote the first draft of the manuscript. All authors revised the draft critically and gave approval of the final version of the protocol.

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**Competing interests**

The authors declare no conflicts of financial interests or other competing interests in relation to the present study.

**Data sharing**

No additional data available.

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Figure 1. Illustration of the investigation of the KOPAL-intervention
Step 1: Development of the KOPAL conversation GUIDE

1. Workshop with patients/relatives
2. Workshop with health care providers
3. Workshop with representatives

Inclusion SPHC-Teams (n=20)
Inclusion general practitioners (n=56)

Step 2: Quantitative investigation of the KOPAL intervention

- Intervention group (n=28)
- Randomisation on practice level
- Control group (n=28)
- Screening & inclusion patients (n=308)
- Screening & inclusion patients (n=308)
- t0 baseline – survey

KOPAL Intervention
- Home visit by SPHC nurse
- Brief SPHC-consultation
- Interdisciplinary telephone case conference

Follow-up-survey after
- (t1) 6 weeks
- (t2) 12 weeks
- (t3) 24 weeks
- (t4) 48 weeks

Care as usual

Additional care offered

Step 3: Qualitative evaluation of the KOPAL intervention

Evaluation of the intervention
- Qualitative Evaluation: interviews with patients, SPHC teams and family doctors; focus groups with relatives
- Quantitative and health economic analysis of the questionnaire survey
| Section/item          | Item No | Description                                                                 | Included page |
|----------------------|---------|-----------------------------------------------------------------------------|---------------|
| Administrative information |         |                                                                             |               |
| Title                | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1             |
| Trial registration   | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry | 14            |
|                      | 2b      | All items from the World Health Organization Trial Registration Data Set     | n.a.          |
| Protocol version     | 3       | Date and version identifier                                                 | 14            |
| Funding              | 4       | Sources and types of financial, material, and other support                 | 16            |
| Roles and responsibilities | 5a   | Names, affiliations, and roles of protocol contributors                      | 1-2, 16       |
|                      | 5b      | Name and contact information for the trial sponsor                          | 16            |
|                      | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16            |
|                      | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 13            |
| Introduction         |         |                                                                             |               |
| Background and rationale | 6a     | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5f            |
|                      | 6b      | Explanation for choice of comparators                                       | 5f            |
| Objectives | Specific objectives or hypotheses |
|------------|----------------------------------|
| Trial design | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

**Methods: Participants, interventions, and outcomes**

| Study setting | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eligibility criteria | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) |
| Interventions | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |

11a Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial |

Outcomes | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |

Participant timeline | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1) | Figure 1 |
| Sample size     | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|----------------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recruitment    | 15 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                                                                                                                                                                                      |

**Methods: Assignment of interventions (for controlled trials)**

| Allocation: | | |
|-------------|| |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial |

**Methods: Data collection, management, and analysis**

| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |

|            | 11, 15 | |
|------------|--------| |
|            | 7      | |
|            | 8      | |
|            | 8      | |
|            | 8      | |
|            | n.a.   | |
|   |   |   |   |   |
|---|---|---|---|---|
| 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10, 14 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 13 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11,12 |
|   | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 12,13 |
|   | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 9 |

**Methods: Monitoring**

| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
|   | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |

**Harms**

| 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13f |

**Auditing**

| 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |

**Ethics and dissemination**
| Section                                      | Item | Description                                                                                                                                                                                                 | Reference |
|----------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| **Research ethics approval**                 | 24   | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval                                                                                                                     | 14        |
| **Protocol amendments**                      | 25   | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14        |
| **Consent or assent**                        | 26a  | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)                                                                                   | 14        |
|                                              | 26b  | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable                                                                           | n.a.      |
| **Confidentiality**                          | 27   | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14        |
| **Declaration of interests**                 | 28   | Financial and other competing interests for principal investigators for the overall trial and each study site                                                                                              | 17        |
| **Access to data**                           | 29   | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators                                                                 | 14        |
| **Ancillary and post-trial care**            | 30   | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation                                                                                 | n.a.      |
| **Dissemination policy**                     | 31a  | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14f       |
|                                              | 31b  | Authorship eligibility guidelines and any intended use of professional writers                                                                                                                                 | n.a.      |
|                                              | 31c  | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code                                                                                              | n.a.      |

**Appendices**

| Section                                      | Item | Description                                                                                                                                                                                                 | Reference |
|----------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| **Informed consent materials**               | 32   | Model consent form and other related documentation given to participants and authorised surrogates                                                                                                           | n.a.      |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n.a. |
Effectiveness of a specialist palliative home care nurse-patient consultation followed by an interprofessional telephone case conference compared with usual care among patients with non-oncological palliative care needs: protocol for the multicentre KOPAL cluster randomised controlled trial

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| --- | --- |
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Scherer, Martin; University Medical Center Hamburg-Eppendorf,
Department of General Practice and Primary Care

Primary Subject Heading: General practice / Family practice

Secondary Subject Heading: Palliative care, Health services research

Keywords: PALLIATIVE CARE, PRIMARY CARE, Heart failure < CARDIOLOGY,
INTERNAL MEDICINE, Chronic airways disease < THORACIC MEDICINE
Effectiveness of a specialist palliative home care nurse-patient consultation followed by an interprofessional telephone case conference compared with usual care among patients with non-oncological palliative care needs: protocol for the multicentre KOPAL cluster randomised controlled trial

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ABSTRACT

Introduction

Progressive chronic, non-malignant diseases (CNMD) like congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and dementia are of growing relevance in primary care. Most of these patients suffer from severe symptoms, reduced quality of life and increased numbers of hospitalisations. Outpatient palliative care, can help to reduce hospitalisation rate by up to 50%. Due to the complex medical conditions and prognostic uncertainty of the course of CNMD early interprofessional care planning among GPs who provide general palliative care and specialist palliative home care (SPHC) teams seems mandatory. The KOPAL study will test the effectiveness of a SPHC nurse-patient consultation followed by an interprofessional telephone case conference.

Methods and analysis

Multicentre two-arm cluster randomised controlled trial KOPAL with usual care as control arm. The study is located in Northern Germany and aims to recruit 616 patients in 56 GP practices (because of pandemic reasons reduced to 191 participants). Randomisation will take place on GP practice level immediately after inclusion (intervention group/control group). Allocation concealment is carried out upon confirmation of participation. Patients diagnosed with CHF (NYHA classification 3-4), COPD (GOLD stage classification 3-4, group D), or dementia GDS stage 4 or above). Primary outcome is a reduced hospital admission within 48 weeks after baseline, secondary outcomes include symptom burden, quality of life, and health costs. The primary analysis will follow the intention-to-treat (ITT) principle. Intervention will be evaluated after the observation period using qualitative methods.

Ethics and dissemination

The responsible ethics committees of the cooperating centres approved the study. All steps of data collection, quality assurance and data analysis will continuously be monitored. The concept of KOPAL could serve as a blueprint for other regions and meet the challenges of geographical equity in end-of-life care.

Trial registration number DRKS00017795.
STRENGTHS AND LIMITATIONS OF THIS STUDY

- The mixed-methods design including multi-perspective evaluation allows insights into acceptance, practicability, beneficial aspects and barriers of the KOPAL-intervention.
- In-depth interviews with health providers and interpretative analysis will reveal possible unconscious obstacles that might hinder early integration of specialist palliative home care in general.
- Analysis of observed telephone case conferences will show details of roles and competencies of interprofessional interaction.
- As KOPAL is cluster-randomised study the risk of selection bias cannot be ruled out, but will be minimized by the standardised patient-screening.
INTRODUCTION

Congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and dementia are among the most common chronic, non-malignant diseases (CNMD) and causes of death in Europe and worldwide. (1–4) Due to demographic change these diseases will be of growing relevance. The course of CNMD is progressive, characterised by ‘long-term limitations with intermittent serious episodes’ (5) and, with increasing age, by higher hospitalisation rate when crises occur. These phases of crisis and wellbeing make the course of the diseases difficult to predict. (5,6) In 2015, the overall hospitalisation rate in Germany for CHF was 20.6%, 11.7% for COPD, and 24-44% of patients with advanced dementia were hospitalised at least once during the end stage of the disease. (7) Hospitalisation may not only be traumatic for patients but also a major cost factor within health expenditure in Germany. (7–10) While most patients wish to be cared for at home, about 46% die in hospitals. (11–13) Studies showed that inpatient as well as outpatient palliative care programs helped to reduce the hospitalisation rate by up to 50% and may reduce hospitalisation cost as well as overall health care costs. (14–20) At the same time research points to an increased unmet demand of specialised palliative care among patients with final stage CNMD (21), yet 80-90% of medical end-of-life care for CNMD patients is provided by general practitioners (GP). (22) During the course of the illness patients are increasingly afflicted with physical and mental impairments, experience a loss of autonomy, change in their social role and reduced quality of life wherefore palliative care focuses on four dimensions of life following WHO definition of palliative care: physical, mental, social, and spiritual. (23)

Due to the complex medical conditions and prognostic uncertainty of the course of CNMD early interprofessional care planning among GPs who provide general palliative care and specialist palliative home care (SPHC) teams seems mandatory. Forming an early collaboration with SPHC teams would allow to form a treatment plan based on the patients’ individual disease and burden management including multiple care providers (e.g. PC nurses, physiotherapists, music therapists, pastors) and volunteers. The complex medical conditions of CNMD patients demand interprofessional collaboration, since evidence points to the necessity of such collaboration. (24,25) An Australian pilot study by Mitchell et al. showed first evidence for the beneficial use of case conferences for CNMD patients with primary care and specialist public sector-based professionals. (26) Mitchell et al. reported a reduction in emergency department visits, number of hospital admissions, and length of stay. Further national and international studies refer to the wish for intensified collaboration among GPs
and SPHC providers. (22,27–30) Mahtani-Chugani et al., however, found barriers to palliative care provision by patients as well as providers (lack of clarity about illness prognosis, the hegemony of the curative approach, avoiding words such as palliative care, and cheating death which is still considered a taboo) that may hinder early collaboration and need to be overcome. (31)

In Germany, GPs and SPHC providers need to consolidate their collaboration and broaden their interconnectedness. Coordination of medical services from different care suppliers is restricted due to the heterogeneous structural conditions in SPHC across the federal states in Germany. Therefore, the KOPAL-study aims to develop and implement a structured palliative care nurse home visit followed by an interprofessional telephone case conference. KOPAL further aims at enhancing the collaboration between GPs and SPHC teams and enabling an early interprofessional care planning for patients with CHF, COPD, and dementia in an advanced stage and thereby improving health care for this special group of patients. We hypothesise a reduction in hospitalisation within 48 weeks (primary outcome) as well as a decrease in symptom burden, use of medication, and increase in quality of life of these patients and collaboration among the medical providers (secondary outcomes).

METHODS AND ANALYSIS

Study design and study setting

The KOPAL study is a multi-centre, two-arm, cluster randomised controlled trial (CRT) with usual care in the control arm (funding period: 01.06.2019 to 31.05.2022). The study is carried out in the cooperation of Departments of Primary Care, Palliative Care, Health Economics and Statistics of four Universities in Hamburg, Hannover, Goettingen, and Oldenburg located in two federal states of northern Germany. The latter ensures to cover different medical service structures of the SPHC teams.

The study will be conducted in three steps: 1) Development of the KOPAL conversation GUIDE, 2) intervention and quantitative investigation, 3) Evaluation: 3a) health economic analyses and 3b) qualitative evaluation of the KOPAL-intervention.

Step 1: Development of the KOPAL conversation GUIDE

The KOPAL conversation GUIDE for the SPHC nurses’ conversation with the patients will be developed based on the British ‘PEPSI COLA aide memoire’ (used with permission from the National GSF Centre in End of Life Care). (32) The PEPSI COLA aide memoire is a holistic
common assessment of supportive and palliative care needs for adults with cancer. It aims to
detect needs in the following areas of life during the interview: physical, emotional, personal,
social support, information/communication, control/autonomy, out of hours/emergency,
living with your illness and after care. For KOPAL, the PEPSI COLA framework will be adapted
to the German health care system with a focus on patients with CHF, COPD and dementia in
an advanced stage. The prefinal KOPAL conversation GUIDE will be discussed and revised in
three workshops with patients of the target group and/or their relatives, with health care
providers (e.g. palliative care providers, GPs), and with scientific experts and representatives,
i.e. the advisory board (see figure 1).

*Insert figure 1 about here*

**Step 2: Quantitative investigation of the KOPAL-intervention**

The second step will investigate the effectiveness of the KOPAL-intervention at five time
points (baseline, after 6, 12, 24 and 48 weeks). Data collection will take place in the broader
region of Hamburg and Lower Saxony.

**Recruitment and eligibility**

In Germany, SPHC teams provide care in a defined local region. All SPHC teams of Hamburg
and Lower Saxony will be assigned to a study centre and invited to participate in written form,
successively. SPHC teams are eligible for participation if the participating nurses and doctors
have a specialised qualification in palliative care. Once a SPHC team will have agreed to take
part all GPs within the respective regions will be invited to participate. Inclusion criteria for
GPs are: specialisation in primary care or internal medicine, focus on primary care medicine,
and a computer-based documentation software which allows to filter for patients according
to their diagnosis and last visit in the last quarter. GPs who work as a palliative care specialist
in a SPHC team will be excluded. Since recruitment of GPs in palliative care research can be
challenging (33), we decided to invite all GPs of the respective regions. Invitation includes a
short description of the main aspects of the study and a short questionnaire on eligibility
criteria. Further, invited GPs will be contacted by phone to ask for willingness to participate
and to ensure eligibility.

After written consent is given by the practice, GPs will be provided with a study folder and
assisted by study staff (via telephone or on site) in case of any difficulties regarding the
screening process. Patients will be screened by the GP according to inclusion criteria: confirmed diagnosis of CHF with NYHA classification 3-4, COPD with GOLD stage classification 3-4, group D, or dementia with stage 4 or above in the Global Deterioration Scale. Additionally, participants must have had at least one consultation with the GP during the last three months, and the ability to give oral/written consent. If possible, participants with dementia will be informed and will sign the consent form. If unable to consent, a legal representative will sign on behalf of the participant. Exclusion criteria for participants are a no hospital admission during the last 12 months in patients with CHF, current cancer diagnosis, current SPHC support, no signed consent form.

Eligible patients will be invited in written form by their GP. Patients or their legal representatives willing to participate can contact the research team of the responsible study centre by sending in the included contact form. After having received the contact form, the research team contacts the patient or the legal representative and arranges a personal meeting at the patient’s home. At this meeting detailed study information will be given in written and oral form. Participation is voluntary. Patients/legal representative’s give their informed consent in written form (translated consent form, see online supplemental file 1).

Randomisation and blinding

Block-Randomisation will take place on practice level immediately after inclusion. Allocation concealment is carried out upon confirmation of participation. Randomisation will be performed by the local research teams using a web-based program provided by the clinical trials unit Goettingen. Since the intervention includes a face-to-face conversation, blinding is not possible for participating patients, providers and researchers, who are involved in data collection. Allocation concealment is ensured when practices confirm their participation.

Intervention

The KOPAL-intervention is a low-threshold and easy-to-use medical concept to strengthen the interprofessional collaboration amongst GPs and SPHC teams. It consists of a) one home visit of approx. 60 minutes by a SPHC nurse to assess the participant’s current life and health situation using the KOPAL conversation GUIDE, b) a brief consultation between SPHC nurse and SPHC physician regarding the patient’s situation, and c) the interprofessional telephone case conference of approx. 30 minutes between the GP, SPHC nurse, and SPHC physician to discuss the patient’s current health and care situation as well as possible PC needs and next
steps of treatment and care. A scientific researcher will be present to protocol the telephone case conference. To evaluate the results from the SPHC’s home visit and telephone case conference, the SPHC nurse will forward the completed KOPAL conversation GUIDE form to the research team. A maximum of 14 days is scheduled between the SPHC home visit and the telephone case conference. Baseline will be assessed one day before the SPHC home visit. Participants of the control group will receive care as usual. Possible prescription of SPHC during the course of the study does not lead to exclusion, but will be documented.

**SPHC training**

To improve intervention protocol adherence, SPHC nurses will be provided with a full online training course on background information of the KOPAL study, the use of the KOPAL conversation GUIDE, and data security before starting the intervention. Additionally, SPHC teams will be provided with a detailed description of their role within the KOPAL study and an intervention checklist.

**Primary and secondary outcome measures**

Primary outcome is the number of hospital admissions 48 weeks after baseline, as documented by participant. In case of missing or invalid data, hospital admissions according to discharge report will be collected from the GP. As for secondary outcomes symptom burden will be measured with the Integrated Patient Outcome Scale (IPOS). (34) The Brief Pain Inventory (BPI) (35) will particularly be used to measure pain and impairment due to pain. To observe pain in non-communicative participants with dementia the Pain Assessment in Advanced Dementia Scale (PAINAD, German version Beurteilung von Schmerzen bei Demenz, BESD) (36) will be used. Health related quality of life will be assessed using EQ-5D-5L. (37) The Questionnaire for Health-Related Resource Use in an Elderly Population (FIMA) (38) will be used to measure health care utilisation including current medication, involved health care providers, and health costs. Participants will be asked about their thoughts on preferred place of death.

**Additional measures**

Diagnosis of hospital admission and discharge as well as the number of days in intensive or palliative care unit, the reason for admission (scheduled or emergency), and collaboration among the medical providers serve as additional secondary outcomes (see table 1).
Participants will receive the ‘KOPAL patient diary’ including visualisation aides for scales used during the interviews (t0-t4) which allows participants to record hospital admissions as well as consultations with doctors and therapists. This diary will help participants in remembering events since the last interview and helps to improve adherence to follow-up interviews.

To describe the sample and to gain knowledge about selected aspects of patients, participants will further be asked about the use of SPHC services, living will and healthcare proxy, sociodemographic questions. In case of drop-out or death of the participants, GPs will provide date, place, and cause of death. Demographic data on GPs specialisation, number of years of experience, and changes in their medical service due to the Coronavirus disease pandemic will be assessed.

Numbers of completed interviews, home visits, case conferences and GP participant interviews will be recorded. In case of drop-out, information on hospital admissions and diagnosis during the last follow-up and time of drop-out will be gathered from the participant’s GP.

Data collection
Data will be collected at baseline and four follow-up time points (after 6, 12, 24, and 48 weeks) by members of the research team, who undergo a prior training. For participants in the control group the follow-up date refers to baseline while for participants in the intervention group it refers to the date of the telephone case conference. All parameters (except sociodemographic data) will be collected at each time point. Baseline will be assessed as face-to-face interview to establish a relationship with persons of this vulnerable group. Data at follow-up will be collected by telephone. GPs data will be assessed via telephone at baseline and at follow-up 48 weeks after baseline or at the time of drop-out/death of the participant.

The electronic data capture system and database (secuTrial®) will be used in this study and was configured by the department for biostatistics and data management of the University Medical Center Goettingen. For instruments and timing see table 1.

Table 1 KOPAL measurements

| Instruments used in KOPAL | Time of measurement |
|--------------------------|---------------------|
| Participants             | t0  | t1  | t2  | t3  | t4  |
|                          | 6 weeks | 12 weeks | 24 weeks | 48 weeks |
Hospital admissions x x x x x*  
Medication x x x x x  
BPI – Brief Pain Inventory x x x x x  
IPOS – Integrated Palliative Care Outcome Scale Patient/Staff x x x x x  
BESD – Beurteilung von Schmerzen bei Demenz x x x x x  
Healthcare proxy x x x x x  
Thoughts on preferred place of death x x x x x  
EQ-5D-5L – Health-related quality of life x x x x x  
FIMA - use of medical and non-medical services in old age x x x x x  
Sociodemographic data x  

general practitioners – participant related questionnaire  
ICD-10 diagnosis x x  
Date of last consultation x x  
Hospital admissions x x  
Prescriptions for palliative care x x  
Changes in medical care due to the Coronavirus pandemic x x  
If applicable: date and place of death x x  
Collaboration with SPHC (for intervention group only) x  
general practitioners – GP related questionnaire  
Sociodemographic data x x  
GP practice features x x  
*Primary endpoint

Sample size and power
Participants with the above-mentioned diseases and severity levels are usually admitted to hospital several times a year; we expect an average of about two admissions per participant per year. A 30% reduction is relevant and realistic. (15,16) Under these assumptions, a case number of 93 participants per group gives a statistical power of 90% for a test comparing two Poisson rates to the usual bilateral significance level of 5%. The distribution of hospital admissions per participant shows some extra-Poisson variation, i.e. the variance is greater than the mean (19). We correct the overdispersion, defined as variance/mean, by multiplying the number of cases by the corresponding factor of 2. (39) We also correct for 20% dropout of participants. This results in a total case number of 465 participants. The cluster randomisation and the expected cluster size of 11 participants per practice, which are based on the assumptions of population-related values for palliative care needs for the selected chronic diseases (cf. (40)), feasibility of the intervention at GP level, and assumed intra-cluster
correlation (ICC) of 0.032 (41), result in a design effect of 1.32 (42). This results in a rounded
total case number of 616 participants (56 practices with 11 participants each, 28 practices per
group). Practices, which drop out, will be replaced. The aim is to recruit 7 GP practices with
11 participants each in all four study centres per condition (intervention and control). Since
literature on annual hospitalisation rates varies and the assumptions on extra-Poisson
variation, ICC and dropout are subject to a certain degree of uncertainty, we will conduct a
sample size review after recruitment of the first 300 participants, and adjust case number
planning accordingly. (43)

However, start of recruitment coincided with the spread of the COVID-19 pandemic. Since the
progression of the pandemic was difficult to predict, the KOPAL study group, in consultation
with the funder, decided to close recruitment at the scheduled time and to recalculate the
study power. Therefore, the sample size was reduced to 191 participants, resulting in 51
practices with approximately 4 participants each. With the same ICC as in the original
planning, the design effect was therefore reduced to 1.096 (down from 1.32 in the original
sample size calculation). Then, using the same methodology as in the original sample size
calculation, a total sample size of 191 participants would be sufficient to prove a significant
difference between intervention and control group with 80% power (down from 90%),
assuming a likewise clinically relevant reduction in hospitalisations of 40% (up from 30%).
Significance level, dropout rate and assumptions on overdispersion were kept as planned
originally. A further review of the sample size was no longer performed as raising the sample
size would not have been possible.

**Statistical analysis**

The primary analysis will follow the intention-to-treat (ITT) principle. The effect of the KOPAL-
intervention on the number of hospital admissions will be analysed using a generalised linear
model with logarithmic link function as well as fixed effects for the intervention and important
prognostic factors at practice and participant-level (e.g. size of the practice, underlying
disease of the participant), and random effects for the practices and the participants. The
data of all recruited participants will be included in the analysis regardless of the time of drop
out or death; the logarithmic follow-up times will be included in the model as offset. The
intervention effect will be reported as an incidence ratio with a 95% confidence interval and
p-value testing the null hypothesis of the incidence ratio being equal to 1. If mortality within
the 48-weeks period is considerable (greater than 20%), a joined frailty model will be applied
to the recurrent hospitalizations and time-to-death will be modelled as a competing event. Further secondary effects will be examined by linear regression analyses in a multi-level model. Binary outcomes will be modelled by logistic regression with mixed effects. Furthermore, GP factors and specific symptom complexes of the participant can be considered as possible confounders. Participant subgroups will be formed based on diagnoses, symptom burden, socioeconomics, etc. and included in the analyses on an exploratory basis. Missing data will be dealt with using multiple imputation methods. The statistical evaluations are further detailed in a statistical analysis plan.

**Step 3 Evaluation**

**Step 3a: Health economic analysis**

Health economic analysis will include the evaluation of health care utilisation, costs and cost-effectiveness from a healthcare payer’s and societal perspective. Health care utilization will be assessed using the FIMA questionnaire, which was adapted to the diseases focused in KOPAL and the palliative care setting. Subsequently, health care utilization will be monetarily valued by standardised unit costs in Germany. (44) Besides descriptive analysis, cost determinants will be evaluated using regression models, which will account for the skewness of costs distributions. For cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) will be calculated. The effectiveness will be measured by quality-adjusted life years (QALYs) based on the EQ-5D-5L index. (45) Finally, uncertainty in the ICER will be evaluated by cost-effectiveness acceptability curves based on the net-benefit regression approach. (46)

**Step 3b: Qualitative evaluation of the KOPAL-intervention**

With regard to the implementation of the KOPAL-intervention qualitative evaluation will assess acceptance and feasibility considering different perspectives: health providers, patients/proxys, and relatives/associates.

Health providers: After follow-up four, all 28 GPs of the intervention group, and all involved members of the SPHC teams will be interviewed individually by trained members of the research team. Narrative interview techniques will be used in order to allow individual accentuation of relevancies. (47) The focus will be on: acceptance, practicability, beneficial aspects and barriers of the KOPAL-intervention, as well as interprofessional communication and consequences on participants care previous to the KOPAL-intervention according to each perspective. Interviews will be audio recorded, transcribed verbatim and analysed with a
Grounded Theory approach (48) using abductive reasoning (49) in order to transfer the practical experiences into a databased theory on interprofessional collaboration in the area of primary and palliative care. We decided to apply an in-depth approach to go beyond a manifest level of reflected attitudes and opinions regarding palliative care provision for non-oncological patients and cooperation with SPHC providers, since the aim of the study is to reveal possible unconscious barriers or reservations which will not be able to be explicated by participants.

Additionally, all telephone case conferences will be observed by a researcher using an observation protocol (non-participating observation (43)). Matters of interest are: course of actions, constellation of interactions, proportion of speech, main focus, omissions, and conclusions. According to Grounded Theory, observation protocols will enrich the analysis of interviews with GPs and SPHC teams.

Participants/proxies and relatives/associates: Semi-structured interviews (43,50) will be conducted with 16 to 22 participants (or proxies respectively) of the intervention group. Two semi-structured focus groups including 5-8 participants each (43) with relatives (or associates respectively) of KOPAL participants on their perception and experiences of the (effects of the) KOPAL-intervention, e.g., relevant changes in daily life and care. Audio recordings of the interviews and focus groups will be transcribed verbatim and analysed with a qualitative content analysis approach. (51) In contrast to analysis of provider interviews, we aim at analysing individual meanings and experiences with intervention reported on a manifest level wherefore we decided the chosen approach to be appropriate.

Findings from the qualitative evaluation will give insights into strengths and limitations of interprofessional collaboration amongst GPs, SPHC nurses and SPHC physicians at the intersection of primary and specialised palliative home care. Considering the needs of participants and their relatives will provide the basis for identifying structural or professional collaboration barriers.

**Monitoring**

All aspects of study design and data collection have been discussed in advance with the advisory board of the KOPAL study. The advisory board, which is independent from the investigator and the sponsor, will supervise the study process at least once a year. The department for biostatistics and data management of the University Medical Center Goettingen will continuously monitor all steps of data collection, quality assurance and data
analysis and will conduct a blinded interim analysis to proof the statistical power. They will oversee the intra-study data sharing process. The main risks of the study are possible negative events for the patients due to talking about their life situation. In case of negative events occurring during data collection the monitoring and safety board will be informed. If the board decides that these events are to be seen in connection with study participation or trial conditions the trial will be stopped. All participating patients receive usual care. In case of early withdrawal, the GP will be informed about the end of further patient related data collection and usual care will continue.

**Patient and Public involvement statement**

Participants affected by COPD and CHF, patient representatives for participants with dementia, and professional caregivers (nurses and physicians) will be involved in the development of the KOPAL conversation GUIDE. Their experiences and opinions will be discussed in three workshops and considered in the final version of the guide. Professional caregivers and patient representatives are members of the advisory board. The general public will not be actively involved.

**ETHICS AND DISSEMINATION**

KOPAL has been approved by the local ethics committee of the Medical Association Hamburg, Germany (no. PV7090) as well as the ethics committees of the University Medical Centre Goettingen, Germany (no. 34/1/20Ü), the Hannover Medical School (no. 8815 BO K 2019), and the University of Oldenburg (no. 2019-145). The trial is registered on the German clinical trial register (registration number DRKS00017795; 17-Nov-2021, version 05). Important protocol modifications will be submitted to the ethical boards as well as they will be communicated to the funder, the trial registry and to participating GPs, SPHC teams and patients.

Study participants will be informed about the study details by members of the respective research team. All participants (including those affected with dementia) will give written informed consent. Additionally for participants with dementia, a legal representative will have to give informed consent on participant’s behalf. Participants and legal representatives have the right to withdraw from the study at any point during the study without giving reasons, or any negative effect on patient care. In this case, the GP will be informed about
withdrawal and no further data will be collected. All study and patient-related information will be stored securely at the study sites.

The KOPAL study will develop and test an intervention of a lowthreshold contributing to strengthen interprofessional collaboration in palliative care and cross-sectoral care. The intervention will be tested in two German federal states. In case of effectiveness, the concept of the KOPAL study could serve a blueprint for other regions and meet the challenges of geographical equity in end-of-life care.

To ensure that the results of this study are accessible to the public, the results will be published in peer-reviewed international and national journals, and disseminated through national and international conferences. The main findings will be published in the German Clinical Trials Register.

**DISCUSSION**

Notwithstanding given differences among countries, an general need of improvement in palliative primary health care (PHC) is observed in European countries. (52) Not only is palliative care underprovided in general, this applies in particular for patients with other conditions than cancer. (53–55) In Germany, palliative care is structurally separated into two coverage areas, primary (general) and specialised palliative care. While the need for SPHC for non-oncological patients is accepted, it is still mostly provided to patients suffering from cancer for historical reasons. The integration of a concept to strengthen the early collaboration of primary and outpatient specialised palliative care providers in general and the interprofessional collaboration in particular could be a relevant step to consider more strongly the palliative care needs of non-cancer patients in primary care. The multicentre KOPAL RCT aims to develop and test an intervention including a home visit by a SPHC nurse using the KOPAL conversation GUIDE followed by an interprofessional telephone case conference.

Unfortunately, the scheduled start of recruitment and data collection coincided with the increase of the COVID-19 pandemic in Germany which had a retarding effect on the study progress. The SPHC teams were faced with a strong increase of SPHC prescriptions. Movable hospitalisations were stopped to keep hospital beds for COVID-19 patients which were often forwarded to SPHC to compensate for homecare needs. During the following months, also GPs reported increase of workload caused by insufficient information, lack of personal
protective equipment, the need to restructure practice procedures, and insufficient individual and structural pandemic preparedness. The fact of the fast worldwide spread and the absence of medication and vaccine led to high additional workload and financial worries. (56) Although this shows the relevance of SPHC providers as well as GPs and thus the relevance of research in this field, recruitment process was challenging and the sample size needed to be reduced in consultation with the funder.

To gain information about possible confounding factors of the pandemic on the effectiveness of the KOPAL-intervention, additional health related questions regarding the COVID-19 pandemic will be collected at baseline with GPs and patients.

Acknowledgements
Scientific experts and representatives (physicians, nurses, researcher and patient representatives) serve as advisory board and counsel the KOPAL study group once a year.

Author contributions
GM, TM, NP, FS, JD, MZ, TA, SB, CM, MF, EH, HvdB, IS, HHK, SST, NSch, FN, TF, MS contributed substantially to the conception of the study. MS (principal investigator), GM (coprincipal investigator), MF, EH, HvdB, IS, HHK, SST, NSch, FN and TF are the applicants of the trial. GM coordinates the trial. TF and TA are the trial statisticians and contributed to the statistical analysis aspect of the protocol. GM, NP, MZ and FS contributed substantially to the qualitative method of the protocol. GM and TM coordinated ethics approval and wrote the first draft of the manuscript. All authors revised the draft critically and gave approval of the final version of the protocol.

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Competing interests
The authors declare no conflicts of financial interests or other competing interests in relation to the present study.
Data sharing

Deidentified data will be available upon reasonable request beginning 1 year and ending 7 years following publication of primary and secondary outcomes. Proposals should be directed to the corresponding author.

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Figure 1. Illustration of the investigation of the KOPAL-intervention
Declaration of consent – copy for the study participant

I have been informed in detail by a study staff member about the nature and objectives of the study and agree with the procedure described in the patient information leaflet. My questions were answered satisfactorily. I have had sufficient time to decide whether to participate and I know that participation is voluntary and not associated with any immediate benefits or disadvantages for me. I know that I can withdraw this consent at any time without giving reasons and without any disadvantages for me.

I was informed of the following details in particular:

1. A study staff member of General Practice and Primary Care of the University Medical Center Hamburg-Eppendorf (UKE) will contact me and interview me in person at the beginning of the study, as well as four further times in writing and by telephone (at the beginning of the study, after 6, 12, 24 and 48 weeks). For this purpose, I will provide my contact information (name, address, telephone number) on a separate data sheet. In the questionnaire and telephone surveys, information about my person, my life situation, my mood, my general state of health and chronic illnesses, as well as the use of the health care system (incl. prescription of drug or non-drug therapies) will be collected, documented and evaluated. All survey data will be pseudonymized, i.e., stored under a personal code.

2. I will receive an additional care offer and will be visited by an outpatient nurse specialized in the treatment of symptoms (SHPC nurse) for a 30-minute conversation about my health and psychosocial situation. For this purpose, I give permission for my data (surname, first name, full address, name of my family doctor, my current medication schedule, date of birth) to be sent via fax to the responsible SHPC team by an employee of the Center for Psychosocial Medicine and Institute of General Medicine.

3. The SHPC team will store my personal data (see 2) in accordance with the current data protection guidelines.

4. Within the framework of the additional care offer, my general practitioner, an SHPC doctor and the SHPC nurse will discuss my health and psychosocial situation as well as my care once by telephone. An employee of the Department of General Practice and Primary Care, UKE will listen in on the case conference and will record it in writing in pseudonymized form. After this telephone call, I will receive regular care.

5. All persons involved in the study are bound to confidentiality according to § 203 StGB.

6. My data from the written or telephone interviews, carried out by the study staff, will not be passed on to third parties - not even to my general practitioner.

7. I have the right to be informed about my data. For this purpose, I contact the persons named as contact persons in the study information in the section on the General Data Protection Regulation (DSGVO).

8. If I terminate my participation in the study prematurely, the data collected from me up to this point may continue to be used in the study in anonymized form, i.e. without naming or the possibility of attribution to my name.

9. The pseudonymized data (using a personal code) collected in the course of the study will be stored electronically in the Department for biostatistics and data management of the University Medical Center Goettingen (UMG) and forwarded to the Department of General Practice and Primary Care (UKE) for data backup after completion of the surveys. In addition, the data from the personal initial survey will be archived in paper form at the Department of General Practice and Primary Care (UKE) in pseudonymized form for a period of 10 years.
10. The pseudonymized data (using a personal code) collected during the study will be evaluated by the Department of General Practice and Primary Care (UKE) and the following cooperation partners and used exclusively for research purposes: Institute for General Practice and Palliative Care, Hannover Medical School (MHH), Department of General Practice, University, UMG, Division of General Practice, Carl von Ossietzky University of Oldenburg, Department of Medical Statistics, UMG, and Department of Health Economics and Health Care Research, UKE. **Scientific publications are made exclusively in anonymized form** and do not allow any conclusions to be drawn about my person.

11. **Medical confidentiality:** My general practitioner will be asked about my current care situation as well as my health and psychosocial situation as part of the study. For the purposes of the study, I release my general practitioner from the duty of confidentiality towards the study staff of the Center for Psychosocial Medicine and Institute of General Medicine (UKE). In addition, I release my general practitioner from the obligation of confidentiality towards the SPHC team (SPHC physician and SPHC nurse), for the one-time telephone conference and for possible further contacts for study purposes.

12. **Professional confidentiality SPHC team:** The SPHC team will participate in a one-time telephone conference with my primary care physician about my current care situation and my health and psychosocial situation as part of the study. For the purposes of the study, I release the SPHC team from the duty of confidentiality towards my general practitioner and the study staff of the Department of General Practice and Primary Care, UKE.

13. **Legal data protection:** The study staff of the Department of General Practice and Primary Care will not pass on information from the surveys to my general practitioner.

14. As soon as the purpose of the study allows, my data will be completely anonymized, i.e. names, addresses and telephone numbers will be destroyed. After the retention period of 10 years has expired, all remaining data collected will be destroyed.

15. I understand and agree that I may be contacted again at the end of the study to be invited for a personal interview about my experiences during the study.

16. If necessary, I agree, that a relative named by me, may also be interviewed about his/her experiences in a group discussion.

I have read and understood the information on the legal basis and the data protection passage on pseudonymization (encryption) and agree to the procedure described. The information collected in the course of the study may be used in pseudonymized form for research purposes by all research centers participating in the study. **I was able to clarify any open questions with the study staff.**

I am aware that if I have any further questions, I can contact my general practitioner or a member of study staff at the Department of General Practice and Family Medicine directly at any time.

**I have received the written information about the study and a copy of this consent.**

**By signing this form, I declare that I agree with the procedure described above.**

**My participation in the study is voluntary. I know that I can revoke this consent at any time and without giving reasons. This will not result in any disadvantage for my further medical treatment.**

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**Place, Date**

**First and surname Participant**

**Signature participant**

**Ort, Datum**

**First and surname study staff**

**Signature study staff**
| Section/item                | Item No | Description                                                                 | Included page |
|-----------------------------|---------|-----------------------------------------------------------------------------|---------------|
| Administrative information  |         |                                                                             |               |
| Title                       | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1             |
| Trial registration          | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry | 14            |
|                             | 2b      | All items from the World Health Organization Trial Registration Data Set     | n.a.          |
| Protocol version            | 3       | Date and version identifier                                                 | 14            |
| Funding                     | 4       | Sources and types of financial, material, and other support                 | 16            |
| Roles and responsibilities  | 5a      | Names, affiliations, and roles of protocol contributors                      | 1-2, 16       |
|                             | 5b      | Name and contact information for the trial sponsor                          | 16            |
|                             | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16            |
|                             | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee) | 13            |
| Introduction                |         |                                                                             |               |
| Background and rationale    | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5f            |
|                             | 6b      | Explanation for choice of comparators                                       | 5f            |
| Objectives  | 7 | Specific objectives or hypotheses | 9 |
|------------|---|-----------------------------------|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6 |

**Methods: Participants, interventions, and outcomes**

| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6, 7 |
|---------------|---|----------------------------------------------------------------------------------------------------------------|---|
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7, 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7,8, figure 1 |
| 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 13f |
| 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 9 |
| 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 14 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 10, table 1 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1) | Figure 1 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|-------------|----|----------------------------------------------------------------------------------------------------------------------------------|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                 |

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
|---------------------|-----|----------------------------------------------------------------------------------------------------------------------------------|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation       | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking)   | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
|                      | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial |

### Methods: Data collection, management, and analysis

| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
|------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------|
18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination
| Item | Description                                                                 | Page |
|------|-----------------------------------------------------------------------------|------|
| 24   | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 14   |
| 25   | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14   |
| 26a  | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 14   |
| 26b  | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n.a. |
| 27   | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14   |
| 28   | Financial and other competing interests for principal investigators for the overall trial and each study site | 17   |
| 29   | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 14   |
| 30   | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n.a. |
| 31a  | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14f  |
| 31b  | Authorship eligibility guidelines and any intended use of professional writers | n.a. |
| 31c  | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n.a. |
| **Appendices** | | |
| 32   | Model consent form and other related documentation given to participants and authorised surrogates | 8    |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n.a. |