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Nurse-led, screening-triggered, early specialised palliative care intervention programme for patients with advanced lung cancer: study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction It has been suggested that palliative care integrated into standard cancer treatment from the early phase of the disease can improve the quality of life of patients with cancer. In this paper, we present the protocol for a multicentre randomised controlled trial to examine the effectiveness of a nurse-led, screening-triggered, early specialised palliative care intervention programme for patients with advanced lung cancer.

Methods and analysis A total of 206 patients will be randomised (1:1) to the intervention group or the control group (usual care). The intervention, triggered with a brief self-administered screening tool, comprises comprehensive need assessments, counselling and service coordination by advanced-level nurses. The primary outcome is the Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT) at 12 weeks. The secondary outcomes include participants' quality of life (FACT-Lung), depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), illness perception (Prognosis and Treatment Perceptions Questionnaire), medical service use and survival. A mixed-method approach is expected to provide an insight about how this intervention works.

Ethics and dissemination This study has been approved by the Institutional Review Board of the National Cancer Center Japan (approval number: 2016-235). The findings will be disseminated through peer-reviewed publications and conference presentations and will be reflected on to the national healthcare policy.

Trial registration number UMIN000025491.

Strengths and limitations of this study

- This is the protocol paper for the first randomised controlled trial in Japan to examine the effectiveness of a palliative care programme integrated into standard cancer treatment in patients with advanced lung cancer.
- We present a low-cost novel model for delivering specialised palliative care, by combining screening and stepped-care approach, referring to it as a nurse-led, screening-triggered, early specialised palliative care intervention programme.
- A possible limitation is that the study only targets patients with advanced lung cancer in two tertiary cancer centres.

INTRODUCTION

Cancer, especially advanced cancer, affects patients both physically and psychosocially. Therefore, provision of comprehensive supportive care to patients, along with anticancer treatments, is an essential aspect of quality cancer care. It has been suggested that provision of palliative care even from the early phase of cancer along with standard oncological care (early palliative care integrated with standard oncological care: EPC) lessens patients' symptom burden and yields beneficial effects on their quality of life (QOL).[1] A breakthrough study by Temel *et al*[2] demonstrated that provision of palliative care integrated into standard cancer treatment soon after the diagnosis of advanced lung cancer improves the QOL, severity of depressive symptoms and overall survival of patients, compared with usual oncology care. Several randomised controlled studies have replicated the efficacy of EPC.[3–5]

However, a few limitations have been pointed out on these EPC studies. First, the results of the studies have been inconsistent.[6–8] Several models of EPC delivery have been described, and while studies where palliative care specialists provided care for all patients from first contact revealed the clinical efficacy of EPC, a study where advanced-level

nurses served as the primary palliative care provider failed to demonstrate significant effects of EPC.[6] As the former approach is costly and is only feasible in facilities with abundant medical resources, exploration/establishment of an effective but more feasible model of EPC is desired.[9]

Theoretically, use of screening can be a solution to implement a cost-effective programme with limited human resources, and its implementation has been recommended 'as granted' in many clinical guidelines.[10 11] However, the effectiveness of distress screening has not yet been confirmed. A randomised controlled study of the effectiveness of a screening programme for ambulatory patients with cancer demonstrated effectiveness in lung cancer, but not in patients with breast cancer.[12] Another randomised trial involving 220 patients with cancer who underwent radiation and/or chemotherapy failed to yield any significant effect of distress screening on patient-reported outcomes, QOL or cost-effectiveness of care.[13] In general, screening per se does not yield meaningful clinical effects and needs to be combined with subsequent second-step evaluation and provision of appropriate care.[14 15]

Another limitation of EPC studies is that the mechanism underlying the beneficial effect of EPC has not been confirmed. Improvement in patients' perception of their illness, discussion between clinicians and patients about methods of coping with the illness, and clinicians' support on patients' decision-making are presumed to mediate the effectiveness of EPC; however, evidence still needs to be collected.[16 17] Studies to uncover the actual core components of EPC interventions are warranted.

Further, the efficacy of palliative care service is influenced by sociocultural situations and the medical system under which it is provided. Therefore, development of a conceptual model that is both feasible as well as desirable under the sociocultural condition where it is provided is important. In Japan, the Basic Plan to Promote Cancer Control enacted by the Japanese government addresses palliative care as an essential component in the care of patients with cancer and promotes the provision of palliative care from the time cancer is first diagnosed.[18] However, an effective model of EPC delivery has not yet been established due to the limited number of palliative care specialists. The rate of use of palliative care services remains low as compared with other countries.

Bearing these issues in mind, the authors conceived of a novel model for delivering specialised palliative care, by combining screening and a stepped-care approach, referring to it as a nurse-led, screening-triggered, early specialised palliative care intervention programme. In this model, patients who are potentially in need of palliative care first undergo a brief screening. A positive screen triggers further assessment by an advanced-level nurse, who provides counselling and serves as a segue to relevant health professionals. We examined the feasibility of this intervention in 50 patients with advanced lung cancer in a single-arm, pre-post design study,[19] where we observed satisfactory feasibility of the intervention and improved QOL and psychological status among the participants. We targeted patients with advanced lung cancer because lung cancer ranks very high both in terms of prevalence and mortality. Mortality is especially high in patients with advanced disease (stage IV non-small cell lung cancer (NSCLC) and extensive disease small cell lung cancer (SCLC), with an estimated median overall survival of 11–14 months and 12–14 months in these two groups, respectively[20 21]), which warrants provision of specialised palliative care.

Therefore, in the study described herein, we aim to examine the effectiveness of our nurse-led, screening-triggered, early specialised palliative care intervention programme using a randomised controlled study design. We hypothesised that our intervention would be more beneficial than standard oncological care in maintaining QOL of patients with advanced lung cancer. We also aim to collect information on the core effective elements of our palliative intervention using a mixed-method analysis approach.

METHODS AND ANALYSIS

This protocol paper is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines[22] (online supplemental material 1).

Design

This is a multicentre, parallel-group, randomised controlled trial. The participants are randomised to the intervention group (nurse-led, screening-triggered palliative care intervention) or to the control group (standard oncological care) at a 1:1 ratio (figure 1). The allocation is stratified by (1) histological type of cancer (NSCLC or SCLC), (2) study site and (3) age of participants (<75 years or ≥75 years). Blinding is impossible due to the nature of the intervention and the analysis of patient-reported outcomes. We will adopt a mixed-method approach for the analysis, as advocated by the UK Medical Research Council, setting multiple secondary endpoints and conducting qualitative analysis.[23]

Setting

This study is being conducted in two comprehensive cancer centres in Japan (National Cancer Center East in Kashiwa and National Cancer Center Hospital in Tokyo). Both facilities are tertiary medical facilities dedicated to cancer treatment and research.

Participants

Eligibility criteria of participants are as follows: (1) pathologically or cytologically confirmed diagnosis of lung cancer; (2) stage IV NSCLC or extensive disease SCLC; (3) negative or unknown status of gene mutations for which molecular targeted therapy is applicable (eg, *EGFR*, *ALK*, *ROS1* or *BRAF*); (4) scheduled for first-line chemotherapy (other than immunotherapy); (5) absence of any

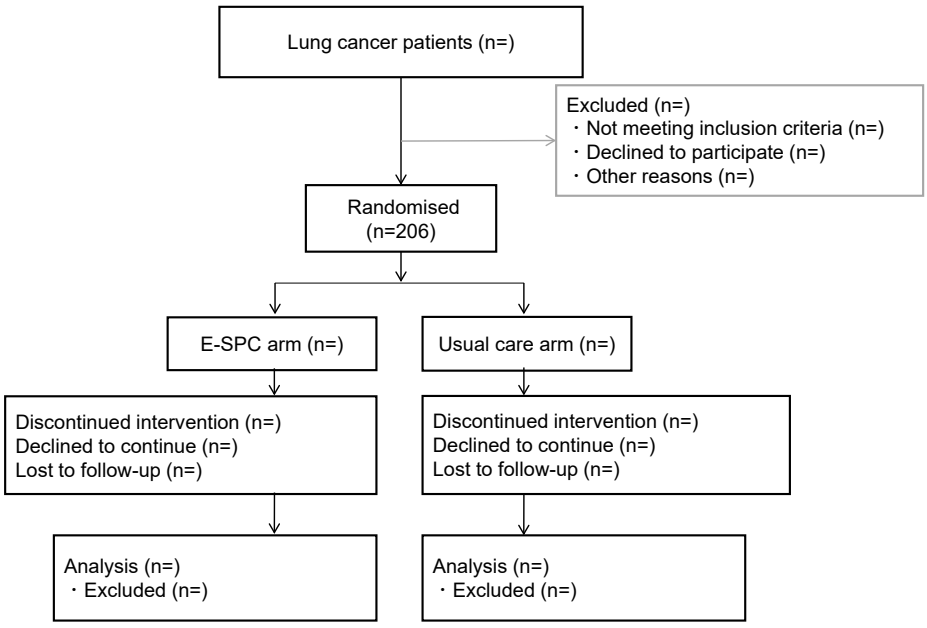

Figure 1 Flow diagram. E-SPC, early specialised palliative care.

previous anticancer treatment for lung cancer (including chemotherapy, surgery, radiation therapy with curative intent and/or immunotherapy); (6) initial administration of first-line chemotherapy in an inpatient setting; (7) age 20 years or over; and (8) willing to provide written informed consent.

Subjects are excluded if they (1) have already received specialised palliative care interventions (including psycho-oncology care); (2) have severe cognitive impairment; (3) are unable to comprehend Japanese; (4) are already participating in other interventional studies which prohibit participation in the current research; or (5) are considered ineligible for this study by the physician in charge.

RECRUITMENT

The participants are recruited from the thoracic oncology divisions of the National Cancer Center Hospital, Tokyo, Japan, and the National Cancer Center East, Kashiwa, Japan. Patients who meet the above-mentioned eligibility criteria are consecutively approached by the research staff. After providing written consent, the participants are allocated to the intervention group or the control group.

SAMPLE SIZE

We recruit 206 participants in total to potentially obtain statistically significant differences in the primary outcome (change in the Trial Outcome Index (TOI) from baseline to 12 weeks) between the intervention group and the control group, with an estimated SD score of 14 and an intraclass correlation of 0.6. With 80% power to detect a significant difference at a 5% alpha level (one-sided) and an estimated attrition rate of 36% by week 12, the required sample size is calculated as 103 participants in each arm. A 5-point difference in the mean TOI score is considered a clinically meaningful change in anticancer treatments.[24] In a cutting-edge study of early palliative care, Temel *et al* demonstrated a 5.1-point difference in mean TOI between the intervention group and the control group.[2] Further, in our previous feasibility study,[19] an improvement in mean TOI by 5.5 points (52.3±14.8 at baseline vs 58.8±13.2 at study completion) was observed.

Interventions

Intervention group

Patients who are allocated to the intervention group receive the nurse-led, screening-triggered, specialised palliative care. This programme comprises the following components.

Screening

Initial intervention starts with the administration of a brief self-completed screening questionnaire. This self-administered screening questionnaire comprises questions in four subscales, namely physical distress, psychological distress, socioeconomic need, and concerns about the illness or its treatment, which will be described later in this manuscript.

Counselling and care coordination by an advanced-level nurse

A positive result of screening for any of physical distress, psychological distress or socioeconomic need subscales of the above-mentioned questionnaire prompts intervention by the specialised palliative care team. One of the advanced-level nurses belonging to the team primarily contacts the patient and conducts a comprehensive assessment using a checklist covering physical, psychological, social and medical/informative aspects. During this process, the advanced-level nurse attempts to provide the following care, based on the findings of a previous palliative care study[17]: (1) building rapport; (2) symptom management; (3) facilitating patients' coping with cancer diagnosis; (4) facilitating patients' understanding of the illness and the treatment; (5) counselling on anticancer treatment and its adverse effects; (6) preparation for cancer progression and end of life; and (7) facilitating family involvement. The advanced-level nurse may achieve these aims by providing the counselling himself/herself or by coordinating referral to other professionals as necessary. For example, he/she refers a patient to a medical social worker if he/she has financial problems. If a patient expresses concern about his/her illness or the treatment, the advanced-level nurse will notify the physician and/or the nurses responsible for the care of the patient.

Interdisciplinary team approach

Participants' care plans are reviewed regularly by an interdisciplinary palliative care team. For hospitalised patients, they are reviewed weekly by a team consisting of palliative care physicians, palliative care nurses, psychiatrists, psychologists, social workers, pharmacists and nutritionists. For ambulatory patients, the plans are reviewed every 2 weeks by one of the advanced-level nurses and a board-certified palliative care physician. Based on this regular review, further specialised palliative care intervention is provided by other professionals.

Follow-up

Once the intervention by the specialised palliative care team begins, it is continued until the end of the study period (5 months). One of the advanced-level nurses meets the participant at least once a month for ambulatory patients and at least once a week for hospitalised patients.

For patients who are found to be negative on screening, the brief screening is repeated every month, with a 3-week margin. The intervention by the specialised palliative care team is withheld until (if ever) the screening turns positive; however, the team provides services on request by patients, their family or the medical professionals attending the patients. Participants continue to receive the usual oncological care during the study period.

The nurses who engage in this intervention (1) need to be an advanced-level nurse (certified nurse or certified nurse specialist) in the relevant specialised fields, which will be described later; and (2) need to have received at least 10 hours of training based on the intervention manual (available on request addressed to the corresponding author). Certified nurses are qualified nurses who have at least 5 years of clinical experience and have received at least 6 months of advanced-level training in one of 21 specialised areas. Certified nurse specialists are master-level nurses who have at least 5 years of clinical experience and have received at least 2 years of advanced-level training in one of 10 specialised areas. Both of the credentials are authenticated by the Japanese Nursing Association.[25] In the current study, certified nurses in palliative care, certified nurses in cancer pain management nursing, certified nurse specialists in cancer nursing and certified nurse specialists in psychiatric mental health nursing are eligible for participation.

Control group

Patients who are assigned to the control group receive usual oncological care. They are not scheduled to meet with the palliative care service team unless it is requested by the patient, by his/her family or by the treating oncologists.

Measurements

Primary outcome

The primary outcome measure in this study is change in TOI from baseline to completion of the intervention (at 12 weeks). The TOI represents the physical situation and the quality of life of patients with lung cancer and is considered an important endpoint in clinical trials.[26] The TOI is calculated as the sum of the scores of the physical well-being subscale, functional well-being subscale and lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L).

Secondary outcomes

Disease-specific QOL

We use the FACT-L to evaluate participants' QOL. The FACT-L is a combination of the Functional Assessment of Cancer Therapy-General (FACT-G) and the LCS. The FACT-G assesses multiple dimensions of QOL (physical, functional, emotional and social well-being) of patients with lung cancer during the previous week. Higher scores indicate better QOL. The LCS evaluates seven symptoms that are specific to lung cancer. The FACT-L is self-administered by patients at three time points in this study: at baseline and at 3 months and 5 months postrandomisation.

Global QOL

We use the EuroQoL 5-Dimension to measure participants' global QOL.[27] The scale consists of two parts: a Visual Analogue Scale (VAS) and a self-classifier. The self-classifier has been recognised as showing better concordance with other QOL measures than VAS; therefore, we use the self-classifier in our study. The self-classifier comprises five items, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents' answer to each question is graded on

a 5-point scale. Combinations of these responses are converted to a single score (health utility value) using a conversion table called 'tariff'. The scale has been widely used in the cancer population and has been validated in the Japanese population.[28 29]

Depression

We use the Patient Health Questionnaire-9 (PHQ-9), a nine-item self-reported instrument, to measure the severity of depression in patients.[30] Higher score indicates greater severity of depression. A total score of 10 or more indicates clinically significant depression. A patient is diagnosed as having major depressive syndrome if he or she answers in the affirmative at least five of the nine symptoms of depression on the scale, with either anhedonia or depressed mood as one of the symptoms. The PHQ-9 has been used in numerous clinical studies of patients with cancer[31] and has been validated in the Japanese population.[32]

Anxiety

We use the Generalized Anxiety Disorder-7 (GAD-7), a seven-item self-reported instrument, to measure the level of anxiety.[33] A score of 10 or more out of a total score of 21 indicates clinically significant anxiety. The GAD-7 has been validated in the Japanese population.[34] Both PHQ-9 and GAD-7 are recommended by the American Society of Clinical Oncology as screening tools to detect psychological distress in patients with cancer.[35]

Brief screening questionnaire

We use a brief screening questionnaire for initial screening and follow-up during the study period. This questionnaire consists of four domains: physical, psychological, social and medical/information needs. Physical distress is assessed with a single question enquiring the level of physical symptoms; the patient indicates his/her response on a 5-point Likert scale (from 0: no physical distress to 4: persistent unendurable physical distress). This question was adopted from the physical domain of the Support Team Assessment Schedule.[36] A score of 2 or over is indicative of physical distress. The psychological domain corresponds to the Distress and Interference Thermometer, a well-established screening tool which has been validated and widely used in the Japanese cancer population.[37 38] The scale consists of a single item to rate the level of psychological distress on a thermometer-shaped numeric scale (from 0: no distress to 10: extreme distress) and a single item to rate the level of interference with daily life activities arising from the distress (from 0: no interference to 10: extreme interference). Based on a previous report, a distress score of 4 or over and an interference score of 3 or over indicate psychological distress.[39] The presence of social distress is evaluated by a single question, that is, 'Do you currently have any concern on financial issues, employment issues or any other issues in daily living?' The participants are asked to select an answer from the following: 'Yes', 'No current concern, but want to talk with someone on these issues' and 'No concern at all'. The first two responses are indicative of social distress. The fourth domain of the questionnaire is designed to enquire about participants' need for more information on their illness and/or treatment, using the following question: 'Do you currently have any concern or do you have anything you want to know further on your illness and/or treatment?'

Illness perception

We measure participants' prognostic perceptions using the Prognosis and Treatment Perceptions Questionnaire. This 13-item questionnaire is used to assess a patient's beliefs regarding (1) the likelihood of cure; (2) the importance and helpfulness of knowing about the prognosis; (3) the primary goal of cancer care; (4) preference about receiving/not receiving information about the treatment; and (5) satisfaction with the quality of information received about the prognosis and treatment. The questionnaire has been validated in a mixed cancer population.[40]

Other clinical outcomes

We collect data on patients' survival (1-year survival rate and overall survival period), medical service use and circumstances of death (date and place of death, number of days of hospitalisation within the last month of life, days and types of the last chemotherapy administration, last administration of intravenous chemotherapy, hospice use, and rate of cardiopulmonary resuscitation). We selected these variables based on well-established quality indicators of end-of-life cancer care and reports from previous studies on early palliative care intervention.[2 3 41] We record contents of and the time spent for the intervention provided by the specialised palliative care. We also compile adverse events according to the Common Terminology Criteria for Adverse Events, Fourth Version. The participants will be followed up for 2 years after study enrolment.

Qualitative evaluation of the intervention

A semistructured interview of patients providing consent for the interview is conducted at week 12. The interview is designed to determine the general impression of the intervention, the components that the participants perceived as being helpful, the components that the participants perceived as being harmful, the subjective changes that were perceived after the intervention as compared with before, and the issues that the participants found as helpful to obtain a better understanding of their illness and treatment.

Schedule of outcome measurements

The schedule of these outcome measurements is shown in table 1.

Statistical analyses

All randomised participants who satisfy the eligibility criteria and receive the study intervention will be included in statistical analyses. For the primary endpoint, point estimates and CIs of the mean change in TOI from baseline to 12 weeks will be calculated for each group and compared between groups

Table 1 Schedule of outcome measurements

Assessment	Time points						
	0 week	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	Follow-up§
Characteristics of participants	●						
Chemotherapeutic regimen							●
Brief screening questionnaire*	●	●†	●†	●†	●†		
EQ-5D, FACT-L, GAD-7, PHQ-9, PTPQ	●			●		●	
Satisfaction with the intervention				●		●	
Semistructured interview‡				●			
Medical service use at the end of life							●
Survival status							●

*Will be evaluated among participants in the intervention group.
†Will be evaluated among participants in the intervention group who have not received intervention up to that time point.
‡Will be conducted among participants in the intervention group who submitted oral consent for the interview.
§Will be conducted in 2 years after the last assessment.
EQ-5D, EuroQoL 5-Dimension; FACT-L, Functional Assessment of Cancer Therapy-Lung; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PTPQ, Physical Therapy Practice Questionnaire.

using a general linear model, with adjustments for allocation factors and baseline TOI. When the number of subjects in each stratum is small, the handling of the allocation adjustment factors will be determined in this analysis plan. The mean change in TOI, after the adjustments, in the groups will be estimated and compared.

Data collection and monitoring

The investigators at each study site maintain individual records for each patient as source data, including a copy of the informed consent, medical records, laboratory data and other records or notes, maintaining confidentiality. All data are collected by the Japan Supportive, Palliative and Psychosocial Oncology Group (J-SUPPORT) Data Center at the Center for Public Health Science, National Cancer Center Japan. The data management centre oversees the intrastudy data sharing process. Patient enrolment, randomisation, data entry, data management and central monitoring are performed using the REDCap electronic data capture application (Vanderbilt University).[42] Central data monitoring reports are compiled by the clinical data managers twice a year and reported to the principal and site investigators. Auditing is not planned for this study.

Ethical considerations and registration

This study is conducted in accordance with the principles of the Declaration of Helsinki and the Ethics Guideline for Clinical Studies of 2014 published by the Japan Ministry of Health, Labour and Welfare. The study has been approved by the Institutional Review Board of the National Cancer Center Japan (approval number: 2016-235). This protocol has been reviewed by the protocol review committee of J-SUPPORT and has been approved as the J-SUPPORT 1603 study. The study has been registered at the Japanese Clinical Trial Registry.

Patient and public involvement

This study protocol was reviewed by patient and public involvement (PPI) representatives. The PPI representatives meet the research team regularly at the progress report meetings, provide advice on the progress of the study and will help the team develop dissemination strategy.

DISCUSSION

This paper presents the protocol of a parallel-group, randomised controlled study to examine the effectiveness of a nurse-led, screening-triggered, early specialised palliative care intervention programme. This programme represents a combination of self-administered screening and subsequent care led by an advanced-level nurse, who undertakes comprehensive assessment, counselling and care coordination. If this programme is proven to be effective in improving QOL and alleviating distress of patients with cancer, it would be considered a universally applicable model of early palliative care.

There are a few limitations to this study. First, our intervention is undertaken only in two tertiary cancer centres, both of which are rich in staff with expertise in cancer care and palliative care, as compared with other medical facilities. It would be difficult, therefore, to exclude the possibility that the programme proves less effective at facilities that are not as well staffed. Second, we target only patients with advanced lung cancer and the findings would need to be verified in other cancer populations.

Trial status

This ongoing study was started in January 2017 and the recruitment of participants was closed in September 2019. The registered participants are currently under intervention or under observation for assessments, which will be continued until September 2021.

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

Section/item	ItemNo	Description	Addressed on page number
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	5, 22
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 23-24
	5b	Name and contact information for the trial sponsor	3
	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	23-24
	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)	21
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	6-9
	6b	Explanation for choice of comparators	6-9

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)	9
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	9-10
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)	10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
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	15-20
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)	14, 16
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	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11

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	9
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	9, 21
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

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	21-22
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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	21-22
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	21

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
	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)	21
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	21-22
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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	20
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
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Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
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)	N/A
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