Statistical analysis plan

Nurse-led Smoking Cessation Intervention with Follow-up in Healthy Life Centers: a Randomized Clinical Trial

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1. Administrative information

The "Nurse-led Smoking Cessation Intervention with Follow-up in Healthy Life Centers: a Randomized Clinical Trial" aims to investigate clinical and health economic effects of a multi-component intervention for smoking cessation following an atherosclerotic cardiovascular disease event.

1.1 Trial registration numbers

This is a (ClinicalTrials.gov Identifier: NCT05049174) multicenter trial that enroll patients from three hospitals within the Vestre Viken Health Trust.

1.2 Protocol version used for preparation of the statistical analysis plan

Protocol version 2.0, 24.08.2022.

1.3 Contributors for preparation of the statistical analysis plan

Project leader/main supervisor John Munkhaugen and PhD candidate Karin Pleym
Statisticians: Harald Weedon-Fekjær and Morten Wang Fagerland (QC)

The SAP has been approved by the NORCOR smoking cessation project steering committee including user representatives.

1.4 Signatures

Project leader

Name: John Munkhaugen

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1.5 SAP Revision

Date of revision	Revision	Justification for revision
06.03.2024	Health-economic analysis in a separate paper	After careful discussions with leading national health economists, we agreed that a comprehensive Markow analysis needs to be elaborated in a separate paper and not included in the main publication.
06.05.2026	Specification of long-term outcomes and changes in the follow-up period	After careful discussions within the research group, we have pre-specified the trial's long-term outcomes into (i) ischemic events and all-cause mortality,

		and (ii) the total number of unplanned hospital admissions. Due to the large event rate during the first 18 months of follow-up and practical considerations regarding data completeness, we have decided to reduce the median follow-up duration for this pre-specified sub-study from 5 years to 3.5 years. Note that we have not yet collected data on recurrent events beyond 18 months, which prevents bias when selecting the timing of this updated analysis. We previously assessed the effect of the nurse-led intervention on smoking cessation outcomes in the proof-of-concept trial and the main trial, in accordance with the original SAP, and found similar rates of smoking cessation. In the present prespecified sub-study, we will evaluate how these cessation rates affect all-cause mortality and unplanned re-hospitalizations, using combined data from the proof-of-concept trial (N=58) and the main trial (N=220).

2. Introduction

2.1 Background and rationale for the study

Cigarette smoking is a major risk factor for numerous diseases including atherosclerotic cardiovascular disease (ASCVD).[1-3] The detrimental health effects from smoking lead to extended disability and premature mortality, quantifiable by disability-adjusted life-years (DALYs).[4] In 2019, tobacco smoking was responsible for more than 7 million deaths and 200 million DALYs worldwide.[5] These figures underscore the substantial burden tobacco smoking places on individuals, healthcare systems, and society at large.[6,7]

Smoking cessation following an ASCVD event mitigates the likelihood of subsequent vascular events and mortality.[8] However, cessation rates remain modest or low among patients with various presentations of ASCVD.[9-11] In a previous study from Norway, we found that half of those smoking preceding an unplanned coronary heart disease event continued smoking after hospital discharge.[12] Correspondingly, up to 60% of smoking patients hospitalized with a stroke or transient ischemic attack (TIA) continue to smoke.[10] A recent study revealed that more than 70% of patients with peripheral artery disease were daily smokers one year after hospitalization.[13] Of these, only 1 in 5 were referred to formal cessation counseling and 1 in 10 were prescribed smoking cessation drugs.[13] Thus, it is crucial to establish and implement smoking cessation

interventions across vascular diagnoses. Extensive evidence for the effectiveness of pharmacological and behavioural smoking cessation measures is available.[14-16] However, implementing this knowledge into clinical practice remains challenging due to individual and systemic barriers.[17-19]

The majority of smoking ASCVD patients have a long history of smoking and come from socio-economically disadvantaged backgrounds.[20-22] Low socio-economic status is associated with low health literacy which in turn may pose a significant barrier to seeking, finding and participating in relevant smoking cessation programs.[23,24] Notably, more than 70% of daily smokers express a desire to quit.[25] An acute ASCVD event and subsequent hospitalization may act as a catalyst for these patients, enhancing their motivation for smoking cessation.[26] In this setting, healthcare providers have an unique opportunity to identify smokers and provide tailored counselling and support.[27] Importantly, smoking cessation interventions for hospitalized patients should extend for a minimum of one month after discharge.[28] This knowledge encourages care coordination between specialist and primary health care.

Unfortunately, only a small minority of ASCVD patients in Norway and Europe currently access or participate in cardiac rehabilitation programs.[29,30] Within the Norwegian primary healthcare system, community-based Healthy Life Centers take part in preventive care alongside general practitioners and cardiac rehabilitation services.[31,32] These centers offer a variety of health-promoting measures, including smoking cessation programs providing cessation drugs at no cost.[33] Patients can initiate contact with the Healthy Life Center themselves, but also be referred by healthcare professionals for participation.

Based on key factors known to promote successful smoking cessation,[34-37] we developed a nurse-led, multi-component cessation intervention tailored for smokers hospitalized with acute ASCVD events. The intervention builds on existing infrastructure of the Norwegian healthcare system. The purpose was to enhance cessation rates by capitalizing on the possible increased readiness to quit related to hospitalization.[26] Accordingly, the intervention began during hospital stay with nurse-led cessation counseling, employing recommended motivational interviewing techniques.[34,38] Furthermore, we aimed to provide a seamless transition to post-discharge follow-up care in community-based Healthy Life Center smoking cessation programs.[35] Thus, nurses actively referred patients by telephone to their local community-based center for continued follow-up. Moreover, staff members from Healthy Life Centers proactively contacted the patient by telephone, inviting them to participate in the cessation program. We hypothesized that this strategy would effectively promote smoking cessation among patients hospitalized with ASCVD. We anticipated that the impact of the intervention would be mediated through motivational counseling, proactive referral, increased participation in smoking cessation programs, and increased use of cessation drugs.

In a recent feasibility study, we assessed the effect of this intervention on participation rate and use of cessation drugs.[39] Compared to the control group, the nurse-led intervention significantly increased participation in the Healthy Life Center cessation programs, with a 48% participation rate versus 7% in the control group. Additionally, the use of cessation drugs was significantly higher in the intervention group.[39] An exploratory evaluation showed promising results in smoking cessation at six months, with 48% of the intervention group successfully quitting compared to 25%

in the control group.[39] Despite the small sample size (N=58), these encouraging results call for a larger-scale, statistically robust trial to determine the effectiveness of the intervention. The primary objective of this pragmatic randomized study is to determine the effect of the multi-component nurse-led intervention on smoking cessation rates at six- and 12 months follow-up after an ASCVD event. Additionally, we aim to conduct a cost-effectiveness analysis of the intervention.

2.2 Objectives

The overall aim is to evaluate the clinical and health economic effects of a nurse-led, multi-component intervention tailored to daily smokers admitted to the hospital with an acute ASCVD event.

2.2.1 Primary objective

To determine the effect of the multi-component nurse-led intervention on self-reported smoking cessation rates at six-month follow-up.

2.2.2 Secondary objectives

Key secondary objective:

To determine the effect of the intervention on smoking cessation verified by carbon monoxide measurements in exhaled breathing air at six-month follow-up.

Other Secondary objectives:

#1. To determine differences between the groups in participation rate at the cessation program.

#2. To determine differences in self-reported use of cessation drugs between the groups.

#3. To determine the effect of the intervention on smoking cessation at 12 months follow-up.

2.2.3 Exploratory objectives

#1. To determine differences in self-reported smoking cessation rates at six-month follow-up in the following subgroups; age, sex, ASCVD diagnosis, somatic comorbidity, and study site.

#2. To explore between-group differences in the composite end-point of all-cause mortality and unplanned re-hospitalizations for ASCVD events at 18 months follow-up (i.e. myocardial infarction, angina/claudication, coronary and peripheral revascularization procedures, stroke/TIA, tachyarrhythmia's and/or heart failure).

2.2.4 Secondary and exploratory objectives for sub-studies

The following objectives pertain to sub-studies planned for subsequent publications.

#1. To perform a cost-effectiveness analysis of the intervention.

#2. To assess the effect of the nurse-led intervention on the composite of all-cause mortality and unplanned re-hospitalizations for ASCVD events after median 3.5 years follow-up using data from the proof-of-concept trial (N=58) and the main trial (N=220).

#3. Investigate whether baseline levels and longitudinal changes in the following PROMs are associated with smoking cessation between treatment arms and in the entire study cohort:

- Symptoms of depression, anxiety, insomnia, and sleep duration.
- Type D personality.
- Metacognitions (as measured by DTQ, MSQ, MCQ-30).

#4. Identify clinical and psychosocial predictors of smoking cessation in a combined analysis, incorporating data from the main trial (N=220) and the proof-of-concept trial (N=58).

3. Study methods

3.1 Trial design and randomization

This is a prospective, randomized, multi-center, parallel-group, open-label, blinded end-point (PROBE) clinical trial evaluating the effect of a multi-component smoking cessation intervention. Patients will be randomized 1:1 to the multi-component intervention or to usual care plus an information leaflet. The randomization will be stratified by study site. The three study sites are Drammen hospital, Kongeberg hospital and Ringerike hospital.

3.2 Intervention

The multi-component intervention includes 1) counselling utilizing motivational interview technique, 2) an information-leaflet, 3) referral to a post-discharge municipal smoking cessation program providing access to free nicotine replacement therapy, 4) a proactive invitation by telephone to participation in the cessation program after hospital discharge and 5) a letter to the general practitioner informing about the inclusion in the study and the option of participating in the Healthy Life center for smoking cessation. The control group received treatment and follow-up care according to routine clinical practice at the participating hospitals and in primary care plus an information-leaflet describing the cessation program and how to initiate contact for participation.

3.3 Framework, sample size and power calculation

The trial will be analyzed as an ordinary superiority trial and is designed to have more than 90% power to detect a between-group difference of 23% (48% vs. 25%) in occurrence of the primary outcome, self-report smoking cessation at six months follow-up (with an alpha of 0.05). The difference is based on results for our pilot study conducted in 2021 (ClinicalTrials.gov Identifier: NCT04772144). With 196 (98 x2) patients we also have 80% power to detect an even more conservative difference in point prevalence of smoking cessation of 19% (44% vs. 25%) between treatment groups. To account for slightly lower effects of the intervention, we will randomize 220 patients. The database will be locked and the study un-blinded when the last randomized patients have been followed for a minimum of 6 months.

3.4 Interim analysis for effect

No interim analyses are planned.

3.5 Timing of final analysis and outcome assessments

The final analyses will be performed when follow-up has ended, and all endpoints have been registered and after database lock. The minimum follow-up period will be 6 months.

Primary, secondary and exploratory endpoints are collected from 1) medical records at the participating hospitals and community-based cessation centers at study end, 2) telephone interviews conducted after one, three, six- and 12-months follow-up, 3) self-report questionnaires collected at baseline and at six months after randomization, and 4) carbon monoxide (CO) measurements collected six months after randomization.

4. Statistical principles

4.1 Confidence intervals and P values

For the primary outcome we will use a significance level of 5% and a confidence interval (CI) of 95% will be reported. The secondary outcomes will be assessed with a CI of 95%. All statistical tests and confidence intervals will be two-sided.

4.2 Protocol deviations

Possible protocol deviations are linked to situations where:

- The patient refuse to participate in the motivational interview conversation
- The nurse for some reason do not refer the patient to community-based Healthy Life Center.
- The Healthy Life Center fail to pro-actively contact the patient and inviting them to participate

Should such situations occur, they will be registered.

4.3 Analysis population

All major comparisons between the randomized groups will be performed according to the principle “intention-to-treat”, i.e., participants will be analyzed, and endpoints counted in the group to which they were assigned at randomization.

5. Trial population

5.1 Screening

Patients admitted to the hospital for an ASCVD event will be screened for inclusion and exclusion criteria at all participating centers. All sites in are consecutively reporting the reasons for not being included in the trial. Collected screening data will be summarized and presented in the main publication.

Screening data registered in the eCRF of all screened patients:

- Site
- Exclusion criteria (see below)

5.2 Inclusion and exclusion criteria

Inclusion criteria	• >18 years • Smoking at least one cigarette daily • Hospitalized with an acute cardiovascular disease event and established atherosclerosis (based on diagnosis and/or treatment with a lipid lowering and antiplatelet)
Exclusion criteria	• Patients not living in or working in the Vestre Viken region • Any condition (psychosis, alcohol abuse, dementia) or situation that may pose a significant risk to the participant, or make participation unethical • Short life expectancy (<12 months) • Not able to understand and write Norwegian • Decline to participate

5.3 Information to be included in the CONSORT flow diagram

- Number of patients assessed for eligibility
- Number of patients excluded and reason for exclusion
- Number of patients randomized
- Number of patients allocated to the intervention or the control group
- Number of loss to follow-up
- Number of patients excluded from analyses and reasons for exclusion

5.4 Withdrawal and loss to follow-up

5.4.1 Withdrawal of informed content

Patient consent withdrawals are possible at any time during follow-up and the day of withdrawal will be registered. Time to withdrawal will be summarized.

5.4.2 Loss to follow up

All non-responders will be categorized as current smokers in the primary analysis according to the Russel criteria.[40]

5.5 Data collection

Data collected from hospital medical records at baseline:

- Demographics
- Information about the qualifying ASCVD event treatment and/or procedures performed during index event
- Major comorbidities summarized into Charlson comorbidity score
- Risk factors

Patient reported outcomes measures collected at baseline and after six months follow-up:

a. **Socio-economic variables:** Education, employment status, marital status (living alone or with others)

b. **Smoking history and behavior:** cigarettes/day, number of years daily smoking, previous quit attempts, smoking partner, motivation to quit (readiness for smoking cessation), nicotine addiction (Fagerstrøm), previous use of nicotine replacement therapy and/or e-cigarettes.

c. **Lifestyle**: Physical activity, alcohol consumption, height and weight calculated into BMI

d. **Other post-discharge follow-up**: participation in cardiac rehabilitation, follow-up with GP.

e. **Screening question for quality of life**: SF-12- Question 1.

f. **Measures of depression and anxiety**: HADS (Hospital Anxiety and Depression Scale)

g. **Measures of sleeping disorder**: Bergen insomnia Scale and average sleep duration

h. **Measures of personality**: Type D (distressed) personality disorder.

i. **Measures of metacognitions:** Desired Thinking Questionnaire (DTQ; Spada & Caselli, 2011), Metacognitions about smoking questionnaire (MSQ; Nikcevic, Caselli, Wells & Spada, 2015) and Metacognition Questionnaire-30 (MCQ-30)

Data collected during follow-up:
Primary, secondary and safety endpoints are collected through questionnaires, medical records at participating hospitals and municipality centers, CO measurements, and telephone interviews throughout the trial as previously described.

5.6 Patient characteristics in main publication

Data at baseline:

- Demographics and social background
    - Age, sex, marital status/living condition (living alone, living with partner or in a care home facility), employment status and education level
- Index cardiovascular event
    - Acute myocardial infarction/stroke vs. other atherosclerotic cardiovascular disease events
- Somatic comorbidities, risk factors and treatment
    - Hypertension (diagnosis and/or treatment), hyperlipidemia (treatment with statins and/or ezetimibe), chronic kidney disease, diabetes (diagnosis/treatment), physical inactivity, alcohol consumption, obesity, antiplatelet
    - Previous cardiovascular disease, Charlson comorbidity score
    - HADS-Score
- Quality of life -single screening questionSmoking frequency, history and motivation
    - Nicotine dependency
        - Fagerstrøms test
        - Time to first cigarette
    - Duration of smoking
    - Living with a daily smoker
    - Previous quit attempt and eventually use of nicotine replacement therapy and/or e-cigarettes.
    - Motivation to quit on a 0-10 Likert scale
- Readiness for smoking cessation
    - Preparation phase, contemplation phase, pre-contemplation phase

Follow-up care after discharge

- Participation in cardiac rehabilitation
- Visits to general practitioner
- Participation in Healthy Life Center

Details of how baseline characteristics will be descriptively summarized
Baseline characteristics will be presented as numbers with percentages for categorical variables and medians with interquartile ranges for continuous variables.

6. Analysis and endpoints

6.1 Endpoints

6.1.1 Primary endpoint

Difference between the groups in the proportion of participants who self-report smoking abstinence at six months follow-up.

6.1.2 Secondary endpoints

Key secondary endpoint:

Difference between the groups in the proportion of participants who self-report smoking abstinence at six months follow-up verified by carbon monoxide (CO) measurements in the exhaled air, according to the Russel standard.[40]

Other secondary endpoints:

#1. The proportion of participants who self-report smoking abstinence at 12 months follow-up.
#2. Participation rate at the cessation program between the groups obtained from medical records at the municipal centers at six months follow-up.

- Number of consultations per participant (digital vs. physical)
- Number of individual and group-based consultations per participant
- Number of vouchers (for 4 weeks use of cessation drugs) delivered (0 to 3) per participant

#3. Patient report use of cessation drugs between the groups at six months follow-up.

6.1.3 Exploratory endpoints

The following exploratory endpoint will be included in the main publication:
#1. The proportion of participants who self-report smoking abstinence at six months follow-up in clinical subgroups as specified in 6.2.4.
#2. The proportion participants with a recurrent event defined as all-cause mortality or unplanned re-hospitalizations for a cardiovascular disease event (i.e. myocardial infarction, angina/claudication, revascularization procedures, stroke/TIA, arrhythmia and/or heart failure) obtained from hospital medical records after median 18 months follow-up

6.1.4 Secondary and exploratory endpoints for future sub-studies

Planned analyses of other secondary and exploratory endpoints for future sub studies are described under 6.2.5.

6.2 Analyses

6.2.1 Analysis of the primary endpoint

The primary assessment will use an intention-to-treat approach among all randomized participants to evaluate the effects of group allocation on the primary endpoint. Main secondary analyses will use an intention-to-treat approach to evaluate the effects of intervention allocation on the proportion of secondary endpoints among all randomized participants.

The primary endpoint is the proportion who self-report smoking cessation assessed after the last patient included has completed 6 months of follow-up. The null hypothesis is that the proportion of the primary endpoint in the allocation groups are equal. The primary analysis will be a binary

logistic regression model with randomization group as the main covariate. The analysis will be adjusted for site (the stratification factor in the randomization). An odds ratio (OR) for intervention vs control group with a 95% confidence interval (CI) will be estimated, and a P-value for the null hypothesis of a odds ratio equal to 1 will be computed.

Decision rule:

- If the estimated OR is > 1 and the 95% CI does not contain 1, superiority of the intervention will be accepted.
- If the estimated OR is < 1 and the 95% CI does not contain 1, superiority of the control group will be accepted.
- If the 95% CI contains 1, no superiority will be accepted

6.2.2 Analyses of secondary endpoints

The key secondary endpoint and other secondary endpoints to be included in the main publication are listed in section 6.1.2. All dichotomous end-points will be analyzed in the same manner as the primary endpoint, except only the CI will be computed and reported, and not the P-value. Secondary discrete numerical endpoints (mean number of events per participant) will be analyzed with linear regression models, where randomized group and site will be covariates. The estimated difference (intervention - control) with a 95% CI will be reported. The health economic analysis are detailed in 6.2.3.

6.2.3 Additional analyses

Exploratory analysis: Numeric differences in (first and all) recurrent cardiovascular events and all-cause mortality between the intervention and control group will be summarized. Due to an expected high probability of type II error, no statistical comparisons are planned.

6.2.4 Planned subgroup analyses

The following subgroup analyses of the primary study end point are planned in the primary publication:

- Age (</≥ median age)
- Gender (male vs. female)
- Charlson comorbidity score (</≥ median score)
- Acute myocardial infarction or stroke vs. other ASCVD events
- Study site (Drammen vs. Kongsberg vs. Ringerike)

The subgroup analyses will be performed by adding an interaction term in the logistic regression model (as described in Section 6.2.1) between the intervention and the subgroup-defining factor. A P-value ≤ 0.05 for the interaction term will indicate a significant subgroup effect. An OR with 95% CI for intervention vs. control group will be estimated for each subgroup and presented in a forest plot. For age and Charlson comorbidity score, the lowest category will be reference value.

Exploratory analyses in the main publication: Nicotine dependency (Fagerstøm score), Readiness for cessation (Stages of change), motivation (0-10 Likert scale), smoking partner, HADS-score Anxiety and Depression.

6.2.5 Secondary and exploratory endpoints and data to be included in sub studies

The following data will be used in sub studies planned for later publications. Study data and planned analyses are not elaborated in detail as these will not be included in the main publication.

#1 Health economic cost-effectiveness analysis:

We will assess the cost-effectiveness of the intervention by capturing outcomes in terms of life years and resource use (costs). The primary analysis will capture costs and outcomes over the first 16 months. The secondary analysis will cover the patients' remaining life time based on extrapolation of costs and outcomes from the primary analysis.

Primary analysis – cost over 16 months – mean per patient for intervention and control group

- Hospital data on in-patient and out-patient hospital care (costing based on DRG codes)
- Intervention costs
    - Staff
    - Training
    - Materials

Primary analysis – outcomes over 16 months – survival

- Number of life days during the 16 months study period based on day of death if applicable

The main result will be expressed as Net Monetary Benefit.

Remaining lifetime

Survival time in the intervention group and control group will be based on survival in the general population, but adjusted down because patients have already had cardiac disease. The relative survival between the control group and the intervention group will be adjusted based on the relative mortality ratio during the initial 16 months.

The annual cost per patient during the remaining lifetime in the intervention and the control group will be the same as for month 10-16 of the study period adjusting for the higher survival in the intervention group.

Life years, and costs during the survival period until death will be discounted at the recommended discount rate in Norway (4%),

#2. The following long-term outcomes will be analyzed:

-Primary outcome: Time to the first occurrence of any component of the composite endpoint — all-cause mortality, non-fatal myocardial infarction, non-fatal stroke (ischemic or hemorrhagic), coronary revascularization (e.g., PCI or CABG), peripheral artery revascularization, or amputation documented in hospital medical records during a median follow-up of 3.5 years. All events will be adjudicated by a blinded endpoint committee.

-Other outcomes: Time to the first occurrence of any unplanned rehospitalizations subcategorized as (i) cardiovascular admissions, (ii) admissions due to COPD or pulmonary infections, or (iii) other admissions, documented in hospital medical records during a median follow-up of 3.5 years.

#3. Differences between the groups in the proportion of participants who self-report smoking abstinence at six- and 12 months follow-up.

6.3 Missing data

Follow-up is through medical records, telephone interviews, and self-report questionnaires as previously described. We anticipate no missing data on the primary or main secondary outcomes since non-responders to the six-month follow-up interview will be classified as smokers according to the Russel standard.[40] We therefore do not plan to replace missing data in the main publication.

6.4 Harms

6.4.1 Safety endpoints

The primary components of the intervention which is motivational interviewing and a pro-active referral approach do not have effects that could cause any harm to participants. However all patients will have access to free nicotine replacement therapy (NRT) if they choose to participate in the community-based smoking cessation offer. The main concern with NRT in ASCVD patients is that nicotine can elevate heart rate and blood pressure. However, the levels of nicotine provided by NRT are usually lower and more stable than the spikes from inhaling cigarette smoke. Furthermore, clinical guidelines indicates that NRT can be used safely in patients with cardiovascular disease who are trying to quit smoking.[1] Thus, no safety analyses are planned.

6.4.2 Adverse events

All unplanned hospitalizations and all-cause death, including potential endpoints, will be registered from hospital medical records

Tables summarizing adverse events:

- All-Cause Mortality:
- Total number of hospitalizations
- Descriptive statistics will be displayed for continuous data and for categorical data.

6.4.3 Details of guidelines for stopping the trial early

The steering committee recommended not to set any criteria for early termination of the trial as all participants has equal access to the community-based smoking cessation program regardless of group assignment.

7. Data handling and record keeping

Data is collected for participants who enter the randomized phase of the study. All source data will be entered into an electronic data system (Ledidi). The dataset will be prepared and stored at the secured research server in Vestre Viken Trust. This dataset forms the basis for all statistical analyses, which will be performed by the study statisticians in collaboration with the QC statistician. The Oslo Center for Biostatistics and Epidemiology will perform internal database quality-control checks.

8. Supplementary materials

Study protocol evaluated by the ethics committee (ref. number: 270267) and the Data protection officer (ref. number: 21/07103-1 / 005) version 2.0, 31.08. 21 (in Norwegian).

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