ATRIAL FIBRILLATION AND LONG-TERM ECG MONITORING OF HEART RHYTHM IN THE TROMSØ STUDY

Atrial fibrillation (AF) is common and increases the risk of mortality, stroke, heart failure and cognitive impairment. AF imposes significant burden to patients and their families, including reduced life years, health related quality of life, societal health and health economy. One of three AF cases are undiagnosed. Several methods for detection of AF exist, but most of them have major limitations and are associated with resource-demanding diagnostic workup in specialist health care services. This randomized clinical trial will evaluate whether self-screening for AF in patients with increased levels of NT-proBNP utilizing a novel Norwegian patch ECG sensor a) reduces AF-related morbidity and mortality in a well-defined cohort and b) identify factors related to individual risk. Identification of individuals at risk and patient-centered early diagnosis through screening can facilitate a personalized preventive health care approach to improve individual physical health and life quality.

1. EXCELLENCE

1.1. STATE OF THE ART, KNOWLEDGE NEEDS AND PROJECT OBJECTIVES

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 33 million people worldwide.[1] AF increases the risk of ischemic stroke (IS), premature death, heart failure and cognitive impairment and provokes significant societal and health economic burden.[2] The prevalence of AF increases with age, reaching from <1% in people aged < 40 years to between 10% and 17% in those aged > 80 years, with a higher prevalence in men than in women.[3] Known risk factors for developing AF include male gender, age, previous heart disease, hypertension, smoking, alcohol consumption and obesity.[4] Future projections suggest that the burden of AF may increase by >60% in 2050,[5] due to ageing populations and increase in major AF risk factors such as obesity, inactivity, and underlying cardiovascular diseases (CVD).[1] Up to one third of AF cases are undiagnosed due to the intermittent and often asymptomatic nature of AF.[6,7]

Studies have shown that 20-30% of all strokes are attributed to AF and that AF confers a 2-10 fold increased risk of stroke dependent on age and presence of other risk factors.[7,8] AF related stroke is particularly debilitating and potentially lethal because the size of embolism that is caused by a left atrial thrombus may lead to obstruction of larger cerebral arteries.[9] A recent estimation from Sweden calculated 5000 yearly strokes due to AF in Sweden with an estimated annual cost of 7,4 billion SEK.[10] AF is also associated with an up to a 30% increased risk of developing dementia[11], independent of clinical stroke events.[12] Cognitive impairment in AF is likely related to micro-embolic events resulting in subclinical brain lesions (revealed by neuroimaging techniques).[12] However, prior research has reported inconsistent findings on the association between AF and morphological changes linked to dementia detected by brain MRI, such as subclinical cerebral infarction, brain atrophy and white matter hyperintensities.[13,14]

Anticoagulation treatment reduces the risk of IS by 70% in patients with AF and may potentially prevent premature death and cognitive impairment.[7] As a large proportion of AF episodes remain asymptomatic[15], timely diagnosis of AF remains a major challenge in clinical practice and oral anticoagulant therapy is often initiated only after a stroke.[16] Early diagnosis and initiation of anticoagulant treatment is key to prevent mutilating stroke sequalae. The diagnosis of AF is made by recording the heart rhythm with an electrocardiogram (ECG). The ECG can be a single recording, intermittent recordings, or continuous recording for hours or days, and several types of devices for ECG monitoring exist. In patients with intermittent (paroxysmal) AF, the diagnosis is often missed by single or repeated ECG recordings, while prolonged continuous ECG-monitoring improves the detection rate.[17] Long-term assessment of the heart rhythm is usually performed by a conventional Holter monitor system which requires a recording device coupled to electrodes on the chest.[18] Although an important diagnostic improvement when implemented in the 1960ies, the Holter monitoring system usually features brief testing intervals (24-72 hours), is susceptible to

disruptions and have high operational expenses. Because of the latter, there is a scarcity of these devices in numerous hospitals, which frequently results in lower utilization rates than recommended, and consequently extensive waiting lists.[19] Other devices for AF-detection include thumb-ECG devices (TED) and implantable loop recorders (ILR). TEDs have been used in previous cohort studies and AF screening studies, but have limited heart rhythm monitoring time and consequently lower sensitivity to intermittent arrhythmias.[20,21] ILRs have also been used in a previous AF screening study[5] and allow for continuous rhythm monitoring over years, but require surgical procedures. Watches with heart rate monitoring based on arterial pressure waves cannot be used for clinical diagnostics.[7] Another alternative is patch ECG-devices, which in smaller studies have been shown to be well suited for AF screening.[22-24]

AF fulfils most criteria for population screening; a severe and prevalent health problem that can be asymptomatic and for which highly effective treatment exists.[25] Systematic rhythm monitoring can enable earlier detection of AF and initiation of anticoagulant therapy.[26,27] Yet, the cost-effectiveness of AF screening is not settled.[28] In the recently published STROKESTOP trial, a strategy with AF screening by TED twice daily for 2 weeks was found to reduce the composite primary outcome (stroke, systemic embolism, bleeding leading to hospitalization and all-cause death) by 4% and the risk of IS by 8%.[21] In the Danish LOOP study, AF screening with ILR resulted in a three-times increase in the number of AF patients detected and anticoagulation initiated and a 20% reduction in the risk of stroke or systemic arterial embolism during follow-up, which did not reach statistical significance (HR 0.80; 95% CI 0.61–1.05; p=0.11).[29] The European Society of Cardiology recommends screening for AF in people >75 years of age and in patients with increased risk of stroke, but gives no clear recommendations for method and frequency.[7]

The CHA_2DS_2-VASc risk score is based on age and traditional CVD risk factors and is currently used to predict the risk of IS among patients with AF and guide initiation of anticoagulant treatment. The score's predictive accuracy is however modest, with a C-statistic of ~0.6 for prediction of thromboembolism.[30,31] N-terminal pro-B-type natriuretic peptide (NT-proBNP) has emerged as a promising biomarker to improve risk prediction. Previous studies have shown that NT-proBNP is elevated in patients with AF and associated with the risk of stroke.[32] Data from several randomized trials showed that adding NT-proBNP to the CHA_2DS_2-VASc score significantly improved the prediction of stroke in patients with AF.[32-34]

The STROKESTOP II study investigates the potential of NT-proBNP as a stratification tool to improve efficacy of AF screening in a randomized population-based study.[35] High and low risk groups were defined according to a cutoff of NT-proBNP ≥125ng/L. New AF was detected in 2.6% of all patients and 4.4% in the high risk group. A recent subgroup analysis from the randomized LOOP study[36] suggests that in an older population with additional stroke risk factors, ILR screening is associated with a significant reduction in stroke risk among participants with baseline NT-proBNP above median but not among those having lower levels.[36] These results support the potential of NT-proBNP to improve the benefit of AF screening and possibly aid in risk stratification for preventive treatment. However, the utility of NT-proBNP for targeting AF screening and prevention of AF consequences needs to be addressed in well-designed randomized trials.

The risk of IS in patients with AF is presumed to arise from emboli generated by structural and functional alterations within the atria, where a pro-thrombotic milieu is established, particularly in the left atrial appendage.[37] Consequently, a new concept of atrial cardiomyopathy has evolved, defined by complex structural, functional and electrophysiological changes, affecting the atria with the potential to produce clinically relevant manifestations.[38] Several transthoracic echocardiographic parameters have emerged as promising biomarkers of AF. These include left arterial volume and left arterial function assessed by strain which are associated with AF in patients at risk[39,40] and in patients with IS of undetermined source.[41,42] However, knowledge of association between echocardiographic parameters and paroxysmal AF in a general population is limited.

Previous studies report that AF is associated with poor health-related quality of life (HRQoL). However, the factors influencing HRQoL in patients with AF are not well understood. A literature review from 2019[43] concluded that patients with AF had consistently lower HRQoL than healthy individuals and patients with other cardiovascular diseases. The most common factor associated with HRQoL in patients with AF was anxiety-specific. This may be related to both to the increased burden of disease associated with AF and to fear of complications from treatment.[44,45] Effects of AF screening on HRQoL is scarcely mapped and highly relevant when considering the benefits of population based screening.

Several knowledge gaps still exist regarding risk stratification, effectiveness, implementation and outcomes of screening programs for AF. Evidence on optimal screening methods in terms of accuracy, cost-effectiveness and feasibility is lacking. Identification of individuals to target for AF screening is essential and the optimal approach to risk stratification for screening purposes remain unclear. Impact of AF screening on clinical outcomes such as stroke prevention, mortality reduction, cognitive function and quality of life is not fully understood and more evidence is needed to assess the long-term effects on patient outcomes, including potential harms associated with overdiagnosis and overtreatment. Subclinical AF refers to episodes of atrial arrhythmia that are asymptomatic and may only be detected through continuous monitoring. It's unclear whether the detection and treatment of subclinical AF lead to improved outcomes compared to clinical AF or if it carries a similar risk of complications such as IS.

The present project is planned as a sub-study of the epidemiological population-based Tromsø Study. In a randomized controlled clinical trial, we plan to test the primary hypothesis that in individuals with elevated NT-ProBNP who are diagnosed with AF through long-term ECG monitoring, anticoagulation treatment according to international guidelines will reduce the incidence of stroke and cardiovascular death in the screening group compared to individuals who do not undergo screening (control group). The study will be performed within a well-defined cohort with extensive available longitudinal and cross-sectional information on risk factors and co-existing conditions. This setup facilitates addressing several knowledge gaps concerning risk stratification including associations between AF and echocardiographic parameters, cognitive impairment, structural changes on brain MRI, and HRQoL.

1.2. NOVELTY AND AMBITION

This project has the potential for providing new knowledge related to the benefit of a stepwise screening approach for AF according to NT-proBNP level, utilizing a novel patch monitor with continuous ECG monitoring and automatic artificial intelligence based (AI) ECG analysis. It can contribute to the identification of a population that is more likely to benefit from AF screening and address the usefulness of CHA_2DS_2-VASc and other novel biomarkers including echocardiographic parameters in the current risk factor era.

The Tromsø Study is an internationally recognized and leading epidemiological study. Data collection includes questionnaires, medical interviews, blood tests and comprehensive clinical examinations with echocardiography, respiratory testing, cognitive testing and MRI of the brain.[46,47] Many participants have attended previous surveys of the Tromsø Study and thus repeated measures are available for several individuals. This approach enables us to identify individual phenotypes with increased risk of AF and AF complications. Information on incident stroke, myocardial infarction, and cause-specific deaths in the participants are obtained through annual linkage to the national registries (the Norwegian Stroke Registry, the Norwegian Myocardial Infarction Registry and the Causes of Death Registry). The combination of clinical data including imaging data with the extensive data collection on both exposure and outcome variables and cross-links between the various sub-projects of the Tromsø Study provides a rich datasource for research, with the potential for several future PhD and postdoc-projects.

Our project group collaborates with major projects within the national AFIB network investigating different aspects related to AF screening and risk stratification. Outcomes in the proposed study are harmonized with these projects, enabling data merging to address central knowledge gaps in larger datasets.

The project focuses on addressing challenges on the path towards a user-centered and sustainable healthcare service through collaboration and use of new technology. The project will provide new knowledge on the utility of novel diagnostic tools for continuous ECG monitoring analyzed with AI based algorithms with high sensitivity and specificity and whether this tool can simplify AF screening, and may thus impact future planning of AF screening. Through the project we will identify biomarkers that would allow stratification of individuals with respect to screening, medical treatment, enable individual precision-based medicine, and ultimately reduce stroke events, with great benefit to patients and the health care system.

1.3. RESEARCH QUESTIONS AND HYPOTHESES, THEORETICAL APPROACH AND METHODOLOGY

The significance and originality of the proposal:
We propose to perform a randomized controlled screening trial within the Tromsø 8 population-based cohort study, applying monitoring of heart rhythm with leading sensor technology (ECG247) in participants with elevated levels of NT-proBNP. We will add important data to ongoing screening trials by including comprehensive clinical assessments of included subjects. The overall aim of the project is to assess the primary hypothesis that continuous ECG-monitoring in individuals with elevated NT-pro-BNP and subsequent anticoagulant treatment according to current international guidelines leads to reduced incidence of the composite outcome ischemic stroke and cardiovascular death.
The work performed by the PhD student for which we seek funding by this application will create new knowledge related to:

1) the age and sex specific prevalence of various burdens of AF (duration, frequency, heart rate and symptoms) and association with repeated measured risk factors in the Tromsø Study
2) the association between AF and echocardiographic parameters
3) the association between AF, findings on brain MRI and results of cognitive tests
4) participants perception of health-related quality of life before and after AF detection by continuous ECG monitoring

The specific research questions which will be addressed in the present PhD project are:

Question 1: What is the age and sex specific prevalence of paroxysmal AF (considering duration, frequency, heart rate and symptoms) and its association with repeated measured cardiovascular risk factors among Tromsø Study participants with elevated levels of NT-Pro-BNP?
Question 2: Can the presence and burden of AF (duration, frequency, heart rate) in the general population with elevated level of NT-ProBNP be predicted by comprehensive echocardiographic evaluation?
Question 3: Is atrial fibrillation associated with cognitive test performance in subjects with elevated NT-proBNP and is this association modified by specific MRI findings?
Question 4: Does detection of AF by continuous ECG monitoring influence health related quality of life?

The project is planned as a randomized controlled screening trial within the 8th survey of the Tromsø Study (T8), which will be ongoing from March 2025 through 2026. All participants will be invited to complete a questionnaire covering lifestyle, HRQoL, risk factors, as well as simple clinical examinations such as height, weight, ECG, blood pressure, and blood tests. Subsets of up to 10 000 participants will be invited to a second visit to undergo more comprehensive examinations, including extended blood tests with NT-proBNP measurements, cognitive tests, MRI of the brain, and echocardiography of the heart. In the planned trial we aim to include 4000 individuals with NT-proBNP above median without previous known AF or ongoing anticoagulant treatment. Participants will be randomized 1:1 to continuous ECG monitoring using the Norwegian produced ECG247 sensor. ECG247 is an efficient, user-friendly and cost-effective continuous ECG monitor approved for both self-testing and use in health care settings.[48] The sensor is connected to the

individual participants' smartphone (Bluetooth technology) and has a flash storage if the smartphone is not available. Single lead ECG data is sent to a cloud-based server intermittently. The system stores information of ECG quality and is evaluated by trained algorithms which classify arrhythmias based on current criteria. The stored data is easily available for the research group, and interpretation, validation, and reclassification if needed. The system fulfills all regulations for a screening tool, as well as handling of sensitive data. Immediate feedback based on an AI based algorithm for analysis will be provided via an app on the participant smartphone if heart rhythm disturbances are detected. ECG247 has been shown to have at least as good diagnostic accuracy for AF and improved user-friendliness compared to conventional Holter technology, enables long-term monitoring and can improve the detection of AF.[48] In most cases, the interpretation is simple and can be performed by other professionals than cardiologists.[49]

Figure 1: Illustration of ECG247 practical setup, modified from www.ecg247.com

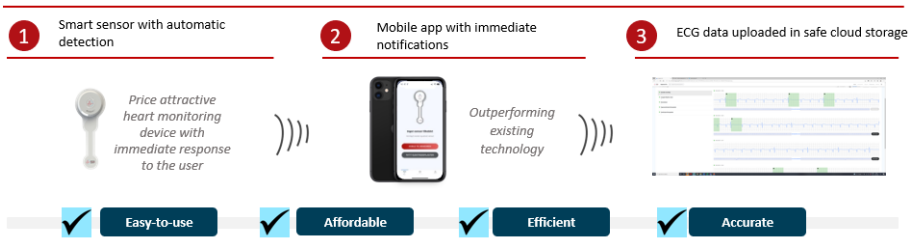

Figure 1: Illustration of ECG247 technical setup, modified from www.ecg247.com

The study design enables cross-sectional and longitudinal assessments of associations between AF and repeated measured traditional risk factors, echocardiographic measures, findings on MRI of the brain, and results of cognitive tests. Long term follow-up enables comparison of the group undergoing ECG247 monitoring to those who have not undergone ECG247 monitoring regarding clinical outcomes (after 6 years).

Study population: A total of 4000 individuals from the general population with NT-proBNP> median fulfilling the inclusion criteria will be included after informed consent for study participation.

Inclusion criteria:

- Age ≥40 years
- NT-proBNP> median level
- Informed consent for participation

Exclusion criteria:

- History of AF (self-reported)
- Use of anticoagulation therapy
- Pacemaker/CRT device
- No available smart phone

Study procedure: Individuals with NT-proBNP > median will be identified when attending the second visit of the Tromsø Study. Eligible participants will be included and automatically randomized (1:1) to ECG247 monitoring or no ECG monitoring. Participants not responding will receive two reminders. Invitation will continue until 4000 study participants have been included.

Intervention: The AF screening device will be sent by post from the study centre to all participants in the intervention group at inclusion, free-of-charge. User guides (paper, digital and video) will be prepared (Norwegian and English), and an "help-desk" located at the Tromsø Study will be available for phone/video assistance. The monitoring of included participants will be handled by trained research nurses. All participants will be requested to fill in a digital questionnaire after having completed the test focusing on usability and adverse events. All ECG recordings will be reviewed by a group of trained and experienced study nurses and physicians. Cardiologists will supervise and verify pathologic ECG findings. The following variables will be registered: Heart rhythm (sinus rhythm, AF, atrial flutter, supraventricular tachycardias (SVT),

ventricular arrhythmias, SA/AV-block, and other arrhythmias), timing, duration, heart rate of arrhythmias, symptoms and duration of the heart rhythm recording. All study participants will receive information about the test results. A new assessment of HRQoL and medication is planned 6 months post intervention. Initiation and adherence to anticoagulation therapy will be assessed both by questionnaires and by linkage to the Norwegian Prescription Register. Incidence of stroke, cardiovascular and all-cause mortality will be obtained from the Tromsø Study through linkage to national registries.

Safety: In the event of clinically relevant arrhythmias, participants will be contacted as soon as possible. Feedback to the participants will be provided by specially trained physicians and nurses. Participants diagnosed with cardiac arrythmia or other cardiac abnormal findings will receive advice on follow-up with their general practitioner or be referred to a cardiologist depending of type of arrythmia. Anticoagulation therapy and other treatments will be recommended if indicated according to current guidelines. The study centre will assist participants who need help to book an appointment for further assessments in cases where this is necessary. An information video about AF will be made in collaboration with the National Association for Heart and Lung Diseases (LHL) to provide general information about AF and potential benefits and risks related to anticoagulant treatment.

Definition of outcomes and other variables of interest: Definition of AF outcome for research question 1 and 2: Paroxysmal AF will be defined as the presence of AF episodes ≥30 seconds. In addition, we will register total time in AF (AF burden), beats per minute and concomitant symptoms. Similarly, other tachycardias as atrial flutter (≥30 seconds), supraventricular and ventricular tachycardias (cut-offs ≥15 seconds and 5 complexes) will also be registered. Initial evaluation will be performed by specially trained research nurses. All positive findings and a similar number of negative tests will be evaluated by a blinded end-point committee of three experts. In case of disagreement the majority will define classification of the outcome. Cognitive test performance outcome for research question 3: Scores on the 12-word immediate recall test, the digit symbol coding test and the Mini-Mental State Examination (MMS-E). AF outcomes will be as for question 1 and 2. "Health related quality of life (HRQoL)" outcome for research question 4: A single summary index value (utility score) using a predefined scoring algorithm of the HRQoL EuroQol-5 Dimension (EQ5D) and health anxiety using the Whiteley Index. EQ5D is a standardized instrument developed by the EuroQol group to measure HRQoL and consists of two parts a descriptive system comprising five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and visual analog scale measured ranging from 0 to 100 where patients rate their perceived health status, with 0 being "worst imaginable health state" and 100 being "best imaginable health state." Whiteley Index consists of 14 items, and participants respond on a scale from "not at all" to "very much" or similar gradations.

Relevant echocardiographic variables are atrial size (LAVI, Left Atrial volume Index) and atrial strain (LA reservoir strain). Relevant MRI measures are global and segmental atrophia, volume of white matter lesions, size, presence and number of clinical and subclinical infarcts and micro hemorrhages.

Statistics and analyses: The associations between the primary outcome defined as AF presence(yes/no) and AF burden (number of hours with AF) and prespecified risk factors (traditional CVD risk factors and novel echocardiographic measures) will be examined using multiple regression analyses taking repeated measures within individuals into account by the use of generalized linear mixed effect models and linear mixed effect models, respectively. Linear and logistic (binary or ordinal) regression models with adjustment for relevant confounders will be chosen as appropriate when examining the cross-sectional associations between cognitive test performance and HRQoL outcomes and AF depending on the type of outcome variable (continuous, dichotomous or ordinal). Incidences will be reported as the number of events per 100 years at risk. Censoring for the composite outcome will be done at an event, death of other cause or end of follow-up. Hazard ratios (HRs) will be obtained by Cox regression with adjustment for relevant cofactors. Suitable statistical software will be used for analyses and an experienced statistician will be consulted.

Power estimates: Power estimates are customized to test the primary hypothesis that continuous ECG-monitoring in individuals with elevated NT-proBNP and subsequent anticoagulant treatment according to current international guidelines leads to reduced incidence of the composite outcome IS and cardiovascular death. According to a previous study performed at Sørlandet[50] with ECG247 the number needed to screen was 45 to detect one unrecognized case of AF in subjects at risk for stroke. When restricting screening to the population with NT-proBNP level > median the number needed to screen may be reduced to 31[36] and even 23[35] in an older population. The 6-year risk of the composite outcome is expected to be 4% in the control group. Risk in the group screened where no AF is found varies from 2 to 3%. In the group screened where AF is found the risk is 10% (30% risk of IS during a 6-year period, reduced by 70% with oral anticoagulant therapy). If the 6-year risk among screened participants without AF is 2,2%, and we include 2000 participants in each group, there is 80% power to detect a significant difference (α=0.05) between control and intervention groups with estimated risk of 4.0% vs. 2.4% for the composite outcome, respectively. Based on the results of the Loop and StrokeStop study and the younger population in the Tromsø study, we expect to reduce risk of the composite outcome from 4% in the control group to 2.4% in the screening group. Compared to previous epidemiological studies, the planned epidemiological projects for the PhD student will have sufficient statistical power to explore meaningful associations.

Data handling and storage: EUTRO is a research administrative tool that will be used for data collection and storage in Tromsø 8. EUTRO provides a complete overview of a study's total research material, including responses to questionnaires, biological material, health data, and project information. EUTRO is integrated within TSD (services for sensitive data located at University of Oslo) which assures and facilitates anonymized data handling and storage according to present regulations and research needs. All data security is taken care of according to the requirements from the Norwegian Data Protection Authority, and privacy is well maintained in the system. The system ensures compliance with the Health Research Act and GDPR requirements for security, handling, and administration of sensitive research data and biological material.

Ethics: Separate applications for approval will be sent both for the Tromsø study as a whole and for the present study. Participants must give an informed signed consent before data collection. The study will be conducted in accordance with the Declaration of Helsinki. We will provide relevant feedback to all participants with specific recommendations including how to follow-up positive results. Participants diagnosed with cardiac arrythmia or other cardiac abnormal findings will receive advice on follow-up. The participant will either be referred to follow-up with their general practitioner or the study team will refer him/her to a cardiologist if indicated. Advise on starting anticoagulant treatment will comply with current guidelines. Appsens AS developed, manufactures and distributes the ECG247 smart heart sensor. Disclosures related to Jortveit being both employer and shareholder in Appsens, as well as inventor will be handled accordingly. No Appsens-affiliated personnel will be involved in data analyses.

Risks and mitigation: • Patients from the Tromsø 8 study may not be willing to participate. Mitigation: A high percentage of patients invited to follow-up studies in previous Tromsø studies attended. Randomization will continue until the planned number of included participants is met • Patients do not have access to smartphones needed for communication between the sensor and the ECG247 platform. Mitigation: We will provide some smartphones for loan to participants in need in the T8 study. • Too optimistic power calculations if the prevalence of AF is lower than expected and the risk of the composite outcome in the included population is lower than expected. Mitigation: The completion of the PhD thesis is not reliant on collection of the composite outcome at after 6 years follow-up.

Gender perspective: Both women and men will be invited to participate in the study. Analyses will be performed sex-adjusted and/or stratified by sex. The research group consists of both female and male researchers. In line with the project owner's gender policy, women will be encouraged to apply for PhD fellowship and preferred if qualifications are otherwise equal.

2. IMPACT

2.1. POTENTIAL IMPACT OF THE PROPOSED RESEARCH

The study will provide new knowledge about risk factors, clinical findings and co-existing comorbidities in individuals that are associated with both increased risk of AF and clinical events. Hence, the study can contribute to identifying new targets and better tools for a more effective, precise and personalized prevention of stroke in patients with AF and provide knowledge about risk groups where long-term ECG monitoring would be beneficial. The project will provide novel insights into the impact of screening on HRQoL in participants who have AF confirmed through screening. In addition, the study will provide data on the prevalence of paroxysmal AF and AF burden detected by new sensor technology both being highly relevant outcomes and risk factors for future Tromsø-Study projects.

In the long term, we will generate new knowledge on whether AF screening utilizing patients centered novel sensor technology in participants with elevated level of NT-proBNP is beneficial for patients' outcomes. The study may impact future European guidelines for the prevention and treatment of AF.

The proposal adds clinical experience and skills related in the use of sensor technology for home-based monitoring of cardiac patients and patient-administered heart rhythm examinations without the need for hospital visits. Hence, more patients may gain benefit from this cost-effective and sustainable non-invasive approach for AF detection. Reducing the need for healthcare resources, transportation, hospital stays away from home and work has the potential of moving health care towards more precise diagnostics and equal care in a sustainable manner, and also be beneficial for health-related costs and the environment.

Using new sensor technology, some participants will through the trial be diagnosed with AF, that they were previously unaware of. This enables initiation of effective preventive treatment that reduces the risk of stroke. Successful self-screening makes AF screening possible at a population level, and consequently has a potential to prevent mortality and severe AF-related morbidity.

Enhanced disease characterization can lead to more precise and personalized clinical decisions. Streamlining heart rhythm monitoring could reduce the need for time-intensive, repetitive manual tasks and patient transportation to hospitals, thereby enhancing both the efficiency and sustainability of healthcare. This is particularly relevant to the United Nations' Sustainable Development Goal 3 (Good Health and Well-being; specifically target 3.4, which aims to reduce premature mortality from non-communicable diseases by one third by 2030 through prevention and treatment, and to promote mental health and well-being), Goal 5 (Gender Equality), Goal 10 (Reduced Inequalities), Goal 11 (sustainable cities and human settlements).

2.2 MEASURES OF COMMUNICATION AND EXPLOITATION

Our goals for communication, dissemination, and engagement are to keep each stakeholder up to date and engaged for the recruitment, continuation, and implementation of the study outputs. Communication and dissemination activities will be conducted by all members of the study group. We anticipate that the findings will capture significant interest from both the media and patient organization. Study results are relevant to patients, health care providers and policy makers. Participants will be informed via letters and websites. In collaboration with the patient's organization LHL we plan to make an information video about AF including general information and information about potential benefits and risks related to anticoagulant treatment. Results are communicated to researchers and healthcare professionals through scientific publications, conferences, regional and national meetings. Information is shared with the public via social media, podcasts, and news reports. Decision-makers and politicians will be informed through information meetings. The LHL will use own information channels (including lhl.no) to disseminate the study's results.

3. IMPLEMENTATION

3.1. RESEARCER AND PROJECT GROUP

This study is based on a broad multidisciplinary collaboration and a synergistic integration between researchers and clinicians is facilitated by the closely located, large multi-disciplinary research environments at the University Hospital of North Norway (UNN) and The Arctic university of North Norway (UiT). The main responsibility for planning and implementation of the study lies at the Department of Neurology, UNN and Institute of Clinical medicine, UiT, with significant contributions from the Institute of Community Medicine, UiT and the Department of cardiology, UNN. Eltoft, senior consultant at the Department of Neurology, UNN, associate professor at the department of Clinical Medicine, UiT, will chair the planned project and serve as the main supervisor. She has completed an epidemiological PhD based on data from the Tromsø Study and was as trial officer part of the management of a large randomized controlled multicenter clinical trial. She is the local principal investigator (PI) for several clinical stroke trials ongoing at UNN and ongoing supervisor for several master and PhD students.

The project group possesses long experience in research project management and has a firm background in clinical research and epidemiology. The project organization ensures a solid foundation for research collaboration and knowledge transfer between the specialist healthcare, primary healthcare and health care planners. The project will be an important meeting place and can provide experience and contacts in planning future research projects. The projects approach facilitates a strong, long lasting and interdisciplinary regional and national research environment anchoring:

Ellisiv B. Mathiesen (Head of Brain and Circulation Research Group, UiT), Maja-Lisa Løchen (Head of Department, Department of Clinical Medicine, UiT), both with extensive experience from the Tromsø Study and AF research. Ekaterina Sharashova (assoc. professor, Dept. of Community Medicine, UiT and principal investigator of the project "Atrial fibrillation in the Tromsø Study 1986-2017: incidence trends, contribution of risk factors and prognostic outcomes"), Hilde Espnes (MD, PhD candidate), Assami Rössner (cardiologist responsible for echocardiography examination in T8) and Iina Marja Javo (consultant cardiologist, UNN), Erin Hald (hematologist, UNN involved in AF research). The last three mentioned participants also hold positions as assoc. professors, Dept. of Clinical Medicine, UiT. Jannike Ringstad is user representative from LHL.

A broad national collaboration is assured by including leading capacities within the field in the project group, namely Halvor Øygarden and Jarle Jortveit (Sørlandet Sykehus) involved in the AF-study and NORSCREEN, Jon Magne Letnes and Håvard Dalen (HUNT/NTNU) chairing AF-studies in HUNT, Håkon Ihle Hansen (Vestre Viken), Guri Hagberg (OUS) involved in AF-studies in ACE 1950. In addition, Renate Schnabel (University Heart Centre Hamburg) is an international collaborator with expertise on AF and biomarkers.

3.2 PROJECT ORGANISATION AND MANAGEMENT

The role of the PhD candidate: The PhD candidate will be recruited and employed in a 50% position from April 2025. Prior to start all relevant approvals (REC and PVO) will be obtained by the project leader. The PhD candidate will work in close collaboration with the Tromsø Study group, utilizing available infrastructure provided by the Tromsø Study. Tromsø 8 starts in march 2025 with the first visit. 10,000 participants will subsequently be invited to visit 2 starting in April 2025, where NT-proBNP is measured. Based on NT-ProBNP results, participants will be selected and long-term recordings with ECG247 are conducted. The infrastructure at T8 will be essential for conducting blood tests and ECG247 sensor logistics. The management of the ECG247 sensor monitoring is performed by specially trained nurses, but the PhD candidate will be involved in this work to have first line details of the workflow. Postal deliveries of sensors for self-administration will be performed together with the research nurses. General feedback to the Tromsø participants will be standardized and provided electronically. The PhD candidate will under supervision develop an information video in collaboration with LHL. The PhD candidate will organize the data bases and perform data analyses,

drafting and revision of manuscripts according to timeline presented the electronic application form and Gantt chart below. The candidate will be affiliated with the research group Brain and Circulation at UiT and have a shared office space with other PhD students. The candidate will join the national AFIB network (afib.no) and the Norwegian PhD school of heart research (NorHeart (norheart.no)). The four manuscripts of the PhD project will address research questions 1-4 and will be published in international peer-reviewed journals. Furthermore, the PhD student will participate in the PhD program for medicine and health sciences at UiT, which includes completing at least 30 credits of required coursework.

Gantt chart of study timeline	**2025**				**2026**				**2027**				**2028**				**2029**				**2030**				**2031**		
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3
Participant recruitment and data collection																											
Mandatory PhD courses																											
Data analysis, drafting, and publication article 1																											
Data analysis, drafting, and publication article 2																											
Data analysis, drafting, and publication article 3																											
Data analysis, drafting, and publication article 4																											
Communication and dissemination																											
Writing, submission of thesis and dissertation																											

User involvement: LHL provides knowledge from the patients' perspective for the studies' design, planning and performance. LHL has been involved in planning of the specified study. Their contribution to the assessment of health-related life quality of life has been valuable and impacted on the project's objectives. They will be included in ongoing discussion related recruitment enhancement, information to the participants as well as experience with the use of ECG247 sensors for monitoring. LHL will also be actively involved in discussion and dissemination of the results. The research staff will participate in meetings arranged by LHL to present relevant findings. These face-to-face meetings will provide valuable feedback to optimize research and clinical implementation towards what is most important for patients with AF and stroke.

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