CLINICAL INVESTIGATION PLAN

Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness

LAGOM

CIV- 24-09-049056

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Sponsor: Västra Götalandsregionen

Sponsor representative and
Coordinating Investigator: Hemen Najar

Revision history

Document version	Date of Issue	Summary of Change
2.0	2024-12-06	The addition of a fifth exclusion criterion: 5) Currently under compulsory care. This change should be reflected on page 10 (under Section 1: Synopsis) and page 22 (under Section 6.3.2: Exclusion Criteria). The addition of: 5) Under behandling med tvångsvård. This change should be reflected on page 13 (under Section Synopsis på Svenska).
3.0	2025-06-10	Correcting the order of the references. Principle investigator has been changed for Öster to Lina Klysing and for Nordost to Elin Saari-Bladmyr. ”psychiatric outpatient clinics” has been changed to “psychosis outpatient clinics” in the synopsis. “Descriptive cost” has been modified to “cost” throughout the document. “Accredited translators” has been changed to “Accredited interpreters” throughout the document” “At the first baseline” has been changed to “Before the first baseline.” throughout the document. **Section 6.5, under care as usual:** “Care as usual takes place over two visits, with some days' interval between them. During the first visit, which lasts approximately 45 minutes, the patient meets with the case manager. At the second visit, which also lasts approximately 45 minutes” Has been changed to: “Care as usual takes place over two visits, which take place within 45 days. During the first visit, which lasts approximately 60 minutes, the patient meets with the case manager. At the

		second visit, which also lasts approximately 60 minutes” Following text has been added: ”The blood test and physical examination provide the cardiometabolic risk indicator values relevant to this clinical trial. Only indicators obtained within the defined visit window will be included. This visit window spans 45 days before and after the second visit of the annual health check, which involves the physician. The window is designed to accommodate the realities of clinical practice, where it may not always be feasible for patients to complete the blood test or physical examination on the scheduled day. This flexibility ensures alignment with routine care. If a patient completes the blood test or undergoes the physical examination after the second visit, a follow-up physician visit is required to review the results and implement necessary management measures.” “As part of care as usual, the case manager sends all patients with self-assessment questionnaires (EQ-5D-5L, AUDIT-C, and a questionnaire on eating habits to be filled at home) and a letter with instructions for blood sample preparation” Has been changed to: “As part of care as usual, the case manager prepares for the annual health check by ordering blood tests, beginning to fill in the worksheet, and sending a letter to the patient with instructions for blood sample preparation. Depending on the case, the case manager may also send the patient self-assessment questionnaires (EQ-5D-5L, AUDIT-C, and a questionnaire on eating habits to be completed at home)” The section describing the data collection procedure for the control group has been moved to follow directly after the description of care as usual, to improve the logical flow. Visits 1, 3, 5, and 7– “Two weeks before the annual health check with the physician” has been changed to “The annual health check with the case manager” Visits 2, 4, 6, and 8 – “The annual health check with the physician” has been changed to “The annual health check with the physician and case manager” Visit 1: A text clarification has been made, that written consent is obtained during the annual health check. “The participant completes the control version of the worksheet and undergoes a somatic examination, as outlined in Table 1, conducted by the case manager.” Has been changed to “The participant is interviewed according to the control version of the worksheet and undergoes a somatic examination, as outlined in Table 1, conducted by the case

		manager." Following text has been added: "In preparation for Visit 1, the case manager begins filling the worksheet for the annual health check by gathering information from various sources, including medical records, telephone interviews with the participant, or the case manager's or physician's prior knowledge of the patient." **Section 6.5, under intervention group:** "After informed consent, the case manager will interview the participants with the intervention version of the worksheet." Has been changed to "After informed consent, the case manager will continue interviewing the participants and fill in the intervention version of the worksheet." A repetitive paragraph has been removed. Visits 1, 8, 15, and 22: – "Two weeks before the annual health check with the physician" has been changed to "The annual health check with the case manager" Visits 2, 9, 16, and 23 – The annual health check with the physician. "and the case manager" has been added. Under Visit 1: "At this visit, patients are screened for eligibility. If eligible, they are invited to join the intervention group by a member of the clinical trial team, and written consent is obtained. The participant completes the intervention version of the worksheet and undergoes a somatic examination, as outlined in Table 1, conducted by the case manager. A blood test is ordered according to clinical practice and should be completed before the baseline visit. The blood sample is collected following the standard clinical procedure used during routine annual health checks. Participants are examined using a body composition analyzer and complete the QRISK3 assessment with their case manager, as outlined in table 1." Has been changed to "The same routine as in Visit 1 (baseline) for the control group, except for inviting to the intervention group and using the intervention version of the worksheet. If written consent is obtained, the participants are examined using a body composition analyzer by their case manager, as outlined in table 1. No study-specific procedures are

		conducted before informed consent is obtained. However, in preparation for Visit 1, the case manager begins filling the worksheet for the annual health check by gathering information from various sources, including medical records, telephone interviews with the participant, or the case manager's or physician's prior knowledge of the patient." Following text has been added to visit 2: "The physician fills in the QRISK3 algorithm with the participant." **Section 7.4:** "the number of completed medical history protocols" has been changed to "the completed worksheets" **Section 8.3:** Following text has been removed "within one week" and the following text has been added: "The first and second checks are performed within 45 days of the second visit of the annual health check. However, during summer, Christmas, and other national holidays, these routines may require additional time due to limited staff availability and scheduling constraints." **Section 9.1:** "One week" has been changed to "45 days" **Section 14.1:** "during the annual health checks" has been added to the sentence "If they are eligible, they will be invited to participate in the clinical trial" in the first paragraph.

3.1	2025-10-21	"Care as usual" has been changed to "usual care" throughout the document. The terms *"intervention group"* and *"control group"* have been revised to *"intervention clinics"* and *"control clinics,"* respectively, where applicable. This change was made to improve clarity and accuracy in describing the trial's cluster-level design. The adjustment has been applied selectively—only in contexts where *"intervention clinics"* and *"control clinics"* more appropriately reflect the organizational level of the intervention rather than the individual participant level. Table 1 Changing "eating habits" to "Dietary habits" An update was made to specify the timing of data collection

		for “Questions about participation in educational sessions and lifestyle sessions.” These assessments occur at baseline, 12 months, 24 months, and 36 months. This information had been omitted in previous versions of the CIP and has now been added for completeness and clarity. 6.3.2 Exclusion criteria Exclusion criteria, “Deemed unsuitable for inclusion at the discretion of the investigator” and “Previous participation in the clinical trial” have been clarified.

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Signatures

Sponsor

I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical trial. I will submit the CIP and all other important clinical investigation-related information to the responsible investigator(s) so that they can conduct the clinical trial correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical trial informed and trained.

Sponsor representative and Coordinating Investigator signature Date

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Hemen Najar

Principal Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical trial. By signing my name below, I agree to conduct the clinical trial in compliance with this Clinical trial plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical trial.

I will submit this CIP and all other important clinical trial-related information to the staff members who participate in this clinical trial, so that they can conduct the clinical trial correctly. I am aware of my responsibility to continuously keep the staff members who work with this clinical trial informed and trained.

I am aware that quality control of this clinical trial will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator’s signature Date

Printed name

Contact information

Role	
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Monitor	To be decided

Funding and research agreement

This is an investigator-initiated clinical trial without any assistance or input from any company.

The clinical trial has got research grants from Sahlgrenska University Hospital's foundations, Göteborgs Läkaresällskap, Innovation fund, and Wilhelm and Martina Lundgren's Science Foundation as well as from Västra Götalandsregionen and Sahlgrenska University Hospital. We will even apply for funding from ALF-medel and Forte.

The clinical trial will be held in 6 outpatient clinics belonging to the Department of Psychotic Disorders in Gothenburg. No site agreement will be signed, as it is the same manager who is responsible for the study being carried out at all 6 sites.

List of used acronyms and abbreviations

Abbreviation	**Term/Explanation**
ADE	Adverse Device Effect
AE	Adverse Event
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
B-HbA1c	Blood Hemoglobin A1C
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index

BMR	Basal Metabolic Rate
Case manager	The person responsible for coordinating the patient's care and treatment. This role may be filled by a nurse, assistant nurse, occupational therapist, or social worker
CE	Conformité Européenne, which is French for "European Conformity"
CIP	Clinical Investigation Plan
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DD	Device Deficiency
eCRF	electronic Case Report Form
Euro	the single European currency
FFM	Fat-Free Mass (FFM)
fP-TAG	fasting Plasma Triacylglycerol
IB	Investigator's Brochure
ICD	International Classification of Diseases
ID	Identification
ICER	Incremental cost-effectiveness ratio
IFU	Instructions For Use
ISF	Investigation Site File
LAGOM	Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness
MAR	Missing At Random
MCAR	Missing Completely At Random
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MI	Multiple Imputation
ML	Maximum Likelihood
MNAR	Missing Not At Random
P-ALP	Plasma Alkaline Phosphatase
P-ALT	Plasma Alanine Transaminase
P-AST	Plasma Aspartate Transaminase
P-CRP	Plasma C Reactive Protein
P-HDL-C	Plasma High Density Lipoprotein Cholesterol
P-LDL-C	Plasma Low Density Lipoprotein Cholesterol

P-TChol	Plasma Total cholesterol
QALY	Quality-Adjusted Life Year
REDCap	Research Electronic Data Capture
Research team	The research team is comprised of research nurses, research assistants, case managers, psychiatrists, physiotherapists, and licensed psychologists
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCORE2	Systematic COronary Risk Evaluation 2
SS-EN ISO	Swedish Standard - European standard International Organization for Standardization
UKCA	United Kingdom Conformity Assessed
WHR	Waist-hip ratio

1. Synopsis

Background and rationale:	Cardiometabolic diseases are prevalent among individuals with psychotic disorders, significantly contributing to their shorter lifespan, reduced quality of life, and economic impact on individuals and society. To improve cardiometabolic health, effective and individualized interventions are crucial. Psychosis outpatient clinics are ideal for these interventions due to regular patient visits and the availability of diverse health professionals. We have developed and want to test a comprehensive intervention program to improve cardiometabolic health, enhance quality of life, and promote healthy lifestyles specifically for people with psychotic disorders at psychosis outpatient clinics in Gothenburg. This longitudinal, multicenter, naturalistic, multicomponent, parallel-group, quasi-experimental, superiority, case-control study, LAGOM (Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness) aims to include 644 individuals with psychotic disorders from six outpatient clinics in the Department of Psychotic Disorders at Sahlgrenska University Hospital in Gothenburg. Two outpatient clinics will provide the LAGOM-intervention, while the other clinics will serve as controls, offering "usual care". The intervention group

	will receive multidisciplinary support integrated into the routine clinical procedures. The intervention includes regular follow-ups and use of motivational tools, including body composition analyzer and cardiovascular risk prediction algorithm (QRISK3). If the intervention effectively improves cardiometabolic health, enhances quality of life for this vulnerable group, and proves cost-effective, it can serve as a model program for implementation in Region Västra Götaland.
Investigational device:	In this clinical trial, we will use two investigational devices that are also visual in the sense that they can create a shared picture, between participants and healthcare providers, of the participants' well-being. These devices are motivational tools and are focused on cardiometabolic health, in line with the project's overall purpose. These are called QRISK3 algorithm and TANITA body composition analyzer, a special type of scale that gives a more holistic view of body composition.
Number of participants:	644
Inclusion criteria:	1) Adults, ≥18 years, meeting ICD-10 diagnostic criteria for any one of the schizophrenia spectrum disorders (F20-F25 or F28-F29). 2) Has the ability to sign informed consent.
Exclusion criteria:	1) Having an electrical medical implant like pacemaker or other mechanical implants. 2) Pregnant women. 3) Deemed unsuitable for inclusion at the discretion of the investigator. 4) Previous participation in the clinical trial. 5) Currently under compulsory care.
Study objectives:	Primary objective: To evaluate whether the intervention is superior to usual care in lowering levels of cardiometabolic risk indicators after 36 months. Secondary and exploratory objective(s): To assess if the intervention is superior to usual care in lowering the risk of cardiovascular disease (CVD) after 36 months. To evaluate whether the intervention is superior to usual care in enhancing the quality of life (EQ-5D-5L) after 36 months.

	To evaluate whether the intervention reduces high-sensitivity CRP and HbA1c after 36 months. To determine the cost per participant and perform a cost-effectiveness analysis where cost neutrality for the intervention is a positive outcome. To evaluate whether the intervention improves the targeted lifestyle after 36 months. To explore the total number and the type of intervention sessions, and the average time interval between consecutive sessions needed per year to achieve a change in the targeted lifestyle. To investigate whether participation in educational sessions by participants and their relatives will motivate participants to adopt a new lifestyle

Study endpoints:	Primary endpoint:
	Cardiometabolic risk indicators:
	• Body mass index (BMI) (kg/m^2)
	• Waist-hip ratio (WHR)
	• Systolic blood pressure (SBP) mm Hg
	• Diastolic blood pressure (DBP) mm Hg
	• Triacylglycerol/high density lipoprotein-cholesterol ratio (TAG/HDL-C ratio)
	• Total cholesterol/HDL-C ratio (TChol/HDL-C ratio)
	• Plasma glucose (mmol/L)
	
	Secondary and exploratory endpoint(s):
	• CVD events or reduction in CVD risk scores according to SCORE2
	• Blood samples
	  ○ High-sensitivity CRP (mg/L)
	  ○ HbA1c (mmol/mol)
	• Questionnaires
	  ○ Quality of life according to EQ-5D-5L
	  ○ Alcohol habits according to AUDIT-C
	  ○ Tobacco habits
	  ○ Eating habits
	  ○ Physical activity
	• Cost-utility analysis
	  ○ Cost description in SEK and EURO
	  ○ Quality-Adjusted Life Years (QALYs) at baseline and at 12, 24, and 36 months

	○ Incremental cost-effectiveness ratio (ICER), comparing the costs between the control and intervention groups at baseline and after 36 months
Planned duration of the clinical trial:	Q1 2025 – Q4 2029

Synopsis på Svenska

Bakgrund and rational:	Kardiometabola sjukdomar är utbredda bland personer med psykossjukdomar, vilket väsentligt bidrar till deras kortare livslängd, minskade livskvalitet och ekonomiska påverkan på individer och samhälle. För att förbättra den kardiometabola hälsan är effektiva och individanpassade interventioner avgörande. Psykos öppenvårdsmottagningar är idealiska för dessa insatser på grund av regelbundna patientbesök och tillgången till olika hälso- och sjukvårdpersonal. Vi har utvecklat och vill testa ett omfattande interventionsprogram för att förbättra kardiometabol hälsa, höja livskvaliteten och främja en hälsosam livsstil specifikt för personer med psykossjukdomar vid psykos öppenvårdsmottagningar i Göteborg. Denna longitudinella, multicenter, naturalistiska, multikomponent, parallell-grupp, quasi-experimentella, överlägsenhet, fall-kontrollstudie, LAGOM (Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness) kommer att inkludera 644 individer med psykossjukdomar från sex öppenvårdsmottagningar inom Psykiatri Psykos vid Sahlgrenska universitetssjukhuset i Göteborg. Två av mottagningarna genomför LAGOM-interventionen och vid övriga mottagningar rekryteras kontroller som får vanlig vård. Interventiongruppen kommer att få multidisciplinärt stöd integrerat i de rutinmässiga kliniska procedurerna. Interventionen inkluderar regelbundna uppföljningar och användning av motiverande verktyg, inklusive kroppsanalysvåg och algoritm för förutsägelse av kardiovaskulär risk (QRISK3). Om interventionen effektivt förbättrar kardiometabol hälsa, förbättrar livskvalité för denna sårbara grupp och visar sig vara kostnadseffektiv kan den fungera som ett modellprogram för implementering inom Västra Götalands Regionen.

Medicinsk teknisk produkt:	I den här kliniska prövningen kommer vi att använda två medicintekniska produkter som också är visuella i den meningen att de kan skapa en delad bild, mellan försökspersoner och vårdgivare, av deltagarnas välbefinnande. Dessa enheter är motiverande verktyg och är fokuserade på kardiometabolisk hälsa, i linje med projektets övergripande syfte. Dessa kallas QRISK3 algoritm och TANITA kroppsanalysvåg, en speciell typ av våg som ger en mer helhetssyn på kroppssammansättningen.
Antal försökspersoner:	644
Inklusionskriterier:	1) Vuxna, ≥18 år, som uppfyller ICD-10 diagnostiska kriterier för någon av schizofrenispektrumsyndrom och andra psykoser (F20-F25 eller F28-F29). 2) Har förmåga att underteckna informerat samtycke.
Exklusionskriterier:	1) Att ha ett elektriskt medicinskt implantat som pacemaker eller andra mekaniska implantat. 2) Gravida kvinnor. 3) Anses olämplig för inkludering efter utredarens bedömning. 4) Tidigare deltagande i prövningen. 5) Under behandling med tvångsvård.
Syfte:	Primärt syfte: Att utvärdera om interventionen är överlägsen vanlig vård för att sänka nivåer av kardiometabola riskindikatorer efter 36 månader. Sekundära och explorativa syften: Att bedöma om interventionen är överlägsen vanlig vård för att sänka risken för hjärtkärlsjukdom efter 36 månader. Att utvärdera om interventionen är överlägsen vanlig vård för att höja livskvaliteten (EQ-5D-5L) efter 36 månader. Att utvärdera om interventionen minskar högkänslig CRP och HbA1c efter 36 månader. Att bestämma kostnaden per försöksperson och utföra en kostnadseffektivitetsanalys där kostnadsneutralitet för interventionen är ett positivt resultat. Att utvärdera om interventionen förbättrar den riktade livsstilen efter 36 månader.

	Att utforska det totala antalet och typen av interventionssessioner, och det genomsnittliga tidsintervallet mellan på varandra följande sessioner som behövs per år för att uppnå en förändring i den riktade livsstilen. Att undersöka om deltagande i utbildningstillfällen av försökspersoner och deras anhöriga kommer att motivera försökspersonerna att anta en ny livsstil.
Utfallsmått:	Primära utfallsmått: Kardiometabola riskindikatorer: • Body mass index (BMI) (kg/m^2) • Waist-hip ratio (WHR) • Systolic blood pressure (SBP) mm Hg • Diastolic blood pressure (DBP) mm Hg • Triacylglycerol/high density lipoprotein-cholesterol ratio (TAG/HDL-C ratio) • Total cholesterol/HDL-C ratio (TChol/HDL-C ratio) • Plasma glucose (mmol/L) Secondära och exploratorativa utfallsmått: • Händelser av hjärtkärlsjukdom eller minskning av riskpoäng för hjärtkärlsjukdom enligt SCORE2 • Blood samples o Högkänslig CRP (mg/L) o HbA1c (mmol/mol) • Questionnaires o Livskvalitet enligt EQ-5D-5L o Alkoholvanor enligt AUDIT-C o Tobaksrökning och snusvanor o Matvanor och Kostindex o Fysisk aktivitet • Cost-utility analysis o Kostnadsbeskrivning i SEK och EURO o Quality-Adjusted Life Years (QALYs) vid baslinjen samt vid 12, 24 och 36 månader o Incremental cost-effectiveness ratio (ICER) där vi jämför kostnaderna mellan kontroll- och interventionsgruppen vid baslinjen och efter 36 månader
Planerad varaktighet av den kliniska prövningen:	Q1 2025 – Q4 2029

2. Identification and description of the investigational device

2.1. Description of the investigational device

2.1.1. QRISK®3-2018 risk calculator

The QRISK3 algorithm was developed in 2007 by a research group in Great Britain and updated in 2017 to the current version-QRISK3 (https://qrisk.org) (1). QRISK3 is a software that calculates a person's risk of developing a heart attack or stroke over the next 10 years. QRISK3 is United Kingdom Conformity Assessed (UKCA)-marked. The UKCA marking set up by the UK is intended to completely replace CE marking in the UK. QRISK3 considers having psychotic disorders and treatment with atypical antipsychotics as independent risk factors. In addition, QRISK3 estimates the risk over a wide age range (25–84 years). QRISK3 is included in the intervention for use in motivational work because it illustrates how reducing the number of cigarettes, losing weight, and improving blood pressure and blood lipids can reduce the absolute risk of CVD. In addition, QRISK3 illustrates the interactive and synergistic relation between the various cardiometabolic risk factors.

The calculator uses

- the QRISK3 algorithm, version 2018.0
- the BMI predictor algorithm, version 2013.0
- the cholesterol ratio predictor algorithm, version 2013.0
- the SBP predictor algorithm, version 2013.0
- the University of Nottingham Townsend score reference table, version 2018.0

2.1.2. Body composition analyzer

TANITA body composition analyzer calculates body composition using Dual Frequency Bioelectrical Impedance Analysis (BIA). The device is CE certified as a class IIa medical device. Safe, low-level electrical signals are passed through the body via the TANITA foot pads on the monitor platform. The signal can flow easily through fluids in muscles and other body tissue but meets resistance as it passes through body fat, because body fat only contains small amount of fluid. This resistance is called impedance. The impedance readings are then entered into medically researched mathematical formulas to calculate body composition.

TANITA is intended for persons aged 5-99 years. This Tanita Body Composition Analyzer is clinically proven to deliver accurate, reliable, and highly repeatable results. It is used globally by health, research, and medical professionals for:

- Medical screening and health assessments
- Monitoring the progress of weight loss during treatment relating for lifestyle diseases such as diabetes, hyperlipidemia, bariatric surgery, hypertension, and fatty liver disease

The analyzer measures weight, impedance, and estimates BMI, total body fat percent and mass, total body water percent and mass, total body muscle mass, bone mass, visceral fat,

basal metabolic rate (BMR), and fat-free mass (FFM) using BIA. It is suitable for healthy children (ages 5-17) and adults with varying levels of physical activity, ranging from inactive to highly active lifestyles.

2.2. Intended purposes

In this clinical trial, **QRISK3** will be used as a motivational tool to encourage lifestyle changes such as reducing smoking, exercising, and improving diet. These healthier habits can lower both absolute and relative risks of CVD, either directly by reducing smoking or indirectly by reducing factors like blood pressure, BMI, and blood lipids. Additionally, QRISK3 is intended to help participants understand the importance of managing these factors to reduce cardiovascular risk.

QRISK3 highlights the interactive and synergistic relation between various cardiometabolic risk factors. It shows how small improvements in multiple risk factors can significantly reduce overall cardiovascular risk. This makes QRISK3 a valuable visual tool, fostering a shared understanding between participants and healthcare providers about the participant's health. It also conveys that even modest changes in different risk factors can be beneficial. Since QRISK3 estimates risk over the next 10 years, it may indicate to the participants that they have time to make meaningful changes without undue pressure.

The **TANITA body composition analyzer** used in this clinical trial further supports participants in making lifestyle changes, aligning with the device's overall intended purpose.

Importantly, the results from QRISK3 and TANITA will not influence medical decisions made by physicians or healthcare professionals. These results will not be shared with other health units, such as primary health care centers. Instead, they will be communicated exclusively to the participants, to motivate lifestyle changes and support healthcare professionals' efforts to improve the participants' cardiometabolic health.

2.3. Manufacturer of the investigational device

2.3.1 QRISK®3-2018 risk calculator

Name: ClinRisk Ltd.
Address: 13-19 Queen St, Leeds, LS1 2TW
Contact: enquiries@clinrisk.co.uk

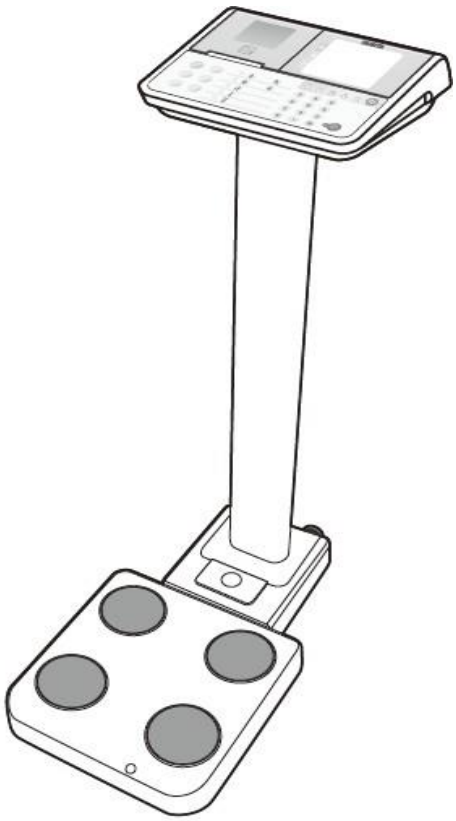
6.3.1. Body composition analyzer DC-430MA

Name: TANITA Corporation
Address: 1-14-2 Maeno-cho, Itabashi-ku, Tokyo 174-8630 Japan
Contact, phone number: +81-(0)3-3968-7048

2.4. Model/type

QRISK3 algorithm: version 2018.0

TANITA body composition analyzer: Model DC-430MA



COLUMN MOUNTED VERSION

2.5. Summary of required training/experience needed

The clinical trial team will undergo both theoretical and practical training before using the QRISK3 software and TANITA body composition analyzer.

3. Background and justification for the design of the clinical trial

3.1. Background

People with schizophrenia and schizophrenia-spectrum disorders (psychotic disorders) are at higher risk for cardiometabolic diseases such as CVD, obesity, and type 2 diabetes mellitus compared with the general population (2). These illnesses can lead to premature death, and people with psychotic disorders have a life expectancy that is 20 years shorter than that of the general population in Sweden (3). This mortality gap has increased in recent decades (4). Cardiometabolic diseases also lead to a poorer quality of life for these individuals (5) and affect the economy through loss of production and increased healthcare costs (6).

Several factors increase the risk for these cardiometabolic diseases in people with psychotic disorders, including the phenomenology of the illness, genetic predisposition, use of psychotropic drugs, unhealthy eating habits, lack of physical activity, tobacco smoking, and risky alcohol use (7). A lower quality of somatic care for people with psychotic disorders compared with the general population is well documented and plays an important role (7, 8). Many of these risk factors can be influenced by the choice of psychotropic drugs and

interventions to change unhealthy lifestyles. However, people with psychotic disorders, especially schizophrenia, find it difficult to change their lifestyle because of difficulties with memory and executive functions, as well as persistent psychiatric symptoms that prevent them from adopting new behaviors (9). Even when learning a new lifestyle, people with schizophrenia have difficulty maintaining it because of illness, cognitive impairment, and side effects of psychotropic medications.

In addition to the difficulties faced by people with psychotic disorders, there are several shortcomings in health care. Healthcare professionals do not consider the vulnerability of individuals with psychosis and place high demands on these individuals to follow the same recommendations as for the public when it comes to changing lifestyles. These recommendations are often given in the form of concise standardized advice, which, according to The Swedish National Board of Health and Welfare (10), should be complemented by more extensive measures. Such measures may include advisory sessions that are adapted to the individual's specific needs and include motivational strategies as well as various tools and aids, or qualified advisory sessions that are similar to advisory sessions but are more time-consuming and require staff to have in-depth knowledge of the subject and are trained in the method used for the session. Another shortcoming in healthcare is the lack of educational programs for both individuals with psychotic disorders and healthcare professionals, to inform about the relation between psychotic disorders, lifestyle choices and the cardiometabolic profile. This profile includes development over time or the collective effect of different cardiometabolic parameters such as weight parameters (waist circumference and BMI), blood sugar, blood lipids, and blood pressure. There is also a large variation among healthcare professionals regarding follow-up and level of knowledge regarding the evaluation of deviations in the cardiometabolic profile and lifestyle habits of individuals with psychotic disorders. In psychiatry, there are recommendations to carry out annual physical health checks, but there are no clear guidelines for these health checks nor follow-up guidelines. These guidelines would ensure the application of interventions aimed at improving the cardiometabolic profile and lifestyles. This has been noticed by the Swedish National Board of Health and Welfare in its report on the national evaluation of care and support for schizophrenia and schizophrenia-spectrum disorders – 2022 (11). Finally, the collaboration between psychiatry and primary health care centers needs to be strengthened to improve the health of people with psychotic disorders.

Some intervention programs succeeded in improving certain components of the cardiometabolic profile in individuals with psychotic disorders. An example is the ACHIEVE trial (12) which lasted 18 months and showed that tailored interventions can help people with psychotic disorders lose weight. Two other studies lasting 30 months showed improvement in all cardiovascular risk factors (13) and reduction in the risk of type 2 diabetes in people with schizophrenia (14).

Although some intervention studies have shown positive results, only a few were naturalistic (13-15) while most intervention studies were designed in a way that limited their effect on the individual's health in everyday clinical practice. Most studies focused on individual lifestyle factors and individual cardiometabolic risk factors rather than the overall cardiometabolic

profile and aggregate cardiovascular risk estimate (12-14, 16-19). In addition, most studies had short intervention periods (16-20), typically one year or less, which did not provide sufficient time to achieve clinically significant improvements in risk factors except for the CRESSOB study (15). An additional challenge was that the health programs often did not take into account how care is delivered in practice, had few patients per healthcare staff (15, 17, 18, 20), and used methods that are not sustainable in the long term, such as providing breakfast and lunch for participants (12), evaluating grocery shopping and cooking through home visits, as well as coaching physical activity at home (20). Many intervention studies also lacked education for patients and staff about the relation between psychotic disorders, the cardiometabolic profile, and lifestyle choices (12, 15, 16). Previous studies had limited inclusion criteria (12-18, 20). Furthermore, most did not consider improvement in the diagnosis and treatment of cardiometabolic abnormalities, which is a well-documented problem (12-14, 16-18).

The LAGOM project (Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness) has been designed to improve the evaluation of cardiometabolic health in people with psychotic disorders. LAGOM is integrated into the daily clinical routine of psychiatry in Gothenburg. This integration enables application of the method in the same clinical environment. The project focuses on the overall cardiometabolic profile and spans 36 months ± 6 months with broad inclusion criteria. LAGOM is an individually tailored program that aims at gradual improvements in lifestyle habits. In addition, the program improves communication with primary health care centers to optimize diagnosis and treatment of cardiometabolic abnormalities. It also offers education for participants, their relatives, and healthcare professionals about the relation between psychotic disorders, the cardiometabolic profile, and lifestyle choices.

At the clinic, we possess clinical and research expertise in using tools that facilitate mutual understanding between healthcare providers and patients regarding the patients' health conditions. For instance, in a quality improvement and research project, we assessed a specific patient-centered technical feature known as a "dashboard." It promoted feedback-informed care as it enabled us to visualize the outcomes of patients' annual health checks, facilitating discussions between healthcare providers and patients (21).

In this project, we will use two other tools that are also visual in the sense that they can create a shared picture, between patients and healthcare providers, of the patients' well-being. In our clinical trial these are focused on cardiometabolic health, in line with the project's overall purpose. These motivational tools are called QRISK3 algorithm and body composition analyzer, a special type of scale that gives a more holistic view of body composition. See below for a more detailed description.

With over 3,000 individuals receiving care within the Department of Psychotic Disorders in Gothenburg, the need for a health promotion program is acute and extensive. However, there is still a lack of knowledge about the effect of comprehensive naturalistic interventions such as LAGOM to improve cardiometabolic health, enhance quality of life, and reduce the risk of premature death in persons with psychotic disorders.

4. Risks and clinical benefits of the investigational device and clinical trial

4.1. Expected clinical benefits and risks

We are not aware of any risks with using the QRISK3 algorithm or the body composition analyzer. Since the clinical trial is integrated into routine clinical practice, the risks are no greater than those typically encountered during usual care. However, there is a concern that participants at the intervention clinics may need to attend additional outpatient clinic visits, which could require more time and energy and potentially impact their compliance with the clinical trial. To mitigate this, participants will be exempt from the costs of these visits and will receive bus tickets to cover transportation for the additional visits associated with the intervention.

The LAGOM program is a proactive response to challenges seen in previous intervention studies and clinical settings, aiming to mitigate cardiometabolic risk factors and improve lifestyle habits for individuals with psychotic disorders. It integrates seamlessly into clinical practice at the Department of Psychotic Disorders in Gothenburg, focusing on patient and family education and professional development for healthcare staff. These efforts are geared towards heightening awareness regarding the intricate interplay between psychotic disorders, cardiometabolic health, and lifestyle choices. LAGOM focuses on overall cardiometabolic health and addresses underdiagnosis and undertreatment of cardiometabolic abnormalities. Its potential long-term impact includes enhancing quality of life, promoting efficient resource allocation, addressing cardiometabolic disease risks, and fostering holistic well-being. If the intervention effectively improves cardiometabolic health, enhances quality of life for this vulnerable group, and proves cost-effective, it can serve as a model program for implementation in Region Västra Götaland. The clinical trial also includes collaboration with the schizophrenia association in Gothenburg to strengthen communication with and potential impact for end users.

4.2. Rationale for benefit-risk ratio

Since we cautiously assume that there are no risks involved in participating in the intervention, the risks are outweighed by the clinical and scientific value. Expected benefit at individual and group level consists in increased knowledge about the prevention and treatment of cardiometabolic abnormalities in people with psychotic disorders. The results have the potential to improve healthcare for the participants but also others who are treated for the same disease. The utility aspect thus prevails.

5. Objectives of the clinical trial

5.1. The purpose of the clinical trial

The overall aim of the clinical trial is to improve cardiometabolic health, promote healthy lifestyles, and enhance quality of life in individuals with psychotic disorders.

5.2. Objectives

5.2.1. Primary objectives

To evaluate whether the intervention is superior to usual care in lowering levels of cardiometabolic risk indicators after 36 months.

5.2.2. Secondary and exploratory objectives

To assess if the intervention is superior to usual care in lowering the risk of CVD after 36 months.

To evaluate whether the intervention is superior to usual care in enhancing the quality of life (EQ-5D-5L) after 36 months.

To evaluate whether the intervention reduces high-sensitivity CRP and HbA1c after 36 months.

To determine the cost per participant and perform a cost-effectiveness analysis where cost neutrality for the intervention is a positive outcome.

To evaluate whether the intervention improves the targeted lifestyle after 36 months.

To explore the total number and the type of intervention sessions, and the average time interval between consecutive sessions needed per year to achieve a change in the targeted lifestyle.

To investigate whether participation in educational sessions by participants and their relatives will motivate participants to adopt a new lifestyle

6. Design of the clinical trial

6.1. General information

The LAGOM clinical trial is a longitudinal, multicenter, naturalistic, multicomponent, parallel-group, quasi-experimental, superiority, case-control clinical trial.

6.2. Endpoints

6.2.1. Primary endpoint

Cardiometabolic risk indicators at 36 months compared with baseline:

- Body mass index (BMI) (kg/m^2)
- Waist-hip ratio (WHR)
- Systolic blood pressure (SBP) mm Hg
- Diastolic blood pressure (DBP) mm Hg
- Blood samples
    - Triacylglycerol/high density lipoprotein-cholesterol ratio (TAG/HDL-C ratio)
    - Total cholesterol/HDL-C ratio (TChol/HDL-C ratio)
    - Plasma glucose (mmol/L)

6.2.2. Secondary and exploratory endpoints

- CVD events or reduction in CVD risk scores according to SCORE2
- Blood samples
  - High-sensitivity CRP (mg/L)
  - HbA1c (mmol/mol)
- Questionnaires
  - Quality of life according to EQ-5D-5L
  - Alcohol habits according to AUDIT-C
  - Tobacco habits
  - Eating habits
  - Physical activity
- Cost-utility analysis
  - Cost description in SEK and EURO
  - Quality-Adjusted Life Years (QALYs) at baseline and at 12, 24, and 36 months
  - Incremental cost-effectiveness ratio (ICER), comparing the costs between the control and intervention clinics at baseline and after 36 months

6.3. Participants

6.3.1. Inclusion criteria

1) Adults, ≥18 years, meeting ICD-10 diagnostic criteria for any one of the schizophrenia spectrum disorders (F20-F25 or F28-F29).

2) Has the ability to sign informed consent.

6.3.2. Exclusion criteria

1) Having an electrical medical implant like pacemaker or other mechanical implants.

2) Pregnant women.

3) Deemed unsuitable by the investigator (A person may be deemed unsuitable for participation in the trial by the clinical investigation team member, based on factors that may affect the ability to participate safely and reliably. Such factors may include, but are not limited to, physical disability that hinder participation, or practical challenges such as long travel distance to the trial site. The assessment is made on an individual basis and aims to ensure both patient safety and trial integrity).

4) Prior participation in the LAGOM trial during a previous inclusion cycle (i.e., participants can only be included once during the trial period).

5) Currently under compulsory care.

6.3.3. Investigation population

All eligible patients visiting one of the six outpatient clinics affiliated with Sahlgrenska University Hospital will be invited to participate in the clinical trial during their annual health checks. Inclusion will proceed consecutively until we reach the specified number of participants at both the intervention and control clinics. The patients are called based on their birth month, meaning that after a full year, all patients following the schedule have been asked to participate in the clinical trial. As the schedule is not always followed in practice, the recruitment period is expected to last longer than 12 months.

The intervention group (n=157) will be recruited from two psychosis outpatient clinics at the Department of Psychotic Disorders (Centrum and Mölndal) with a total of over 650 listed patients. The control group (n=487) will be recruited from four other psychosis outpatient clinics (Hisingen, Nordost, Väster, and Öster) with a total of over 2000 listed patients. The target group for these outpatient clinics includes individuals who have psychotic disorders and who live within the respective catchment areas, which have a total of 768,574 inhabitants according to the population statistics from Statistics Sweden as of December 31, 2023 (22).

6.3.4. Criteria and procedures for participant withdrawal or discontinuation

Participants can discontinue their participation in the clinical trial at any time without any consequence to his/her continued treatment.

If the participant discontinues the clinical trial, follow-up of this participant will be performed according to the clinic's routine.

Discontinuation criteria for individual participants:

- Inappropriate enrollment (violation of inclusion/exclusion criteria)
- Withdrawal of consent
- Pregnancy
- Receiving an electrical medical implant, such as a pacemaker, or other mechanical implants
- Relocating to another city or country, or being registered at a different outpatient clinic

The reason for discontinuation should be recorded in the eCRF.

6.4. Methods to minimize bias

In this clinical trial, possible sources of bias have been identified and strategies to minimize them have been implemented:

Selection Bias: The psychosis clinics are located in different socio-economic areas with diverse ethnic groups, due in part to immigration, and there are variations in patients' language skills. To minimize bias, we will stratify the data and adjust for confounders in the analysis, such as socioeconomic status and ethnicity. Accredited interpreters, familiar with both patients and healthcare providers, will be used as part of standard care practice. Including outpatient clinics with a majority of immigrant populations helps reduce selection bias, as these clinics represent a crucial part of the target population.

Confounding Bias: Including a diverse sample addresses confounding bias, as factors like socioeconomic status and ethnicity can influence cardiometabolic risk. Adjusting for these variables during data analysis will further mitigate confounding effects.

Information Bias: To minimize information bias, a standardized medical history protocol for data collection has been developed. Additionally, blood pressure equipment will be calibrated and examined annually. In cases of missing or incorrect data in the protocols, research nurses and assistants will rectify these during initial and secondary reviews before data entry.

Recall Bias: To reduce recall bias, information prone to this error will be cross-checked with medical records to ensure accuracy.

Question Order Bias: The order of questions has been carefully considered to minimize the impact of question order bias.

Performance Bias: To ensure consistency in the intervention across healthcare providers, a flowchart and standardized procedures will be used in all intervention outpatient clinics. Training workshops will also be conducted to maintain uniformity. A medical history protocol will standardize data collection for both the intervention and control groups.

Attrition Bias: Attrition bias is expected to be minimal in the intervention group due to the individualized nature of the intervention methods. However, it cannot be completely ruled out in the control group.

6.5. Description of the clinical procedures and diagnostic methods relating to the clinical trial

Usual care: Usual care describes the present health care situation for all individuals with psychotic disorders in Gothenburg. In Sweden, a comprehensive healthcare system ensures that all citizens are registered with a primary health care center, which assumes responsibility for addressing abnormal cardiometabolic risk factors. Even patients receiving specialist psychiatric care remain linked to their primary health care centers. Presently, individuals with psychotic disorders in Gothenburg undergo an annual health check, constituting the standard "usual care" practice. Usual care takes place over two visits, which take place within 45 days. During the first visit, which lasts approximately 60 minutes, the patient meets with the case manager. At the second visit, which also lasts approximately 60 minutes, the patient meets with both the case manager and the psychiatrist or attending physician (henceforth referred to both as the physician).

Usual care includes ordering fasting blood samples and physical examinations such as blood pressure measurement and weight assessment. The results of these tests and examinations are evaluated by the physician by comparing them to established reference intervals, which serve as the primary evaluation tool. Sometimes the physician uses risk algorithms for future CVD as Systematic COronary Risk Evaluation 2 (SCORE2) (23).

The blood test and physical examination provide the cardiometabolic risk indicator values relevant to this clinical trial. Only indicators obtained within the defined visit window will be included. This visit window spans 45 days before and after the second visit of the annual health check, which involves the physician. The window is designed to accommodate the realities of clinical practice, where it may not always be feasible for patients to complete the blood test or physical examination on the scheduled day. This flexibility ensures alignment with routine care. If a patient completes the blood test or undergoes the physical examination after the second visit, a follow-up physician visit is required to review the results and implement necessary management measures.

Depending on the physician’s assessment, further management may be considered, which could include referral to the primary health care center. Occasionally, discussions regarding lifestyle factors, particularly physical activity, diet, and substance use (such as tobacco and

alcohol), are initiated during these appointments.

In cases where the case manager or the physician identifies deviant lifestyle habits, they offer the patient simple advice. Additionally, patients may be referred to a health promoter for support in reducing tobacco smoking, receiving dietary guidance, participating in group physical activities (e.g., pole walking or water aerobics), or consulting with a dietitian or primary health care center for further assistance.

The total clinical trial is scheduled to span 36 months per participant ± 6 months. Before their first baseline visit for the annual health check at one of the four control outpatient clinics (Hisingen, Nordost, Väster, or Öster), patients will be screened for eligibility. If eligible, they will be invited to participate in the trial and join the control group during the annual health check. Those who agree to participate will sign written informed consent. Rescreening is permitted if a patient meets the exclusion criteria in one year but not in the following year, in which case they may be included. The clinical trial does not modify usual care, except for standardizing the information collected during annual health checks through the use of a medical history protocol (henceforth referred to as the worksheet). There are two versions of this worksheet: one for the intervention clinics (Appendix 1) and one for the control clinics (Appendix 2). While both versions include the same annual blood tests, the physical examination in the intervention worksheet is more extensive, as detailed in the intervention section and in Table 1.

Patients who decline participation, whether from the control or intervention outpatient clinics, will continue to receive usual care.

As part of usual care, the case manager prepares for the annual health check by ordering blood tests, beginning to fill in the worksheet, and sending a letter to the patient with instructions for blood sample preparation. Depending on the case, the case manager may send the patient self-assessment questionnaires (EQ-5D-5L, AUDIT-C, and a questionnaire on eating habits to be completed at home). These procedures are standard clinical routines and remain unchanged regardless of the patient’s participation in the clinical trial.

Data collection procedure:

Control clinics (Usual care)

Baseline visits

Visit 1 – The annual health check with the case manager

Before this visit, patients are screened for eligibility. If eligible, they are invited to join the control group by a representative of the clinical trial team, and written consent is obtained during the annual health check. The participant is interviewed according to the control version of the worksheet and undergoes a somatic examination, as outlined in Table 1, conducted by the case manager. A blood test is ordered according to clinical practice and is expected to be completed before the baseline visit. The blood sample is collected following the standard clinical procedure used during routine annual health checks. In preparation for Visit 1, the case manager begins filling the worksheet for the annual health check by gathering information from various sources, including medical records, telephone interviews with the participant, or the case manager’s or physician’s prior knowledge of the patient.

Visit 2 – The annual health check with the physician and the case manager

During the scheduled annual health check, the participants meet with the physician to review the worksheet, physical examination results, and blood test analysis. The participant, case manager, and physician collaborate to determine a suitable management plan based on clinical routines.

Continuing Annual Health Checks

Visits 3, 5, and 7 – The annual health check with the case manager

The same routine as in Visit 1 (baseline) at the control clinics.

Visits 4, 6, and 8 – The annual health check with the physician and case manager

The same routine as in Visit 2 (baseline) at the control clinics.

Intervention clinics

The total clinical trial is scheduled to span 36 months per participant ± 6 months, during which case managers at outpatient clinics will maintain their routine practice of contacting patients for annual health checks. Before the first baseline visit to one of the two intervention outpatient clinics (Centrum or Mölndal), patients are screened for eligibility and, if eligible, are invited to join the intervention group during the annual health check, with written consent obtained. Rescreening is permitted if a patient meets the exclusion criteria in one year but not in the following year, in which case they may be included. After informed consent, the case manager will continue interviewing the participants and fill in the intervention version of the worksheet.

The annual health checks at the intervention clinics follow the same structure of two visits as in routine usual care, with the primary difference being the content of the visits.

At the annual health checks a comprehensive mapping will be conducted by the physician and the case manager, using a flowchart (Appendix 3) to assess the cardiometabolic health and lifestyle habits. The mapping process unfolds over the course of the two visits. During the initial visit, which lasts approximately 45 minutes, the case manager fills in the intervention version of the worksheet and conducts lifestyle and somatic examinations according to table 1 for all eligible participants. The participant then meets with the physician and case manager for another 45-minute session during the second visit. The physician assesses the cardiometabolic profile by carefully monitoring changes in various cardiometabolic parameters over time, using the clinically used algorithm of SCORE2 to provide a contextual estimate of the risk for CVD, and evaluating the fulfillment of the criteria for metabolic syndrome (24) as outlined in the intervention worksheet. Assessment of risk behavior in lifestyle habits is linked to the participant’s state of health and illness as well as to the gains the participants make by stopping their unhealthy lifestyle. Upon identifying unhealthy lifestyle habits or deviations in the cardiometabolic profile, the results are communicated to the participant, who receives advisory support from healthcare professionals. This step involves the use of motivational interview techniques and motivational tools to tailor individualized plans. These motivational tools include the QRISK3 algorithm and TANITA body composition analyzer. Based on the outcomes of these intervention-specific steps—mapping and motivational efforts—the physician conducts a

medical evaluation to determine if referrals to internal resources, such as health promoters or physiotherapists, are needed for further assessment and support. Additionally, referrals to external resources, including primary health care centers, may be made for targeted treatments and interventions, with an emphasis on individualized care.

The case manager has a main role to follow up and ensure that the participant has come into contact with the internal or external resources. This is done via regular follow-up sessions throughout the year. The follow-ups are estimated to take approx. 15–30 minutes. They consist of motivational and counseling conversations and can be conducted in-person or remotely. These follow-ups are individually tailored and can therefore vary in frequency, number, and type. Type of sessions includes the four lifestyle habits: dietary habits, physical activity, alcohol habits, and tobacco habits. Lifestyle changes are based on small adjustments, taking into account the participant's cognitive impairments and increased sensitivity to stress.

According to routine clinical practice, when the participant has established contact with either the internal (such as the health promoter or the physiotherapist), or external (such as the primary health care center) resources, the responsibility is left to those resources to follow up on their specific efforts during the follow-up year, which is the time between two annual health checks.

However, the case manager is responsible for documenting the number of different sessions with the internal and external resources at the annual health checks in the worksheet the following year through asking the participant or checking the participants medical records. This will make it possible to evaluate adherence and fidelity to the intervention program.

The participants undergo physical examinations every two months to monitor the development of blood pressure, pulse, waist measurement, hip measurement, weight and other parameters according to the body composition analyzer according to table 1. The intervention also includes group education sessions for participants and their relatives once a year. These education sessions are adapted to LAGOM's concept and aim to deepen the understanding of the connection between psychotic illnesses, lifestyle habits and cardiometabolic health. The education sessions are physical and take 45 minutes. The clinical trial team will hold the education sessions. It is not necessary for a relative to be involved in the education sessions. If a relative is included, no data will be reported for this person.

Data collection procedure:

Intervention clinics

Baseline visits

Visit 1 – The annual health check with the case manager

The same routine as in Visit 1 (baseline) for the control clinics, except for inviting to the intervention group and using the intervention version of the worksheet. If written consent is obtained, the participants are examined using a body composition analyzer by their case manager, as outlined in table 1. No study-specific procedures are conducted before informed

consent is obtained. However, in preparation for Visit 1, the case manager begins filling the worksheet for the annual health check by gathering information from various sources, including medical records, telephone interviews with the participant, or the case manager's or physician's prior knowledge of the patient.

Visit 2 – The annual health check with the physician and the case manager

During the scheduled annual health check, the participants meet with the physician to review the worksheet, physical examination results, and blood test analysis. The physician fills in the QRISK3 algorithm with the participant. The participant, case manager, and physician collaborate to determine individually adapted interventions based on the mapping process. They also agree on a follow-up plan with the case manager.

Continuing Annual Health Checks

Visits 8, 15, and 22 – The annual health check with the case manager

The same routine as in Visit 1 (baseline) at the intervention clinics.

Visits 9, 16, and 23 – The annual health check with the physician and the case manager

The same routine as in Visit 2 (baseline) at the intervention clinics.

Visits 3–7, 10–14, and 17–21 – Follow-up every other month with physical examination

During the year following the annual health check, participants at the intervention clinics will attend follow-up visits every two months at the outpatient clinic for a physical examination, as outlined in Table 1.

The intervention also includes an educational session for participants and their relatives once a year.

Table 1. Data collection schedule according to worksheet

Collected data	**Baseline**		**Every other month ± 14 days Visits 3–7***	**12 months ± 60 days Visits 8+9*** **Visits 3+4**	**Every other month ± 14 days Visits 10–14***	**24 months ± 60 days Visits 15+16*** **Visits 5+6**	**Every other month ± 14 days Visits 17–21***	**36 months ± 60 days Visits 22+23*** **Visits 7+8**
	Visit 1	**Visit 2[#]**						
Check for eligibility	**X**							
Informed consent	**X**							
Inquire about adverse event*			**X**	**X**	**X**	**X**	**X**	**X**
Social and background questions	**X**			**X**		**X**		**X**
Medical anamnesis	**X**			**X**		**X**		**X**
Questions about participation in educational sessions and lifestyle	**X**			**X**		**X**		**X**

sessions								
Lifestyle questionnaires								
• Alcohol habits according to AUDIT-C • Tobacco habits • Dietary habits • Physical activity	**X**			**X**		**X**		**X**
Blood tests								
P-high-sensitivity CRP (mg/L)	**X**			**X**		**X**		**X**
fP-Triacylglycerol (mmol/L)	**X**			**X**		**X**		**X**
P-HDL-cholesterol (mmol/L)	**X**			**X**		**X**		**X**
P-LDL-cholesterol (mmol/L)	**X**			**X**		**X**		**X**
P-Total cholesterol (mmol/L)	**X**			**X**		**X**		**X**
P-non-HDL-cholesterol (mmol/L)	**X**			**X**		**X**		**X**
fP-Glucose (mmol/L)	**X**			**X**		**X**		**X**
B-HbA1c (mmol/mol)	**X**			**X**		**X**		**X**
P-Kreatinin (µmol/L)	**X**			**X**		**X**		**X**
P-ALAT (µkat/L)	**X**			**X**		**X**		**X**
P-ASAT (µkat/L)	**X**			**X**		**X**		**X**
P-ALP (µkat/L)	**X**			**X**		**X**		**X**
P-bilirubin (µmol/L)	**X**			**X**		**X**		**X**
Physical examination								
Height (cm)	**X**			**X**		**X**		**X**
Weight according to SECA 799 (kg)	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Waist circumference (cm)	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Hip circumference (cm)	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Systolic blood pressure mmHg	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Diastolic blood pressure mmHg	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Pulse (bpm)	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Assessment scales								
EQ-5D-5L	**X**			**X**		**X**		**X**
Fulfillment of criteria of metabolic syndrome*	**X**			**X**		**X**		**X**
SCORE2*	**X**			**X**		**X**		**X**
QRISK3*	**X**			**X**		**X**		**X**
Measurements according to TANITA body composition analyzer*								
• Weight (kg) • Total body fat mass (kg) • Total body water mass (kg) • Total body muscle mass (kg) • Bone mass (kg) • Metabolic age	**X**		**X**	**X**	**X**	**X**	**X**	**X**
* Only intervention clinics # Visit 2 involves no new data entry but complements Visit 1 by ensuring that all data from Visit 1 is complete. Eligibility screening and informed consent are always completed during Visit 1.								

6.6. End of the clinical trial

The clinical trial ends when the last participant has completed the last visit (Visit 8 at the control clinics and 23 at the intervention clinics). The sponsor will notify the Swedish Medical Products Agency within 15 days after the end of the clinical trial and send the clinical trial report within 1 year after the end of the clinical trial including an easily understandable summary.

7. Quality control

7.1. Monitoring

The clinical trial will be monitored by an independent monitor before the clinical trial begins, during the clinical trial conduct, and after the clinical trial has been completed, so as to ensure that the clinical trial is carried out according to the CIP and that data is collected, documented, and reported according to SS-EN ISO 14155:2020 and applicable ethical and regulatory requirements. The monitor is appointed by the sponsor and independent in relation to the principal investigator and site staff.

7.2. Monitoring plan

Monitoring will be risk-based, which means the extent of the monitoring is based on the sponsor's risk-assessment and is performed as per the investigation's monitoring plan. Monitoring is intended to ensure that the participant's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

7.3. Source data

The investigator must keep source documents for each participant in the clinical trial. A document describing what has been classified as source data in the clinical trial (source data reference document) should be included in the Investigation Site File (ISF). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities. Source data is defined before clinical trial starts at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.

Access to investigation-related documentation, such as participants' medical records, CRFs, other source data and other clinical trial documentation will be provided for monitoring and auditing purposes. Access to participants' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the investigational site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.

7.4. Quality assurance and quality control

Quality assurance refers to activities that promote the collection of high-quality data, and quality control refers to activities that detect new data problems with sufficient time to implement appropriate corrective actions. Our approach to quality assurance includes: 1) development of a flowchart for the intervention (Appendix 3); 2) development of a medical history protocol (worksheet) (appendices 1 and 2); 3) train all data collectors through workshops; 4) regular meetings with data collectors; 5) following the manufacturer's maintenance instructions of the blood pressure devices, SECA scale, and TANITA body composition analyzer. Our quality control strategy includes: 1) monitoring the completed worksheets via research nurses and research assistants; 2) in case of missing data or incorrect data registration in the protocols, rectify the deficiencies via research nurses during the first review of the protocols and research assistant before entering the data from the protocols into the database; 3) record data entry lag time and 4) regular meetings with

research nurses and research assistants to review missing data, out-of-range values, or illogical data relations.

8. Statistical considerations

8.1. Analytical procedures

The clinical trial will involve longitudinal comparisons within and between the intervention group and the control group. The analyzes are carried out with linear regression models for continuous variables, logistic regressions for categorical variables, and Poisson or negative binomial regressions for count data (e.g., number of different sessions with the internal and external resources). The dependent variables in the primary analysis will be the following cardiometabolic risk indicators: BMI, WHR, SBP, DBP, TAG/HDL-C ratio, TChol/HDL-C ratio, and plasma glucose. These cardiometabolic risk indicators will be limited to those obtained within the visit window. The visit window is specified as 45 days before and after the second visit of the annual health checks (where the physician participates). Clinical trial site, age, and sex will be included for adjustment in the analysis model. Other covariates not balanced between groups will be considered for adjustment. Cardiometabolic risk indicators outside the visit window will be used to evaluate their impact on conclusions in a sensitivity analysis. To assess the impact on outliers, sensitivity analyzes will be run both with and without those outliers.

For the secondary outcome, the CVD risk measured by SCORE2 will be analyzed using linear regression methods while CVD risk measured by the time to CVD events will be analyzed using survival analysis techniques such as Cox regression and Kaplan-Meier estimator. All statistical tests will be two-sided, using an alpha of 0.05 to control for type I error.

Cost-utility analysis: To illuminate the costs in the clinical trial, we will use three different methods. First, through a cost description in SEK and EURO. Second, we will calculate Quality-Adjusted Life Years (QALYs) at baseline and at 12, 24, and 36 months. (cost-indexed based on the clinical trial's end date). We will compare the costs for the intervention group both with themselves and with the costs for the control group. Finally, we will perform an incremental cost-effectiveness ratio (ICER), comparing the costs between the control and intervention groups at baseline and after 36 months. To test the model, we will also conduct a sensitivity analysis with a variation of +/-20%. We will not include the education cost for personnel as an additional cost in the analysis, nor will we consider the extra cost for managing the clinical trial (trial costs). However, we will consider the additional time required for the intervention in the clinical trial population, as well as the time it takes for regular treatment. This may result in slightly more frequent and sometimes longer visits for the intervention group compared with the control group, which needs to be studied and considered in the final calculation. Cost neutrality for direct and indirect costs yields a positive outcome for the clinical trial.

8.2. Sample size calculation

The estimated number of participants needed to achieve the clinical trial objectives is based on the expected level of clinical significance. To be clinically significant, the difference in mean value between the intervention and control groups should be at least: 1 kg/m^2 in BMI

(25), 1 cm in waist circumference or 0.01 unit in WHR (26), 10 mm Hg in SBP (27), 2 mm Hg in DBP (28), 1 unit in TAG/HDL-C ratio (29, 30), 1 unit in TChol/HDL-C ratio (31), or 1 mmol/L in plasma glucose (32). Table 2 shows the power calculation of the number of participants per group. Of the 2650 patients listed at the six psychosis outpatient clinics in Gothenburg, we need to recruit 157 people from the intervention clinics and 487 from the control clinics.

Table 2. Power calculation for minimum number of participants per group

Variable	Standard deviation (ref.)	Expected difference	Two-tailed significance level	Power %	Expected dropout %	Sample size for intervention group	Sample size for control group
WHR	0.08 (33)	0.03	0.05	80	40	125	389
BMI	4.5 (34)	1.5	0.05	80	40	157	487
SBP	14.4 (33)	10	0.05	80	40	37	115
DBP	9 (35)	3	0.05	80	40	157	487
TAG/HDL-C ratio	0.9 (36)	1	0.05	80	40	15	47
TChol/HDL-C ratio	1.1 (36)	1	0.05	80	40	24	74
Glucose	0.8 (34)	1	0.05	80	40	14	42

8.3. Missing data

We have a two-step strategy to minimize the occurrence of missing data. The first step involves the review of completed worksheets by a research nurse after the second visit of the annual health check. In the second step, a research assistant signals any missing data after the first check. The first and second checks are performed within 45 days of the second visit of the annual health check. However, during summer, Christmas, and other national holidays, these routines may require additional time due to limited staff availability and scheduling constraints.

We will analyze the following factors for the missing data: missing data levels of analysis (item-, construct-, and person-level) and missing data mechanism (missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR)) (37). This analysis will guide the strategy (maximum likelihood (ML), multiple imputation (MI), listwise and pairwise deletion) for handling missing data. The effect that any missing data may have on the results as well as the robustness of the measure for handling missing data will be assessed through a sensitivity analysis.

9. Data management and protection

Participants in the clinical trial are coded with a specific record ID according to REDCap. All participants are registered in a participant identification list (participant enrolment and

identification list) that connects the participant's name and personal number with the record ID.
All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

9.1. Case Report Form and data cleaning

The research nurse will organize and collect completed worksheets from the case managers and physicians and store them in the respective physical individual folders for the participants. Information is gathered using paper-based methods. Additionally, within 45 days of the second visit of the annual health check, the research nurse will ensure the worksheet is complete and accurate by addressing any missing information or questionable data. This will involve gathering details from various sources, such as the participant, case manager, physician, or medical records. All data must be finalized within 45 days of the second visit of the annual health check before the worksheets are handed over to the research assistant for entry into the electronic case report form (eCRF). At a later stage and within 45 days of the second visit of the annual health check, a research assistant enters all the data into the eCRF, ensuring that missing data and abnormal variables are identified. Examples of such abnormal variables include swapping weight and height values or reversing systolic and diastolic readings. Another example is indicating the absence of a somatic illness while also noting the use of antihypertensive or antidiabetic medications. All participants' information will be considered confidential. Access to the secure eCRF will be encrypted, password protected and restricted to trained and authorized personnel. In addition, authorized personnel will have different permissions and will only be able to access specific areas (e.g. edit data or only read data). All data that are stored electronically will be encrypted and saved on a secure server housed in Region Västra Götaland using REDCap.

9.2. Archiving

The PI and sponsor will maintain the essential clinical trial documents in the investigation site files archive and sponsor files archive, respectively. The sponsor shall keep all documentation and data for at least 10 years after the clinical trial has ended. The PI will archive all local investigation documentation for at least 10 years or as long as stipulated by the local institution.

9.3. Data protection

All participants in LAGOM will receive a journal entry stating that they are participating in the clinical trial and what it entails. Confidentiality will be guaranteed through several mechanisms. For the clinical trial, each participant will be assigned a record ID. When the eCRF is ready for analysis, it will not contain the actual identities of the participants. When not in use, all study forms and paper records containing participant information will be stored in secure, locked areas at the respective outpatient clinic. Such material, when used, will be kept away from public scrutiny. In addition, access to the locked areas containing all participant data and information will be restricted to authorized personnel. The results will only be reported at the group level. The data will not be presented in such a way that the identity of individual participants can be deduced.

The content of the informed consent form shall comply with relevant integrity and data protection legislation. In the participant information and the informed consent form, the participant will be given complete information about how collection, use and publication of

their clinical trial data will take place. The participant information and the informed consent form will explain how clinical trial data are stored to maintain confidentiality in accordance with national data legislation.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical trial, including the participant's medical history.

10. Amendments to the CIP

Amendments to the CIP will be agreed upon between the sponsor/coordinating investigator. Substantial modifications must be approved by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency before implementation.

11. Deviations from the CIP

Investigator(s) are not allowed to deviate from the CIP except if it is for the protection of the participant´s rights, safety, or well-being under emergency circumstances.
All such deviations shall be documented and reported to the sponsor, the Swedish Medical Products Agency and/or the Swedish Ethical Review Authority (as applicable) as soon as possible. All deviations shall be documented with an explanation and reported to the sponsor. Deviations will be reviewed by the sponsor and reported to the appropriate regulatory bodies as required.

12. Device traceability and accountability

The TANITA body composition analyzer will be used in the clinical trial according to the clinical investigation plan. The TANITA body composition analyzer will be held by the clinic after the clinical trial.

The TANITA body composition analyzer will be used in the clinical trial according to the clinical trial plan. As the TANITA body composition analyzer is a CE-marked medical device, we intend to use it in normal clinical practice after the clinical trial is finished.

The TANITA body composition analyzer will be marked with a label stating "Medicinteknisk produkt i klinisk prövning" (Medical device in a clinical trial). It will also be entered in the hospital inventory system. Periodic maintenance will be performed according to manufacturer's instruction stated in the IFU (instructions for use). The inventory system records the physical location, date of receipt and batch/serial number of the device. Marking, registration and periodic maintenance will be performed by the Biomedical Engineering Department at Sahlgrenska University Hospital.

All medical devices used in the study will be placed in the hospital inventory system and periodic maintenance will be performed according to manufacturer's instructions.

13. Statements of compliance

13.1. Compliance to the investigational plan, good clinical practice, and regulations

The clinical trial will be conducted in accordance with the CIP, the ethical principles of the Declaration of Helsinki, the principles of SS-EN ISO 14155:2020 and current national and international regulations governing this clinical trial. This is to ensure the safety and integrity of the participants as well as the quality of the data collected. The clinical trial shall not begin until the required regulatory and ethical assessments have been completed with non-negative outcomes, in accordance with Medical Device Regulation (MDR) and national legislation. Any additional requirements imposed by the Ethics Committee or regulatory authority shall be followed.

13.2. Insurance

The participants in the clinical trial will be covered by Swedish Patient Insurance (patientskadeförsäkring) and liability insurance (ansvarsförsäkring).

14. Informed consent process

14.1. General process for informed consent

Before the first baseline visit at the annual health checks, patients will be screened for eligibility according to inclusion and exclusion criteria. If they are eligible, they will be invited to participate in the clinical trial during the annual health checks.

A representative of the clinical trial team at each outpatient clinic will introduce the clinical trial to eligible patients and ensure that these patients receive full and adequate oral and written information about the clinical trial, its purpose, potential risks and benefits, and inclusion and exclusion criteria. The patients must also be informed that they are free to discontinue their participation in the clinical trial at any time without having to provide a reason. Patients shall be given the opportunity to ask questions and be allowed time to consider the information provided and participation in the clinical trial. Upon agreement the patient will be referred to as participant and both the participant and the representative of the clinical trial team shall sign the informed consent form. In connection with the information, the participant has the right to decline registration and is informed of the right to end his/her participation in the register at any time, without this affecting the treatment. A copy of the participant information as well as a copy of the informed consent form shall be provided to the participant. The participant’s signed and dated informed consent must be obtained before performing any activity specific to the clinical trial. The process shall be documented in the participant’s source documents and the signed informed consents shall be maintained with the essential documents. If new information becomes available that can significantly affect a participant’s future health and medical care, that information shall be provided to the affected participant(s) in written form. If new information is added to the clinical trial, the participant has the right to reconsider whether he/she will continue their participation.

15. Adverse events, adverse device effects and device deficiencies

15.1. Definitions

15.1.1. Adverse Event

An Adverse Event (AE) is untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical trial, whether or not related to the investigational device.

This definition includes events that are anticipated as well as unanticipated events

This definition includes events occurring in the context of a clinical trial related to the investigational device or the procedures involved.

15.1.2. Adverse Device Effect

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

15.1.3. Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that led to any of the following:

a) death,

b) serious deterioration in the health of the participant, that resulted in any of the following:
   i. life-threatening illness or injury,
   ii. permanent impairment of a body structure or a body function,
   iii. hospitalization or prolongation of patient hospitalization,
   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
   v. chronic disease,

c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect

15.1.4. Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

SAEs related to procedures imposed by the clinical trial plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

15.1.5. Unanticipated Serious Adverse Device Effect

An Unanticipated SADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a

device shall be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the CIP but not with the use of the device shall not be considered Serious Adverse Device Effects.

15.1.6. Device Deficiency

A Device Deficiency (DD) is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

15.2. Recording and Reporting

15.2.1. Recording

The principal investigator or an authorized designee will record:

- all AEs except the following events specified not to be recorded; The symptoms and signs that are clearly related to psychotic disorders and the expected course of the condition and to the adverse effects of medications used. In addition, AEs will not be followed or recorded at the control clinicssince these participants will not be exposed to any of the devices.
- all SAEs
- all DDs
- any new finding in relation to any of the above-mentioned events.

15.2.2. Reporting

The investigators will report all SAEs and DDs to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel’s awareness of the event.

The sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

- any SAE that has a causal relationship with the investigational device or the investigation procedure, or where such causal relationship is reasonably possible;
- any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and
- any new findings in relation to any event referred to above.

Reporting by the sponsor will be done by filling out the “Summary Reporting Form” (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/participants, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

15.2.3. Assessment of Causality

The relationship between each adverse event and the investigational device and the investigation procedure will be assessed and recorded by the investigator and sponsor. For assessment of causality, the IB and the risk analysis report will be consulted. The sponsor and investigator will distinguish between SAEs related to the investigational device and those related to the procedures, relatedness to both is possible.

Each SAE will be classified according to four different levels of causality:

1. Not related
   Relationship to the device or procedures can be excluded when:
   – the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
   – the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   – the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   – the event involves a body-site or an organ that cannot be affected by the device or procedure;
   – the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   – the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
   In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.
2. Possible
   The relationship with the use of the investigational device or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.
3. Probable
   The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. Causal relationship
   The SAE is associated with the investigational device or with procedures beyond reasonable doubt when:
   – the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   – the event has a temporal relationship with investigational device use/application or procedures;
   – the event involves a body-site or organ that
      - the investigational device or procedures are applied to;
      - the investigational device or procedures have an effect on;

– the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
– the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
– other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
– harm to the participant is due to error in use;
– the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

16. Premature termination of the clinical trial

The sponsor may suspend or prematurely terminate either the clinical trial at an individual clinical trial site or the entire clinical trial for significant and documented reasons. The Swedish Medical Products Agency may suspend or prematurely terminate the clinical trial at the applicable clinical trial sites.

If suspicion of an unacceptable risk to participants arises during the clinical trial, or when so instructed by the Medical Products Agency, the sponsor will suspend the clinical trial while the risk is assessed. The sponsor will terminate the clinical trial if an unacceptable risk is confirmed. The sponsor will inform all investigators.

The sponsor shall consider terminating or suspending the participation of a particular clinical trial site or investigator in the clinical trial if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If, in the opinion of the investigator, the clinical observations in the clinical trial suggest that it may be unsafe to continue the clinical trial at the site, the investigator may terminate participation in the investigation after consultation with the sponsor. A written statement fully documenting the reasons for such termination will be provided to the sponsor. If the clinical trial is prematurely terminated, the investigators shall promptly inform the participants and take necessary steps to finalize their engagement in the clinical trial. All relevant investigation material must be collected, and accountability completed.

If the clinical trial is interrupted or terminated prematurely the sponsor will report to the Medical Products Agency within 15 days together with a justification. If the sponsor has temporarily halted or prematurely terminated the clinical trial on safety grounds, the Medical Products Agency will be informed within 24 hours. A clinical trial report will be prepared within three months of the early termination or temporary halt, irrespective of the results. In the event that the clinical trial is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical trial report until the clinical trial has been completed.

The final clinical trial report shall include details with respect to the temporary halt.

17. Publication policy

The clinical trial will be registered in a publicly accessible database before the start of recruitment activities and the content will be updated throughout the conduct of the clinical trial and the results entered at completion of the clinical trial. The results will be submitted for publication in scientific journals. The first results are expected to be available in 2027. Results will also be disseminated through, for example, national and international conferences, meetings at the relevant county councils, or in the media.

18. References

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19. Appendix

Appendix	File name
Medical history protocol (Intervention clinics)	Appendix_bilaga 1_LAGOM
Medical history protocol (Control clinics)	Appendix_bilaga 2_LAGOM
Flowchart	Appendix_bilaga 3_LAGOM