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Kontigo Care

Clinical Study Protocol

TripleA-enhanced aftercare after basic treatment of alcohol dependence in outpatient care

KC102-001

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Not applicable for the first version of the protcol.

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INNEHÅLLSFÖRTECKNING

1. Summary

TripleA-enhanced aftercare after basic treatment of alcohol dependence in outpatient care **KC102-001**	
Study design	A randomized, controlled, open-label study comparing conventional therapy with and without enhancement of TripleA.
Length (intervention and follow up period)	12 months
Investigational product	The TripleA product consists of an alcohol meter that is connected to a mobile app that is installed on a mobile phone, as well as caregiver portal.
Interventional arm	TripleA - a medical technology system that can frequently and space-boundly measure whether a person has drunk alcohol - in addition to conventional treatment.
Control arm	Conventional treatment (without addition of Triple A)
Study population	Adults with alcohol dependence. The clinical study intends to frequently and place-bound, through several measurements per day, monitor sobriety for patients in outpatient care and aftercare during alcohol treatment. The population refers to patients undergoing conventional outpatient treatment with medication (eg disulfiram [Antabus], acamprosate [Campral], naltrexone [Naltrexone Vitaflo] and nalmefene [Selincro]) and / or with various therapies (CBT, MI call, 12- step treatment).
Number of subjects	106 randomised patients, distributed 1:1 between test arm and control arm
Inclusion criteria	• Patients for whom there is a care commitment for the alcohol program at the Addiction and Neuropsychiatry, Uppsala University Hospital • 18 years or older • Meets at least 2 of the criteria for addiction / substance syndrome according to DSM-5 • Ability to undestand and communicate in Swedish

	• Ability to handle the technical equipment used in the study (breathalyzer + smartphone) • Has a fixed point (accommodation, night rest place with possibility to charge the phone)
Exclusion citeria	• Schizophrenia • Substance syndrome related to substances other than alcohol and nicotin • Impaired lung function (not able to achieve adequate exhalation volume for breathalyzer function) • The patient is cared for within the framework of LVM • Unsuitable to participate in the study according to the examiner's assessment • Has not consumed any alcohol during the 4 weeks that baseline Time Line Follow Back refers to. • Normalized CDT and PEth-values in blood samples collected at visit 1.
Study Objectives	Primary objective The primary objective of the study is to investigate differences in alcohol consumption patterns between alcohol dependents who receive only conventional treatment and alcohol dependents who receive conventional treatment enhanced with TripleA. Secondary objectives • Investigate whether more patients can achieve and maintain sobriety if conventional treatment is enhanced with TripleA • Investigate whether TripleA can help reduce the number of relapses and whether the relapses may be delayed • Investigate whether TripleA can help fewer patients discontinue treatment • Collect data on health outcomes as a basis for health economic analyzes • To use interviews to evaluate how users experience the product TripleA in different respects

Outcomes	Primary Outcome Difference between the treatment arms in proportion of patients with no heavy drinking days during the 4-weeks period before the 12 months follow-up visit. Secondary Outcomes Difference in proportion of sober patients during the four weeks period before the 6 and 12 months visit, respectively. Difference in total amount consumed alcohol per 4 weeks period before 6 and 12 months visit, respectively, compared to baseline. Difference in number of heavy drinking days per 4 weeks period before 6 and 12 months visit, respectively, compared to baseline. Difference in number of sober days per 4 weeks period before 6 and 12 months visit, respectively, compared to baseline. Difference in number of standard glasses per drinking day during the four weeks period before the 6 and 12 months visit, respectively. Time to relapse Clinical Global Impression improvement after 6 and 12 months, respectively. Change in health outcome measured with EQ5D Proportion of patients who have reduced their AUDIT score after 12 months. Proportion of patients who have reduced their AUDIT score with at least one zone. Proportion of patients having a risk level <II (i.e. less than 6 AUDIT points for women, 8 AUDIT points for men) after 12 months. Change in degree of alcohol dependence measured as the difference in SADD-points at 12 and 6 months respectively, compared to baseline. Compliance with agreed treatment. Change in the presence of the alcohol metabolites PEth and CDT in the blood at 6 and 12 months respectively compared to baseline.

2. Introduction

Problematic Alcohol consumption

The WHO's Global Status Report on Alcohol and Health 2014 contains comprehensive statistics on alcohol consumption from 2010. It shows that the part of the world's population that was 15 years or older in 2010 consumed 6.2 liters of pure alcohol per person, which corresponds to 13.5 grams per person and day. Many people do not drink alcohol at all, but of those who drink and are 15 years or older, 16% globally, almost 23% in Europe and as much as 34.5% in Sweden, regularly drink heavily, i.e. drink 60g of alcohol or more at one and the same time at least once a month.

The prevalence of alcohol dependence is stated in the WHO report to be 4.7% of the population in Sweden (15 years or older), which is higher than the European average. If you combine harmful use and dependence, the figure is 8.9%.

There are several different terms and definitions of having a problematic relationship with alcohol and other drugs. The terms used also have different meanings depending on the business and occupational group.

In the medical field, the terms are mainly linked to the diagnostic classifications used. In Sweden, ICD-10 is mainly used in the diagnosis of diseases in the health care system. DSM is used in research and to some extent in psychiatric activities. Until recently, the DSM-IV was used which distinguished between alcohol dependence and abuse. In the latest version of DSM, DSM-5, however, there has been talk of substance abuse syndrome. Substance syndrome is a combination of the two previous concepts of addiction and substance abuse. For diagnosis, at least two criteria must be met. The degree of difficulty is stated as “mild” if 2–3 criteria are met, as “moderate” if 4–5 criteria are met, and as “severe” if more than 5 criteria are met.

Heavy drinking has many negative consequences and is one of the leading causes of premature death and illness in Europe. The costs of this, which can be linked to health care, drunk driving, unemployment, absenteeism from work, reduced productivity of those who work despite drinking, premature mortality and the harm to people in the environment, are enormous. The most recent estimate of Swedish annual costs was made in 2002 and the estimated amount was then close to SEK 30 billion (Johansson 2006).

Treatment goals

The goal of the treatment of alcohol dependence used to be almost always complete sobriety, but in recent decades the idea of controlled drinking where one achieves a significant risk reduction without total abstinence has gained ground. Controlled drinking can be a way of accepting treatment for one's alcohol dependence even if one is not prepared to give up completely, and can significantly reduce the physical and psychosocial consequences of alcohol use. However, it is not uncommon during the course of treatment to need to re-evaluate the goal when the patient realizes that he or she is unable to control drinking, and then may become more motivated to try to stay completely sober instead. There are results that indicate that regardless of whether the goal of treatment is risk reduction via controlled drinking or complete sobriety, you get equivalent outcomes. However, the fact that patients themselves can be involved in choosing their treatment goal increases the possibility that the treatment will be successful. (van Amsterdam and van den Brink, 2013).

A new product to enhance the treatment

TripleA is a new product based on measuring alcohol in the exhaled air place-bound, discreetly and frequently (several times a day). Measurement of alcohol (ethanol) in breath tests is an established method for detecting or dismissing the influence of alcohol, for example in connection with sobriety checks in traffic and in alcohol locks. Exhalation tests are also used in healthcare, prison care and in working life. TripleA conveys information about the results of the alcohol measurements to the patient's regular care contact. The idea with the product TripleA is that it should function as a complement to the treatment regardless of the goal and type of treatment.

Two separate clinical trials are being conducted to evaluate the product in two different contexts: KC102-001 and KC102-002. Both studies are briefly described in the following sections. This study protocol then describes the implementation of KC102-001.

KC102-001 – Clinical study of TripleA in diagnosis, care and aftercare of alcohol dependence in outpatient care

The study KC102-001 is carried out in connection with outpatient care at the Academic Hospital's Addiction Clinic. It is possible here to introduce the product already during the assessment phase, when information is gathered and an assessment is made of what treatment the patient needs. TripleA can be continued (or initiated) even during the treatment phase as patients have close contacts with their therapist and often also start drug treatment. Drug treatment can be alone or in combination with other therapy which can be motivational conversations, cognitive behavioral therapy, etc. Exhalation and blood sampling are common. Biofeedback, which means that you return the test results to the patient and can link changes in drinking patterns to changes in the result when taking samples, is a way to make the patient aware and interested in how alcohol affects the body. The patient can see in black and white that reduced alcohol consumption has improved health.

When the primary treatment is completed and switched to follow-up / aftercare with sparse recurrences, TripleA continues to support the patient and maintains contact with the caregiver. At Akademiska sjukhuset, both complete sobriety and risk reduction through controlled drinking are used as treatment goals, which is adapted individually for each patient.

KC102-002 – Clinical study of TripleA-enhanced aftercare after basic treatment of alcohol dependence in treatment homes

The study KC102-002 is carried out in connection with inpatient care at Nämndemansgården's treatment home. Nämndemansgården's operations use the 12-step program. After at least one month of intensive treatment in a boarding school, the patients switch to aftercare activities that involve meetings every week or month. The 12-step program aims for complete sobriety. Aftercare involves more frequent follow-up compared with the University Hospital's model, but no samples are taken and no medication is prescribed. Patients are provided with TripleA before leaving the treatment home or at the first aftercare.

3. The alcohol program at the Academic Hospital

3.1. The three phases of the alcohol program

Patients are welcome to contact the addiction clinic for advice and / or self-report. Patients are also admitted on referral from somatic care, other psychiatry, primary care and other actors such as the prison service, social services, student health and occupational health care. All referrals are assessed via an outpatient round. The staff group consists of a team with different professions to ensure adequate care where both medical and psychosocial factors are taken into account.

The efforts of the alcohol program are divided into three different phases: the way in, the way through and the way forward.

In the first phase - the way in - the focus is on assessment and investigation. The first phase ends with the patient receiving an oral and written summary of what has emerged during the assessment interviews.

If the patient then chooses to proceed, phase two begins - the way through. Here, the patient, together with their therapist, will weigh the advantages and disadvantages of a change and make a plan for how the change will take place and which treatment options suit the individual. The treatment is evaluated continuously and at follow-up meetings after the end of treatment.

In the last phase - the way forward - there is either a conclusion or an in-depth assessment based on social complications, somatic complications, psychiatric comorbidity and / or resource level. The results provide guidance on whether the patient should be referred to another instance or whether other interventions may be relevant within the framework of the alcohol program.

Within the alcohol program, drugs are combined with methods such as relapse prevention with motivational conversations. Within the framework of the current study, all study participants will undergo some form of conventional treatment, i.e. any or a combination of the following treatment methods. The intervention group will also have access to TripleA. The description of the conventional treatment methods in section 3.2 below is taken from the Clinical Handbook 2014 Alcohol - Risk use, addiction and dependence, Alcohol syndrome A decision support in the investigation and treatment of Tobias Eriksson, Chief Physician Addiction & Neuropsychiatry, Academic Hospital.

3.2. Conventional treatment at the addiction medicine clinic

3.2.1. Relapse prevention

Relapse prevention has its origins in cognitive behavioral therapy (CBT), which is about re-learning and reorientation based on the mapping of dysfunctional thoughts and behaviors.

You can individually or in groups, among other things, handle cravings, say no to alcohol, plan for emergencies and handle incipient relapses. You get to learn about the brain's reward system and problem solving. The concept of post-acute abstinence is highlighted, where the imbalance in the reward system gives different symptoms long after acute symptoms have subsided.

The treatment is usually carried out during eight sessions, each of which takes approximately 45-90 minutes, depending on whether it is individual or in a group. Between the sessions, the participant is given homework that translates theory into practice and provides tools for dealing with everyday life.

3.2.2. Motivating conversation

Here, the treatment is focused on the patient's own will for change, which requires a lot of motivation as you have to bring about a change in habits that have been around for a long time.

The therapist in motivational conversation therapy is neutral during the sessions and does not describe what is good to do, but should instead help to get the patient to express arguments for and against drug consumption and then make their own decisions that lead to change in the right direction.

This is a treatment model that suits risk users and those with more limited problems.

3.2.3. Drug treatment

Acamprosate (drug name Campral, Aotal) inhibits the effect of excitatory neurotransmitters in the brain. The drug prevents the increase of glutamate extracellularly in the brain in connection with alcohol withdrawal and the reward system is favorably affected. Tablets of 333mg are dosed 2 + 2 + 2 at body weight over 60kg and 2+ 2 if the body weight is below 60kg. The drug reduces the positive experience of alcohol and prolongs the time to alcohol consumption or relapse.

Naltrexone is an opiate receptor antagonist and reduces the effect of the endorphins released during alcohol intake, this affects the reward system which clinically manifests itself as reduced cravings, and increases the number of non-alcoholic days. 50mg tablets are dosed once daily.

Nalmefen (drug name Selincro) is an opioid system modulator with effect on my, delta and kappa receptor. Due to rapid uptake works in need procedure.
The drug affects the brain's motivational system with the end result of reducing the desire for alcohol intake and avoiding loss of control.

The preparation has the indication reduction of alcohol consumption and may be relevant in the treatment of risk consumption where the desire is a reduction rather than completely stopping consuming alcohol. 18 mg tablets are taken 1x1 if needed. The patient should take the preparation before any alcohol consumption, preferably the drug should be taken 1-2 hours before presumed consumption but can have an effect even if you take it when you start drinking. You should not take more than one tablet per day.

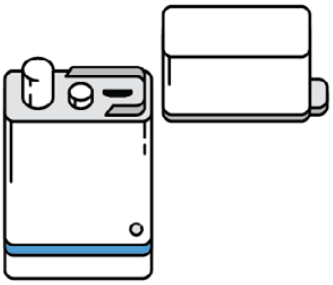
Disulfiram (Antabus) is an old, well-proven aversion drug based on the principle that it should be so unpleasant to drink alcohol that one refrains.

Alcohol is broken down in the body via two steps where the latter means that acetaldehyde becomes acetic acid and water with the help of the enzyme aldehyde dehydrogenase. This enzyme is blocked by disulfiram and an accumulation of acetaldehyde when consuming alcohol causes symptoms in the form of flatulence, flushing, palpitations, throbbing headache, nausea and vomiting. Antabus is an excellent preparation for motivated individuals and the best evidence can be noted when it is given supervised. Tablets of 400mg are taken three times a week, in case of side effects you can prescribe 200mg daily. Should be supervised if possible.

4. Identification and description of the test product

4.1. TripleA

The TripleA system consists of an alcohol meter, an app, a caregiver portal and a database. The care recipient uses the alcohol meter and the associated app for sobriety tests and in some cases for registration of meetings. Sobriety tests and meeting participation are controlled from the caregiver portal. All information is handled in accordance with the Personal Data Act. The care provider delivers TripleA to the care recipient. TripleA can be used immediately.



Alcohol meter

The alcohol meter measures and analyzes alcohol in the exhaled air. The information is transmitted wirelessly to the app.

Application

A message from the caregiver portal urges the user to take a sobriety test..

The user opens the app and starts the alcohol meter, after which the devices ate connected via Bluetooth.

The user starts a sobriety test using the app and does a breath test. During sampling, a photo is taken to ensure the correct identity of the sampler. The test result is displayed in the caregiver portal for the caregiver. In the app, you can also check in for meetings by registering the GPS coordinates for the meeting you visit.

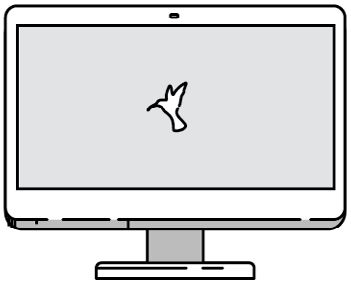
Database

The database stores all information regarding sobriety testsm photis and reigsterd meetings. All data is stored securely in accordance with the Personal Data Act.

Caregiver portal

In the caregiver portal, the caregiver registers his patients and can create an inividual plan for sobriety tests and meeting participation..

Via the caregiver portal, the caregiver can check the results from sobriety tests and meeting participation as well as personal identification.



4.2. Manufacturer

Kontigo Care AB, Box 11008, 750 11 Uppsala.
Visiting address: Dragarbrunnsgatan 35, Uppsala.

4.3. Product identification

TripleA 1.0.

TripleA is a CE-marked medical device and meets the requirements of the Medical Products Agency's regulations LVFS 2003: 11 .. TripleA has been developed in accordance with the European Medical Directive 93/42 / eec. TripleA is developed for professional use and meets applicable requirements for accuracy in accordance with SS-EN 15964: 2011.

TripleA is classified as a Class I product according to rules 5 and 12 of MEDDEV 2.4 / 1. The product has a measuring function but does not fully meet the criteria for class Im according to MEDDEV 2.1 / 5.

4.4. Traceability

Each alcohol meter has a unique serial number and is paired with a specific mobile phone with associated app. The information is stored in Kontigo Care's database. Via the care provider portal, it is registered which meter has been distributed to which study patient, which ensures traceability and the possibility of delivering a new unit to the patient when it is time for calibration or if a unit needs to be replaced due to a malfunction. Only staff authorized by Kontigo Care have access to patients' personal data and a secure login is required to view data. Unauthorized staff at Kontigo Care cannot see a patient's personal information

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4.5. Intended use

TripleA is intended for medical use by caregivers and patients in the treatment of alcohol dependence. TripleA is a complement to other methods available to the caregiver to control patients' sobriety and compliance with therapy over time and to motivate patients to maintain sobriety. The product consists of an alcohol meter for exhaled air controlled via an app, a web-based care provider portal for handling patients and a database for collecting and storing information and measurement data.

TripleA is intended for use by patients for:

Frequent and site-bound sobriety measurement.

• Registration of participation in planned treatment meetings such as AA meetings.

TripleA is intended to be used by caregivers for:

• Supervision and control of sobriety measurements and meeting participation.

• Evaluation of measurement results and management of the outcome of patients' compliance with therapy.

4.6. Composition of the test product

The test product TripleA consists of an alcohol meter, a mobile phone with an installed app, a micro-USB charger, instructions for use and extra blow nozzles. The blowing nozzle that will be placed in the user's mouth is made of a biocompatible plastic material (Cycoloy HC1204HF-8H5D003).

Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are conjugated ethanol metabolites that are commonly measured in urine samples but can also be measured in blood and hair samples. EtG and EtS in urine are used as markers to detect alcohol consumption or confirm sobriety during the last 24 hours. A minor to moderate alcohol intake can be detected for up to 1 day and intoxication for up to a couple of days afterwards. EtG and EtS are eliminated more slowly than ethanol and therefore they can be used even after the ethanol has disappeared from the body. (Helander 2011).

Phosphatidylethanol (PEth) is a group of membrane lipids formed from phosphatidylcholine in the presence of ethanol and measured in whole blood. PEth is used as a marker to demonstrate regular alcohol consumption and "risk use" or to confirm sobriety in recent weeks (Helander 2011). PEth is specific for alcohol, but does not detect occasional intoxication. The half-life is 4-7 days (Helander 2011, Helander et al 2012). The concentration of PEth-16: 0/18: 1 in the blood reflects the alcohol consumption of recent weeks. PEth-16: 0/18: 1 values lower than 0.05 µmol / L indicate no or low sporadic alcohol consumption. Values between 0.05-0.30 µmol / L speak for regular moderate consumption, but even occasional very large intakes of alcohol can probably give measured values in this range. (Sampling instructions B-Phosphatidylethanol, Karolinska University Laboratory).

Low carbohydrate transferrin (CDT) shows alcohol-induced change in the glycosylation pattern of transferrin, which is measured in serum samples. CDT is used as a marker to demonstrate regular alcohol consumption and «risk use / abuse«, where the measured value reflects the intake during the last weeks - the month. Single major alcohol intakes do not affect CDT levels. The specificity is controversial, as an elevated CDT value may have causes other than alcohol.

Within the framework of the current study, PEth and CDT will be analyzed.

4.7. Evaluation of the results of the relevant preclinical tests/assessments performed to justify the use of the test product in human subjects

The product meets the essential requirements according to the Medical Products Agency's regulations for medical devices, LVFS 2003: 11. The product has undergone the required safety tests and meets the requirements of the European standards IEC 60601-1 and 60601-11. Product documentation can be found in the technical file that forms the basis for the CE marking of the product. Electrical safety and EMC have been tested by Intertek.

4.8. Evaluation of clinical data relevant to the current clinical study

Prior to the CE marking of the product, a review of clinical data regarding safety and performance for TripleA and similar products is compiled in the Clinical Evaluation Report. In summary, there is limited data for equivalent products, as TripleA is a system with several components. There is dock data that supports each component itself is secure and has effects and features that can contribute to the composite system.

5. Risks and benefits of the test product and the clinical study

5.1. Expected clinical benefits

TripleA is expected to support the patient in his decision to reduce or completely abstain from alcohol consumption, by reducing the space where one can otherwise drink without anyone else finding out. Via TripleA, the therapist and patient also receive more reliable data on the patient's alcohol intake patterns and can, based on this, find strategies for managing risk situations. TripleA also means that any relapses can be noticed more quickly and further treatment can be initiated if necessary.

5.2. Expected side effects from the test product

The use of TripleA entails a significant restriction on the patient's privacy as information about alcohol intake is communicated to the care provider. However, this is one of the main points of the method and a prerequisite for the use of TripleA both within the framework of the current study and addiction care in general is that it is voluntary for the patient to use TripleA as enhanced support for other interventions.

Probably even a sober patient experiences a strong stress if you do not have the opportunity to perform a prescribed sobriety test within a given time, or discover that you have missed a test. How this is experienced will be mapped in focus group interviews. The patient is also given the opportunity to prove his sobriety by providing an extra blood sample if desired.

5.3. Remaining risks associated with the test product

For the risk management process, Kontigo Care has complied with the harmonized standard ISO 14971: 2012 Medical devices - Application of a risk management system for medical devices.

Appropriate measures have been taken for all foreseeable safety risks that could have been linked to the use of TripleA as intended, or that could arise in the event of a malfunction of any of the components in the system.

5.4. Risks associated with participation in the study

A safety aspect that should be taken into account for the relevant patient group is that an abrupt release of alcohol in people who have had a long-term and high consumption of alcohol is associated with a risk of severe withdrawal symptoms, which can be life-threatening. However, this is not linked to the use of TripleA per se, but a consequence of the release of alcohol.

5.5. Interactions

TripleA does not affect concomitant pharmacological treatment.

5.6. Risk reduction measures

Usual clinical procedures must be applied to manage the risks of discontinuation of alcohol and can e.g. is about gradual reduction of alcohol intake or hospitalization for detoxification.

5.7. Risk-benefit motivation

The benefit of TripleA is judged to outweigh the risks of the current patient population, especially given that the method in the current study does not replace any other treatment but is used as a supplement to, and reinforcement of, patients' regular care.

The risks mentioned in sections 6.3 and 6.4 above must also be set in relation to the consequences of continued alcohol consumption, both with regard to the patient's own health and for the co-dependents, consequences that may be considered significantly more serious.

6. The study´s objectives and hypotheses

6.1. Objectives

6.1.1.Primary objective

The primary objective of the study is to investigate differences in alcohol consumption patterns between alcohol dependents who receive only conventional treatment and alcohol dependents who receive conventional treatment enhanced with TripleA.

6.1.2. Secondary objectives

- Examine whether more patients can achieve and maintain sobriety if conventional treatment is enhanced with TripleA
- Investigate whether TripleA can contribute to fewer patients relapsing and whether relapse can be delayed
- Investigate whether TripleA can help fewer patients discontinue treatment
- Collect data on health outcomes as a basis for health economic analyzes
- To use interviews to evaluate how users experience the product TripleA in different respects

6.2. Hypotheses

By strengthening TripleA with the conventional hospital care of alcohol addicts (medicines and therapy calls), a larger proportion of patients is obtained who significantly reduce their alcohol consumption or become completely sober, thereby reducing their risk of somatic and / or mental injuries.

6.3. Claims and performance to be verified

The desired effect of treatment for alcohol dependence is to improve physical and psychosocial parameters. As a surrogate variable, however, it is accepted that you measure changes in the drinking pattern, which can be either absolute sobriety, or a reduction in the number of heavy drinking days. Regardless of how one chooses to evaluate treatments for alcohol dependence, a basic attitude is that if the treatment does not change the drinking pattern in a positive direction, it has not been successful. In this verification study, the hypothesis is that the use of TripleA enhances conventional treatment so that the drinking pattern with TripleA means a clinically relevant reduction in alcohol intake, compared with the drinking pattern without TripleA. Clinically relevant is that heavy drinking days do not occur.

6.4. Risks and adverse effects

Experiences with regard to invasion of privacy, etc. will be mapped via questionnaires to the participating patients / focus group interviews.

Risks and expected undesirable effects of the test product are assessed in advance as small, but safety reporting during the course of the study is essential in order to be able to capture any unexpected effects and risks with TripleA. See also section 18 (Safety reporting).

7. Study design

7.1. Generally

7.1.1. Type of clinical study

The study is a 12-month open and randomized comparison between the control group receiving conventional therapy only and the intervention group receiving conventional therapy enhanced with TripleA.
The study is open because it is the overall concept TripleA that is to be evaluated, which means that both the patient and the therapist must use the tool. A single-blind design could have been used if the goal had been to study the system's components, e.g. only changed patient behavior due to increased support or how therapists' efforts change with or without the information that TripleA can provide. If you want to study the combination effect, the study cannot be blinded.
Many treatments work to achieve sobriety or controlled drinking in the short term, but it is more difficult to maintain the effect over time, as the problems behind drinking do not necessarily disappear because you stop drinking or reduce your drinking. The EMA and the FDA, respectively, recommend 12 or 6-month studies, as the drinking pattern at these times has been shown to be predictive of long-term outcomes.
In the current studies, patients will be followed for 12 months to cover all the holidays of the year and other regularly recurring challenges for those who try to refrain from drinking alcohol. An interim analysis is performed after 6 months to obtain data that can support the system patent for TripleA.

7.1.2. Baseline

The process leading up to a treatment intervention can look very different for different patients. Some will therefore have been sober or significantly reduced alcohol consumption for a long time before it becomes relevant with visit 1. To then always use the 4 weeks preceding visit 1 as a baseline for Time Line Follow Back will be very wrong. It is therefore up to the care provider to, in consultation with the patient, define which four-week period is to be counted as the baseline in each individual case. It should be a continuous period of four weeks, and the most recent four-week period that has a representative alcohol intake pattern for the period before the decision to seek help / initiate treatment was made.

7.1.3. Measures taken to minimize or avoid bias/impact

7.1.3.1. Randomization

Randomization of study participants is important to avoid the caregiver consciously or unconsciously distributing TripleA treatment to a certain category of patients. The patient population is heterogeneous, but demographic and social differences between the study arms should be due to chance and not other factors. The randomization takes place according to the principle of permuted blocks in order to distribute the patients as far as possible so that the individual therapists do not treat only one study arm. Each caregiver will have access to their own randomization list. See also section 8.8.2.

7.1.3.2. Sampling as a complement to TLFB

The TimeLine Follow Back method relies on patients remembering and wanting to talk about their alcohol consumption. To improve reliability, TLFB will be combined with sampling of biomarkers for blood alcohol.

7.2. Efficacy endpoints

7.2.1.Primary efficacy endpoint

Proportion of patients who do not have heavy drinking days
Clinically relevant for treatment focused on risk reduction is that patients do not have heavy drinking days. The measurement tool will be TLFB (see Appendix C) where the number of days with large consumption over a four-week period is calculated.
Heavy drinking days are the same as days with heavy consumption, which means consumption of 4 or more standard glasses of alcohol per day for women and 5 or more standard glasses of alcohol per day for men.
How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit. The primary measure of effectiveness is the difference between the treatment arms in the proportion of patients who do not have heavy drinking days during the 4-week period preceding the 12-month visit.

7.2.2. Secondary efficacy endpoints

Difference between the treatment arms in the proportion of completely sober patients during a 4-week period at 6 and 12 months, respectively.

The proportion of completely sober patients is measured with TLFB. To be considered sober, the patient must have entered 0 standard glasses consumed during the 4-week period preceding the 6- and 12-month visits, respectively.

The difference in the total amount of alcohol consumed per 4-week period after 6 and 12 months, respectively, compared with baseline

The total amount of alcohol consumed per 4-week period is measured in standard glasses using TLFB, and is the sum of the number of glasses for the entire period. How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit.The difference in the number of heavy drinking days per 4-week period at 6 and 12 months, respectively, compared with baseline

The number of heavy drinking days is measured with TLFB. Heavy drinking days are the same as days with heavy consumption, which means consumption of 4 or more standard glasses of alcohol per day for women and 5 or more standard glasses of alcohol per day for men. How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit.

The difference in the number of drink-free days per 4-week period at 6 and 12 months, respectively, compared with baseline.

The measuring tool becomes TLFB where the number of days of consumption specified as zero standard glass during a four-week period can be calculated. How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit..

The measuring tool becomes TLFB where the number of days of consumption specified as zero standard glass during a four-week period can be calculated. How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit.

The measuring tool becomes TLFB, where the sum of the number of standard glasses for the entire 4-week period is divided by the number of days when alcohol is consumed. How TLFB is to be determined at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit.

Time to relapse

Depending on the goal of treatment, a relapse can be either a day of heavy consumption or drinking at least one standard glass of alcohol. Both recurrence measures will be evaluated.

• The number of days before the first alcohol intake (at least one standard glass) according to the patient's own information.

• The number of days before the first heavy drinking day according to the patient's own information.

Clinical Global Impression improvements after 6 and 12 months, respectively

The patients who after 12 months are “significantly improved” or “greatly improved”, ie they receive a value of 1 or 2 on the CGI-I scale (see section 8.3.6) are considered to have responded to the treatment (responders). Patients with a value of 3 or higher are classified as non-responders. The proportion of responders will be compared between the treatment arms.

Change in quality of life measured with EQ-5D

EQ-5D is an accepted and widely used measure of quality of life, and the form is recommended by TLV (Dental and Pharmaceutical Benefits Agency). A general quality of life measure such as EQ-5D provides an overall picture of the study participants' perceived health, and is a good basis for health economic analyzes.

AUDIT improvement

The National Board of Health and Welfare prioritises AUDIT as a tool for identifying alcohol problems. The treatment arms will be compared with respect to:

• Proportion of patients who after 12 months have lowered their AUDIT score

• Proportion of patients who after 12 months have lowered their AUDIT score to at least one zone

• Proportion of patients who after 12 months have a risk level <II

(i.e. less than 6 AUDIT points for women, 8 AUDIT points for men).

SADD improvement

Change in alcohol dependence measured as the difference in SADD scores at 12 and 6 months, respectively, compared with baseline).

Compliance with agreed treatment

The patient remains in treatment

At each study-related visit, it is documented whether the patient remains in treatment or has interrupted his or her treatment. The proportion of patients who remain in treatment will be compared between the patient groups over time.

Compliance with TripleA

For the TripleA arm, the proportion of measurements performed compared to announced measurements will be reported. The information is retrieved from the TripleA database where all notifications and measurements are logged. Corresponding information is not available for the control arm for obvious reasons.

If the patient has a valid explanation for the lack of an individual blow, the caregiver can state this in the system, and indicate whether or not there should have been alcohol in the exhaled air at the time in question.

Compliance with the agreed plan for visits to the care provider and / or visits to AA meetings

In cases where the caregiver and patient have agreed that the patient should participate in certain activities, such as e.g. relapse prevention course or MI call, compliance with this plan will be evaluated. The ratio between the number of occasions the patient participated relative to the planned number is calculated and expressed as a percentage. The calculation is made per type of activity, eg:

• The number of treatment meetings that the patient has participated in the last 4 weeks divided by the number of planned treatment meetings for the corresponding period.

• The number of AA meetings visited in the last 4 weeks divided by the agreed number of AA meetings the patient would have attended for the corresponding period.

For the TripleA arm, this information can be retrieved from the TripleA database if that function has been used. However, the comparison between the treatment arms is based on the information noted in the CRF during the visits when the patient is asked about his or her participation. For the TripleA arm, an analysis is then made of how large the correspondence is between the registrations in TripleA and the data in CRF.

Compliance with drug treatment

Adherence to drug treatment will not be evaluated in the context of the study.

Change in the presence of the alcohol metabolites PEth and CDT in the blood at 6 and 12 months, respectively, compared with baseline.

Phosphatidylethanol (PEth) is analyzed at Karolinska Laboratory. The concentration of PEth-16: 0/18: 1 is given in the unit µmol / L. The PEth level in the blood reflects the alcohol consumption of recent weeks. PEth-16: 0/18: 1 values lower than 0.05 µmol / L indicate no or low sporadic alcohol consumption. Values between 0.05-0.30 µmol / L speak for regular moderate consumption, but even occasional very large intakes of alcohol can probably give measured values in this range.

Low carbohydrate transferrin (CDT) shows alcohol-induced change in the glycosylation pattern of transferrin, which is measured in serum samples. CDT is used as a marker to demonstrate regular alcohol consumption and «risk use / abuse«, where the measured value reflects the intake during the last weeks - the month. Single major alcohol intakes do not affect CDT levels.

Analyzed at the Academic Laboratory and reported in%. Reference interval <2.0%.

7.3. Methods and times for measuring, registering and analyzing variables

7.3.1. Short Alcohol Dependence Data (SADD)

SADD consists of 15 questions that measure the degree of alcohol dependence using a points scale. The form can be answered by the therapist interviewing the patient or filling in by the patient himself. Estimated time consumption max 5 minutes. See Appendix B

Time: Made at visit 1 to collect baseline data, and at 6 and 12 months.

7.3.2. Alcohol calender– Time-Line Follow-Back

Time-Line Follow-Back (TLFB) is a method that can be used to obtain information about patients' alcohol consumption. (Sobell, Maisto et al 1979). In short, it means that as far back as 3 months ago, you retrospectively reconstruct how many standard glasses you have consumed per day. It is accepted that the reporting is not an exact representation of the alcohol intake, but also that it

provides a decent benchmark, which is also sensitive to changes in the drinking pattern. An alcohol calendar (see Appendix C) is used for this purpose. For study purposes, alcohol consumption reported via TLFB is used for the 4 weeks preceding each visit. How to determine the TLFB at baseline is stated in section 8.1.2.

When filling in TLFB, the patient and therapist must consult and results of blood tests and for the intervention arm, TripleA measurements must also be taken into account to identify if and when alcohol intake has occurred.

Information about missed measurements or measurements that show alcohol in the exhaled air (both for TripleA and for regular measurements at the care provider) should be used in the TLFB call and should in the alcohol calendar correspond to a number greater than 0 standard glasses on the current day. There may be discrepancies between what the patient is willing to state in the TLFB and the information that the caregiver has available in the TripleA caregiver portal or from other sources. The caregiver should talk to the patient about this, and give the patient the opportunity to update the information in the TLFB if necessary, but should not force the patient to enter a number greater than 0 or change information provided by the patient without the patient's consent.

In CRF, it is possible for the care provider to state whether there are signs of alcohol intake that do not correspond to reported intake in TLFB.

Time: At each visit.

AUDIT (The Alcohol Use Disorders Identification Test)

AUDIT (See Appendix D) is a well-validated instrument that is useful for identifying both alcohol problems and high alcohol consumption. However, AUDIT is not a diagnostic tool. You get a picture of consumption and the degree of difficulty of the problem. AUDIT consists of ten short questions and check boxes for the answers. It takes 2-3 minutes to answer the form that deals with last year's alcohol consumption. The first three questions are about how often and how much you drink, the rest about the consequences of drinking.

Time: Made at visit 1 (refers to the year before baseline), 5 and 6.

Risknivå	AUDIT-poäng	Tolkning
Zon I	Man 0-7 Woman 0-5	Low risk alcohol habits
Zon II	Man 8-15 Woman 6-13	Risky alcohol habits with not necessarily an addiction
Zon III	Man 16-19 Woman14-17	Problematic alcohol habits likely there is an alcohol-related diagnosis
Zon IV	Man 20+ Woman 18+	Very problematic alcohol habits probably exist one alcohol-related diagnosis

7.3.3. DUDIT (The Drug Use Disorders Identification Test)

DUDIT (Appendix E) has been developed as a parallel instrument to AUDIT, with the aim of assessing whether problems with drugs (including addictive drugs) occur. Based on aggregated points and the distribution of these, the instruments provide information on consumption levels, signs of addiction development and injuries related to consumption.

Time: Made at visit 1

7.3.4. Questions about motivation and belief in one´s own ability

The intention is to measure how motivated the patient is to change their drinking and whether it is the patient's own initiative or pressure from other parties that is behind it. The patient may also value confidence in their own ability to succeed with the change. The patient's own confidence in their ability has been shown to be predictive of treatment outcome, and a simple instrument with only one question has better predictive ability than more complex instruments (Ludwig et al, 2013). The questionnaire can be found in Appendix F.
Time: Made at visit 1

7.3.5.CGI (Clinical Global Impression) Severity and Improvement Scales

CGI is an abbreviation for Clinical Global Impression, which has been translated as "overall clinical impression".

CGI-Severity (CGI-S) means that the caregiver makes an assessment of the severity of the disease based on the question: "In the light of your clinical experience of this particular patient population, how seriously mentally ill is the patient currently?"

An answer option can be specified:

○ Not assessed

○ Normal, not sick at all

○ Limit cases for mental illness

○ Mildly ill

○ Moderately ill

○ Significantly ill

○ Seriously ill

○ Among the most extremely ill patients

Time: Done at visit 1

The initial CGI-S assessment then forms the basis for assessing whether the patient has improved or deteriorated, as indicated on the Clinical Global Impression - Improvement Scale (CGI-I) which is a scale from 1-7 where 1 corresponds to "significantly improved" , 2 "much improved", 3 "slightly better", 4 "unchanged", 5 "slightly worse", 6 "much worse", and 7 "significantly worse".

CGI-I is done at visits 5 and 6.

7.3.6. EQ-5D

The EQ-5D is a standardized instrument for measuring and describing health outcomes. The EQ-5D contains a descriptive questionnaire and a vertical visual analog scale (EQ VAS).

The descriptive questionnaire in EQ-5D consists of questions where the individual can classify their own health in five different dimensions: mobility, hygiene, main activities, pain / discomfort and fear

/ depression on a three-point scale (no, moderate and severe discomfort). The individual's answers to these questions form a health profile that represents a specific health condition.

There are a total of 243 possible combinations of health conditions. On the thermometer-like scale (EQ VAS), the individual can describe how good or bad he feels by putting a cross on the scale from 0 to 100. Where 0 is the worst possible health and 100 is the best possible health. In this way, EQ VAS generates an individual self-rated state of health, so-called VAS score.

Time: Made at visits 1, 5 and 6.

7.3.7. Biological samples (blood and urine)

Samples are ordered via the medical record system, taken and handled according to regular clinical routine. Patients are instructed to leave the samples some week before the visits, so that test results are available for the visit.

For sampling instructions, refer to the latest updated versions on the Academic Laboratory's website.

Urine samples for drug screening usually include amphetamine, benzodiazepines, burprenorphine, cannabis, cocaine, methadone metabolites, opiates. Verification analysis in the event of a positive result on a urine dipstick is performed if clinically relevant

Time: Done at visit 1

Phosphatidylethanol (PEth) is analyzed at Karolinska Laboratory. The concentration of PEth-16: 0/18: 1 is given in the unit µmol / L. The PEth level in the blood reflects the alcohol consumption of recent weeks. PEth-16: 0/18: 1 values lower than 0.05 µmol / L indicate no or low sporadic alcohol consumption. Values between 0.05-0.30 µmol / L speak for regular moderate consumption, but even occasional very large intakes of alcohol can probably give measured values in this range.

Time: Made at each visit

Low carbohydrate transferrin (CDT) shows alcohol-induced change in the glycosylation pattern of transferrin, which is measured in serum samples. CDT is used as a marker to demonstrate regular alcohol consumption and «risk use / abuse«, where the measured value reflects the intake during the last weeks - the month. Single major alcohol intakes do not affect CDT levels.

Analyzed at the Academic Laboratory and reported in%. Reference interval <2.0%.

Time: Made at each visit

7.3.8. The assessment phase

The assessment phase must be documented in CRF with the date of the assessment interview and whether the patient chooses to continue with any type of treatment. If the patient refuses treatment efforts, the patient's participation in the study must be terminated.

Time: At visit 1 and while the assessment phase is ongoing.

7.3.9. Conventional treatment

The treatment interventions that have begun, are ongoing or have ended must be documented in CRF. Start date, end date and scope must be stated for psychosocial interventions. For medicinal products, the substance, dosage form, route of administration, strength and dose frequency and start and end dates are indicated. Time: Made at each visit.

7.3.10. Treatment goal

The goal of the treatment ("To become alcohol-free" or "To reduce alcohol consumption") is documented at visit 1 and any changes in goals are followed up at each visit. If the goal is to reduce alcohol consumption, a target level is documented. At each visit, the caregiver also makes an assessment of whether the patient has achieved his or her own treatment goal or not.

7.3.11. Compliance with treatment and meeting participation

In cases where the caregiver and patient have agreed that the patient should participate in certain activities, such as relapse prevention courses or AA meetings, compliance with this plan will be evaluated. The ratio between the number of occasions the patient participated relative to the planned number is calculated and expressed as a percentage. The calculation is made per type of activity, eg: • The number of treatment meetings that the patient has participated in the last four weeks divided by the number of planned treatment meetings for the corresponding period. • The number of AA meetings visited in the last four weeks divided by the agreed number of AA meetings the patient would have attended for the corresponding period. Time: Done at visits 2, 3, 4, 5 and 6.

7.3.12. TripleA

Random measurements of alcohol in exhaled air, with identity control via mobile camera. Made on request via notification in mobile app - only in the TripleA arm. Reporting of results to the therapist takes place via the caregiver portal.

Timing: Sleep breaks can be added by a therapist. Thereafter, the alcohol tests take place according to schedule daily just before and after the sleep break. A third alcohol test will take place during the waking time between the 2 previous tests. If desired, this can be planned to happen randomly.

The care provider checks the care portal before each patient visit, but does not have continuous supervision of the system within the framework of the study, which is technically but not organizationally possible.

In order for TripleA to always be usable, the mobile phone has been provided with a subscription that allows free calls and SMS, as well as data traffic up to 1GB per month. Kontigo Care is responsible for the subscription fee. The patient can use the phone during the study at no extra cost.

7.3.13. Safety reporting

Patients in the TripleA arm should be asked at each visit if there have been any incidents related to the use of TripleA.

Alcohol-related hospitalization since the previous visit must be noted in CRF for all study participants.

Time: Made at each visit.

7.3.14. Study overview

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Protocol section**
Time point	**Month 0**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 12**	
Informed consent	X						17, **Error! Reference source not found.**
Inclusion and exclusion criteria	X						**Error! Reference source not found.**, **Error! Reference source not found.**
Anamnesis and medical examination	X						7.8.2
Demographic data	X						7.8.2
Beverage history	X						7.8.2
SADD	X*				X	X	7.3.1
TLFB	X*	X	X	X	X	X	7.3.2
AUDIT	X*				X	X	8.3.3
DUDIT	X						7.3.3
Motivation questions	X						**Error! Reference source not found.**
CGI (S and I, respectively)	X^S				X^I	X^I	7.3.5
EQ-5D	X				X	X	7.3.6
Urine sample	X						7.3.7
Blood samples	X	X	X	X	X	X	7.3.7
Documentation of assessment and conventional	X	X	X	X	X	X	**Error! Reference source not found.**,

treatment including drugs							**Error! Reference source not found.**
Compliance to treatment		X¤	X¤	X¤	X¤	X¤	**Error! Reference source not found.**
Safety reporting	X	X	X	X	X	X	7.3.13, **Error! Reference source not found.**
Randomization	X						7.8.2
TripleA dividend and registration in caregiver portal#	X				X		7.8.2
TripleA return#					X	X	7.8.8

*) Refers to baseline
S) CGI-Severity
I) CGI-Improvement Scale
¤) Participation in agreed therapy meetings, AA meetings etc
#) Only intervention arm. TripleA needs to be calibrated after 6 months use and will therefore be replaced at visit 5.

7.4. Equipment to be used in the clinical study to meaasure variables

In addition to the study product, laboratory equipment is used in an accredited laboratory for routine analyzes of alcohol metabolites.

7.5. Loss

7.5.1. Loss of patients

The reason why a patient discontinues treatment or study must be documented and these patients must be followed up. Patients who discontinue the study will not be reimbursed. The loss will be reported.

7.5.2. Loss of individual values

Missed blows are discussed with the patient during the visits. If the patient has a plausible explanation for the lack of a single puff, the caregiver can state this in the system, and indicate whether or not there should have been alcohol in the exhaled air at the time in question. A patient who so wishes may submit an extra blood sample to prove that he has been sober during the period when measurement values are missing.

7.6. Test product(s) and comparator(s)

7.6.1. Description of the exposure of the test product (s) or comparative product, if used.

The test product TripleA is used by the patients in the intervention group throughout the study period, a total of 12 months. The patient is instructed to always carry the breathalyzer and the associated mobile phone. SMS notification indicates that it is time to make a measurement. The patient then needs to complete the measurement within 60 minutes.

Measurement can not be done on the patient's own initiative, but only after activation via SMS notification. SMS notifications occur randomly several times a day, which means that the patient does not know in advance when it is time for the next measurement. The caregiver can set a break for night rest when notifications are not sent.

7.6.2. Justification for the choice of comparative product

Not applicable no comparator will be studied.

7.6.3. List of other medical devices or drugs to be used during the clinical study

No other medical devices or drugs will be linked to the study. However, study participants will be allowed to continue or start using other products and medicines in parallel with the study, provided that this is documented in the patient's medical record.

7.6.4. The number of product units used, and justification for this

One TripleA unit per study participant is used at a time. At 6 months, the unit will need to be calibrated and the study participant will then be assigned a new TripleA to not be without when the first one is sent back to Kontigo Care for calibration.

A total of approximately 200 units are estimated to be used within the framework of the study.

7.7. Subjects

7.7.1. Inclusion criteria for selection of subjects

• Patients for whom there is a care commitment for the alcohol program at the Addiction and Neuropsychiatry, Akademiska sjukhuset
• 18 years or older
• Meets at least 2 of the criteria for addiction / substance syndrome according to DSM-5
• Ability to understand and communicate in Swedish
• Ability to handle the technical equipment used in the study (breathalyzer + smartphone)
• Has a fixed point (accommodation, night rest place to charge the phone)

7.7.2. Exclusion criteria for selection of subjects

• Schizophrenia
• Substance syndrome related to substances other than alcohol and nicotine
• Impaired lung function (not able to achieve adequate exhalation volume for breathalyzer function)
• The patient is cared for within the framework of LVM
• Unsuitable to participate in the study according to the examiner's assessment
• Has not consumed any alcohol during the 4 weeks that baseline Time Line Follow Back refers to.
• Normalized CDT and PEth values in blood samples taken at visit 1.

7.7.3. Criteria and procedures for removing subjects from the study or suspending their participation

Substance syndrome related to substances other than alcohol and nicotine: Screening with urine sample and DUDIT is done at inclusion. The test result does not have to be available before the subject is included in the study, but should a positive screening test be reported, the subject should be removed from the study. No further samples are taken within the framework of the study.

Should the patient lose or otherwise lose the test product, it can be replaced (a limited number of times) and the patient does not need to be removed from the study if alcohol consumption is reported during the days when the measurements could not be performed and blood tests are performed to determine a new level of PEth / CDT . Phones that have fallen into the wrong hands or are misused in other ways can be deactivated by Kontigo Care. Contact Kontigo Care should this occur.

7.7.4.Time for inclusion in the study

A subject is considered to be included in the study when the consent form is signed by both the subject and the study staff.

7.7.5.Expected total time required for the clinical study

The study is expected to start in August 2015 and end in November 2016, ie a total of 16 months. Recruitment of study participants is estimated to last for 4 months and each study participant is followed for 12 months.

7.7.6.Expected total time required for the individual subject´s participation

The first visit is estimated to take about 1 hour. The following visit takes about half an hour.

7.7.7.Number of subjects to be included in the study

A total of 106 patients are expected to be included in the study, divided 1: 1 between control arm and TripleA arm.

7.7.8.Estimated time required to include this number of subjects

The recruitment period is estimated to last 4 months.

7.8. Procedures

7.8.1.Case Report Form (CRF)

In connection with each visit, the study staff must fill in the relevant section of the CRF and update the ongoing logs that follow the patient during the study.

7.8.2. Visit 1

• Obtaining informed consent (see also section 17)

• Control of inclusion and exclusion criteria (see sections 8.7.1 and 8.7.2)

• Baseline data that reflects the initial position before the patient begins the current care contact, i.e. before enrolling in the alcohol program. At visit 1, the study participants need to answer the following form with the period before enrollment in mind.

o SADD see section 8.3.1 above and Appendix B

o TLFB see sections 8.1.2 and 8.3.2 above and Appendix C

o AUDIT see section 8.3.3 above and Appendix D

If this data is available from a time representative of Baseline, and has been obtained as part of a regular routine before the patient signs the informed consent to participate in the current study, the forms do not need to be filled in again.

• General history and medical examination (medical, neurological and psychiatric) and consequences of alcohol dependence on the patient's cognitive, psychological and physiological functions. In particular, lung function should be considered, given the ability to use TripleA.

• Demographic data are noted in the CRF

o age

o sex

o weight

o socio-economic factors

• Beverage history is noted in CRF

o Age when drinking began

o Number of years of heavy drinking

o Age when addiction began

o Episodic or chronic drinking

o previous attempts to remain sober, how long the period of sobriety was and what treatment was used

• DUDIT (Drug Use Disorders Identification Test) See section 8.3.4 and Appendix E

• CGI Severity (Clinical Global Impression Severity Score) is noted in CRF, see section 8.3.6

• EQ-5D: See Section 8.3.7 and Appendix G

• Documentation of the goal that the patient and the care provider have agreed on (controlled drinking or total sobriety) See Appendix F Motivation questions.

• Blood samples are taken (see section 8.3.8)

• Urine test for drug screening (see section 8.7.3)

• Assessment phase and / or Conventional treatment is documented in CRF

• Randomization to one of the treatment arms takes place by the care provider identifying the next available patient number on its list. The patient numbers must be distributed consecutively and for each patient number there is a code envelope that the care provider opens to find out whether the patient should participate in the control arm or use TripleA.

If the patient is randomized to TripleA:

• Distribution of TripleA

• Registration of the patient in the care provider portal.

• The patient is instructed on how to use TripleA and may practice using the equipment under the supervision of the study staff before taking the equipment home.

• If any incidents with TripleA occur during the visit, these must be reported (see section 18 Safety reporting)

Note that the assigned device number must be registered both in the care provider portal and on a separate list of study equipment.

The source text is required if you want further information about the translation

Send feedback

Side panels

7.8.3. Before all the following visits:

7.8.3.1. Checking patient status in the caregiver portal (TripleA arm only).

Prior to each study visit, the study staff checks the patient's status in the care provider portal with regard to

- If completed blows were performed by the right person (ID check via photo).
- If completed blows indicate alcohol intake or not.
- Participation in agreed meetings (if applicable).

7.8.3.2. Measures in the event of noted deviations in the care provider portal

Deviations in the form of a positive or missed sobriety test must be discussed with the patient at the visit and allowed to influence the TLFB responses.

The caregiver has the opportunity to enter status comments for an individual test, which means that the database will contain supplementary information - without overwriting the basic status. The following options are available:

If the basic status is "Missed", the following status comments can be selected:

- No alcohol
- Alcohol could not be excluded
- Technical issue.

If the default status is "Alcohol could not be excluded", the following status comments can be selected:

- No alcohol
- Technical issue.

If the basic status is "Technical error", the following status comments can be selected:

- No alcohol
- Alcohol could not be excluded

7.8.3.3. Measures in case of detected relapses (regardless of information source)

The normal process when patients have relapsed is followed, which means that for each individual is discussed and decided what is best in the current situation - whether it is relevant to change something in the treatment, work with motivation or management of triggers. If necessary, MI, relapse prevention and / or medication are offered.

7.8.4. Visit 2 (Follow-up after 1 month)

- TLFB - See section 8.3.2 and Appendix C.
- Blood test - See section 8.3.8.
- Note changes in medication and other conventional treatment. Update relevant assessment phase information (WP2 only) - See sections 8.3.9 and 8.3.10
- Compliance - See section 8.3.12
- Safety reporting - See section 18

7.8.5. Visit 3 (Follow-up after 2 months)

- TLFB - See section 8.3.2 and Appendix C.
- Blood test - See section 8.3.8.
- Note changes in medication and other conventional treatment. Update assessment phase information if relevant - See sections 8.3.9 and 8.3.10
- Compliance - See section 8.3.12
- Safety reporting - See section 18

7.8.6. Visit 4 (Follow-up after 3 months)

- TLFB - See section 8.3.2 and Appendix C.
- Blood test - See section 8.3.8.
- Note changes in medication and other conventional treatment. Update the assessment phase information if relevant - See sections 8.3.9 and 8.3.10
- Compliance - See section 8.3.12
- Safety reporting - See section 18

7.8.7. Visit 5 (Follow up after 6 months)

• TLFB - See section 8.3.2 and Appendix C.

• Blood test - See section 8.3.8

• AUDIT - See section 8.3.3 above and Appendix D

• CGI Improvement Scale (Clinical Global Impression Severity Score): See section 8.3.6

• EQ-5D: See Section 8.3.7 and Appendix G

• SADD: See section 8.3.1 and Appendix B

• Note changes in medication and other conventional treatment - See section 8.3.10

• Compliance - See section 8.3.12

• Safety reporting - See section 18

• Check that the patient has had a new TripleA device sent home and returned the old one for calibration

7.8.8. Visit 6 (Close-out visit after 12 months)

• TLFB - See section 8.3.2 and Appendix C.

• Blood test - See section 8.3.8

• AUDIT - See section 8.3.3 above and Appendix D

• CGI Improvement Scale (Clinical Global Impression Severity Score): See section 8.3.6

• EQ-5D: See Section 8.3.7 and Appendix G

• SADD: See section 8.3.1 and Appendix B

• Note changes in medication and other conventional treatment - See section 8.3.10

• Compliance - See section 8.3.12

• Safety reporting - See section 18

• Return of TripleA.

• End the patient in the caregiver portal

7.8.9. Follow up and treatment after the study

The caregiver decides how the patient should be followed up and possibly treated after the end of the study. Any continued use of TripleA takes place within the framework of ordinary care.

7.8.10. Sponsors activities

Kontigo Care performs calibration of equipment and technical support for TripleA.

7.8.11. Factors that can affect the result

How motivated the patient is to abstain from alcohol will have an impact on whether one succeeds in abstaining from drinking alcohol during the course of the study. However, in order to make a study as realistic as possible, patients will not be selected depending on how motivated they are.

On the other hand, motivational factors will be mapped (see Appendix F) and thus you can get information on whether the degree of motivation in the two treatment groups is comparable or not, and whether it is possible to link the degree of motivation to the treatment result. The degree of severity of the dependence and the possible impact of demographic and social factors on the result will also be taken into account with exploratory analyzes.
The trust between therapist and patient can be of great importance for the treatment result and even if the methodology applied by the therapists is the same, it is conceivable that it matters which therapist you meet. Therefore, the randomization procedure will ensure that each therapist treats patients in both treatment arms to the greatest possible extent.
The treatment the patient receives may play a role in how the patient succeeds, but there is a lack of unambiguous data that suggests that a certain treatment works better than others, both in general and for specific patient groups. We therefore allow a wide range of treatment methods as background treatment in the clinical studies with TripleA. Descriptive statistics will be presented for what the distribution of treatment methods looks like in the various treatment arms. The patient material in the current study is probably too small to be able to draw any conclusions as to whether any treatment works better or worse in combination with TripleA, but exploratory subgroup analyzes will be performed.
The efficacy measures based on self-reported TLFB data may be affected if patients provide incorrect information in an attempt to protect their addiction and to conceal their possible drinking. In this study, the probability of a recurrence being detected is lower in the control arm than in the TripleA arm. This risks giving an incorrect comparison as frequent measurements in the TripleA arm (at least 3 times a day) increase the possibility of detecting the use of alcohol, which would otherwise have gone unnoticed. TLFB data can also be affected and provide more honest reporting as the patient knows that even shorter relapses risk being detected through the frequent alcohol tests. This could mean that even if the actual alcohol use in the TripleA arm is lower than in the control arm, we get more reports of alcohol use in the TripleA arm.
However, it is reasonable to assume that even if more alcohol intake is detected with TripleA, the actual alcohol intake pattern is not worse in the TripleA arm than in the control arm. It is also an advantage that relapses and alcohol intake become clear to both the patient and the therapist, in order to be able to work with relapses and the factors that trigger them within the framework of the treatment. The earlier you can stop a risky alcohol intake, the less the consequences for both the patient and the environment.
Although more relapses would be detected in the TripleA arm due to the frequent measurements, there is a possibility that the support that the system provides to maintain sobriety leads to more patients completing the entire treatment and participating in aftercare throughout the study period. Our hypothesis is therefore that the proportion of patients without heavy drinking days is more and the proportion who carry out the entire aftercare is more in the arm where the care and aftercare has been strengthened with TripleA.
When the study was designed, it was considered within the framework of the study to carry out more frequent checks of biomarkers to get a "real" result also for the control arm's alcohol intake, but the choice was made not to introduce more frequent biomarker controls (which in itself can have a deterrent effect on alcohol intake, to the price of further restrictions in the patient's daily life and increased costs for laboratory analyzes). One of the reasons for this choice is that the results of the study should be able to be compared with the interventions the patients currently receive.

8. Monitoring plan

The planned monitoring of the study, including verification of source data, is described in a separate monitoring plan.

9. Statistical considerations

9.1. Statistical design, method and analysis procedure

9.1.1. General

Continuous data will be summarized using descriptive statistics where the following parameters will be reported: number of observations, number of missing observations, mean, standard deviation, median, minimum and maximum. Categorical data will be presented with number (n) and percentage (%).
In addition to evaluation of all study data from the entire study period (12 months), 6-month data will also be evaluated.
Factors such as gender, severity of addiction, motivation, form of therapy and socio-economic factors will be considered as covariates in the statistical analyzes.

9.1.2.Efficacy evaluation

9.1.2.1. Primary efficacy endpoint

Proportion of patients who do not have heavy drinking days. A logistic regression model will be used to compare the groups.
Clinically relevant for treatment focused on risk reduction is that patients do not have heavy drinking days. The measurement tool will be TLFB (see Appendix C) where the number of days with large consumption over a four-week period is calculated.
Heavy drinking days are the same as days with heavy consumption, which means consumption of 4 or more standard glasses of alcohol per day for women and 5 or more standard glasses of alcohol per day for men. How to determine the TLFB at baseline is stated in section 8.1.2. Follow-up TLFB is then made at each visit.

9.1.2.2. Secondary efficacy endpoints

i) Change in total amount of alcohol consumed per 4-week period after 6 months from “baseline.” An ANOVA model for repeated measurements will be used to compare the groups.

ii) Change in total amount of alcohol consumed per 4-week period after 12 months from “baseline.” An ANOVA model for repeated measurements will be used to compare the groups.

iii) Proportion of completely sober patients at 12 months A logistic regression model will be used to compare the groups.

iv) Proportion of completely sober patients at 6 months. A logistic regression model will be used to compare the groups.

v) Change from baseline in the number of heavy drink days per 4-week period at 6 and 12 months, respectively. An ANOVA model for repeated measurements will be used to compare the groups.

vi) Change from “baseline” in the number of non-drinking days per 4-week period at 6 and 12 months, respectively. An ANOVA model for repeated measurements will be used to compare the groups.Förändring från ”baseline” i antalet standardglas per dryckesdag per 4-veckorsperiod vid 6 and 12 months, respectively. vii) Time to relapse (ie first alcohol intake). For

patients with the goal of becoming alcohol-free, relapse is defined as the first day after “baseline” where alcohol consumption was found, while relapse for patients with the goal of reducing alcohol consumption is defined as the first day after “baseline” where heavy alcohol consumption is found. Heavy consumption is defined for women as a day with 4 or more glasses, while for men it is defined as a day with 5 or more glasses. The data sources TripleA, TLFB or blood samples are used to detect recurrence. To compare the survival curves, ie. the variable time to recurrence, between the treatment groups a log-rank test will be used.

vii) CGI improvement. The proportion of respondents at follow-up visits is compared between the groups with a logistic regression model.

viii) EQ-5D. The groups are compared regarding change from “baseline” with ANOVA model. No significant difference is expected, as quality of life forms are generally not particularly sensitive to change after treatment.

ix) Participation in treatment. To compare the survival curves, ie. the variable time until the treatment is stopped, between the treatment groups a log-rank test will be used.

x) Compliance with TripleA. The proportion of measurements performed by those announced is calculated and reported for the TripleA arm.

xi) Compliance with the agreed plan for visits to the care provider and / or visits to AA meetings. The treatment groups are compared with respect to the proportion of visits performed based on CRF data with a logistic regression model. For the TripleA arm, the corresponding data collected via TripleA and the correspondence between TripleA and CRF data are also evaluated.

xii) Alcohol metabolites in the blood. Changes from baseline to 6 and 12 months, respectively, in PEth and CDT levels are calculated and the treatment groups are compared with an ANOVA model for repeated measurements.

xiii) Evaluation of AUDIT data. The treatment arms will be compared with respect to:

xiv) - The proportion of patients who after 12 months have lowered their AUDIT score

xv) - The proportion of patients who after 12 months have lowered their AUDIT score to at least one zone

xvi) - Proportion of patients who after 12 months have a risk level <II (i.e. less than 6 AUDIT points for women, 8 AUDIT points for men).

xvii) Evaluation of the number of "reds" and the number of missing blows in TripleA.

TripleA generates new types of high-resolution data that need to be handled in this and future clinical trials. In the simple case, the patient performs all agreed alcohol tests. For these, we can easily calculate the frequency of negative and positive alcohol tests in relation to a limit value for alcohol in the exhaled air. A fully sober patient has then probably performed 90 (3 / day) negative alcohol tests for 30 days in a month and can be considered 100% sober. A positive alcohol test (> 0.1 mg / ml = 0.2 ‰) gives a sobriety that is 1/90 = ~ 99% or if it is calculated per day it will be 96.6% (29/30). What can be more complicated is to correlate this new type of high-resolution data with e.g. the number of days with large consumption from

patient-reported data in TLFB form. If there are 3 positive blows in one day, it is very likely also a heavy drinking day (≥4 standard glasses / day for women, ≥5 standard glasses / day for men), which is medically serious. If there are alcohol tests performed in the evening 3 different days with just over 0.2 ‰, it can correspond to 2 glasses of wine for dinner - which can be completely acceptable if the goal is to reduce drinking and its somatic and psychological consequences (risk reduction). If you detect around 0.2 ‰ in the morning 3 different days, it can be serious and very well mean 3 heavy drinking days where the alcohol consumption took place after the last alcohol test in the evening and the body did not have time to burn all alcohol before the next test in the morning.

The second thing to deal with is missed alcohol tests. These may be due to the patient being sober but for various reasons not being able to perform the alcohol test in time (not noticed the notification, flight, mobile data shadow, etc.) or relapse into alcohol consumption. Here, the patient can contact the care provider (or vice versa) and clarify what happened.

The caregiver has the opportunity to enter a new classification for an individual test in the caregiver portal, which means that the database will contain supplementary information - without overwriting the basic status. The following options are available for missed tests:

- No alcohol
- Alcohol could not be excluded
- Technical issue.

If the default status is "Alcohol could not be excluded", the following status comments can be selected:

- No alcohol
- Technical issue.

If the basic status is "Technical error", the following status comments can be selected:

- No alcohol
- Alcohol could not be excluded

The patient also has an opportunity to show that they have not had a relapse by submitting blood samples for analysis of PEth and CDT. The caregiver can then reclassify the missed alcohol tests as above.

Even if the caregiver indicates a new classification on a test performed or missed, the original data always remains, which is so that the percentage sobriety can be calculated in two ways:

o Proportion of sober tests based on all alcohol tests performed.

o Corrected proportion of sober tests where both performed and missed alcohol tests are taken into account, with the classification made by the care provider as above.

9.1.3. Explorative analyses

We will initially summarize data from the TripleA alcohol tests as the proportion of sober days (both based on tests performed and corrected values (as above)) over a 4-week period immediately before a visit (1, 2, 3, 6.11 months). A positive alcohol test is> 0.10 mg / L alcohol in the breath test. The effect will be calculated against TLFB data transformed in a similar way. We will also perform correlation studies between TripleA and reported levels of PEth and CDT in blood samples.

The primary and secondary efficacy measures analyzed based on TLFB data will be compared with corresponding analyzes that also take into account blood test data and TripleA results.

9.2. Sample size, significance level and statistical strength

The primary endpoint is the proportion of patients who do not have heavy drinking days during a 4-week period after 12 months from baseline. Assuming that the proportion is 30% in the control group and you want to be able to detect a difference of 30% between the TripleA and the control group, 42 patients are needed per treatment group to achieve a strength of 80% with a double-sided test of 5% significance level. Assuming that the proportion of patients who do not complete the study is about 20%, a total of 106 patients need to be randomized, ie 53 per group.

Expected loss

The drop-out rate in alcohol studies is usually quite large.

At inclusion, the patient is asked to provide at least one contact person that the study staff can contact if the patient is absent from agreed meetings, interrupts treatment and / or stops blowing. Patients who do not wish to continue their treatment should be informed that they are welcome to continue using TripleA and / or alcohol, or otherwise report their alcohol consumption, as this is valuable information for the study. If the patient wants to stop the study completely, the study staff should at least ask the question "how many standard glasses have you drunk the most in one day since we were last seen?". This gives the opportunity to assess whether there has been a heavy drinking day or not.

A certain loss of patients during the course of the study is expected. Three types of missing data can be identified.

1. Patients who choose to discontinue treatment and study participation.

2. Patients who choose to discontinue treatment but who continue to provide information on alcohol intake (i.e. remain in the study)

Patients who continue treatment but who do not provide complete information on alcohol intake.

4. Patients who miss occasional visits.

All efficacy evaluations will be performed on two analysis populations, a population consisting of all randomized patients contributing efficacy data from at least one baseline visit (ITT) and a population consisting of all patients who completed the study according to the protocol (PP).

In the first population, missing values will be handled primarily according to the principle of multiple imputation (MI). In this approach, the missing values according to type 1 in the list above will be directly imputed according to the MI principle while values of type 2 in the list above, i.e. which are collected after treatment interruption, will remain as missing values, which are then imputed. Missing values of type 3 in the list above, ie. incompletely completed alcohol intake data, are replaced according to the principles described for each variable in section 8.3, ie. in these situations there is data and thus MI does not need to be used. For missing values of type 4 in the list above, MI is used.

In addition to the MI approach, any exploratory analyzes will be made where the principle of last-observation-carried-forward (LOCF) can be used, as well as an analysis where only observed values are included in the evaluation.

In addition to the above, a separate evaluation will be made for patients according to type 2 in the list above where collected values after treatment interruption are used. When tabulating alcohol intake data from visit 1 to visit 6, this group will be reported on three lines where line 1 indicates the number of patients in this group who remain on the treatment at each visit, while line 2 indicates the number of patients in this group who discontinued treatment from each visit . The third row then constitutes the sum of row 1 and row 2, i.e. the whole group of patients in the active group who discontinued treatment at some point after visit 1 but still remained in the study.

The analyzes performed on the ITT population will be considered as the primary ones.

The safety assessment will be based on the ITT population.

9.3. Interim analysis

In order to support the system patent for TripleA, an interim analysis will be made of the following data insofar as they are available before 4 May 2016:

• The proportion of patients who remain in treatment / aftercare in each study arm.

• Proportion of patients who have relapsed in each study arm.

• The app contains questions about daily mood. Modeling will be done on the relationship between daily mood and recurrence rate.

The results will only be summarized in a report that must be attached to a patent application. Data will not be available more than for the limited group performing the analysis. The results will not be available to those who work practically with the study.

10. Data management

Procedures for data management are described in a separate data management plan.

11. Changes to the study protocol

Changes to the study protocol must be decided by a representative of Kontigo Care AB and documented in writing. An updated version of the Protocol, with a new version number and date, shall be distributed to all interested parties. If the patient information is affected by the change, a new version of the patient information must also be produced. Depending on what the change is, it can be decided that the new version will be distributed to already recruited study participants, and / or that it will be used in connection with the consent process for new study participants.

Kontigo Care decides whether the change in the study protocol and / or the patient information is of a material nature and due to this needs to be approved by the ethics review board. The responsible researcher then needs to submit an amendment application to the Ethics Review Board and await approval before the amendment can be implemented.

12. Deviations from the study protocol

The examiner may not deviate from the study protocol, except in emergency situations where deviations from the protocol may be made without the approval of the sponsor or the ethics review board, if this is necessary to protect human rights, safety and well-being. Such deviations must be documented and reported to the sponsor and the ethics review board as soon as possible.

Deviations / changes that affect the subjects' safety, rights and well-being, or the scientific integrity of the study must be submitted to the Ethics Review Board before they are implemented, except for the emergencies mentioned above.

Deviations from the study protocol must be reported to and documented by the project manager. The project manager discusses with the sponsor each deviation in order to reach an agreement on what measures are appropriate to take. When the study is analyzed and reported, this must include any deviations from the study protocol.

13. Responsibility for the test products

Access to the test products must be limited and the test products may only be used within the clinical study and in accordance with the study protocol.

The sponsor must keep documentation of the physical location of all test products from the time they are sent to the test site until they are returned or destroyed.

The principal examiner or a delegated staff member shall maintain a distribution log of the receipt, use, return and destruction of the test products, which shall include:

• date of receipt,

• identification of each test product (batch number / serial number or unique code),

• expiry date, if applicable;

• date of use,

• subject ID,

• date when the test product was returned / removed from the subject, if applicable,

• date of return of unused, expired or malfunctioning test products, if applicable.

14. Compliance with laws, guidelines and standards

This clinical study shall be conducted in accordance with the ethical principles that originate in the Declaration of Helsinki (Declaration of Helsinki, 2013) in accordance with the international standard ISO 14155: 2011 and European and Swedish legislation.

The clinical study shall not begin until approval / positive opinion has been obtained from the ethics review board.

If the Ethics Review Board sets any additional requirements in its opinions, these will be complied with.

15. Insurance

The study participants are covered by the care provider's patient injury insurance with Patientförsäkringen LÖF (County Council's Mutual Insurance Company).

16. Informed consent

Patients are informed before the start of the study both orally and in writing by study staff at the reception. It is emphasized that participation is voluntary and that the subject can withdraw his or her consent at any time without this affecting the patient's future care and treatment. The patient must have the opportunity to ask questions to the staff and have them answered before taking a position on the participation. If the patient chooses to participate after reading the patient information, the consent form is signed and dated by both the patient and the study staff. The patient must be sober when taking a stand

The patient may keep a copy of the entire patient information, including the consent form.

17. Safety reporting

17.1. Definitions

17.1.1. Adverser Event (AE)

An adverse medical event, accidental illness or injury, or adverse clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not the event is related to the evolving medical device.
NOTE 1: This includes events related to the test product or comparison product.
NOTE 2: This includes events related to the procedures involved (all procedures in the study protocol)
NOTE 3: For users and other people, this is limited to events related to the test product.

17.1.2. Adverse Device Effect (ADE)

Adverse medical event related to the use of a medical device under development.

NOTE 1- This includes unwanted medical events due to deficiencies or inaccuracies in the instructions for use, setup, implantation, installation, use or function of the medical device under development.

NOTE 2- This includes events caused by user errors or unintentional misuse.

17.1.3. Device deficiency

Deficiencies in a medical device that are linked to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or user error and lack of labeling.

17.1.4. Serious Adverse Device Effect (SADE)

Adverse medical event related to the use of a medical device under development which has resulted in any of the following characteristics of a serious adverse medical event.

17.1.5. Serious Adverser Event (SAE)

Adverse medical event such as:

a) led to death;

(b) has led to a serious deterioration in health which either:

1) resulted in a life-threatening illness or injury or

2) resulted in a permanent disability or permanent bodily injury, or

3) required hospitalization (hospitalization) or extended an already ongoing hospitalization, or

4) resulted in a medical or surgical measure being taken to prevent life-threatening illness, damage a permanent disability or permanent bodily injury

c) led to fetal effects, fetal death, congenital abnormalities or malformations.

NOTE 1: This includes product defects that could have caused a serious adverse medical event if a) appropriate action had not been taken or b) action had not been taken or c) if circumstances had been less successful. These must be handled within the SAE reporting system.

NOTE 2: A planned hospital stay for an existing medical condition, or a procedure required by the study protocol, without serious deterioration of health is not considered a serious adverse medical event.

17.1.6. Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse event occurring related to the use of a medical device under development, which by its nature, occurrence, severity or consequence has not been described in the most recent version of the risk analysis report.

NOTE: Foreseen: An effect that by its nature, occurrence, severity or consequence has been described in the latest version of the risk analysis report

17.2. Time frames for reporting

When a CE-marked product is studied within the intended use, the general obligation for manufacturers according to LVFS 2003: 11 applies, which is clarified in the Medical Products Agency's guide “Manufacturers' obligation to report accidents and incidents with medical devices” revised 2011-11-10

The manufacturer is obliged to report accidents and incidents, ie:

Any malfunction or deterioration of a product's properties or performance as well as defects and deficiencies in the labeling or instructions for use that may lead to or have led to

The death of a patient, a user or another person, or

• a serious deterioration in the health of a patient, a user or another person.

The manufacturer must report incidents to the relevant authority, in Sweden the Medical Products Agency IMMEDIATELY, which in turn requires rapid reporting from the responsible examiner to the manufacturer.

The following time frames for reporting apply in the event of an accident or incident with a medical device that involves:

Serious danger to public health: IMMEDIATELY (without delay which cannot be justified). This means that the notification should not be made later than 2 calendar days after the manufacturer has become aware of the danger.

Death or unexpected serious deterioration of health: IMMEDIATELY (without delay which cannot be justified) after the manufacturer has clarified the link between the product and the accident or incident. This means that the report should not be made later than 10 calendar days after the accident or incident became known to the manufacturer.

Other: IMMEDIATELY (without delay which cannot be justified) after the manufacturer has clarified the link between the product and the accident or incident. This means that notification should not be made later than 30 calendar days after the accident or incident became known to the manufacturer.

The caregiver's obligations are found in the National Board of Health and Welfare's regulations SOSFS 2008: 1, see excerpt below.

Investigation and assessment

If a negative event or incident has occurred with a medical technician

product, shall

• an investigation is initiated as soon as possible and

• an assessment is made as to whether what happened should be reported.

Before the investigation of the incident or incident is completed, the reasons for what happened must be determined as far as possible. If the investigation shows that there are shortcomings in the quality of the business, improvement measures must be taken. The investigation, assessment and measures taken must be documented.

Duty to report

Notification to the manufacturer and to the Medical Products Agency of a negative event or incident with a medical device must be made as soon as possible on the form "Report of adverse events and incidents with medical devices"

The notification obligation must be fulfilled by the person who has been appointed as the person responsible for notification by the operations manager.

The report must be made in the event of a malfunction and deterioration of a product's properties or performance, as well as in the event of errors and deficiencies in the labeling or instructions for use that may lead to or have led to

The death of a patient, a user or another person, or

• a serious deterioration in the health of a patient, a user or another person.

Disposal of medical device

The product identity must be ensured for each medical device that has been involved in a negative event or incident.

The product or products, together with the instructions for use and packaging, must be used to enable a further investigation of the incident or incident.

However, the product or products may still be used before the investigation is completed, if alternative medical devices are lacking in the business and the purpose is to protect people's lives and health.

Additional information about and examination of medical device

The care provider must assist the manufacturer and the Medical Products Agency with the additional information, in addition to notification, that may be needed to investigate a negative event or incident.

The care provider must also, as soon as possible after a notification has been received and on conditions specified by the care provider, provide the manufacturer with an opportunity to examine the medical device that has been used in the care provider's premises.

17.3. Content of the report

The reporting shall state:

• Date when the unwanted medical event began '

• How it was treated

• How it went

• The doctor's assessment of the severity of the event and the causal relationship with the test product.

The information is filled in the form "Report of adverse events and incidents with medical devices" (Inspektionen för Vård och Omsorg)

17.4. Malfunction reporting

Malfunctions and deviations that have occurred must be reported in accordance with the care unit's own routine for deviation reporting. In addition, Kontigo Care must be informed. The appropriate format is the IVO form "Reporting of adverse events and incidents with medical devices"

At Kontigo Care AB, errors and deviations are documented in non-conformity form, which are reported on to the company's QA manager. The QA Manager is responsible for maintaining a non-conformity log of all discrepancies.

17.5. Expected adverse medical events

As patients will be monitored for alcohol use in the study, some patients may be expected to choose to use other drugs instead, which may be considered undesirable from a medical point of view. Within the framework of the study, drug screening will not be done, but to the extent that routine care reveals that patients use drugs, this must be reported as an undesirable medical event.

If the meter is tampered with, damaged or has not been calibrated within the given time frame, the meter may give incorrect results. If this is suspected, the patient should contact the care provider so that a compensation meter can be obtained.

Oral alcohol caused e.g. of mouthwash, food, exposure to solvent vapors and the use of rubbing alcohol may be sufficient to give a positive result in an alcohol test in exhaled air, even though the patient is sober and has no alcohol in his blood. TripleA is therefore programmed so that the patient has the opportunity to do a new test within 15 minutes, which overwrites the first result.

The care portal in TripleA is developed to fit a limited number of browsers, and can work poorly in other versions. In order to avoid disturbances, the care provider should check that the browser used is supported by Kontigo Care AB.

17.6. Contact information for reporting

To report serious adverse events and serious adverse events related to the use of TripleA, the CRF form must be scanned and emailed to Kontigo Care:

email: markku.hämäläinen@kontigocare.com

and / or sent to

Kontigo Care AB

Att: Markku Hämäläinen

Box 11008

750 11 Uppsala

17.7. Data Monitoring Committe

Not applicable.

18. Exposed/extra vulnerable population

Some of the patients who may be eligible for the current study have conditions associated with the treatment for alcohol dependence. This may be, for example, that employment, the possibility of regaining a driving license or contact with minor children is affected by how one handles their treatment and where there are sometimes agreements or agreements that regulate the care provider to report deviations. The fact that the patient participates in this study could mean that the care provider becomes aware of information that would not otherwise have emerged, which in turn could have significance in situations described above. However, the fact that a possible relapse is noticed and that the patient receives help to deal with this is judged to have long-term positive effects for the patient.

19. Interruption or premature termination of the clinical trial

The study may be terminated prematurely if:

• Kontigo Care AB gets into financial difficulties or ceases

• It is not possible to recruit a relevant number of subjects within a reasonable time.

• The safety profile of the product is changed so that the risk-benefit balance is no longer acceptable.

• Kontigo Care AB has business reasons to discontinue the study.

In the event that the subject's participation in the study is interrupted for any of the reasons above, the conventional underlying treatment shall continue according to plan. Only study-related studies and the use of TripleA will be discontinued.

20. Interview study

To investigate users' experience of TripleA, a qualitative interview study on user experiences will be conducted with participants from this and another clinical study. The advantages and disadvantages of the technology will be explored, with a special focus on goal fulfillment, usability and integrity issues.

Issues

• Does the patient feel that Triple A is a support for achieving stable sobriety? If so, in what way? What factors are decisive?

• How does the patient experience the usefulness? Advantages and disadvantages of the technology from an integrity point of view?

• What could be changed to achieve the greatest possible benefit for the patient?

Interviews are conducted with 12-15 patients of both sexes who have used TripleA. The interviews, which are estimated to take a maximum of one hour, are semi-structured with an interview guide that includes the above-mentioned question areas. After a test interview, any adjustments are made to questions. Collected data is analyzed with deductive content analysis,

coded and combined into categories. A separate patient information for participation in the interview survey will be used.

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21. Publication policy

Kontigo Care AB has the right to delay the publication of discoveries and inventions related to the company's product TripleA by 6 months to patent new inventions and to strengthen already filed patent applications.

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Risk analysis report Kontigo Triple-A 1.0, KC001-028V02

System Hazard Analysis Kontigo Triple-A 1.0, KC001-06V03

van Amsterdam J and van den Brink W.,(2013) Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence, Journal of Psychopharmacology 27(11) 987-997

World Health Organization (WHO) Global status report on alcohol and health 2014

Appendix A

Alcohol use syndrome according to DSM-5

A problematic pattern of alcohol use leading to clinically significant impairment or suffering, manifested in at least two of the following over a 12-month period:

1. Often drink alcohol in larger quantities or for a longer period than intended.

2. There is a persistent desire or unsuccessful attempt to limit or control drinking.

3. A lot of time is spent acquiring alcohol, drinking alcohol or recovering after drinking alcohol.

4. Alcohol craving, or a strong desire or longing to drink alcohol.

5. Repeated drinking which leads to the person failing to fulfill his duties at work, at school or at home.

6. Continued drinking despite constant or recurring problems of a social or interpersonal nature caused or exacerbated by the effects of alcohol.

7. Important social activities, occupational or leisure activities are abandoned or reduced due to drinking.

8. Repeated drinking in situations where it entails significant risks of physical harm.

9. Drinking continues despite knowledge of persistent or recurrent physical or mental disorders that are likely to be caused or exacerbated by alcohol.

10. Tolerance, defined as either of the following:

a. Need for significantly increased amount of alcohol to achieve intoxication or other desired effect.

b. Significantly reduced effect with continued consumption of unchanged amount of alcohol

11. Abstinence, as manifested in either of the following:

a. An abstinence syndrome that is typical of alcohol (see criteria A and B for alcohol abstinence below).

b. Alcohol (or a similar substance, such as a benzodiazepine preparation) is used for the purpose of relieving or avoiding abstinence symptoms.

Alcohol abstinence according to DSM-5 (excerpt only criteria A and B, not complete text).

A. The person has stopped or reduced long-term and intense alcohol use.

B. At least two of the following have developed within a few hours to a few days after cessation (or reduction) of alcohol consumption according to criterion A:

Autonomic hyperactivity (eg sweating or heart rate above 100 beats / min).

2. Increased hand tremor.

3. Sleep disturbance.

4. Nausea or vomiting.

5. Transient visual, tactile or auditory hallucinations or illusions.

6. Psychomotor agitation.

7. Anxiety.

8. Generalized tonic-clonic seizures.Källa: Mini-D 5 : diagnostiska kriterier enligt DSM-5 / American Psychiatric Association ; [översättning till svenska av Jörgen Herlofson] Stockholm: Pilgrim Press, 2014

Appendix B

Short Alcohol Dependence Data Questionnaire (SADD)

These questions give an idea of the severity of alcohol dependence.
The questions are about how you think and act around alcohol. Read each question carefully, but do not think too long before answering. Think about how you have been drinking lately.

DO THIS:

Answer each question by calling the option that applies to you.

QUESTIONS	NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
1. Is it hard for you to stop thinking about alcohol?	0	1	2	3
2. Is it more important for you to keep drinking than to eat?	0	1	2	3
3. Are you planning your day according to when and where you can drink?	0	1	2	3
4. Do you drink in the morning, in the afternoon and in the evening?	0	1	2	3
5. Do you drink to achieve a certain effect, without caring about what you drink?	0	1	2	3
6. Do you drink as much as you want without taking into account what to do the next day?	0	1	2	3
7. Would you drink too much even though you know that many problems are caused by alcohol?	0	1	2	3
8. Do you know that it is impossible for you to stop drinking once you have started?	0	1	2	3
9. Are you trying to control your drinking by quitting altogether for a few days or weeks at a time?	0	1	2	3
10. Do you need a restorer to get started in the morning after an evening when you have been drinking a lot?	0	1	2	3
11. Do your hands shake so that others can see it after an evening when you have drunk a lot?	0	1	2	3
12. Do you wake up and vomit after drinking a lot?	0	1	2	3
13. Do you try to avoid other people in the morning after an evening when you have drunk a lot?	0	1	2	3
14. After drinking heavily, do you then see scary things that you then discover were just imagination?	0	1	2	3

15. Does it happen that after drinking you do not remember what happened?	0	1	2	3

Raistrick, D., Dunbar, G., & Davidson, R., (1983). Development of a questionnaire to measure alcohol dependence. British Journal of the Addiction, 78, 89-95.

Bilaga C

Alkoholkalender för Time Line Follow Back

SYFTE

Att få en bild av vilken mängd alkohol du dricker och mönster för alkoholkonsumtionen.

INSTRUKTIONER

1. Ta fram din egen almanacka, dagbok eller liknande.
2. Börja med att notera minnesvärda händelser de senaste fyra veckorna. Det kan vara helgdagar, fester, födelsedagar, resor, något som inträffade på jobbet, speciella evenemang (t ex konserter, fotbollsmatcher) etc.
3. Skriv in dessa händelser i alkoholkalendern fyra veckor bakåt och fram till dagens datum. Med hjälp av detta är det sedan lättare att komma ihåg när, hur och hur mycket alkohol du druckit.
4. Ta en vecka i taget och försök komma ihåg vilka dagar du druckit alkohol och mängden räknat i glas (se fig. nedan). Skriv i för varje dag hur många glas du druckit. Det är viktigt att alla rutor fylls i (de dagar du inte druckit skriver du 0).
5. Börja med den senaste hela kalenderveckan, dvs. måndag till söndag. Gå därefter bakåt en vecka i taget. Vecka 1 är den senaste veckan; vecka 2 är veckan dessförinnan; vecka 3 är veckan dessförinnan den osv.

MED ETT GLAS MENAS:

VECKA	MÅNDAG	TISDAG	ONSDAG	TORSDAG	FREDAG	LÖRDAG	SÖNDAG	SUMMA ANTAL GLAS PER VECKA
1								
2								
3								
4								

GLAS/VECKA

Lägg samman antalet glas för hela perioden (4 veckor):

Dela totala antalet glas med 4:

GLAS/DRYCKESDAG

Räkna antalet dagar som du druckit någon alkohol:

Dela antalet glas för hela perioden (se ovan) med antalet dagar som du druckit någon alkohol:

DAGAR MED STORKONSUMTION

(Kvinna) Dagar då du druckit 4 eller fler glas:

(Man) Dagar då du druckit 5 eller fler glas:

Bilaga D

AUDIT

Här är ett antal frågor om Dina alkoholvanor

Vi är tacksamma om Du besvarar dem så noggrant och ärligt som möjligt genom att markera det alternativ som gäller för Dig.

Med ett ”glas” menas:


50 cl folköl


33 cl starköl


1 glas rött el vitt vin


1 litet glas starkvin


4 cl sprit, t. ex. whisky

Hur gammal är du? ____ **år** **Man** ☐ **Kvinna** ☐

1.	Hur ofta dricker Du alkohol?	Aldrig ☐	1 gång i månaden eller mer sällan ☐	2-4 gånger i månaden ☐	2-3 gånger i veckan ☐	4 gånger/vecka eller mer ☐
2.	Hur många ”glas” (se exempel) Dricker Du en typisk dag då Du dricker alkohol?	1 - 2 ☐	3 - 4 ☐	5 – 6 ☐	7 – 9 ☐	10 eller fler ☐
3.	Hur ofta dricker Du *sex* sådana ”glas” eller *mer* vid samma tillfälle?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
4.	Hur ofta under det senaste året har Du inte kunnat sluta dricka sedan Du börjat?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
5.	Hur ofta under det senaste året har Du låtit bli att göra något som Du borde för att Du drack?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
6.	Hur ofta under senaste året har Du behövt en ”drink” på morgonen efter mycket drickande dagen innan?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
7.	Hur ofta under det senaste året har Du haft skuldkänslor eller samvets-förebråelser på grund av Ditt drickande?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
8.	Hur ofta under det senaste året har Du druckit så att Du dagen efter inte kommit ihåg vad Du sagt eller gjort?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
9.	Har Du eller någon annan blivit skadad på grund av Ditt drickande?	Nej ☐	Ja, men inte under det senaste året ☐		Ja, under det senaste året ☐	
10.	Har en släkting eller vän, en läkare (eller någon annan inom sjukvården) oroat sig över Ditt drickande eller antytt att Du borde minska på det?	Nej ☐	Ja, men inte under det senaste året ☐		Ja, under det senaste året ☐	

Översatt och bearbetat av prof. Hans Bergman, Karolinska Institutet, Stockholm

Har Du besvarat alla frågor? - Tack för Din medverkan!

Bilaga E

DUDIT

Drug Use Disorders Identification Test

Här är ett antal frågor om droger. Vi är tacksamma om du svarar så noggrant och ärligt som möjligt genom att markera det alternativ som gäller för dig.

☐ **Man** ☐ **Kvinna** **Ålder** ☐☐

1. Hur ofta använder du andra droger än alkohol? (Se droglistan på baksidan.)	Aldrig ☐	1 gång i månaden eller mer sällan ☐	2-4 gånger i månaden ☐	2-3 gånger i veckan ☐	4 gånger/vecka eller mer ☐
2. Använder du fler än en drog vid ett och samma tillfälle?	Aldrig ☐	1 gång i månaden eller mer sällan ☐	2-4 gånger i månaden ☐	2-3 gånger i veckan ☐	4 gånger/vecka eller mer ☐
3. Hur många gånger tar du droger under en typisk dag då du använder droger?	0 ☐	1 - 2 ☐	3 – 4 ☐	5 – 6 ☐	7 eller fler ☐
4. Hur ofta blir du kraftigt påverkad av droger?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
5. Har du under senaste året upplevt att din längtan efter droger varit så stark att du inte kunnat stå emot?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
6. Har det hänt att du under senaste året inte kunnat sluta ta droger sedan du börjat?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
7. Hur ofta under senaste året har du tagit droger och sedan låtit bli att göra något som du borde ha gjort?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
8. Hur ofta under senaste året har du behövt ta någon drog på morgonen efter stort drogintag dagen innan?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
9. Hur ofta under senaste året har du haft skuldkänslor eller dåligt samvete på grund av att du använt droger?	Aldrig ☐	Mer sällan än en gång i månaden ☐	Varje månad ☐	Varje vecka ☐	Dagligen eller nästan varje dag ☐
10. Har du eller någon annan blivit skadad (psykiskt eller fysiskt) på grund av att du använt droger?	Nej ☐	Ja, men inte under det senaste året ☐		Ja, under det senaste året ☐	
11. Har en släkting eller vän, en läkare eller sjuksköterska, eller någon annan oroat sig över att du använder droger eller sagt till dig att du bör sluta med droger?	Nej ☐	Ja, men inte under det senaste året ☐		Ja, under det senaste året ☐	

Vänd för att se listan över droger

DROGLISTA

(OBS! EJ ALKOHOL)

Cannabis	Amfetamin	Kokain	Opiater	Hallucinogener	Lösningsmedel	GHB och övriga
Marijuana	Metamfetamin	Crack	Rökheroin	Ecstasy	Thinner	GHB
Hasch	Fenmetralin	Freebase	Heroin	LSD	Trikloretylen	Anabola steroider
Hascholja	Khat	Kokablad	Opium	Meskalin	Bensin	Lustgas
	Betelnöt			Peyote	Gas	Amylnitrat (poppers)
	Ritalina			PCP	Solution	Antikolinergika
				Psilocybin	Lim	
				DMT		

TABLETTER – LÄKEMEDEL

Tabletter räknas som droger när du tar

- läkemedel mer eller oftare än läkaren sagt att du ska göra det
- tabletter för att du vill ha kul, må bra, bli "hög", eller undrar vad du får för effekt av dem
- tabletter som du fått av en släkting eller vän
- tar tabletter som du köpt "svart" eller stulit

SÖMNMEDEL/LUGNANDE MEDEL

Alprazolam	Halcion	Sobril
Apodorm	Heminevrin	Sonata
Apozepam	Iktorivil	Stesolid
Diazepam	Imovane	Stilnoct
Dormicum	Mogadon	Temesta
Fenemal	Nitrazepam	Triazolam
Flunitrazepam	Oxascand	Xanor
Fluscand	Rohypnol	Zopiklon

SMÄRTSTILLANDE

Actiq	Durogesic	OxyNorm
Cocillana-Etyfin	Fentanyl	Panocod
Citodon	Ketodur	Panocod forte
Citodon forte	Ketogan	Paraflex comp
Dexodon	Kodein	Somadril
Depolan	Maxidon	Spasmofen
Dexofen	Metadon	Subutex
Dilaudid	Morfin	Temgesic
Distalgesic	Nobligan	Tiparol
Dolcontin	Norflex	Tradolan
Doleron	Norgesic	Tramadol
Dolotard	Opidol	Treo comp
Doloxene	OxyContin	

Tabletter räknas INTE som droger när du fått dem utskrivna av läkare och du tar dem i rätt mängd.

Bilaga F

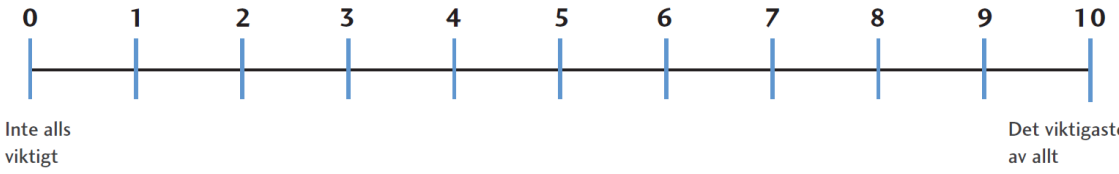
MÅL OCH MOTIVATION

Målsättning

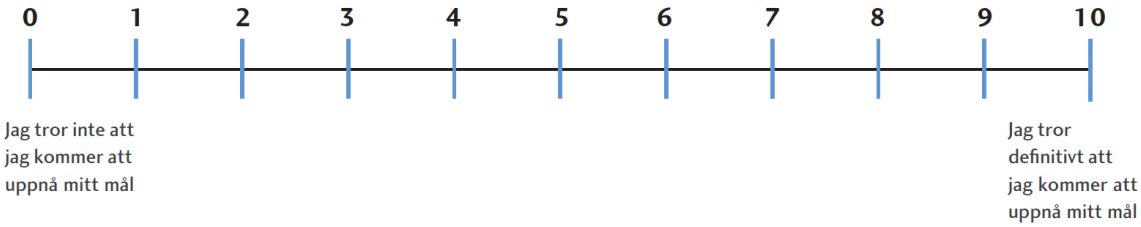
☐ Att bli alkoholfri
☐ Att minska alkoholkonsumtionen → Om målet är att minska alkoholkonsumtionen ange målnivå ex. max antal standardglas per dag eller vecka: _____

☐ Annat: _____

Just nu, hur viktigt är det för dig att uppnå ditt uppgivna mål?



Just nu, hur säker är du på att kunna uppnå ditt uppgivna mål?



Har andra än du själv påverkat ditt beslut att söka hjälp för dina alkoholproblem?

☐ Ja, i hög grad
☐ Till viss del
☐ Inte alls

Vem har påverkat dig? Max 2 alternativ

☐ Anhörig
☐ Arbetsgivare
☐ Kriminalvården
☐ Socialtjänsten
☐ Annan_____

Bilaga G

Hälsoenkät

Svensk version

(Swedish version)

Markera, genom att kryssa i en ruta i varje nedanstående grupp (så här ☑), vilket påstående som bäst beskriver Ditt hälsotillstånd i dag.

Rörlighet
- Jag går utan svårigheter ❑
- Jag kan gå men med viss svårighet ❑
- Jag är sängliggande ❑

Hygien
- Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning ❑
- Jag har vissa problem att tvätta eller klä mig själv ❑
- Jag kan inte tvätta eller klä mig själv ❑

Huvudsakliga aktiviteter *(t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)*
- Jag klarar av mina huvudsakliga aktiviteter ❑
- Jag har vissa problem med att klara av mina huvudsakliga aktiviteter ❑
- Jag klarar inte av mina huvudsakliga aktiviteter ❑

Smärtor/besvär
- Jag har varken smärtor eller besvär ❑
- Jag har måttliga smärtor eller besvär ❑
- Jag har svåra smärtor eller besvär ❑

Oro/nedstämdhet
- Jag är inte orolig eller nedstämd ❑
- Jag är orolig eller nedstämd i viss utsträckning ❑
- Jag är i högsta grad orolig eller nedstämd ❑

Till hjälp för att avgöra hur bra eller dåligt ett hälsotillstånd är, finns den termometer-liknande skalan till höger. På denna har Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.

Ditt nuvarande hälsotillstånd