RESEARCH PROTOCOL

Transmural collaborative care model for cardiovascular risk management and medication review for patients using antipsychotics (TACTIC): a cluster randomised stepped wedge trial

PROTOCOL TITLE 'Transmural collaborative care model for cardiovascular risk management and medication review for patients using antipsychotics: a cluster randomised stepped wedge trial'

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Coordinating investigator/project leader	K.J. van den Brule-Barnhoorn, MSc MD Department of Primary and Community Care Radboud university medical centre P.O. Box 9101, Internal Code 117 6500 HB Nijmegen The Netherlands Tel.: +31 24 36 13 237 E-mail: karlijn.vandenbrule-barnhoorn@radboudumc.nl
Principal investigator (in Dutch: hoofdonderzoeker/ uitvoerder)	Dr. E. Bischoff, MD PhD Department of Primary and Community Care Radboud university medical centre P.O. Box 9101, Internal Code 117 6500 HB Nijmegen The Netherlands Tel.: +31 24 36 13 237 E-mail: erik.bischoff@radboudumc.nl
Junior researcher	Drs KM Jakobs Department of Primary and Community Care Radboud university medical centre P.O. Box 9101, Internal Code 117, 6500 HB Nijmegen

	The Netherlands Tel.: 00 31 24 36 13 237 Email: Kirsti.Jakobs@radboudumc.nl kjakobs@onzehuisartsen.nl
Research team member from the department of Primary and Community Care	Dr MCJ Biermans Department of Primary and Community Care Radboud university medical centre P.O. Box 9101, Internal Code 117, 6500 HB Nijmegen The Netherlands Tel.: 00 31 24 36 13 237 Email: Marion.Biermans@radboudumc.nl
Research team member from the department of IQ healthcare	Dr J van Lieshout Department of IQ healthcare Radboud university medical centre Email: Jan.vanLieshout@radboudumc.nl
Psychiatrist-researcher/advisor from the department of Psychiatry	Dr J Janzing Department of Psychiatry Radboud university medical centre Postbus 9108, 6500 HB Nijmegen The Netherlands Tel.: 00 31 24 36 66 495 Email: Joost.Janzing@radboudumc.nl
Pscyhiatrist-researcher/advisor form the department of Psychiatry University Medical Centre Utrecht	Prof. dr. W. Cahn Department of Psychiatry Heidelberglaan 100 3584 CX Utrecht The Netherlands Tel. 00 31 88 755 5555 Email: w.cahn@umcutrecht.nl
Sponsor (in Dutch: verrichter/opdrachtgever)	Radboudumc

Subsidising party	ZonMw (Goed Gebruik Geneesmiddelen open ronde 9)
Independent expert	Mark van der Wel Wijkgezondheidscentrum Lindenholt Horstacker 1644 6546 EX Nijmegen Tel: 024 - 378 18 18 / 06 22 63 96 05 Email: Mark.vanderWel@radboudumc.nl
Laboratory sites	n.a.
Pharmacy	n.a.

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: Prof. Dr. Aura Timen Department of Primary and Community Care		
Principal Investigator: Dr. Erik Bischoff Department of Primary and Community Care		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AP	**Antipsychotic (medication)**
AR	**Adverse Reaction**
BMI	**Body Mass Index**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRSWT	**Cluster randomised stepped wedge trial**
CV	**Curriculum Vitae**
CVD	**Cardiovascular disease**
CVR(M)	**Cardiovascular risk (management)**
DSMB	**Data Safety Monitoring Board**
EMR	**Electronic medical record**
EQ-5D-5L	**EuroQol 5 Dimensions 5 Levels questionnaire for quality of life**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GP	**General practitioner/practice**
IC	**Informed Consent**
MDM	**Multidisciplinary meeting**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MHI-5	**Mental Health Inventory**
QRISK3	**Predicted 10-year cardiovascular risk score**
(S)AE	**(Serious) Adverse Event**
SF-36	**36-item Short Form health survey for quality of life**
SMI	**Severe mental illness**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical**

	company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it, is not regarded as the sponsor, but referred to as a subsidising party.
TACTIC	**Transmural collaborative care model for cardiovascular risk management and medication review for patients using antipsychotics**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The use of antipsychotic medication is increasing worldwide (1-3). It is well established that patients with a severe mental illness and patients treated with atypical antipsychotics have excess metabolic dysfunction (4) and are at an increased risk of cardiovascular disease (4, 5). Currently, monitoring of usage and effects of antipsychotic treatment (5-7), as well as cardiovascular risk screening in patients with severe mental illness or antipsychotic treatment (6) is not sufficient. General practitioners experience barriers regarding knowledge, collaboration with psychiatrists, and patient compliance (6). To overcome these barriers, the primary care cooperative Onze Huisartsen Arnhem BV developed in close collaboration with Radboudumc a transmural collaborative care model for cardiovascular risk management and medication review for patients using atypical antipsychotics in general practice (TACTIC). We have recently explored the feasibility of TACTIC in a pilot study (CMO 2020-7240) and used our findings to optimize the intervention for assessment of its effectiveness.

Objective: To assess the effectiveness of TACTIC regarding predicted cardiovascular risk and mental quality of life. The secondary objective is to assess its cost-effectiveness.

Study design: Incomplete cluster randomised stepped wedge trial.

Study population: Adult patients (>25yrs) from general practices, using atypical antipsychotics prescribed by their general practitioner.

Intervention: TACTIC is a one-time transmural intervention comprising three steps: 1) online information video to inform patients about the cardiovascular risks of antipsychotic use and about the procedures of the multidisciplinary meeting, 2) a multidisciplinary meeting with the patient to review his or her antipsychotic use and cardiovascular risk and to provide tailored treatment advice, and 3) a follow-up contact with the general practitioner to translate the treatment advice into an individualised action plan through shared decision making. TACTIC complements the current regular cardiovascular risk management programme for primary prevention of cardiovascular diseases of the primary care cooperative Onze Huisartsen BV that has been based on the specific guidelines of Dutch College of General Practitioners (NHG) and has been used in the Arnhem region since several years

Main study parameters/endpoints: Change in cardiovascular risk, as measured with the QRISK3 score, and change in mental quality of life, as measured with the MHI5 questionnaire.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Burden and risk associated with the intervention:
Patients who are eligible and who want to participate in the study will be included in the regular cardiovascular risk management programme of the Arnhem primary care cooperative. This programme includes, according to current Dutch guidelines, 1 to 5 consultations with the GP and/or the practice nurse in which physical examination, i.e. measuring blood pressure and body weight, and blood and urine sample collection will take place. The frequency depends on the severity of the cardiovascular risk and the corresponding follow-up period. On top of the regular cardiovascular care patients who participate in the study will also receive the three-step TACTIC intervention. This is a one-time intervention. Patients who are eligible but who do not want to participate in the study will be included in the regular cardiovascular risk management programme, but will not receive the TACTIC intervention.

There is a potential risk associated with participation, as patients whose antipsychotic medication is altered during participation may destabilize mentally. However, this risk is expected to be low. Changes in medication will only take place after this advice has been given in *Step 2* (i.e. multidisciplinary meeting including the patient's GP, a psychiatrist, and the patient self) and has been followed in *Step 3* (i.e. shared decision making between the patient and his/her GP). The advice to change medication will only be given in *Step 2* as the psychiatrist, the GP, and the patient consider this option to be safe. Besides, the advice will only be followed in *Step 3* if both patient and GP feel safe with it. In addition, TACTIC contains precautionary measures to prevent destabilisation, i.e. any change in antipsychotic medication is accompanied with the advice of follow up consultations with the general practitioner or mental health nurse, and all patients who alter their antipsychotic medication will have a crisis prevention plan to ensure safety.

The potential benefit of participation is high, as changes in antipsychotic medication and appropriate cardiovascular risk screening and management will result in decreased cardiovascular risk.

Burden and risk associated with outcomes measurements:
Patients fill in questionnaires at baseline and every 5 months during follow-up. Based on our experiences in the pilot study, we expect that it will take approximately 20 minutes to fill in

the questionnaire. For the assessment of the primary outcome QRISK3 score routinely collected data from the cardiovascular risk management programme, i.e. blood pressure, body weight, smoking behaviour, and blood cholesterol and glucose levels.

INTRODUCTION AND RATIONALE

Antipsychotic medication is effective for a variety of psychiatric disorders, such as schizophrenia, bipolar disorder, schizoaffective disorder, or major depressive disorder. Remarkably, however, a large proportion of patients on antipsychotics do not have a diagnosis of a severe mental illness (6). Jakobs et al. found that, among patients in general practices who use antipsychotic medication, up to 68% did not have a registered diagnosis of a severe mental illness. These patients are using antipsychotics off-label. Reasons for off-label prescription can be anxiety, dementia, or sleep- and personality disorders.

The use of antipsychotic medication is increasing worldwide (1-3), but this is not without risk. It is well established that patients with a severe mental illness and patients treated with antipsychotics have excess metabolic dysfunction (4) and are at an increased risk of cardiovascular disease (4, 5). The increased risk of cardiovascular disease is multifactorial. Patients with a severe mental illness or on antipsychotic medication tend to have a high incidence of lifestyle risk factors, such as poor diet, lack of exercise, stress and smoking, besides possible genetic susceptibility (8, 9). Furthermore, there is evidence that people with severe mental illness are less likely to receive standard levels of care (5).
Moreover, antipsychotics can cause weight gain, hypertension, glucose intolerance and dyslipidaemia, and can cause cardiac toxicity (10).

Although these factors may contribute as independent risk factors for cardiometabolic dysfunction and cardiovascular disease, having a severe mental illness itself is also an important independent risk factor (5), as well as antipsychotic treatment, particularly for certain drugs and for vulnerable patients (9). In a large prospective open cohort study in England, severe mental illness was associated with a 14% increased risk for women and a 13% increased risk for men (11). This was independent of the risk associated with atypical antipsychotics. Atypical antipsychotics were associated with an increased cardiovascular risk of 29% in women and 15% in men. In addition, antipsychotics cause a dose-related increased risk of sudden cardiac death (12). All in all, this results in a 8-20 years reduction in life expectancy (11).

In the Netherlands, it is common that psychiatrists initiate treatment with antipsychotic medication, but when patients reach a stable state, care is shifted to the general practice. This includes monitoring of treatment effects, adherence and side effects, as well as management of cardiovascular risk. However, monitoring of usage and effects of antipsychotic treatment as well as cardiovascular risk screening in patients with severe mental illness or on antipsychotic treatment is currently not sufficient (5-7). Lifestyle factors

are relatively easy to measure, but are barely considered for screening. Baseline testing of important physical parameters, prior to starting antipsychotic medication, is insufficiently performed (5). This is a serious aspect that needs to be addressed, even more since the adverse effects of antipsychotic medication may also impair the patient's adherence to treatment (13).

The increased cardiovascular risk in patients taking antipsychotic medications can be treated in a primary care setting, with lifestyle counselling as well as pharmacological interventions, in the same way as managing cardiovascular risk in other patient groups. The advantage of cardiovascular risk management in primary care is that general practices are very experienced in providing such care and are able to reach a broad population and detect the patients at risk. This also includes patients with mental disorders using antipsychotics who are in a stable phase and, as a consequence, are not under regular specialist care. However, general practitioners are generally not as familiar with the (long-term) side effects of antipsychotic use as psychiatrists, which may lead to a lack of follow-up. They often renew prescriptions that were initiated by the psychiatrist, without thorough check up. Furthermore, general practitioners and psychiatrists often do not collaborate in reducing cardiovascular risk in patients using antipsychotics. All healthcare professionals must learn to recognize the factors indicating antipsychotic-related cardiometabolic problems to prevent progression to type II diabetes, cardiovascular events and premature death (9).

To address both problems of potential overtreatment with antipsychotic medication and undertreatment of cardiovascular risk, we have developed a one-time transmural collaborative care model for structured antipsychotic medication review and cardiovascular risk management for patients in general practices (TACTIC). During TACTIC, the general practitioner closely collaborates with the patient, a carer (optional), a patient coach with lived experience, and a psychiatrist in a structured multidisciplinary meeting. This review results in tailored advice on antipsychotic treatment (continuation, lowering the dosage, switching to other medication, or discontinuation) and management of cardiovascular risk (e.g. losing weight, treatment of hypertension, regulation of cholesterol). Subsequently, the advice is converted to an individualised action plan through shared-decision making by GP and patient.

We have recently conducted a pilot study in which we assessed the feasibility of TACTIC (CMO 2020-7240). We followed three general practices who provided the TACTIC intervention to 28 patients in total. The feasibility appeared to be high. Based on the positive experiences and after the necessary adjustments in the procedures of the 3-step TACTIC

approach, the primary care cooperative decided to continue with TACTIC in an implementation process including a cluster randomised controlled trial. The pilot study was not powered nor designed to detect a statistically significant and clinically relevant difference, but did show a trend towards a positive health benefit regarding cardiovascular risk, particularly in patients with a moderate to high baseline QRISK3 score, i.e. score ≥ 5%. Pre-post analyses showed a decrease in predicted 10-year cardiovascular risk of 1.9% (SD 3.4) (*unpublished data*). Qualitative analysis, including individual interviews with patients and carers, and focus groups with healthcare professionals, gave us input to optimize the TACTIC procedures prior to assessing its effectiveness in the upcoming cluster RCT (*unpublished data*).

To our knowledge, TACTIC is the first intervention focussing on both medication review and primary prevention of cardiovascular disease in patients on atypical antipsychotic medication in general practice. With this study, we aim to contribute to better healthcare for this particular population, which is at a significantly higher risk of developing cardiovascular disease, but up until now seems to be forgotten in Dutch primary care.

1. OBJECTIVES

Primary objective: to assess the effectiveness of TACTIC in patients using atypical antipsychotics in general practice on cardiovascular risk and mental quality of life.
Secondary objectives: to assess cost effectiveness of the intervention TACTIC and its effectiveness regarding individual risk factors for cardiovascular disease.

2. STUDY DESIGN

We will conduct an incomplete cluster randomised stepped wedge trial including 32 general practices. Clusters (units of a general practitioner and his/her practice nurse) will be randomly allocated to four sequential steps over a 22-month period to implement TACTIC (Figure 1). Clusters will be randomised to time points at which they will receive the intervention. To minimize patient burden, data collection is not continuous, but undertaken on a selective number of occasions, which causes an “incomplete” stepped wedge design (14). Recruitment of clusters will start in September 2022, follow-up of the first step will start in March 2023. Follow-up of the last step will end in December 2024.

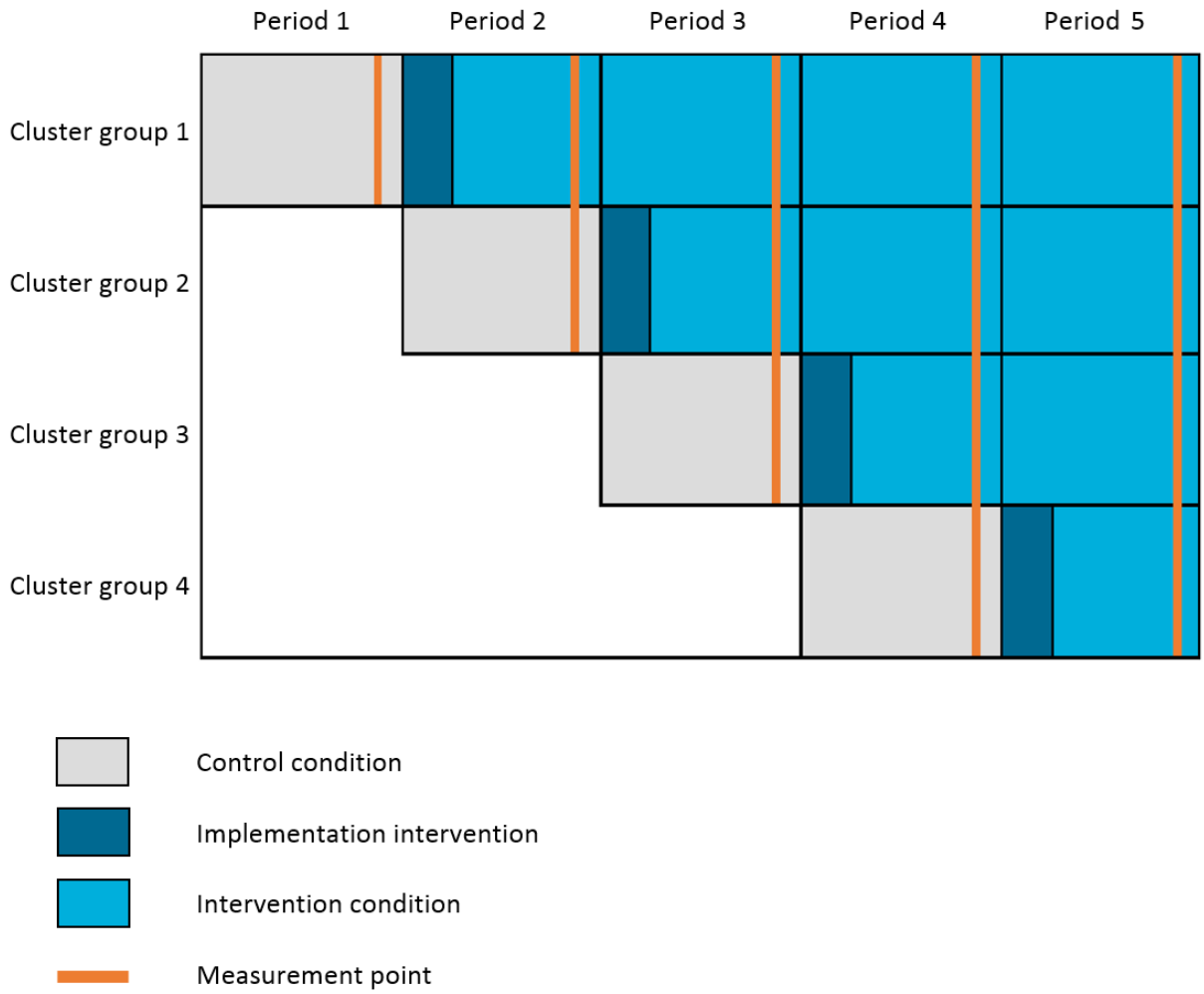

Fig. 1. Incomplete stepped wedge study design; rows are steps to which clusters will be randomised; columns are time periods of each 5 months.

3. STUDY POPULATION

3.1 Setting and population

This study will be conducted in the primary care cooperative 'Onze Huisartsen BV Arnhem'. This primary care cooperative serves around general practices with > 360,00 registered patients of whom approximately 4,000 patients use antipsychotics. Based on our pilot study we know that around 80 practices are sufficiently equipped to participate in our trial, i.e. they use the General Practice Information Systems Medicom or Promedico ASP and VIPlive, which are necessary for requesting digital consultations with the psychiatrist. A cluster is defined as a duo (or unit) of a general practitioner with his of her practice nurse. As a result, large general practices may provide multiple clusters when consisting of multiple duos.

3.2 Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria: 1) aged between 25 and 84 years, 2) using atypical antipsychotic medication for at least 3 months at baseline, 3) the atypical antipsychotic medication is prescribed by the general practitioner, and 4) a 10-year cardiovascular risk of at least 5% at baseline (moderate to severe risk).

3.3 Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study: 1) diagnosis of dementia or organic psychosis, 2) diagnosis of cardiovascular disease (acute myocardial infarction, acute coronary syndrome, heart failure, ischemic stroke, transient ischemic attack, peripheral artery disease, aortic aneurysm or a revascularization procedure, i.e. percutaneous coronary intervention or coronary artery bypass grafting).

3.4 Sample size calculation

The sample size calculation is based on the following findings and expectations. Our pilot showed a reduction of the mean QRISK3 score of 1.9 points. This was after a follow-up period of 3 months, and under suboptimal intervention conditions, e.g. unclear expectation management, modified information meeting due to the corona pandemic. The standard deviation of the difference of QRISK3 score was 3.4 and the standard deviation of a single measurement was 12. This means there is a high reliability on patient level.

$$r_s = 1 - \frac{\left(SD_{diff}/SD\right)^2}{2} \approx 0.95$$

We expect that in the trial, after optimalisation of the TACTIC procedures, we will be able to detect a reduction of a clinically relevant mean QRISK3 score of 2.5 points in the intervention group, compared to the control condition. Given an SD of 12, an intracluster correlation (ICC) of 0.10, and an α of 0.05, 500 simulated trials indicate that 32 general practices with each 12 patients are needed to provide a power of at least 80%. Given drop-out rates of 20% observed in our pilot study and less than 10% in a UK primary care study evaluating a comparable intervention (15), we include 15 patients per cluster. The required total number of participants will be 480 patients in 32 (or more) clusters.

This calculated sample size has also enough power to detect a clinically relevant improvement of 5 points on de mental health inventory, the mental domain of the SF36, which will be our second primary outcome.

4. TREATMENT OF SUBJECTS

Investigational treatment

A transmural taskforce in the region of Arnhem has previously developed the TACTIC intervention. This taskforce consists of all relevant stakeholders: patients with lived experience from the patient organization 'Vitale Verbindingen', general practitioners from the primary care group 'Onze Huisartsen', psychiatrists from 'Pro Persona' and 'GGNet', mental health nurses from primary and secondary care (including addiction care), pharmacists, life style coaches and members of the municipal social welfare team. The TACTIC intervention has been tested in a recent pilot study which provided valuable input for improving the feasibility and effectiveness of the intervention. We followed the Medical Research Council framework for developing and evaluating complex interventions (16).

TACTIC is a one-time intervention that takes place in the general practice setting. It entails three consecutive steps in addition to usual care, i.e. regular cardiovascular risk management programmes:

Step 1: All participating patients are invited to watch an information video in which they are informed about the multidisciplinary meeting. This information video aims to motivate and prepare patients (and their carers) to participate in the multidisciplinary meeting. The healthcare professionals who take part in the multidisciplinary meeting will introduce themselves and tell about their expertise. After the information video, patients are able to contact their healthcare professional for questions. The information video will take approximately 20 minutes. If desired, patients can meet their pharmacist or the experience expert in advance of the multidisciplinary meeting.

Step 2: A 15-minute multidisciplinary meeting per patient will be held. The general practitioner will open a digital consultation for each patient at least one week before the meeting, enabling the psychiatrist to prepare. When a consultation is initiated digitally, the psychiatrist has access to a part of the electronic medical record of the general practitioner, including diagnosis, medication use, blood pressure, Body Mass Index, and laboratory results. The most recent letter from the psychiatrist will be enclosed (if applicable), together with the results of the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) questionnaire (17), the results of a custom-made questionnaire

on antipsychotic use, and the QRISK3 score at baseline (see Methods 6.1.2. Secondary study parameters).
During the multidisciplinary meeting, the participating patient (and carer), the general practitioner, a psychiatrist, the primary care nurse, and if desired an experience expert (patient coach who lived the experience) will review the patient's antipsychotic use and all other relevant medication (if applicable). Also, possible cardiovascular risk factors will be addressed, such as smoking status, blood pressure, Body Mass Index, blood glucose and cholesterol levels. The multidisciplinary meeting will result in a set of individualised treatment suggestions, including advice on antipsychotic use (e.g. continuation, deprescribing, or switching) and reducing cardiovascular risk.
Step 3: A week after the multidisciplinary meeting, the patient has a consultation with the general practitioner during which the set of individualised treatment suggestions will be translated into an action plan through shared-decision making. This shared-decision making process will benefit the adherence and outcome of the plan. The plan will also define the tasks and responsibilities of the various healthcare providers. Potential actions are altering antipsychotic use, initiating antihypertensive medication or statins, referral to the chronic care nurse (in Dutch: POH-S) for example for smoking cessation, referral to the primary care mental health nurse (in Dutch: POH-GGZ), the dietician, the physical therapist, or a life style coach.

The effects of TACTIC in addition to usual care will be compared to usual care alone, in which patients will be their own comparator, prior to treatment initiation.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameters

- Our first primary outcome measure is the QRISK3 score (11). The QRISK3 algorithm (www.qrisk.org/three) calculates a person's risk of developing a cardiovascular event (e.g. a heart attack or stroke) over the next 10 years. The score presents the average risk of people with the same risk factors as those entered for that person. The QRISK3 is the preferred algorithm for assessing cardiovascular risk according to the NICE guideline Cardiovascular Disease (18). It includes severe mental illness and use of atypical antipsychotics as predictors for cardiovascular disease, which makes it suitable for use in our study.
The QRISK3 score is calculated based on age, gender, ethnicity, Townsend deprivation score, smoking status, diabetes status, having chronic kidney disease,

atrial fibrillation, migraines, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness or a family history of premature coronary heart disease in a first degree relative, being on blood pressure treatment, on regular steroid tablets, or on atypical antipsychotic medication, having a diagnosis of or treatment for erectile disfunction, levels of cholesterol/HDL ratio, systolic blood pressure, standard deviation of blood pressure, and Body Mass Index. As the Townsend deprivation score is not applicable to the Dutch population, we will set this to 0, meaning neither deprived nor affluent, as is advised by the authors. The QRISK3 score can range from 0 to 100%. We consider a decrease of 2.5%-points as clinically relevant.
- Our other primary outcome measure is the Mental Health Inventory, five-item version (MHI-5), which is a measure for the mental quality of life (19). The MHI-5 is a derivative of the 36-item short form health survey, the SF36, and assesses symptoms of depression and anxiety, loss of behavioural or emotional control, and psychological well-being in the prior four weeks. The MHI-5 ranges from 0 to 100, where a score of 100 equals perfect mental health. A score of 60 or higher is seen as good mental health, whereas a score below 60 is seen as poor mental health. We will consider an increase of 5 points as clinically relevant.

5.1.2 Secondary study parameters

- Health-related quality of life will be measured with the EuroQol-5D-5L (EQ-5D). This instrument is available in a validated Dutch translation. The EQ-5D comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index is obtained by applying predetermined weights to the five domains, and ranges from 0 to 1, where a score of 1 equals perfect health.
- We will measure change in side effects using the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (17).
- We will use the 8-item Client Satisfaction Questionnaire (CSQ-8) to measure participants' satisfaction with care. This questionnaire is recommended for use in psychiatric patients (20),(21) and has a Dutch validated version (22).
- Number of groups meetings (Step 1), multidisciplinary meetings (Step 2), and GP contacts (Step 3);
- Number and content of individualized treatment plans;
- Percentage of patients who attend group meeting (Step 1);
- Percentage of patients who attend multidisciplinary meeting (Step 2);
- Percentage of patients who contact GP to discuss individualized treatment plan (Step 3);

- Reasons for drop-out.
- Numbers and type of (serious) adverse events.
- Numbers and type of advice given in Step 3 of the intervention, and numbers and type of advice followed up or executed.
- Healthcare utilization as measured with the Dutch version of the Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) questionnaire;
- Costs related to health care, such as medication, visits to the general practice, visits to relevant medical specialists.
- Patient costs, such as travel costs, time costs and over the counter medication
- Costs in other sectors, such as health promotion costs within budget of municipalities

5.2 Randomisation, blinding and treatment allocation

Clusters will be randomised to either of the four steps, or cluster groups, as described in figure 1. The randomisation program we will use, will be custom made by an investigator with no clinical involvement in the trial. Blinding and treatment allocation are not applicable, as it is not possible to blind clusters.

5.3 Study procedures

After enrolment of the general practice, a list with all eligible patients will be generated in VIPlive. A computerized programme will randomly select 30 eligible patients per general practice, who will receive a letter from their general practitioner, informing the patient about the upcoming trial. Patients will be invited to contact the general practice when they are interested in participation. An appointment for a regular cardiovascular risk management consultation at the general practice will then be made. Patients who did not reply to the letter, will be contacted by phone. In the context of the existing regional cardiovascular risk management programme patients will undergo physical examination (for measuring length, weight and blood pressure), venapunction and urinalysis (for measuring risk factors, i.e. HbA1c, blood glucose, lipid spectrum and kidney function), and will be asked about their ethnicity, smoking status and family history of coronary heart disease. All other information will be derived from their medical file, e.g. having atrial fibrillation, migraines, or rheumatoid arthritis. In addition to the usual SCORE calculation, the QRISK score will also be calculated specifically for this study. When the QRISK3 score is below 5%, the patient does not meet the inclusion criteria and will be followed by the general practitioner according to the regular cardiovascular risk management

programme. Patients with a QRISK3 ≥5% will be invited to sign informed consent for participation in the TACTIC intervention study.

After signed informed consent and inclusion, baseline measurement will take place and patients will fill in a digital questionnaire using Castor EDC, containing MHI-5, EQ-5D-5L, TIC-P and LUNSERS. As part of the preparation for the multidisciplinary meeting, patients will be asked to fill in a custom-made questionnaire on antipsychotic use. This questionnaire will help healthcare professionals prepare for the meeting and will give the patient insight in possible topics that can be addressed during the meeting. In case patients do not have an email address, we will send the questionnaires by mail.
Patients will then watch the information video at home, attend the multidisciplinary meeting, and attend a consultation with their general practitioner, as described in section 5. At five months follow-up, patients will be invited for follow-up (monitoring) measurements at the general practice as part of the regular regional cardiovascular risk management programme (usual care|), to undergo physical examination (measuring weight and blood pressure), venapunction and urinalysis (for measuring risk factors, i.e. HbA1c, blood glucose, lipid spectrum and kidney function). As part of the evaluation. patients will also fill in questionnaires, containing MHI-5, EQ-5D-5L, LUNSERS, TIC-P and general questions about smoking status and family history of coronary heart disease. Depending on which step the cluster has started, patients will undergo one to four follow-up measurements, every five months. This is in line with the routine check-ups patients will have in the regular cardiovascular risk management programme. During the last follow-up measurement, they are also asked to fill in the CSQ-8. Table 1 presents the schedule of assessments.
No diagnostic procedures or treatment will be postponed.

	Visit general practice	Digital information	Physical examination	Laboratory tests	Question-naires
Week 1 Routine screening and inclusion after informed consent	X		X	X	
Week 2 Baseline measurement					X
Week 3 Information video		X			
Week 4/5	X				

Multidisciplinary meeting					
Week 5/6 Consultation with GP	X				
Month 5 Routine consultation as part of usual care. Follow-up measurement 1 Start Step 2 at Week 1	X		X	X	X
Month 10 Routine consultation as part of usual care. Follow-up measurement 2 Start Step 3 at Week 1	*X*		*X*	*X*	*X*
Month 15 Routine consultation as part of usual care. Follow-up measurement 3 Start Step 4 at Week 1	*X*		*X*	*X*	*X*
Month 20 Routine consultation as part of usual care. Follow-up measurement 4 Finish Follow-up all clusters	*X*		*X*	*X*	*X*

Table 1. Schedule of assessments.

5.4 Withdrawal of individual subjects

Patients can leave the study at any time for any reason if they wish to do so, without any consequences. If a patient moves to a different general practice during the study, the patient will be excluded from analysis from the moment of changing practice.
The investigator can decide to withdraw a patient from the study for urgent medical reasons. If a patient withdraws from the study, they will continue to receive care as usual.

5.5 Replacement of individual subjects after withdrawal

Patients can be replaced in case of withdrawal of another patient, provided that coming measurements are under the same conditions as they would be for the withdrawing

patient, i.e. when a patient is in the intervention condition at the time of withdrawal, this patient can only be replaced by a patient who is also in the intervention condition.

5.6 Follow-up of subjects withdrawn from treatment

In case of withdrawal from treatment, we will strive to collect all necessary data for analysis, unless, of course, informed consent is also withdrawn. This is according to the intention-to-treat principle.

5.7 Premature termination of the study

The study will be terminated in its current design as recruitment of the necessary number of cluster fails.

In case the study will be terminated prematurely, we will fill in the form “Melden beëindiging studie” on www.ccmo.nl and notify the medical research ethics committee within 15 days.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise patient health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all patients are kept informed.

6.2 AEs and SAEs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the trial procedure or the experimental intervention. All adverse events reported spontaneously by the patient or observed by the general practitioner, his staff, or the investigator will be recorded.

6.2.2 Serious adverse events (SAEs)

During the control period, patients receive care as usual, so no AE and SAE are expected, and if they do, they are part of the usual care process and cannot be considered a consequence of participating in the study.

We will instruct all general practitioners to warn the investigator about every SAE occurring during the study, i.e. psychosis, (attempted) suicide, requirement of the crisis intervention team, and death. We will examine every case to see whether the trial procedure or the intervention caused the SAE. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening, followed by a period of maximum 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general practitioner or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

6.4 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Given the low-risk character of the study, no Data Safety Monitoring Board is installed or interim analyses are planned.

7. STATISTICAL ANALYSIS

All measured data will be assembled in a computer database and analysed using SPSS 25.

7.1 Primary study parameters

As mentioned in chapter 6.1.1, the QRISK3 score is calculated based on several parameters that are collected during regular cardiovascular risk management consultations as part of usual care. For age, we will use age at baseline (T0) at all measurement points. Since the QRISK3 score cannot be calculated when individual items are missing, we will use the following values:

- In case ethnicity is missing, we will use “white or not stated”.

- In case smoking status is missing, we will use “non-smoker”.
- In case the patient is a smoker, but the amount of cigarettes is not stated, we will use “moderate (10-19)”.
- In case cholesterol/HDL ratio is missing, we will use 4.4 for men and 3.7 for women (11). In case systolic blood pressure is missing, we will use the latest measurement of this value, or, if no measurements are available, we will use 129mmHg for men and 123mmHg for women (11).
- In case standard deviation of systolic blood pressure is missing, we will use “0”.
- In case either weight or both length and weight are missing, we will use the latest measurement of the Body Mass Index, or, if no BMI is available, we will use Body Mass Index values as mentioned in table 2.
- In case only length is missing at all measurement points, we will use values as mentioned in appendix … for calculating Body Mass Index.
- In case calculated Body Mass Index is <20kg/m^2, the value is set to 20kg/m^2, as the algorithm is not validated for values of Body Mass Index lower than 20kg/m^2.

Age (years)	Men	Women
25-39	25.2	24.4
40-49	26.2	24.7
50-59	26.5	25.7
60-84	26.8	26.4

Table 2. Mean Body Mass Index (kg/m^2) by age and gender, based on RIVM 2012.

- In case family history of premature coronary heart disease in a first degree relative is “yes” at any measurement point, all measurement points will be set to “yes”, as this factor might not be manifest at the start of enrolment, but does contribute to the patient’s cardiovascular risk, regardless to the moment this factor becomes manifest. This also applies for the factors migraines, rheumatoid arthritis, systemic lupus erythematosus, and erectile dysfunction.
- In case a patient starts blood pressure treatment due to the intervention, all prior measurement points will be set to “yes”, as the indication for blood pressure treatment would have been present provided the patient was on appropriate usual care.

The MHI-5 consists of five questions with each six answer categories: continuously-mostly-often-sometimes-rarely-never. The answers of the positively formulated questions (questions 3 and 5) will be assigned the values 5, 4, 3, 2, 1, and 0, respectively. The

answers of the negatively formulated questions (questions 1, 2, and 4) will be assigned the values 0, 1, 2, 3, 4, and 5, respectively. Subsequently, a sum score will be calculated, multiplied by 4, resulting in an MHI-5 score ranging from 0 to 100, where a score of 100 equals perfect mental health.

Data analysis will be performed according to the intention-to-treat principle. Data from patients who discontinued follow-up will be included in the analysis up to the point of dropout. Descriptive analyses will be performed to describe the patient characteristics. Mean and standard deviation (std) or median and interquartile range for continuous characteristics and number and percentages for categorical characteristics will be determined. The relationship between treatment and outcome measures measured at 5, 10, 15, and 20 month follow up will be analysed with mixed three level linear or logistic regression, taking into account that the times of measurement are clustered within patients, and patients within general practices. We will perform a model with a random intercept and all other variables fixed. To test the effect of the intervention a model with time, group (intervention or control) and the interaction between time and group will be performed. A value of $p<0.05$ will be considered statistically significant for all analyses, based on two-sided testing. Analyses will be performed using the Statistical Package for Social Sciences (SPSS, IBM Corp., Armonk, NY) version 25.

We will present QRISK3 scores and MHI-5 scores as means (SDs) for every measurement point, with notification of the number of patients included in the calculation.

7.2 Secondary study parameter(s)

We will convert the EQ-5D index into a utility score, using the Dutch algorithm. The utility score has a maximum of 1, indicating optimal health. A utility score of 0 equals death, but the score can also be negative, as some conditions are thought to be worse than death. By multiplying the utility score with the amount of time in which the score is applicable and then aggregating these scores over the relevant timeframe (trapezium method), we will compute quality-adjusted life years (QALYs) (22).

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) is self-rating scale for measuring the side-effect of antipsychotic medications. LUNSERS was developed by researchers within the University of Liverpool to indicate the extent of side-effects experienced by patients medicated with neuroleptic drugs. The scale consists of 41 known side effects of neuroleptics. Each ‘side-effect’ listed is scored on a five point

rating scale of 0 – 4, i.e. 0 = ‘Not at all’ and 4 = Very much. A total score can be calculated by adding all item scores and then be graded into ‘very low’, ‘low’, ‘average’, ‘high’, and ‘very high’, based on the percentiles (16). who have a clinically relevant improvement of at least the minimal clinically important difference (MCID), defined as 0.5 x SD of the baseline mean

7.3 Other study parameters

We will perform a sub analysis on the QRISK3 score, determining the proportion of patients reaching 1) an absolute risk reduction of 2.5%, which we consider as clinically relevant, and 2) a proportional risk reduction of 20% of their optimal achievable reduction. To give an example: a patient has a 10-year cardiovascular risk of 20%, but after perfectly optimising all changeable risk factors, is able to reach a 10-year cardiovascular risk of 10%. When, after the intervention, the patient reaches a QRISK3 score of 17%, this means the patient reached a 3% absolute risk reduction (i.e. 20% - 17%), and a 30% proportional risk reduction (i.e. 3% / (20% - 10%)).

As mentioned in chapter 6.1.1, the Townsend Deprivation Score is not applicable to the Dutch population. We do know, however, that deprivation has impact on cardiovascular risk. Therefore, we want to perform a secondary analysis on the QRISK3 score in which we use the Dutch equivalent of deprivation (“achterdstandsindex”). In the Netherlands, we use a deprivation index for patients with low social economic status, based on employment, income and percentage of non-western immigrants. This deprivation index is applicable for approximately 10% of the Dutch population.

We decided to apply the Townsend Deprivation Score at p20 (below which are the 20% most deprived of the British population) for the 10% most deprived patients in our population. By choosing p20 instead of p10, we stay on the safe side and might underestimate the effect of deprivation, but we find this more important than overestimating its impact.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki of 2013.

8.2 Recruitment and consent

Recruitment of patients has been described in section 6.3 Study procedures. After being found eligible for participation, the investigator will contact the patient for informed

consent. The patient has the opportunity to ask additional questions before giving consent. If desired, the patient can contact an independent physician, who knows about the study, but is not involved in execution of the study.
The patient information letter and informed consent form can be found attached to this research protocol. Together with the patient information letter for adults, we provide an "easy reading" version for patients with low literacy, which is based on the patient information letter model for children under 16 years of age, provided by the CCMO.

8.3 Objection by minors or incapacitated subjects (if applicable)

Some eligible patients live in supervised communities (for instance RIBW) and are incapacitated. However, patients who are registered in a general practice are usually less incapacitated then those who are for example cared for by an intellectual disability physician. It is important that these patients have the opportunity to participate in this study because, both individually and as a group, they often are at risk of being overtreated with antipsychotic medication and undertreated for cardiovascular risk (24). It is important to study whether TACTIC is suitable for these patients as well. Caregivers and legal representatives will be involved in invitation, the informed consent procedure and during the entire study.

8.4 Benefits and risks assessment, group relatedness

Potential benefit of the intervention

The potential benefit of participation is high, as changes in antipsychotic medication and appropriate cardiovascular risk screening and management will result in decreased cardiovascular risk. The intervention has been developed by the primary care cooperative Onze Huisartsen BV with the intention to implement it in the Arnhem region after demonstrating its feasibility and its (cost-)effectiveness. The intervention is in line with the current guideline of the European Society of Cardiology on cardiovascular disease prevention in clinical practice, which recognises the increased cardiovascular risk for patients with mental disorders (25).

Burden and risk associated with the intervention:

Patients who are eligible and who want to participate in the study will be included in the regular cardiovascular risk management programme of the Arnhem primary care cooperative. This programme includes, according to current Dutch guidelines, 1 to 5 consultations with the GP and/or the practice nurse in which physical examination, i.e. measuring blood pressure and body weight, and blood and urine sample collection will take

place. The frequency depends on the severity of the cardiovascular risk and the corresponding follow-up period. On top of the regular cardiovascular care patients who participate in the study will also receive the three-step TACTIC intervention. This is a one-time intervention. Patients who are eligible but who do not want to participate in the study will be included in the regular cardiovascular risk management programme, but will not receive the TACTIC intervention.

There is a potential risk associated with participation, as patients whose antipsychotic medication is altered during participation may destabilize mentally. However, this risk is expected to be low. Changes in medication will only take place after this advice has been given in *Step 2* (i.e. multidisciplinary meeting including the patient's GP, a psychiatrist, and the patient self) and has been followed in *Step 3* (i.e. shared decision making between the patient and his/her GP). The advice to change medication will only be given in *Step 2* as the psychiatrist, the GP, and the patient consider this option to be safe. Besides, the advice will only be followed in *Step 3* if both patient and GP feel safe with it. In addition, TACTIC contains precautionary measures to prevent destabilisation, i.e. any change in antipsychotic medication is accompanied with the advice of follow up consultations with the general practitioner or mental health nurse, and all patients who alter their antipsychotic medication will have a crisis prevention plan to ensure safety.

Burden and risk associated with outcomes measurements:
Patients fill in questionnaires at baseline and every 5 months during follow-up. Based on our experiences in the pilot study, we expect that it will take approximately 20 minutes to fill in the questionnaire. For the assessment of the primary outcome QRISK3 score routinely collected data from the cardiovascular risk management programme, i.e. blood pressure, body weight, smoking behaviour, and blood cholesterol and glucose levels. At the end of follow-up we will conduct focus-group interviews with a purposive sample of participants to explore experiences with the TACTIC intervention.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

For the transfer of data, an agreement will be signed by the participating general practices and the Department of Primary and Community Care of the Radboud university medical centre, which states that the study will be performed according to the code of conduct for health research (in Dutch: Gedragscode Gezondheidsonderzoek); and the

Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet AVG).

All study findings will be stored in a computer database at the Radboudumc and handled strictly confidentially. All personal data will be kept secret, with identification by research number only. The database will be accessible to the principal investigators and those employees actively involved in the study. The key to the identification code will be safeguarded by the two junior investigators. Coded data will be kept after closure of the study and can only be used for ancillary studies after strict approval of the principal investigators.

All coded documents will be stored for 15 years after the study has ended.

9.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

9.3 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.4 Public disclosure and publication policy

The study will be registered at www.clinicaltrials.gov before trial commencement.
Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the sponsor.

Results of the study will be published in peer reviewed journals.

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