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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus treatment as usual in patients with mental disorders in primary care: The COMET study.

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Keywords:	stepped care, collaborative care, mental disorders, comorbidity, guideline-based health care

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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus treatment as usual in patients with mental disorders in primary care: The COMET study.

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Abstract

Introduction: Mental health care is one of the biggest challenges for health care systems. Comorbidities between different mental disorders are common and patients suffer from a high burden of disease. While collaborative and stepped care models have been shown their effectiveness for single disorders, comorbid mental disorders have rarely been addressed in such care models. The aim of the present study is to evaluate the effectiveness of a collaborative and stepped care model for depressive, anxiety, somatoform and alcohol use disorders within a multiprofessional network compared to treatment as usual.

Methods and analysis: In a cluster-randomized, prospective, parallel-group superiority trial n=570 patients will be recruited in primary care practices (n=19 practices per group). The intervention is a newly developed collaborative and stepped care model in which patients will be treated with treatment options of various intensities within an integrated network of outpatient general practitioners, psychiatrists, psychotherapists and inpatient institutions. It will be compared to enhanced treatment as usual with regard to effectiveness, cost-effectiveness and feasibility, with the primary outcome being a change in mental-health-related quality of life from baseline to 6 months. Patients in both groups will undergo an assessment at baseline, 3, 6 and 12 months after study inclusion.

Ethics and dissemination: The study has been approved by the ethics committee of the Hamburg Medical Association (No. PV5595) and will be carried out in accordance with the principles of the Declaration of Helsinki. For dissemination, the results will be published in peer-reviewed journals and presented on conferences. Within the superordinate research project Hamburg Network for Health Services Research (HAM-NET), the results will be communicated to relevant stakeholders in mental health care.

Registration: The study is registered at clinicaltrials.gov under the ID NCT03226743.

Keywords: stepped care; collaborative care; mental disorders; comorbidity; guideline-based healthcare

Article summary

Strengths and limitations of this study

- To our knowledge, the present randomized controlled trial is the first to investigate the effects of a stepped and collaborative care model which addresses comorbidity by including the most frequent mental disorders (depressive, anxiety, somatoform and alcohol use disorders).
- The prospective study design with collecting outcomes at 6 and 12 months follow-up enables to examine mid-term effects.
- Collecting data on health services use and cost-relevant data allows a full health economic evaluation.
- The digital systematic screening and diagnosis for mental disorders in both the intervention and control group might limit the intervention's effect size.
- The study will not be able to determine the effectiveness of single diagnostic and therapeutic elements due to its complex intervention model.

Word count: 5626 words

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT03226743
Date of registration in primary registry	07/10/2017

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Protocol version	Issue date: 01/02/2019 Protocol amendment number 1
Revision chronology	07/10/2017: Original 01/02/2019: Amendment 1: - The study power was reduced from 90% to 80%, a common size in clinical trials thus improving international comparisons. This change resulted in a reduced number of practices (38 vs. 50) and patients (570 vs. 750) needed and increases the chances to reach the sample size. - After consultation with the advisory board and in agreement with the funding body the time point for the primary outcome measure was changed from 12 to 6 months after baseline. In many international studies on mental disorders, the primary outcome (symptom improvement, quality of life, etc.) is assessed after 6 months.
Secondary identifying numbers	01GY1602
Source(s) of monetary or material support	Federal Ministry of Education and Research (BMBF)
Primary sponsor	University Medical Center Hamburg-Eppendorf (UKE), Center of Psychosocial Medicine Prof. Dr med Dr phil. Martin Härter Martinistraße 52 20246 Hamburg m.haerter@uke.uni-hamburg.de www.uke.uni-hamburg.de Telefon:+49 (0) 40 7410-52978 Fax: +49 (0) 40 7410-58170 Contact: Sabine Pape (Secretary) Telefon: +49 (0) 40 7410-52863 Fax +49 (0) 40 7410-58170
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Public title	Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers: A Cluster-Randomized Controlled Trial (COMET)
Scientific title	Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers: A Cluster-Randomized Controlled Trial (COMET)
Countries of recruitment	Germany
Health condition(s) or problem(s) studied	Depressive Disorder Anxiety Disorder Somatoform Disorder Alcohol Use Disorder
Interventions(s)	Study intervention: Collaborative and stepped care Control intervention: Enhanced treatment as usual
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years; Sexes eligible for study: both; Accepts healthy volunteers: no; Inclusion

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	criteria: adult patient (≥ 18), diagnosed one of the health conditions studied, sufficient German language knowledge; Exclusion criteria: ongoing Psychotherapy
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: no blinding Primary purpose: treatment
Date of first enrolment	12/07/2018
Target sample size	38 General Practitioners, 570 Patients
Recruitment status	Recruiting
Primary outcome(s)	Change in health-related quality of life at 6 months
Key secondary outcomes	Change in disorder-specific symptoms, acceptability, feasibility, cost-effectiveness

1 Introduction

1.1 Background and rationale

Care provision for mental disorders constitutes a big challenge in health care worldwide. 17.6% of the world's population meets the criteria for a mental disorder during the last 12 months and about 29.2% experiences a mental disorder at some time in their life[1]. It is predicted that by 2020, the burden of mental and neurological disorders will have increased to 15% of lost disability-adjusted life years (DALYs)[2]. According to the WHO Mental Health Atlas 2011, there is a substantial gap between the burden caused by mental disorders and the resources available to prevent and treat them. Resources in health care systems are inequitably distributed and inefficiently utilized[3]. In high income countries 35.5% to 50.3% of serious cases received no treatment while in low and middle income countries even 76.3% to 85.4% received no treatment[4]. Comorbidity of mental disorders is frequent with 44% of patients having two and 22% three or more mental conditions simultaneously[5]. Alike, there is a large overlap between mental syndromes in primary care[6 7] calling for comprehensive health care approaches to address concurrent mental disorders in primary care settings[8].

One approach to account for comorbidity is collaborative care, an evidence-based form of treatment which focuses on systematically integrating multi-professional health care providers (e.g., general practitioners (GPs), specialized mental health professionals)[9 10]. Systematic reviews have found collaborative care for single mental disorders to be moderately effective[11-15] as well as cost-effective[16 17] for patients with depression and/or anxiety disorders[11], partly also for patients with comorbid physical conditions, e.g. diabetes and depression[18].

Often, collaborative care is combined with stepped care, a guideline-recommended approach in which patients are treated within different intervention steps of varying intensity based on current symptom burden. In this model, patients can be stepped up or down into a more or less intensive treatment depending on their response to treatment, as assessed by systematic monitoring[19]. Stepped care has proven to be effective for the treatment of depressive symptoms, however further investigation is required regarding effectiveness and the best manner of delivering this form of care[19-21].

Some trials examined the effects of stepped care on both symptoms of depression and anxiety[11 22 23]. Finally, a stepped care model for panic and generalized anxiety disorders was found to be effective and cost-effective[12 24]. The evidence of effectiveness of stepped care approaches for alcohol use disorders are limited[25-28]. UK-based stepped care approaches that were proven to be feasible in primary care with initially higher costs but probably with greater health benefits in the long term[29]. For the development of stepped care models for alcohol use disorders, German guidelines provide

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recommendations on the assignment of patients to adequate levels of care and the respective screening and interventions[30].

While there is scarce but promising evidence that collaborative and stepped care might improve the management of somatoform disorders[31 32], these approaches have rarely been implemented and evaluated in practice[33]. Somatoform disorders are not only a frequent phenomenon, but are also often accompanied by comorbid depression or anxiety disorders[34]. Thus, there is a necessity to substantiate an integrated multidisciplinary health care approach targeting persistent somatic symptoms, anxiety and depression at the same time[6].

The majority of current studies for collaborative and stepped care models for mental disorders do not fully correspond to the needs of primary care in that they only addresses one condition or two conditions maximally. For example, a systematic review on comorbidity in stepped care approaches found that of 39 studies only 5 studies addressed comorbidity of mental disorders and only one study included more than two mental disorders[35].

So far, research on collaborative and stepped care for mental disorders has been predominantly carried out in the United States (US)[11]. However, most health care systems outside the US are structured differently to the US which is why evidence for stepped and collaborative care might not be generalized to other health care systems[36].

Taken together, the development of an overarching integrative collaborative and stepped treatment model, which provides evidence and guideline-based treatment for the most common comorbid mental disorders (depression, anxiety, somatoform and alcohol use disorders) in primary care and taking into account the comorbidity between these disorders is necessary. This treatment approach needs to be examined with regard to effectiveness, cost-effectiveness as well as its barriers and facilitators for implementation into routine practice[8].

1.2 Objectives

The primary objective of the *Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers (COMET)-Study* is the effectiveness evaluation of an innovative collaborative and stepped care model (COMET) for patients with depressive, anxiety, somatoform and/or alcohol use disorders. Secondary objectives are the assessment of cost-effectiveness and feasibility of the model. The collaborative and stepped care approach is expected to improve healthcare by optimizing the use of existing resources.

The primary hypothesis is that patients treated with COMET will have a higher change in mental health-related quality of life 6 months after baseline than patients with augmented treatment as usual (aTAU).

2 Methods and Analysis

This study protocol is written according to the SPIRIT reporting guidelines[37].

2.1 Study design

The trial is a cluster-randomized, prospective, parallel-group, superiority study comparing the effectiveness of COMET and aTAU with allocation ratio of 1:1 in a consecutive sample of primary care patients with depressive, anxiety, somatoform and/or alcohol use disorders. Patients in aTAU will follow the same recruitment process as patients in COMET and will receive the same computer-aided screening and guideline-based diagnostic tool, which is not part of clean treatment as usual. Participants in the aTAU-group will have unrestricted access to usual care for their mental health problems. General practitioners (GPs) in aTAU will be instructed to continue treatment with affected patients in the same way as they would do outside the study. We decided to compare the intervention to enhanced usual care as this is a health care services research project which investigates in research to improve routine care for patients with mental health disorders. Usual care is defined as control group because the treatment strategies used in the intervention group are not part of usual-care practices. Moreover, in a pragmatic trial where the research question is to determine the collaborative

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and stepped care intervention is superior to usual care, it is obvious to have usual care as the control group. Patients will be assessed at baseline, at month 3 and 6 during treatment and at 12 months follow-up. The study started in February 2017 with a preparation phase. Recruitment and intervention were initiated in July 2018. The study is expected to end in July 2020 with the primary outcome available in February 2020. We did not involve patients or the public in our work.

2.2 Setting

Patients will be recruited in 38 primary care practices (19 aTAU and 19 COMET practices) by GPs in Hamburg in Germany. Patients in COMET will be treated in the COMET network by GPs, psychotherapists and psychiatrists as well as inpatient clinics in Hamburg. Patients in aTAU will be treated in usual care. The list of all participating care providers can be requested from the study coordinator (Daniela Heddaeus; d.heddaeus@uke.de).

2.3 Eligibility criteria

GP's inclusion criteria for participation in the study will be to have an approval as GP in an outpatient practice by the Association of Statutory Health Insurance Physicians of Hamburg. Psychotherapists, psychiatrists and inpatient institutions must have an approval of the Association of Statutory Health Insurance Physicians of Hamburg. All care providers have to sign a cooperation contract to participate in the study.

For patients, inclusion criteria will be a minimum age of 18, informed consent and one or more of the following ICD-10-diagnoses by their GP: depressive episode (F32), recurrent depressive disorder (F33), dysthymia (F34.1), agoraphobia (F40.0), social phobia (F40.1), panic disorder (F41.0), generalized anxiety disorder (F41.1), mixed anxiety and depressive disorder (F41.2), somatoform disorders (F45), and/or mental and behavioral disorders due to use of alcohol (F10). Patients with insufficient knowledge of the German language or a health situation that does not allow questionnaire completion and the participation in telephone interviews as well as patients already receiving current in- or outpatient psychopharmacotherapy or psychotherapeutic care will be excluded. Neither somatic nor mental comorbidities will be exclusion criteria.

2.4 Recruitment

General Practitioners

In order to recruit participating primary care practices all registered GPs of the city of Hamburg will be informed about the project by mail and invited to a information event where they will be informed about the study except for details concerning the intervention itself. Subsequently, they will be asked to participate in the study and to sign a cooperation contract. To increase willingness for participation, GPs will also be contacted via telephone and, if desired, also get a personal introduction to the study in their practices. All participating GPs will be visited by the study team to implement study procedures. They will receive detailed patient information materials, informed consent forms in order to hand them out to the patients and a tablet computer for the recruitment and screening procedure.

Patients

Participating GP practices will define recruitment days, on which each patient entering the practice will be informed about the study. After giving informed consent to participate in a computerized screening procedure he or she will receive a tablet computer. In line with the recommendations of practice guidelines[30 38-40] the computerized consists of selected modules of the German version of the Patient Health Questionnaire (PHQ-D)(PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module), the Somatic Symptom Disorder-B Criteria Scale (SSD-12) and the Alcohol Use Disorders Identification Test (AUDIT). After the screening the patient hands over the tablet computer to the GP who discusses the results with the patient. Screening results may or may not be used by the physician for diagnostic purposes. Integrated ICD-10 diagnostic criteria checklists support the GP in the selection of the diagnosis. If a

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patient receives one or more study relevant diagnoses and gives his or her informed consent, the patient will be included in the study.

Psychotherapists, psychiatrists, psychosomatics and inpatient institutions
All in Hamburg established psychotherapists, psychiatrists and inpatient institutions will be informed about the project by mail and invited to an information event where they will be informed about the study and their tasks in detail. All psychotherapists, psychosomatics and psychiatrists will receive detailed instruction on the study procedures by phone.

2.5 Participant timeline

Figure 1: Participant timeline

2.6 Allocation of treatment

Cluster-randomization will be performed in order to control for potential bias in order to increase internal validity. In this study, a cluster-randomization will be performed at the level of GP practices, which will be randomly assigned to COMET and aTAU in a ratio of 1:1 and a block length of 4 by a list of computer-generated random numbers without any stratification variables. The randomization list will be created by a research associate of the Department for Medical Biometry and Epidemiology of the University Medical Center Hamburg-Eppendorf, not involved in the implementation of the research project. With the aim to ensure recruiter blinding, the study coordinator, who will not be involved in the recruitment of GPs, will receive the computer-generated randomization list, preserve it in a place accessible only to her and carry out the allocation of participating GPs. Incoming cooperation contracts will be assigned to COMET vs. aTAU according to the randomization list by the study coordinator. GPs will then be informed about their allocation status. Included patients will receive either COMET or aTAU depending on their GP's allocation. This means that even though the allocation is determined by the ranking of the list preventing a bias, strictly speaking the allocation is not totally blinded. Blinding of randomization status cannot be granted for the study team, care providers or patients due to reasons of study implementation.

2.7 The COMET Intervention

The intervention will be a collaborative and stepped care program provided in the city of Hamburg, Germany by established outpatient GPs, psychotherapists, psychiatrists, psychosomatics and inpatient or day-care clinics embedded in the standard health care system in Germany. Number of sessions, treatment schedule and the intensity of care will be tailored individually for each patient. The intervention will contain the following elements:

Collaborative network
Outpatient GPs, psychotherapists, psychosomatics and psychiatrists in as well as inpatient or day care facilities will be integrated into the COMET network to enhance information exchange about their work in general and individual cases of patients and facilitate immediate referral from GP to specialized care providers. An online scheduling platform enables psychotherapists and psychiatrists to indicate available treatment resources and GPs of the network to book those resources. This tool has been developed and successfully implemented in a former project "Health network depression"[21]. At the beginning of the study, network participants will obtain initial training regarding the evidence-based guidelines of conditions in focus[30 38-40] and the planned care model. Additionally, further quality assessment and exchange is provided in quarterly network meetings. In contrast to an often-used approach which brings external care managers into GP practices, we will systematically integrate the resources and competencies of cooperating care providers (GPs, psychotherapists, psychiatrists, psychosomatics, and inpatient facilities) which can more readily create the structures needed to provide a broad spectrum of interventions.

Computer-assisted and guideline-based diagnosis and treatment decisions

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Following the diagnostic process (see 2.4), the GP will continue with the treatment selection. The algorithm of the program on the tablet computer will provide the GP with one or more treatment recommendations for the individual patient that will be based on guideline recommendations for the diagnosed disorder and its degree of severity[30 38-41]. Additionally, several factors will be taken into account when making a treatment decision: patient preferences, possible comorbidities, and specific characteristics of the disorder(s). While these recommendations will offer an orientation for therapeutic decisions, the actual treatment decision for one of the evidence-based treatment options will be carried out in cooperation with the patient by integrating individual preferences and needs, thus following the principles of patient-centered care and shared decision-making.

Collaborative and stepped care interventions

Within the COMET intervention, patients may be offered eight different interventions structured in three steps of varying intensity and setting (Table 1). The complex intervention will be delivered by different care providers and increase in intensity.

Table 1: Guideline-based treatments in the COMET intervention

Step	Description		Care provider	Setting
1a	Basic psychosocial care, psychoeducation	Establishment of a working alliance, the provision of psycho-educative materials, psychosocial counselling and treatment of possible comorbid somatic symptoms[30 38-40] including systematic monitoring	GP (or mental health specialist)	Outpatient
1b	Bibliotherapy	Disorder-specific cognitive-behavioral-therapy oriented self-help books[42-47] accompanied by systematic monitoring	GP (or mental health specialist)	Outpatient
1c	Internet-based self-management	Internet-based self-help program with a cognitive-behavioral-therapy oriented evaluated and certified computer program accompanied by systematic monitoring[48-50]	GP (or mental health specialist)	Outpatient
1d	Single brief interventions (for alcohol use disorders)	Up to five sessions of less than one hour, during which the patient receives individual feedback on alcohol consumption and advice as well as agreed goals[30]	GP	Outpatient
2a	Psychotherapy	Face-to face cognitive-behavioral therapy or psychodynamic psychotherapy either individual or in a group	Psychotherapist	Outpatient
2b	Pharmacotherapy	Medication according to guideline recommendations	GP or mental health specialist	Outpatient
3a	Pharmacotherapy plus psychotherapy	Intensified combination therapy of psychopharmacotherapy and face-to-face-psychotherapy	GP or mental health specialist and psychotherapist	Outpatient
3b	Intensified treatment	Intensified treatment carried out by a multi-professional treatment team	Multiprofessional team	Day hospital or inpatient facility

The materials for step 1 will be provided to the GP by the study team (i.e. psycho-educative materials, self-help books, licenses for the self-help internet programs). In case of referral to a specialized care

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provider in step 2 or 3, the GP will use the online scheduling platform to book free treatment capacity in the collaboration network. The patient will be instructed to call the booked care provider to confirm the appointment.

Previous studies have shown that among patients with mental disorders especially those with a high symptom severity do not receive the treatment they need (e.g.[51-53]). It is still unknown if this is caused by barriers in the referral process, insufficient motivation on patient side or other difficulties. In order to address this problem, a case management will be implemented. A psychologist of the study team will follow the treatment pathways of patients with severe disorders or high comorbidity based on the digital diagnostic information and the monitoring forms filled out by the care providers and will inform the responsible care provider if he detects a possible deficient care is detected.

COMET patients will be monitored regularly by their responsible care provider with monitoring forms in order to ensure that sufficient treatment response will be achieved and potential under- or oversupply will be corrected as quickly as possible.

To improve the adherence of care providers to the intervention protocol they will receive an initial training about the study procedures for three hours. Further trainings (three hours each) will cover the guideline recommendation for the four relevant disorders. Additionally, there will be a network meeting for the COMET-group each quarter. Furthermore all care providers will obtain detailed instruction manuals, prepared materials and they will be visited in their practice at the beginning as well as when any questions or problems occur. There will be a close contact between the study team and the participating care providers. Screening, diagnostic and monitoring information will be sent to the study team promptly. Thus, the study team will be able to early recognize and intervene if there is any deviation from the study protocol and to contact the care provider.

Patients of the COMET group will be free to use any other additional care, if needed. Other care utilization will be recorded in the data collection interviews (T2 and T3).

2.8 Outcomes

Primary outcome measure

Following the primary hypothesis that COMET patients will have a higher change in mental health-related quality of life at 6-month than aTAU patients, the primary outcome parameter will be a change in mental health-related quality of life (Short Form Health Survey, SF-36 mental health score[54]) from baseline to 6 months.

Secondary outcome measures

Secondary outcome parameters will be the change in disorder-specific symptoms as measured with the German versions of the major depressive[55], generalized anxiety[56], panic and somatoform modules of the PHQ[57], the SSD-12[58-60] and the AUDIT[61]. Further secondary outcomes will be disorder-specific response (at least 50% symptom reduction at 6 months on the disorder-specific screening instrument) and remission (obtaining a value below the respective clinical cut-off value of the disorder-specific screening instrument at 6 months), health-related quality of life assessed with the SF-36 physical health score, change in health-related quality of life according to the EQ-5D-5L and health care utilization.

The cost-effectiveness will be a further secondary outcome. For the calculation of direct and indirect costs health care utilization, reduced productivity at work and work loss days will be measured by a modified version of the Client Sociodemographic and Service Receipt Inventory (CSSRI[62]). The utilization of inpatient care, outpatient physician services, outpatient non physician services, medication, as well as formal and informal (long-term) care will be assessed. To assess health effects, quality-adjusted life years (QALYs) will be calculated based on utilities derived from the EQ-5D-5L questionnaire.

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Additionally, to allow for exploratory analyses, relevant process outcomes will be assessed: implementation, functionality, acceptability and sustainability of the network, including attributes of the health care model (e.g. relative advantage, compatibility, trialability), adoption/assimilation (e.g. needs, motivation, values, preferences, acceptance and skills of involved actors, including patients), communication and influence (diffusion and dissemination, including social networks, opinion leadership, change agents), the context (antecedents and readiness for innovation, incentives, reimbursement regulations), and the implementation process (support and advocacy of implementation process, feedback on progress).

2.9 Sample size

We aim for a sample size that permits the detection of a small to moderate standardized mean difference (Cohen's d of 0.35); [63] between the COMET and aTAU for the primary outcome (change in the SF-36 mental health score after 6 months) with a statistical power of 0.80 at a type I error rate of 0.05 (two-sided). Assuming a correlation of 0.50 between baseline and follow-up measurements, this requires analyzable data from 95 patients per group (190 in total) for a linear model with the baseline measurement as covariate [64] if randomization took place at the patient level. With an average cluster size (number of patients per practice) of 12 and an intra-cluster correlation (ICC) of 0.05, this sample size should be multiplied by a design effect of 1.55 [65], leading to 156 patients in 13 practices per group and 312 patients in 26 practices in total. As our experience suggests that up to 30% of the randomized practices and up to 20% of the recruited patients may drop out of the study, we aim to recruit 38 practices (19 per group) including 15 patients each, resulting in a target sample size of 570 recruited patients in total (285 per group).

2.10 Data collection methods

Data collection via tablet computer

Data on screening, diagnostics, severity degree of the disorder, indication and treatment decision as well as the baseline assessment of the primary outcome (SF-36) will be collected on a tablet computer using a specially developed web-based screening and diagnostic software (for tests used for the screening see 2.4 Recruitment). The program will also ask for reasons for GP consultation, age, gender and if the patient already receives psychotherapy or psychopharmacotherapy.

Telephone-based patient interviews

The telephone-based patient interviews will take place at four time-standardized measurement points (baseline, 3, 6 and 12 months after baseline, see Fig. 1). For questionnaires used see table 2. All staff members conducting telephone interviews underwent a special training for the Composite International Diagnostic Interview (CIDI[66]), which is part of the baseline interview and received detailed guidelines and standard operating procedures for the interviews. To conduct the interview, the responsible staff member will call the patient to make an appointment for the interview. At the appointment the staff member will call the patient and carry out the interview. All contact attempts and contacts will be documented. Telephone interviews instead of written questionnaires were chosen to improve the response rate and the quality of the data collected.

Monitoring forms

In COMET, care providers will be instructed to monitor their patients in regular time intervals. Time intervals will depend on the conducted treatment and will be at least once a quarter. Care provider will document the result of the monitoring on a standardized monitoring form that include frequency of consultations since the last visit, treatment decision at the last visit, realized treatment and reasons for deviations, symptom changes (deterioration, improvement), impairment due to symptoms, new diagnoses, remitted diagnoses, serious adverse events and future treatment plans.

Measurement instruments are summarized in Table 2.

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Table 2: data-collection instruments

		measurements			
Instrument	**Description**	***T0***	***T1***	***T2[1]***	***T3***
Sociodemographics	Date of birth, gender, native country, nationality, native country of the parents, family status, postal code, educational level, occupation, professional status	*x*	-	-	-
Composite International Diagnostic Interview (CIDI) (sections for depressive, anxiety, somatoform and alcohol use disorders)	Comprehensive interview procedure consisting of 40 modules that enables the standardized diagnosis of mental disorders (ICD-10, DSM-IV) for the entire lifetime (longitudinal section) or last 12 months (cross-section). For this study only modules for the investigated disorders are used with regard to the last 12 months[66].	*x*	-	-	-
Short Form Health Survey (SF-36)[2]	Measures the disease-spanning, health-related subjective quality of life[54]. It comprises 8 dimensions (physical functioning, physical role functioning, physical pain, general health perception, vitality, social functioning, emotional role functioning and psychological well-being), which can be assigned to the two main scales "physical health" and "mental health". Answers are Likert scaled. They are weighted, added and transformed to the range 0 to 100. High values mean a high health-related quality of life. It is an internationally used, test-theoretically validated instrument with a German reference population[67].	***4***	***x***	***x***	***x***
PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module from the Patient Health Questionnaire (PHQ-D)[3]	German adaptation of the PHQ, a screening instrument based on the criteria of the DSM-IV that covers various syndromes and is a practicable and well validated instrument[57 68 69]. The following modules are used in this study: • The PHQ-9 (9 items) for the identification of depressive syndromes covers main and secondary symptoms of depression on a four-step scale according to their frequency[55]. • The GAD-7 (7 items) to detect generalized anxiety disorder[56] and the PHQ panic module (15 items) for panic disorder. The GAD-7 is measured on a four-step scale. On the PHQ panic module each item corresponds to a DSM-IV panic disorder criterion and is answered "Yes" or "No" [68]. • The PHQ-15 (15 items) identifies the somatoform syndrome measured on a three-step scale.	*4*	*x*	*x*	*x*
Somatic Symptom Disorder-B Scale (SSD-12)[3]	Measures the new psychological criteria of the Somatic Symptom Disorder (DSM-5) with 12 items that refer to three subscales to capture cognitive, affective and behavioral aspects. In a first validation study in an outpatient sample, the scale showed very good psychometric properties[60].	*4*	*x*	*x*	*x*
Alcohol Use Disorders Identification Test (AUDIT)[3]	Instrument developed by the World Health Organization to identify patients with problematic alcohol consumption in different settings. It is nationally and internationally recognized and includes 10 items related to alcohol consumption, dependence and abuse, with a choice of 3 to 5 alternatives[61 70].	*4*	*x*	*x*	*x*

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collaboRATE	Three-item scale of the shared decision making process to measure the dimensions explanation of the health issue, elicitation of patient preferences and integration of patient preferences on a 0 to 9 scale. It has a concurrent validity with other measures of SDM, good interrater reliability and sensitivity to change[71].	[4]	-	*x*	*x*
Quality of Life Questionnaire EQ-5D-5L[3]	Generic health-related quality of life questionnaire consisting of five items that measure current problems on the dimensions mobility, self-care, usual activities, pain discomfort and anxiety/depression on five levels. It can be used as a simple health classification system to detect differences in the health status of population groups. Based on the 3,125 possible unique health states derived from the EQ-5D-5L, index scores can be assigned through a set of preference valuations of the general population regarding different health states[72]. It also contains a visual analogue scale for the general assessment of health-related quality of life, which allows easy comparisons with the general population.	*x*	-	*x*	*x*
Modified Client Sociodemographic and Service Receipt Inventory (CSSRI-D) [3]	Modified version to measure the utilization of services adapted to the specifics of German health care and serves to assess mental health care costs. It collects data about employment and income (employment status, occupation, days of incapacity to work, type and amount of social benefits), use of care services (inpatient, day-care, outpatient and complementary care) as well as medication (type and name of medication taken, dosage, number and size of medication packs collected from the pharmacy, price). The instrument has proven itself in practical use, enables statements to be made on direct and indirect costs and provides information on the utilization and medication profiles[62].	*x*	-	*x*	*x*
Illness Perception Questionnaire Brief (IPQ-B)	9-Item tool for recording illness perceptions. 8 items measure on scales of 0-10 the dimensions perceived consequences of the disease, chronicity, perceived personal control and control over treatment, identity, concerns about the disorder, coherence and emotional representation of the disorder. Higher scores reflect a stronger representation of this dimension. The last item serves to identify the three most subjectively relevant causes of the disease. The IPQ-B has a predictive and discriminatory validity and change sensitivity was confirmed in a systematic review [73].	*x*	-	-	-
Questionnaire on the intensity of the general practitioner commitment (F-HaBi)	Measures the utilization behavior of primary care patients. It distinguishes patients with close primary care coordination from those who access further care without prior contact to the GP. 9 items indicate whether the patient has a GP, how often the GP is consulted, how/if the patient uses the GP as a coordinator and patient satisfaction with the GP and the specialists. Answers are given on a five-step scale. Higher values indicate that the patient is more likely to perceive and use the GP as a coordinator.	*x*	-	*x*	*x*

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Health care utilization and satisfaction with received treatments in the last 3 resp. 6 months	These items ask for the treatments received in the last 3 resp. 6 months on a "yes/no" scale and the patient's satisfaction with the received treatments on a five-step scale.	-	*x*	*x*	*x*
Questionnaire on satisfaction in outpatient care - focus on patient participation (ZAPA)	Four-item questionnaire to measure patient satisfaction in outpatient medical care taking into account the concept of patient participation. It has a one-dimensional structure. Its brevity makes it suitable for use in studies to measure patient satisfaction in outpatient care settings [74].	*x*	-	-	*x*
Process evaluation (quantitative)	Implementation of the COMET study (information, acceptance, time expenditure, incentives) will be evaluated with 4 items. An open-ended question at the end offers the opportunity to comment on the satisfaction with the study.	-	-	*x*	-

T0: baseline, T1: 3 months after baseline, T2: 6 months after baseline, T3: 12 months after baseline,
[1]primary measurement time point,
[2]primary outcome,
[3]secondary outcome,
[4] baseline data collection for these instruments is carried out via the tablet computer-based screening and after study inclusion in the waiting room in the primary care practice as described in 2.12.

Process evaluation

For the process evaluation, semi-structured qualitative interviews will be conducted at the beginning and at the end of the study with patients, GPs, psychotherapists, psychosomatic specialists and psychiatrists of the COMET-group and the aTAU-group. We will use semi-structured interview guides on implementation, functionality, acceptance and sustainability of the interventions of the COMET-model. The interview guides include possible beneficial and impeding aspects referring to the implementation process, the care model, adoption/assimilation, communication/impact and context. Questions about the implementation of the study will be integrated in the patient interview at T2. For a separate evaluation of the care process, practitioners will be asked at baseline and T3 using standardized short questionnaires. Moreover, process evaluation with care providers will be involved in the quarterly network meetings.

Retention and Discontinuation

All care providers will receive financial incentive for those activities that are additional to their usual care. GPs receive expense allowances up to 120€ per patient, psychotherapists up to 290€ and psychiatrists up to 150€ per patient.
Patients will receive a voucher worth 10€ for each of the four conducted interviews. Patients will be contacted up to five times for each of the telephone interviews. If the patient is not available even after five attempts, the GP who included the patient in the study will be informed and the patient will be called again at the next measurement point. Neither termination of the selected treatment nor termination of the relationship to the recruiting GP will be reasons for a subsequent exclusion of the study and participation in further interviews, respectively. Only if the patient explicitly wishes to terminate study participation and does not want to take part in interviews anymore, he or she will be excluded from the study. The data collected so far will only be deleted, if he or she explicitly demands this. All drop-outs will be documented on a drop out form that will include age, gender, drop-out date and reasons for drop-out.

2.11 Data management

Data collected with the web-based screening- and diagnostic tool on the tablet computer will be entered electronically by the patient and the GP and stored pseudonymously in an encrypted database

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on a server of the University Medical Center Hamburg-Eppendorf. The program will include range checks for data values. Data collected during the telephone interviews will be entered directly into a password-protected uniform data entry mask by the interviewing researcher. The data entry masks will be pre-programmed (with the program EpiData) to ensure valid values and prevent entry errors. Data collected via monitoring forms will be documented by the responsible care providers of the network and sent to the study team. A student assistant will enter the data into a digital data mask. All collected data will be stored in a database on the UKE internal server in a pseudonymous form. All participant files will be maintained in storage for a period of ten years after completion of the study. The principal investigators and the study team will have access to the cleaned and final data sets. All data sets will be cleared of any identifying participant information and password-protected.

2.12 Monitoring

The study will be monitored by an international advisory board that is meeting once a year to review the study progress. It consists of five international scientists with expertise in the field of health care services research in mental health and collaborative and stepped care models. Progress, challenges and possible adjustments will be presented by the study team and discussed with the advisory board. The board is independent from the sponsor. A data monitoring committee will not be established. Data will be monitored by the study coordinator who has no competing interests.

2.13 Adverse events

We define adverse events as any adverse medical or psychological incident in a patient. Adverse events will be documented by the care providers and the study team whenever they occur. Serious adverse events will be reported to the ethics committee and include suicidality, significant burden, severe or permanent disability, prolonged or unplanned hospitalization, functional impairment, significant hazard or life threatening condition. For suicidality a standard operating procedure was developed.

2.14 Statistical methods

The descriptive statistics will be presented by group and for the total sample. The primary analysis will be based on the intention-to-treat (ITT) population which includes all practices and patients randomized and included in the study. A linear mixed model for the changes from baseline of SF-36 will be calculated with group (COMET / aTAU) and time as a fixed effect, practice and patients as random effects and the baseline value of the SF-36 mental health score as a covariate. The time by group interaction will be tested, if the interaction is not significant, the interaction will not be included in the model. The coefficient test, comparing the adjusted SF-36-values between the randomized groups, will be performed using the direct maximum likelihood as the statistical estimation procedure, which results in unbiased estimators under the missing-at-random-assumption. The contrast between both groups at the 6-month follow up will be assessed in a confirmatory manner. The analysis will be repeated in the per protocol (PP) population. To investigate the effects of the missing values on the result of the primary analysis, sensitivity analyses will be carried out with different methods for missing value imputation (e. g. multiple imputation, last observation carried forward). The secondary endpoints will be examined in an exploratory manner. For the binary secondary endpoints, we will conduct a mixed logistic regression and for the continuous secondary endpoints we will carry out a linear mixed model. The other model parameters will be set as in the primary endpoint analysis. The following subgroup analysis are planned: diagnosis, sex, age, socio-economic status and symptom severity. Adjusted means and odds ratios, respectively, with their 95% confidence intervals and p values were reported. The two-sided type I error will be set at .05. The safety endpoints will be determined using frequency tables and if possible using mixed logistic regressions to compare the event frequencies. Interim analyses are not planned. A detailed statistical analysis plan will be prepared and finalized before the code is broken. Results will be reported according to the CONSORT statement extended for cluster randomized trials.

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Variable	Hypothesis	*Outcome Measure*	*Methods of analysis*
Health-related quality of life mental health scale	Improvement COMET > aTAU	Short Form Health Survey (SF-36)	Linear mixed model
Change in disorder-specific symptoms	Improvement COMET > aTAU	PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module, SSD-12, AUDIT	Linear mixed model
Response of diagnosed disorder(s)	Improvement COMET > aTAU	PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module, SSD-12, AUDIT	mixed logistic regression
Remission of diagnosed disorder(s)	Improvement COMET > aTAU	PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module, SSD-12, AUDIT	mixed logistic regression
Patient-centeredness and shared decision-making	Improvement COMET > aTAU	CollaboRATE	Linear mixed model
Health care utilization	Improvement COMET < aTAU	Questionnaire, CSSRI	Generalized linear mixed model
Change in quality of Life	Improvement COMET > aTAU	EQ-5D-5L	Generalized linear mixed model
Cost-effectiveness	Improvement COMET > aTAU	CSSRI, EQ-5D-5L	QALYs, ICER, CEAC based on net monetary benefit
Relationship to GP	Improvement COMET > aTAU	F-HaBi	Linear mixed model
Patient satisfaction	COMET > aTAU	Questionnaire, ZAPA	Linear mixed model

Additional analysis

Direct and indirect costs will be calculated from the societal perspective based on health care utilization, reduced productivity at work and work loss days measured by a modified version the CSSRI [62]. For the monetary valuation of resources, German standard unit costs will be applied [75 76]. Indirect costs will be calculated based on the human capital approach by applying gross income plus nonwage labor costs [77]. For assessing health effects, QALYs will be calculated based on utilities (i.e., preference-based scores of health-related quality of life measured on a scale from 0=very bad health to 1=perfect health) derived from the EQ-5D-5L questionnaire. Costs and effects of COMET will be compared to standard care in incremental analyses. This will be done by calculating incremental cost-effectiveness ratios (ICERs)[78]. The ICER is defined as the ratio of the difference in cost and the difference in health effects between intervention and control group. As the ICER is a point estimate which does not consider statistical uncertainty in the data nor the effect of potential confounding variables, cost-effectiveness acceptability curves (CEACs) by means of a series of net benefit regressions using different willingness-to-pay margins will be constructed [79].

Process Evaluation: Data of the patient survey will be analyzed using descriptive statistics (i.e. frequencies, means, and standard deviations). The qualitative data will be analyzed using structuring content analysis based on the above mentioned categories of facilitating and inhibiting factors of implementation and sustainability of the COMET-model [80 81].The qualitative interviews will be transcribed and coded using a deductive category system (e.g. attributes of the health care concept, adoption/assimilation, communication/influence, context and implementation process), which will be further elaborated inductively.

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3 Ethics and Dissemination

The ethics committee of the Hamburg Medical Association has approved the study design and intervention (PV5595) in September 2017 prior to commencing recruitment. We confirm that the study will be carried out in accordance with the principles of the Declaration of Helsinki. Any severe adverse events as well as any protocol changes will be reported to the ethical committee and the advisory board without delay. Written informed consent will be obtained from all patients by their GPs. There are no obvious risks for patients participating in the study. The study does not involve any restriction to standard care. The study has been registered at clinicaltrial.gov NCT03226743 in October 2017.

Personal information about participants

Personal information will be collected on the informed consent form, where the patient gives his or her name and telephone number. This form also includes a unique patient code. The telephone number is needed to call the patient for the patient interviews. The GP sends the form via fax to the study coordinator. The study coordinator receives the fax digitally on her computer, extracts the patient code, name of including GP and telephone number, sends this information to the study team and saves the fax as password-protected files where only she has access to. The study team contacts the patient without knowing his or her name and conducts the interview. At the end of the interview the patient will be asked, if he or she is interested in an expense allowance in form of a 10€ gift coupon. If so, he or she will be asked for the postal address. The address will not be saved but eliminated immediately after the coupon is sent.

Dissemination policy

The results and findings of the study will be published in peer-reviewed journals and presented at conferences and congresses. It will be disseminated also via the multiple partnerships within the superordinate project Hamburg Network for Health Services Research (HAM-NET). Results will also be reflected to the participating health care providers.

Data statement

A completely anonymized data set will be delivered to an appropriate data archive for sharing purposes. No professional writers will be employed.

Conclusion

In line with the primary hypothesis, the intervention condition is expected to be superior to the control condition. This means that COMET is expected to provide more effective treatment than routine care in terms of improving health-related quality of life 6 months after treatment initiation. In addition, COMET is expected to outperform standard care in secondary outcomes, cost-effectiveness, and process variables. A significant knowledge gain is expected on whether it is possible and effective to treat a wide range of mental disorders (depression, anxiety, somatoform and alcohol-related disorders) within a collaborative and stepped care model based on evidence-based recommendations. This is a challenge for the care provider and the whole network. Particular interest will be given to how the central issue of comorbidity is dealt with. As far as we know, this is the first randomized and controlled study dealing with complex co-morbidity patterns.

4 Author contributions

MH, BL, OvdK, MS, IS, HHK, KV and DH designed the study and obtained funding. MH, JD and DH are responsible for its conduct and overall supervision. HHK, CB, TG, KW and AD contributed to specific methodical and health economic issues. DH, JD, SP, KM, SW, AW, TZ, BS, MR and MH worked out study processes, treatment pathways and materials. DH coordinates the study with support from JD and MH. DH, SP, KM and SW organize the network and carry out the recruitment process, network meetings and data collection. DH is responsible for data management. DH, JD and MH wrote the manuscript. All authors contributed, reviewed and approved the final manuscript.

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5 Funding statement

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6 Competing interests

The authors declare that they have no competing interests.

7 Roles and responsibilities

7.1 Coordinating Center: Principal investigator and research team

- Design and conduct of COMET
- Preparations of protocol and revisions
- Study planning
- Preparation of care provider brochure and case report forms
- Recruitment of general practitioners and further health care provider
- Organization of network meeting and trainings
- Network management
- Practice visits
- Publication of study reports
- Preparation of materials for participating health care providers and patients
- Development of the internet transferal platform and the eDiagnostic tool
- Responsible for trial master file
- Budget administration and contractual issues
- Randomization
- Data verification
- Maintenance of trial IT system and data entry

7.2 Steering committee/advisory board

- Agreement of final protocol
- Reviewing progress of study and if necessary agreeing changes to the protocol
- Consultation in clinical, methodological and content-related issues

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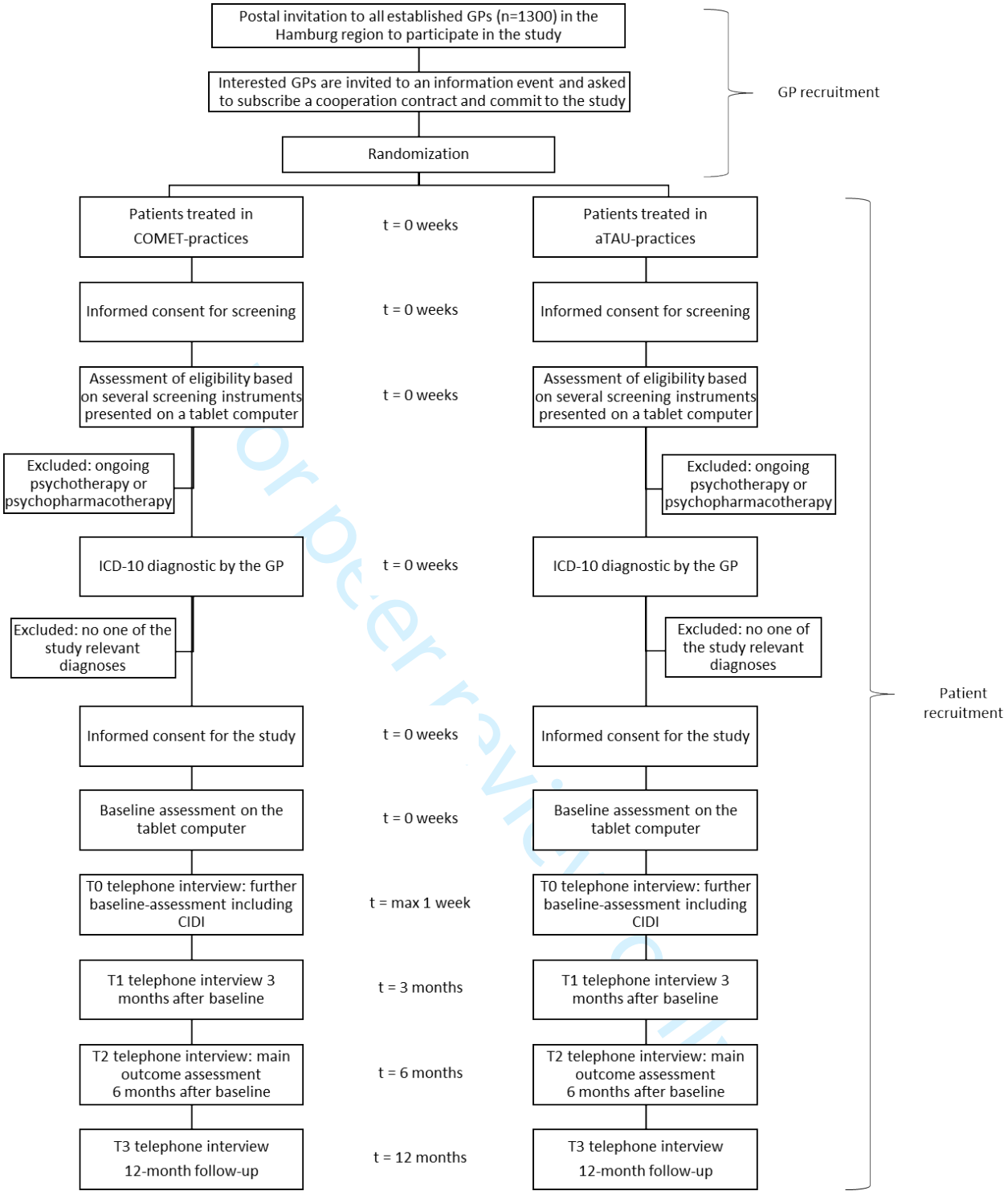

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ETHIK-KOMMISSION DER
ÄRZTEKAMMER
HAMBURG
Körperschaft des öffentlichen Rechts

Mr.
Prof. Dr. med. Dr. phil. Dipl. Psych Martin Härter
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University Medical Center Hamburg-Eppendorf
Martinistr. 52, W26
20246 Hamburg

08.09.2017
Ku/Vo

For peer

Reference number: **PV5595**
Study title: **Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers (COMET)**

Dear Mr. Häter,

The Ethics Committee discussed the above-mentioned project submitted for primary consultation in detail at its meeting on 05.09.2017.

The project complies with ethical and legal requirements. The Ethics Commission approves the project.

The Commission points out that the responsibility of the investigator for the research project and its implementation is not affected by the vote of the Commission.

In the event that the study is carried out in centers of other chamber areas, the Commission assumes that the locally responsible ethics committee will be involved.

The Ethics Committee asks to be informed of any serious or unexpected events that occur during the study and that endanger the safety of the study participants.

The Commission assumes that the personal data of the subjects/patients will be treated in accordance with data protection laws.

In addition, the Commission would like to give some comments and recommends to revise the documents accordingly. Any revised documents submitted subsequently will not be re-examined, as the Commission's deliberations have ended with this letter.

Weidestraße 122 b | 22083 Hamburg Telefon 040 / 20 22 99-240 | Fax 040 / 20 22 99-410

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Reference Number.: PV5595

1. Patient information p.2 "The Ethics Committee of the Hamburg Medical Association has reviewed this scientific study": The EC advises research projects in accordance with professional law; we ask to correct this wording accordingly.

2. The informed consent for the “short questionnaire” does not mention that the participant will be given a copy of the informed consent.

The Ethics Committee expects to receive a final report at the end of the project (stating the reference number) indicating the success or failure of the study and whether the study was discontinued or changed, or whether recourse claims were made.

With binding recommendation
on behalf of the Commission

Prof. Dr. med. M. Carstensen
Deputy chairman

P.S. The Ethics Committee works on the basis of German law and professional law as well as on the basis of the iCH-GCP.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 & 3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3 & 16

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Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 16, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants,			

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interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	10

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		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	10

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		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	14

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		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13

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Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	16
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus augmented treatment as usual in patients with mental disorders in primary care: The COMET study.

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Secondary Subject Heading:	General practice / Family practice, Health services research, Patient-centred medicine, Pharmacology and therapeutics
Keywords:	stepped care, collaborative care, mental disorders, comorbidity, guideline-based health care

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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus augmented treatment as usual in patients with mental disorders in primary care: The COMET study.

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Abstract

Introduction: Mental health care is one of the biggest challenges for health care systems. Comorbidities between different mental disorders are common, and patients suffer from a high burden of disease. While the effectiveness of collaborative and stepped care models has been shown for single disorders, comorbid mental disorders have rarely been addressed in such care models. The aim of the present study is to evaluate the effectiveness of a collaborative and stepped care model for depressive, anxiety, somatoform and alcohol use disorders within a multiprofessional network compared to augmented treatment as usual.

Methods and analysis: In a cluster-randomized, prospective, parallel-group superiority trial n=570 patients will be recruited from primary care practices (n=19 practices per group). The intervention is a newly developed collaborative and stepped care model in which patients will be treated using treatment options of various intensities within an integrated network of outpatient general practitioners, psychiatrists, psychotherapists and inpatient institutions. It will be compared to augmented treatment as usual with regard to effectiveness, cost-effectiveness and feasibility, with the primary outcome being a change in mental-health-related quality of life from baseline to 6 months. Patients in both groups will undergo an assessment at baseline, 3, 6, and 12 months after study inclusion.

Ethics and dissemination: The study has been approved by the ethics committee of the Hamburg Medical Association (No. PV5595) and will be carried out in accordance with the principles of the Declaration of Helsinki. For dissemination, the results will be published in peer-reviewed journals and presented at conferences. Within the superordinate research project Hamburg Network for Health Services Research (HAM-NET), the results will be communicated to relevant stakeholders in mental health care.

Registration: The study is registered at clinicaltrials.gov under the ID NCT03226743.

Summary

Strengths and limitations

- To our knowledge, the present randomized controlled trial is the first to investigate the effects of a stepped and collaborative care model, addressing comorbidity by including the most frequent mental disorders (depressive, anxiety, somatoform and alcohol use disorders).
- The prospective study design with collecting outcomes at 6- and 12-month follow-up enables us to examine mid-term effects.
- Collecting data on health care utilization and cost-relevant data allows a comprehensive health economic evaluation.
- The digital systematic screening and diagnosis for mental disorders in both the intervention and control group might potentially limit the intervention's effect size.
- The study will not be able to determine the effectiveness of single diagnostic and therapeutic elements due to its complex intervention model.

1 Introduction

1.1 Background and rationale

Care provision for mental disorders constitutes a substantial challenge in health care worldwide. 17.6% of the world's population meets the criteria for a mental disorder during the last 12 months, and about 29.2% experiences a mental disorder at some time in their life[1]. The burden of mental disorders (including substance use disorders) has increased to 22.8% of years lived with disability (YLD)[2].

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According to the WHO Mental Health Atlas 2011, there is a substantial gap between the burden caused by mental disorders and the resources available for preventing and treating them. Resources in health care systems are inequitably distributed and inefficiently utilized[3]. In high-income countries, 35.5% to 50.3% of serious cases received no treatment, while in low- and middle-income countries, up to 76.3% to 85.4% received no treatment[4]. The most prevalent mental disorders are depression, anxiety, somatoform and alcohol use disorders[5]. Comorbidity of mental disorders is frequent, with 44% of patients having two and 22% having three or more mental conditions simultaneously[6]. In addition, there is a significant degree of overlap between the symptoms of these disorders as well as mixed forms[7 8], which calls for comprehensive health care approaches for addressing concurrent mental disorders in primary care settings[9].

One approach to address comorbidity is collaborative care, an evidence-based form of treatment which focuses on systematically integrating multi-professional health care providers (e.g., general practitioners (GPs), specialized mental health professionals)[10 11]. Systematic reviews have found collaborative care for single mental disorders to be moderately effective[12-16] as well as cost-effective[17 18] for treating patients with depression and/or anxiety disorders[12], and partly so for treating patients with comorbid physical conditions, for example, diabetes and depression[19].

Collaborative care is often combined with stepped care: a guideline-recommended approach by which patients are treated within different intervention steps of varying intensity based on current symptom burden. In this model, patients can be stepped up or down into a more or less intensive treatment, depending on their response to treatment, as assessed by systematic monitoring[20]. Stepped care has proven effective for the treatment of depressive symptoms, however, further investigation is required regarding effectiveness for treating other specific disorders, such as somatoform disorders and alcohol-related disorders as well as for comorbid conditions and in order to determine the best manner of delivering this form of care[20-22].

Regarding comorbidity, some trials have examined the effects of stepped care on both symptoms of depression and anxiety[12 23 24]. A stepped care model for panic and generalized anxiety disorders was found to be effective and cost-effective[13 25]. For alcohol use disorders the evidence of the effectiveness of stepped care approaches is limited[26-29]. UK-based stepped care approaches were proven to be feasible in primary care with initially higher costs albeit probably with greater health benefits in the long term[30]. For the development of stepped care models for alcohol use disorders, German guidelines provide recommendations on the assignment of patients to adequate levels of care and respective screening and interventions[31].

While there is scarce but promising evidence that collaborative and stepped care might improve the management of somatoform disorders[32 33], these approaches have rarely been implemented and evaluated in practice[34]. Somatoform disorders are not only a frequent phenomenon but are also often accompanied by comorbid depression or anxiety disorders[35]. Thus, there is a necessity to substantiate an integrated multidisciplinary health care approach targeting persistent somatic symptoms, anxiety and depression at the same time[7].

The majority of current studies for collaborative and stepped care models for mental disorders do not fully address the needs of primary care in that they only treat one condition or a maximum of two conditions. For example, a systematic review on comorbidity in stepped care approaches found that of 39 studies only 5 studies addressed the comorbidity of mental disorders, and only one study included more than two mental disorders[36].

Thus far, research on collaborative and stepped care for mental disorders has been carried out predominantly in the United States (US)[12]. However, most health care systems outside the US are structured differently to the US, which is why US evidence for stepped and collaborative care might not be generalizable to other health care systems[37].

Taken together, the development of an overarching integrative collaborative and stepped treatment model is necessary for providing evidence and guideline-based treatment for the most common mental disorders (depression, anxiety, somatoform and alcohol use disorders) in primary care, taking into account the comorbidity between these disorders. This treatment approach needs to be examined

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with regard to effectiveness, cost-effectiveness as well as its barriers and facilitators for implementation into routine practice[9].

1.2 Objectives

The primary objective of the *Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers (COMET)-Study* is the effectiveness evaluation of a collaborative and stepped care model (CSC) for patients with depressive, anxiety, somatoform and/or alcohol use disorders. Secondary objectives are the assessment of cost-effectiveness and feasibility of the model. The collaborative and stepped care approach is expected to improve health care by optimizing the use of existing resources.

The primary hypothesis is that patients treated in CSC will exhibit a greater degree of improvement in mental health-related quality of life 6 months after baseline than patients with augmented treatment as usual (aTAU).

2 Methods and Analysis

2.1 Study design

The study is a cluster-randomized, prospective, parallel-group, superiority trial comparing the effectiveness of the CSC intervention and aTAU with allocation ratio of 1:1 in a consecutive sample of primary care patients with depressive, anxiety, somatoform and/or alcohol use disorders. We selected treatment as usual as the control condition because the research question is to determine whether collaborative and stepped care is superior to usual care. In order to ensure the comparability of intervention and control condition, both groups are to be recruited identically. This recruitment procedure includes a computer-based screening and guideline-based diagnostic process including feedback on the screening results and a diagnostic checklist. Since this computer-based screening and diagnostic procedure is not part of German routine care, we consider the comparison condition as an augmented treatment as usual (aTAU). Participants in the aTAU-group will have unrestricted access to usual care for their mental health problems. General practitioners (GPs) in aTAU will be instructed to continue treatment with affected patients in the same way as they would outside of the study. Clusters are defined as primary care practices. A cluster randomization design was chosen, because part of the intervention was an initial training for the GPs to improve their skills and practice visits from the study team to implement study procedures and instruments. We assume that GPs and primary care practices who have been trained and have access to the intervention would no longer be able to treat their patients under control conditions and thus the intervention and control conditions would be mixed. Patients will be assessed at baseline, at months 3 and 6 during treatment and at 12-month follow-up. The study started in February 2017 with a preparation phase. Recruitment and intervention were initiated in July 2018. The primary outcome will be available in February 2020.

2.2 Setting

Patients will be recruited in 38 primary care practices (19 aTAU and 19 CSC practices) by GPs in Hamburg in Germany. Patients in CSC will be treated in the CSC network by GPs, psychotherapists, psychosomatic specialists and psychiatrists as well as inpatient clinics in Hamburg. The list of all participating care providers can be requested from the study coordinator (Daniela Heddaeus; d.heddaeus@uke.de).

2.3 Eligibility criteria

Cluster level (GP-practices): inclusion criteria for participation in the study will be to have the approval as a GP in an outpatient practice by the Association of Statutory Health Insurance Physicians of Hamburg. Psychotherapists, psychiatrists and inpatient institutions must have the approval of the

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Association of Statutory Health Insurance Physicians of Hamburg. All care providers have to sign a cooperation contract in order to participate in the study.

Individual level (patients): Inclusion criteria will be a minimum age of 18, informed consent and one or more of the following ICD-10-diagnoses, as determined by their GP: depressive episode (F32), recurrent depressive disorder (F33), dysthymia (F34.1), agoraphobia (F40.0), social phobia (F40.1), panic disorder (F41.0), generalized anxiety disorder (F41.1), mixed anxiety and depressive disorder (F41.2), somatoform disorders (F45), and/or mental and behavioral disorders due to use of alcohol (F10). Patients with insufficient knowledge of the German language or a health situation that does not allow questionnaire completion and the participation in telephone interviews as well as patients already receiving current in- or outpatient psychopharmacotherapy or psychotherapeutic care will be excluded. Neither somatic nor mental health comorbidities will be exclusion criteria.

2.4 Recruitment

Cluster level: Primary Care Practices

In order to recruit participating primary care practices, all State Health Insurance GPs of the city of Hamburg will be informed about the project by mail and invited to an information event where they will be informed about the concept of study, the research aims and study procedures but not given details concerning the intervention itself. Subsequently, they will be asked to participate in the study and to sign a cooperation contract. To increase their willingness to participate, GPs will also be contacted via telephone and, if desired, also receive a personal introduction to the study in their practices. All participating GPs will be visited by the study team to implement study procedures. They will receive detailed patient information materials, informed consent forms, in order to hand them out to the patients, and a tablet computer for the recruitment and screening procedure.

Individual level: Patients

Participating GP practices will determine certain days on which recruitment fits in well with their schedule and practice procedures. On these days each patient entering the practice will be informed about the study. After giving informed consent to participate in a computerized screening procedure, each patient will receive a tablet computer. In line with the recommendations of practice guidelines[31 38-40] the screening procedure consists of selected modules of the German version of the Patient Health Questionnaire (PHQ-D)(PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module), the Somatic Symptom Disorder-B Criteria Scale (SSD-12) and the Alcohol Use Disorders Identification Test (AUDIT). After the screening, the patient hands over the tablet computer to the GP who will discuss the results with the patient. The patient's screening scores are presented to the doctor, along with the relevance of the score and the cut-off of each test. Screening results may or may not be used by the physician for diagnostic purposes. Integrated ICD-10 diagnostic criteria checklists for the diagnoses under investigation (depressive, anxiety, somatoform and/or alcohol use disorders) support the GP in the selection of the diagnosis. In addition to the selection of the ICD-10-Code, the GP indicates the severity of the disorder by classifying it as mild, moderate or severe. If a patient receives one or more of the above mentioned ICD-10 diagnoses and gives their informed consent, the patient will be included in the study.

Further care providers for the CSC network: Psychotherapists, psychiatrists, psychosomatic specialists and inpatient institutions

All State Health Insurance psychotherapists, psychiatrists and inpatient institutions in Hamburg will be informed about the project by mail and invited to an informational event at which they will be informed about the study in detail. All psychotherapists, psychosomatic specialists and psychiatrists will receive detailed instruction on the study procedures by phone.

2.5 Participant timeline

Figure 1 shows the participant timeline.

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2.6 Allocation of treatment and blinding

Cluster-randomization will be performed in order to control for potential bias and increase internal validity. In this study, a cluster-randomization will be performed at the level of GP practices, which will be randomly assigned to CSC and aTAU in a ratio of 1:1 and a block length of 4 by a list of computer-generated random numbers without any stratification variables. The randomization list will be created by a research associate of the Department for Medical Biometry and Epidemiology of the University Medical Center Hamburg-Eppendorf, who is not involved in the implementation of the research project. With the aim to ensure recruiter blinding, the study coordinator, who will not be involved in the recruitment of GPs, will receive the computer-generated randomization list, preserve it in a place accessible only to her and carry out the allocation of participating GPs. Incoming cooperation contracts will be assigned to CSC vs. aTAU according to the randomization list by the study coordinator. GPs will then be informed about their allocation status. Included patients will receive either CSC or aTAU depending on their GP's allocation. This means that even though the allocation is determined by the ranking of the list designed for preventing bias, strictly speaking the allocation is not totally blinded. Blinding of randomization status cannot be granted for the study team, care providers or patients due to study implementation constraints. Nevertheless, the researchers who perform the statistical analysis will be blinded.

2.7 The CSC Intervention

The intervention will be a collaborative and stepped care program provided in the city of Hamburg, Germany by outpatient Statutory Health Insurance GPs, psychotherapists, psychiatrists, psychosomatic specialists and inpatient or day-care clinics embedded in the standard health care system in Germany. Number of sessions, treatment schedule and the intensity of care will be individually tailored to each patient. The intervention will contain the following elements:

Collaborative network

In contrast to an often-used approach which brings external care managers into GP practices, we will systematically integrate the resources and competencies of cooperating care providers (GPs, psychotherapists, psychiatrists, psychosomatic specialists, and inpatient facilities), which can more readily create the structures needed to provide a broad spectrum of interventions. Outpatient GPs, psychotherapists, psychosomatic specialists and psychiatrists as well as inpatient or day care facilities will be integrated into the CSC network to enhance the exchange of information about their work in general as well as individual cases of patients and facilitate immediate referral from GPs to specialized care providers. An existing online scheduling platform enables psychotherapists and psychiatrists to indicate available treatment resources and GPs of the network to book those resources. This tool has been developed and successfully implemented in a former project "Health network depression"[22]. At the beginning of the study, network participants will obtain initial training regarding the evidence-based guidelines of conditions in focus[31 38-40] and the planned care model. Additionally, further quality assessment and exchange will be provided in quarterly network meetings.

Computer-assisted and guideline-based diagnosis and treatment decisions

Following the diagnostic process (see 2.4), each GP will continue with the treatment selection. The algorithm of the program on the tablet computer will provide the GP with one or more treatment recommendations for the individual patient that will be based on guideline recommendations for the diagnosed disorder and its degree of severity[31 38-41]. While these recommendations will offer an orientation for therapeutic decisions, the actual treatment decision for one of the evidence-based treatment options will be carried out in cooperation with the patient by integrating individual preferences and needs, thus following the principles of patient-centered care and shared decision-making. Additionally, possible comorbidities and specific characteristics of each of the disorders are to be taken into account.

Collaborative and stepped care interventions

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Within the CSC intervention, patients may be offered eight different interventions structured in three steps of varying intensity and setting (Table 1). The complex intervention will be delivered by different care providers and increase in intensity.

Table 1: Guideline-based treatments in the CSC intervention

Step	Description		Responsible care provider	Setting
1a	Basic psychosocial care, psychoeducation	Establishment of a working alliance, the provision of psychoeducational materials, psychosocial counselling and treatment of possible comorbid somatic symptoms[31] [38-40] including systematic monitoring	GP (or mental health specialist)	Outpatient
1b	Bibliotherapy	Disorder-specific cognitive-behavioral-therapy-oriented self-help books[42-47] accompanied by systematic monitoring	GP (or mental health specialist)	Outpatient
1c	Internet-based self-management	Internet-based self-help program with a cognitive-behavioral-therapy-oriented evaluated and certified computer program accompanied by systematic monitoring[48-50]	GP (or mental health specialist)	Outpatient
1d	Single brief interventions (for alcohol use disorders)	Up to five sessions of less than one hour, during which the patient receives individual feedback on alcohol consumption and advice as well as agreed upon goals[31]	GP	Outpatient
2a	Psychotherapy	Face-to face cognitive-behavioral therapy or psychodynamic psychotherapy either individually or in a group	Psychotherapist	Outpatient
2b	Pharmacotherapy	Medication according to guideline recommendations	GP or mental health specialist	Outpatient
3a	Pharmacotherapy plus psychotherapy	Intensified combination therapy of psychopharmacotherapy and face-to-face-psychotherapy	GP or mental health specialist and psychotherapist	Outpatient
3b	Intensified treatment	Intensified treatment carried out by a multi-professional treatment team	Multiprofessional team	Day hospital or inpatient facility

GP: General Practitioner

The materials for step 1 will be provided to the GP by the study team (i.e., psychoeducational materials, self-help books, licenses for the self-help internet programs). For step 1d, the single brief interventions for alcohol use disorders, GPs obtain special training in the context of one of the first network meetings. In case of referral to a specialized care provider in step 2 or 3, the GP will use the online scheduling platform to book free treatment capacity in the collaboration network. The patient will be instructed to call the booked care provider to confirm the appointment.

Patients will be monitored regularly by their responsible care provider(s) (see table 1) with monitoring forms in order to ensure that sufficient treatment response will be achieved and potential under- or oversupply will be corrected as quickly as possible. Completed monitoring forms will be sent to the study team.

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Previous studies have shown that among patients with mental disorders, those with a high symptom severity in particular do not receive the treatment they need (e.g.,[51-53]). It is still unknown whether this is caused by barriers in the referral process, insufficient motivation on the part of the patient or other difficulties. In order to address this problem, case management will be implemented. Based on the digital diagnostic information assessed by the GP during the diagnostic process, a member of the study team will follow the treatment pathways of those patients who are diagnosed with a disorder of a high degree of severity. In those cases, the existing monitoring forms filled out by the care providers will be reviewed, and the responsible care provider will be informed if possible deficiencies in care are detected.

In order to improve the adherence of care providers to the intervention protocol, each provider will receive an initial three-hour training about the study procedures. Further trainings (also three hours each) will cover the guideline recommendation for the four relevant disorders. Additionally, there will be a network meeting for the CSC care providers each quarter. Furthermore all care providers will obtain detailed instruction manuals, prepared materials, and they will be visited in their practice at the beginning as well as in the event that any questions arise or problems occur.

Patients in CSC will be free to use any other additional care, as needed. Other care utilization will be recorded in data collection interviews (T2 and T3).

2.8 Outcomes

Primary outcome measure

Following the primary hypothesis that CSC patients will exhibit greater improvement in mental health-related quality of life at 6-month than aTAU patients, the primary outcome parameter will be a change in mental health-related quality of life (Short Form Health Survey, SF-36 mental health score[54]) from baseline to 6 months.

Secondary outcome measures

Secondary outcome parameters will be the change in disorder-specific symptoms as measured using the German versions of the major depressive[55], generalized anxiety[56], panic and somatoform modules of the PHQ[57], the SSD-12[58-60] and the AUDIT[61]. We will analyze disorder-specific response (at least 50% symptom reduction at 6 months on the disorder-specific screening instruments) and remission (obtaining a value below the respective clinical cut-off value of the disorder-specific screening instruments at 6 months) for these outcome measures. Further secondary outcomes will be health-related quality of life assessed by the SF-36 physical health score, change in health-related quality of life according to the EQ-5D-5L and health care utilization. Table 2 gives an overview of the outcomes.

Table 2: Outcomes

Variable	Outcome Measure	Outcome	Baseline/ T0	T1	T2	T3
Primary Outcome						
Health-related quality of life mental health scale	SF-36 (36 Items)	change in mental health-related quality of life from baseline to 6 months	X	X	X	X
Secondary Outcome						
Disorder-specific symptoms	PHQ-9 (9 Items) GAD-7 (7 Items)	change in disorder-specific symptoms from baseline to 6 months	X	X	X	X

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Response of diagnosed disorder(s)	PHQ-15 (15 Items) PHQ-Panic module (15 Items) SSD-12 (12 Items) AUDIT (10 Items)	at least 50% symptom reduction at 6 months on the disorder-specific screening instrument(s)	X	X	X	X
Remission of diagnosed disorder(s)		obtaining a value below the respective clinical cut-off value of the disorder-specific screening instrument at 6 months	X	X	X	X
Health-related quality of life physical health scale	SF-36 (36 Items)	change in physical health-related quality of life from baseline to 6 months	X	X	X	X
Health care utilization	Questionnaire, CSSRI (26 Items)	Change in health care utilization at 6 and 12 months	X		X	X
Quality of life	EQ-5D-5L (5 Items)	Change in quality of Life at 6 and 12 months	X		X	X

SF: Short Form Health Survey; PHQ: Patient Health Questionnaire; GAD: generalized anxiety disorder; SSD: Somatic Symptom Disorder-B Scale; AUDIT: Alcohol Use Disorders Identification Test; CSSRI: Client Sociodemographic and Service Receipt Inventory

Economic evaluation

For the calculation of direct and indirect costs health care utilization, reduced productivity at work and work loss days will be measured by a modified version of the Client Sociodemographic and Service Receipt Inventory (CSSRI[62]). The utilization of inpatient care, outpatient physician services, outpatient non-physician services, medication, as well as formal and informal (long-term) care will be assessed. To assess health effects, quality-adjusted life years (QALYs) will be calculated based on utilities derived from the EQ-5D-5L questionnaire.

Process evaluation

Additionally, to allow for exploratory analyses, relevant process outcomes will be assessed: implementation, functionality, acceptability and sustainability of the network, including attributes of the health care model (e.g. relative advantage, compatibility, trialability), adoption/assimilation (e.g., needs, motivation, values, preferences, acceptance and skills of involved actors, including patients), communication and influence (diffusion and dissemination, including social networks, opinion leadership, change agents), the context (antecedents and readiness for innovation, incentives, reimbursement regulations), and the implementation process (support and advocacy of implementation process, feedback on progress). For the assessment semi-structured qualitative interviews will be conducted at the beginning and at the end of the study with patients, GPs, psychotherapists, psychosomatic specialists and psychiatrists of the CSC-group and the aTAU-group. We will use semi-structured interview guides on implementation, functionality, acceptance and sustainability of the interventions of the CSC. The interview guides include questions regarding possible beneficial and impeding aspects referring to the implementation process, the care model, adoption/assimilation, communication/impact and context. Questions about the implementation of the study will be integrated in the patient interview at T2. For a separate evaluation of the care process, care providers will be asked at baseline and T3 using standardized short questionnaires. Moreover, process evaluation with care providers will be involved in the quarterly network meetings.

2.9 Sample size

We aim for a sample size that permits the detection of a small to moderate standardized mean difference (Cohen's d of 0.35); [63] between CSC and aTAU for the primary outcome (change in the SF-36 mental health score after 6 months) with a statistical power of 0.80 at a type I error rate of 0.05 (two-sided). Assuming a correlation of 0.50 between baseline and follow-up measurements, this

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requires analyzable data from 95 patients per group (190 in total) for a linear model with the baseline measurement as covariate [64] if randomization takes place at the patient level. With an average cluster size (number of patients per practice) of 12 and an intra-cluster correlation (ICC) of 0.05, this sample size should be multiplied by a design effect of 1.55 [65], leading to 156 patients in 13 practices per group and 312 patients in 26 practices in total. As our experience suggests that up to 30% of the randomized practices and up to 20% of the recruited patients may drop out of the study, we aim to recruit 38 practices (19 per group) including 15 patients each, resulting in a target sample size of 570 recruited patients in total (285 per group).

2.10 Data collection methods

Data collection via tablet computer

Data on screening, diagnostics, severity of the disorder, indication and treatment decision as well as the baseline assessment of the primary outcome (SF-36) will be collected on a tablet computer using specially developed web-based screening and diagnostic software (for tests used for the screening see 2.4 Recruitment). The program will also ask for reasons for GP consultation, age, gender and whether the patient is already receiving psychotherapy or psychopharmacotherapy at baseline.

Telephone-based patient interviews

The telephone-based patient interviews will take place at four standard measurement points (baseline, 3, 6 and 12 months after baseline, see Fig. 1). All staff members conducting telephone interviews have undergone a special training for the Composite International Diagnostic Interview (CIDI[66]), which is part of the baseline interview, and received detailed guidelines and standard operating procedures for the interviews. In order to conduct the interview, the responsible staff member will call the patient to make an appointment for the interview. At the appointment the staff member will call the patient and carry out the interview. All contact attempts and contacts will be documented. Telephone interviews rather than written questionnaires were chosen to improve the response rate and the quality of the data collected.

The following questionnaires will be used for data assessment:

Short Form Health Survey (SF-36) (Primary Outcome): This questionnaire assesses the disease-unspecific, health-related subjective quality of life[54]. It comprises 8 dimensions (physical functioning, physical role functioning, physical pain, general health perception, vitality, social functioning, emotional role functioning and psychological well-being), which can be assigned to the two main scales "physical health" and "mental health". Answers are Likert scaled. They are weighted, added and transformed to the range 0 to 100. High values indicate a high health-related quality of life. It is an internationally used, test-theoretically validated instrument with a German reference population[67] The baseline assessment for this instrument is carried out via the tablet computer-based screening after study inclusion in the waiting room of the primary care practice, as described in 2.12.

Sociodemographic Questionnaire*:* Sociodemographic data will be collected only at baseline assessment and comprise date of birth, gender, country of origin, nationality, parental country of origin, marital status, postal code, educational level, occupation and professional status.

Composite International Diagnostic Interview (CIDI): This comprehensive interview procedure will be conducted at baseline and consists of 40 modules, which enables the standardized diagnosis of mental disorders (ICD-10, DSM-IV) for the entire lifetime (longitudinal section) or the last 12 months (cross-section). For this study only the sections for depressive, anxiety, somatoform and alcohol use disorders will be used with regard to the last 12 months[66].

PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module from the Patient Health Questionnaire (PHQ-D): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the

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waiting room in the primary care practice, as described in 2.12. It is the German adaptation of the PHQ, a screening instrument based on the criteria of the DSM-IV, which covers various syndromes and is a practical and well validated instrument[57 68 69]. The following scales and subscales are used in this study:

- The PHQ-9 (9 items) for the identification of depressive syndromes covers main and secondary symptoms of depression on a four-step scale according to their frequency[55]
- The GAD-7 (7 items) to detect generalized anxiety disorder[56] and the PHQ panic subscale (15 items) for panic disorder; The GAD-7 is measured on a four-step scale. On the PHQ panic subscale, each item corresponds to a DSM-IV panic disorder criterion and is answered with "Yes" or "No" [68].
- The PHQ-15 (15 items) identifies the somatoform syndrome measured on a three-step scale.

Somatic Symptom Disorder-B Scale (SSD-12): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the waiting room in the primary care practice, as described in 2.12. It measures the new psychological criteria of the Somatic Symptom Disorder (DSM-5) with 12 items that refer to three subscales to capture cognitive, affective and behavioral aspects. In a first validation study in an outpatient sample, the scale showed very good psychometric properties[60].

Alcohol Use Disorders Identification Test (AUDIT): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the waiting room in the primary care practice, as described in 2.12. The AUDIT is an instrument developed by the World Health Organization to identify patients with problematic alcohol consumption in different settings. It is nationally and internationally recognized and includes 10 items related to alcohol consumption, dependence and abuse, with a choice of 3 to 5 alternatives[61 70].

Collaborate: This three-item scale will be assessed at baseline, T2 and T3 to evaluate the shared decision-making process. It measures the dimensions *explanation of the health issue*, e*licitation of patient preferences* and *integration of patient preferences* on a 0 to 9 scale. It evidences concurrent validity with other measures of SDM, good interrater reliability and sensitivity to change[71].

Quality of Life Questionnaire EQ-5D-5L: This generic health-related quality of life questionnaire consists of five items that measure current problems on the dimensions of mobility, self-care, usual activities, pain discomfort and anxiety/depression on five levels. It can be used as a simple health classification system to detect differences in the health status of population groups. Based on the 3,125 possible unique health states derived from the EQ-5D-5L, index scores can be assigned through a set of preference valuations of the general population regarding different health states[72]. It also contains a visual analogue scale for the general assessment of health-related quality of life, which allows easy comparisons with the general population.

Modified Client Sociodemographic and Service Receipt Inventory (CSSRI-D): This is the modified version of a questionnaire for measuring the utilization of services, which has been adapted to the specifics of the German health care system and serves to assess mental health care costs. It collects data about employment and income (employment status, occupation, days of incapacity to work, type and amount of social benefits), use of care services (inpatient, outpatient and complementary care) as well as medication (type and name of medication taken, dosage, number and size of medication packs collected from the pharmacy, price). The instrument has proven itself in practical use, as it allows conclusions to be drawn regarding direct and indirect costs, while providing information on the utilization and medication profiles of patients[62].

Illness Perception Questionnaire Brief (IPQ-B): This 9-Item tool for recording illness perceptions will be used at baseline. 8 items measure the dimensions of perceived consequences of disease, chronicity,

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perceived personal control and control over treatment, identity, concerns about specific disorders, coherence and emotional representation of said disorders on scales of 0-10. Higher scores reflect a stronger representation of this dimension. The last item serves to identify the three most subjectively relevant causes of the disease in question. The IPQ-B has predictive and discriminatory validity, and change sensitivity was confirmed in a systematic review [73].

Questionnaire on the intensity of the general practitioner commitment (F-HaBi): This questionnaire will be used at baseline, T2 and T3. It measures the utilization behavior of primary care patients. It distinguishes patients with close primary care coordination from those who access further care without prior contact to the GP. 9 items indicate whether the patient has a GP, how often the GP is consulted, how/whether the patient uses the GP as a coordinator, and patient satisfaction with the GP and the specialists. Answers are given on a five-point scale. Higher values indicate that the patient is more likely to perceive and use the GP as a coordinator.

Health care utilization and satisfaction with received treatments in the last 3 or 6 months: These items ask for the treatments received in the last 3 or 6 months on a "yes/no" scale and the patient's satisfaction with the received treatments on a five-point scale.

Questionnaire on satisfaction in outpatient care - focus on patient participation (ZAPA): This four-item questionnaire will be applied at T2 and T3 to measure patient satisfaction in outpatient medical care, taking into account the concept of patient participation. It has a one-dimensional structure. Its brevity makes it suitable for use in studies measuring patient satisfaction in outpatient care settings [74].

Process evaluation (quantitative): These four items will be asked at T2 to evaluate the implementation of the COMET study (information, acceptance, time expenditure, incentives). An open-ended question at the end will offer participants the opportunity to comment on their satisfaction with the study.

Monitoring forms

In CSC, care providers will be instructed to monitor their patients in regular time intervals. Time intervals will depend on the treatment conducted and will be at least once per quarter. The care provider will document the result of the monitoring on a standardized monitoring form that includes items on the frequency of consultations since the last visit, treatment decision at the last visit, realized treatment and reasons for deviations, symptom changes (deterioration, improvement), impairment due to symptoms, new diagnoses, remitted diagnoses, serious adverse events and future treatment plans.

Retention and Discontinuation

All care providers will receive financial incentives for those activities that are additional to their usual care. GPs receive expense allowances up to 120€ per patient, psychotherapists up to 290€ and psychiatrists up to 150€ per patient.

Patients will receive a voucher worth 10€ for each of the four conducted interviews. Patients will be contacted up to five times for each of the telephone interviews. If the patient is not available even after five attempts, the GP who included the patient in the study will be informed, and the patient will be called again at the next measurement point. Neither termination of the selected treatment nor termination of the relationship to the recruiting GP will be reasons for a subsequent exclusion from the study and participation in further interviews. Only if the patient explicitly wishes to terminate study participation and does not want to take part in interviews anymore, will they be excluded from the study. The data collected up until that time will only be deleted if the patient explicitly insists upon this. All drop-outs will be documented on a drop-out form that will include age, gender, drop-out date and reasons for drop-out.

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2.11 Data management

Data collected with the web-based screening- and diagnostic tool on the tablet computer will be entered electronically by the patient and the GP and stored de-identified in an encrypted database on a server of the University Medical Center Hamburg-Eppendorf. The program will include range checks for data values. Data collected during the telephone interviews will be entered directly into a password-protected uniform data entry mask by the interviewing researcher. The data entry masks will be pre-programmed (with the program EpiData) to ensure valid values and prevent entry errors. Data collected via monitoring forms will be documented by the responsible care providers of the network and sent to the study team. A student assistant will enter the data into a digital data mask. All collected data will be stored in a database on the UKE internal server in a pseudonymous form. All participant files will be maintained in storage for a period of ten years after completion of the study. The principal investigators and the study team will have access to the cleaned and final data sets. All data sets will be cleared of any identifying participant information and password-protected.

2.12 Monitoring

The study will be monitored by an international advisory board that meets once a year to review the study progress. It consists of five international scientists with expertise in the field of health care services research in mental health and collaborative and stepped care models. Progress, challenges and possible adjustments will be presented by the study team and discussed with the advisory board. The board is independent from the sponsor. A data monitoring committee will not be established. Data will be monitored by the study coordinator, who has no competing interests.

2.13 Adverse events

We define adverse events as any adverse medical or psychological incident experienced by a patient. Adverse events will be documented by the care providers and the study team whenever they occur. Serious adverse events will be reported to the ethics committee and include suicidality, significant burden, severe or permanent disability, prolonged or unplanned hospitalization, functional impairment, significant hazard or life-threatening conditions. In order to address suicidality, a standard operating procedure was developed.

2.14 Statistical methods

The descriptive statistics will be presented by group and for the total sample. The primary analysis will be based on the intention-to-treat (ITT) population, which includes all practices and patients randomized and included in the study. A linear mixed model for the changes from baseline of SF-36 will be calculated with group (CSC / aTAU) and time as fixed effects, practice and patients as random effects, and the baseline value of the SF-36 mental health score as a covariate. The time by group interaction will be tested, and if the interaction is not significant, the interaction will not be included in the model. The coefficient test, comparing the adjusted SF-36-values between the randomized groups, will be performed using the direct maximum likelihood as the statistical estimation procedure, which results in unbiased estimators under the missing-at-random-assumption. The contrast between both groups at the 6-month follow-up will be assessed in a confirmatory manner. The analysis will be repeated in the per protocol (PP) population. To investigate the effects of the missing values on the result of the primary analysis, sensitivity analyses will be carried out with different methods for missing value imputation (e.g., multiple imputation, last observation carried forward). The secondary endpoints will be examined in an exploratory manner. For the binary secondary endpoints, we will conduct a mixed logistic regression, and for the continuous secondary endpoints we will carry out a linear mixed model. The other model parameters will be set as in the primary endpoint analysis. The following subgroup analyses are planned: diagnosis, sex, age, socio-economic status and symptom severity. Adjusted means and odds ratios, respectively, with their 95% confidence intervals and p values were reported. The two-sided type I error will be set at .05. The safety endpoints will be determined using frequency tables and using mixed logistic regressions to compare the event

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frequencies, if possible. Interim analyses are not planned. A detailed statistical analysis plan will be prepared and finalized before the start of the analysis. Results will be reported according to the CONSORT statement extended for cluster randomized trials.

Additional analysis

Direct and indirect costs will be calculated from the societal perspective based on health care utilization, reduced productivity at work and work loss days measured by a modified version the CSSRI [62]. For the monetary valuation of resources, German standard unit costs will be applied [75 76]. Indirect costs will be calculated based on the human capital approach by applying gross income plus nonwage labor costs [77]. For assessing health effects, QALYs will be calculated based on utilities (i.e., preference-based scores of health-related quality of life measured on a scale from 0=very bad health to 1=perfect health) derived from the EQ-5D-5L questionnaire. Costs and effects of CSC will be compared to standard care in incremental analyses. This will be done by calculating incremental cost-effectiveness ratios (ICERs)[78]. The ICER is defined as the ratio of the difference in cost and the difference in health effects between intervention and control group. As the ICER is a point estimate which neither considers statistical uncertainty in the data nor the effect of potential confounding variables, cost-effectiveness acceptability curves (CEACs) will be constructed by means of a series of net benefit regressions using different willingness-to-pay margins [79].

Process Evaluation: Data of the patient survey will be analyzed using descriptive statistics (i.e., frequencies, means, and standard deviations). The qualitative data will be analyzed using structuring content analysis, based on the above mentioned categories of facilitating and inhibiting factors of implementation and sustainability of CSC [80 81].The qualitative interviews will be transcribed and coded using a deductive category system (e.g., attributes of the health care concept, adoption/assimilation, communication/influence, context and implementation process), which will be further elaborated upon inductively.

Patient and Public Involvement

Research questions and outcome measures where not informed by patients' priorities, experience or preferences. Patients were not involved in the design of this study. Patients were not involved in the recruitment for and the conducting of the study. The results will be disseminated to the participating care providers by sending them reports about the study results. Patients will evaluate the impact of the intervention.

3 Ethics and Dissemination

The ethics committee of the Hamburg Medical Association approved the study design and intervention (PV5595) in September 2017, prior to commencing recruitment. We confirm that the study will be carried out in accordance with the principles of the Declaration of Helsinki. Any severe adverse events as well as any protocol changes will be reported to the ethical committee and the advisory board without delay. Written informed consent will be obtained from all patients by their GPs. There are no foreseeable risks for patients participating in the study. The study does not involve any restriction to standard care. The study has been registered at clinicaltrial.gov NCT03226743 in October 2017.

Personal information about participants

Personal information will be collected on the informed consent form, on which the patient provides their name and telephone number. This form also includes a unique patient code. The telephone number is needed to call the patient for the patient interviews. The GP sends the form via fax to the study coordinator. The study coordinator receives the fax digitally on her computer, extracts the patient code, the name of referring GP and the telephone number, sends this information to the study team and saves the fax as a password-protected file to which only the GP has access. The study team contacts the patient without knowing the patient´s name and conducts the interview. If the landline telephone number is given, the interviewer will ask for the person who is taking part in the COMET-study. At the end of the interview, the patient will be asked whether they are interested in an incentive

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in form of a 10€ gift coupon. If so, the patient will be asked for their postal address. The address will not be saved but will instead be eliminated immediately after the coupon is sent.

Dissemination policy

The results and findings of the study will be published in peer-reviewed journals and presented at conferences and congresses. It will be disseminated also by mean of the multiple partnerships within the superordinate project Hamburg Network for Health Services Research (HAM-NET). Results will also be relayed to the participating health care providers. A completely anonymized data set will be delivered to an appropriate data archive for sharing purposes. No professional writers will be employed.

Conclusion

In line with the primary hypothesis, the intervention condition is expected to be superior to the control condition. This means that CSC is expected to provide more effective treatment than routine care in terms of improving health-related quality of life 6 months after treatment initiation. In addition, CSC is expected to outperform standard care in secondary outcomes, cost-effectiveness, and process variables. A significant contribution to the knowledge relating to whether it is possible and effective to treat a wide range of mental disorders (depression, anxiety, somatoform and alcohol-related disorders) within a collaborative and stepped care model based on evidence-based recommendations is expected. This is a challenge for the care providers and the whole network. Particular interest will be given to how the central issue of comorbidity is dealt with. As far as we know, this is the first randomized and controlled study dealing with complex co-morbidity patterns.

4 Authors' contributions

MH, BL, OvdK, MS, IS, HHK, KW and DH designed the study and obtained funding. MH, JD and DH are responsible for its conduct and overall supervision. HHK, CB, TG, KW and AD contributed to specific methodical and health economic issues. DH, JD, SP, KM, SW, AW, TZ, BS, MR and MH worked out study processes, treatment pathways and materials. DH coordinates the study with support from JD and MH. DH, SP, KM and SW organize the network and carry out the recruitment process, network meetings and data collection. DH is responsible for data management. DH, JD and MH wrote the manuscript. All authors contributed to, reviewed and approved the final manuscript.

5 Funding statement

The study is funded by the German Federal Ministry of Education and Research (BMBF) under the grant number 01GY1602. The sponsor does not have any influence on study design, collection, management, analysis, interpretation of data, writing or publication process.

6 Competing interests

The authors declare that they have no competing interests.

7 Roles and responsibilities

7.1 Coordinating Center: Principal investigator and research team

- Designing and conducting of COMET
- Preparations of protocol and revisions
- Study planning
- Preparation of care provider brochure and case report forms
- Recruitment of general practitioners and further health care providers
- Organization of network meeting and trainings
- Network management
- Practice visits

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- Publication of study reports
- Preparation of materials for participating health care providers and patients
- Development of the internet transferal platform and the eDiagnostic tool
- Responsibility for trial master file
- Budget administration and contractual issues
- Randomization
- Data verification
- Maintenance of trial IT system and data entry

7.2 Steering committee/advisory board

- Approval of final protocol
- Study progress review and approval of changes to the protocol, as needed
- Consultation in clinical, methodological and content-related issues

8 Literature

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Legend: Figure 1: Participant timeline
GP: general practitioner; aTAU: augmented treatment as usual; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CIDI: Composite International Diagnostic Interview

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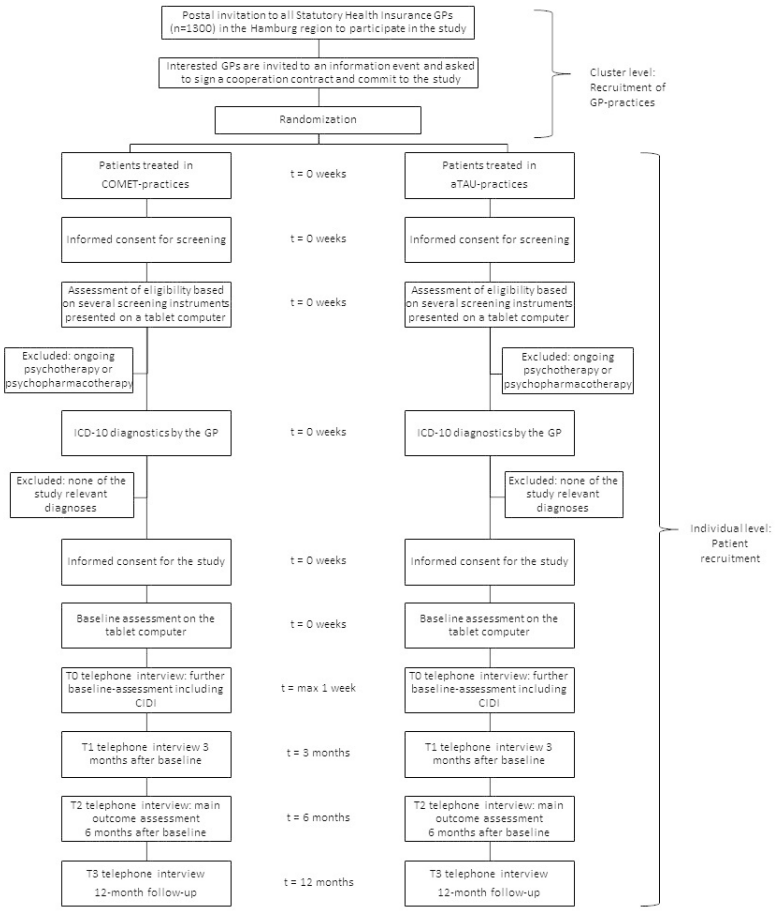

Figure 1: Participant timeline
GP: general practitioner; aTAU: augmented treatment as usual; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CIDI: Composite International Diagnos-tic Interview

80x108mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 15

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 & 15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

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Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8 & 12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6

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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

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Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus treatment as usual in patients with mental disorders in primary care: The COMET study.

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Study protocol for a cluster-randomized, prospective, parallel-group, superiority trial to compare the effectiveness of a collaborative and stepped care model versus treatment as usual in patients with mental disorders in primary care: The COMET study.

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Abstract

Introduction: Mental health care is one of the biggest challenges for health care systems. Comorbidities between different mental disorders are common, and patients suffer from a high burden of disease. While the effectiveness of collaborative and stepped care models has been shown for single disorders, comorbid mental disorders have rarely been addressed in such care models. The aim of the present study is to evaluate the effectiveness of a collaborative and stepped care model for depressive, anxiety, somatoform and alcohol use disorders within a multiprofessional network compared to treatment as usual.

Methods and analysis: In a cluster-randomized, prospective, parallel-group superiority trial n=570 patients will be recruited from primary care practices (n=19 practices per group). The intervention is a newly developed collaborative and stepped care model in which patients will be treated using treatment options of various intensities within an integrated network of outpatient general practitioners, psychiatrists, psychotherapists and inpatient institutions. It will be compared to treatment as usual with regard to effectiveness, cost-effectiveness and feasibility, with the primary outcome being a change in mental-health-related quality of life from baseline to 6 months. Patients in both groups will undergo an assessment at baseline, 3, 6, and 12 months after study inclusion.

Ethics and dissemination: The study has been approved by the ethics committee of the Hamburg Medical Association (No. PV5595) and will be carried out in accordance with the principles of the Declaration of Helsinki. For dissemination, the results will be published in peer-reviewed journals and presented at conferences. Within the superordinate research project Hamburg Network for Health Services Research (HAM-NET), the results will be communicated to relevant stakeholders in mental health care.

Registration: The study is registered at clinicaltrials.gov under the ID NCT03226743.

Summary

Strengths and limitations

- To our knowledge, the present randomized controlled trial is the first to investigate the effects of a stepped and collaborative care model, addressing comorbidity by including the most frequent mental disorders (depressive, anxiety, somatoform and alcohol use disorders).
- The prospective study design with collecting outcomes at 6- and 12-month follow-up enables us to examine mid-term effects.
- Collecting data on health care utilization and cost-relevant data allows a comprehensive health economic evaluation.
- The digital systematic screening and diagnosis for mental disorders in both the intervention and control group might potentially limit the intervention's effect size.
- The study will not be able to determine the effectiveness of single diagnostic and therapeutic elements due to its complex intervention model.

1 Introduction

1.1 Background and rationale

Care provision for mental disorders constitutes a substantial challenge in health care worldwide. 17.6% of the world's population meets the criteria for a mental disorder during the last 12 months, and about 29.2% experiences a mental disorder at some time in their life[1]. The burden of mental disorders (including substance use disorders) has increased to 22.8% of years lived with disability (YLD)[2]. According to the WHO Mental Health Atlas 2011, there is a substantial gap between the burden caused

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by mental disorders and the resources available for preventing and treating them. Resources in health care systems are inequitably distributed and inefficiently utilized[3]. In high-income countries, 35.5% to 50.3% of serious cases received no treatment, while in low- and middle-income countries, up to 76.3% to 85.4% received no treatment[4]. The most prevalent mental disorders are depression, anxiety, somatoform and alcohol use disorders[5]. Comorbidity of mental disorders is frequent, with 44% of patients having two and 22% having three or more mental conditions simultaneously[6]. In addition, there is a significant degree of overlap between the symptoms of these disorders as well as mixed forms[7 8], which calls for comprehensive health care approaches for addressing concurrent mental disorders in primary care settings[9].

One approach to address comorbidity is collaborative care, an evidence-based form of treatment which focuses on systematically integrating multi-professional health care providers (e.g., general practitioners (GPs), specialized mental health professionals)[10 11]. Systematic reviews have found collaborative care for single mental disorders to be moderately effective[12-16] as well as cost-effective[17 18] for treating patients with depression and/or anxiety disorders[12], and partly so for treating patients with comorbid physical conditions, for example, diabetes and depression[19].

Collaborative care is often combined with stepped care: a guideline-recommended approach by which patients are treated within different intervention steps of varying intensity based on current symptom burden. In this model, patients can be stepped up or down into a more or less intensive treatment, depending on their response to treatment, as assessed by systematic monitoring[20]. Stepped care has proven effective for the treatment of depressive symptoms, however, further investigation is required regarding effectiveness for treating other specific disorders, such as somatoform disorders and alcohol-related disorders as well as for comorbid conditions and in order to determine the best manner of delivering this form of care[20-22].

Regarding comorbidity, some trials have examined the effects of stepped care on both symptoms of depression and anxiety[12 23 24]. A stepped care model for panic and generalized anxiety disorders was found to be effective and cost-effective[13 25]. For alcohol use disorders the evidence of the effectiveness of stepped care approaches is limited[26-29]. UK-based stepped care approaches were proven to be feasible in primary care with initially higher costs albeit probably with greater health benefits in the long term[30]. For the development of stepped care models for alcohol use disorders, German guidelines provide recommendations on the assignment of patients to adequate levels of care and respective screening and interventions[31].

While there is scarce but promising evidence that collaborative and stepped care might improve the management of somatoform disorders[32 33], these approaches have rarely been implemented and evaluated in practice[34]. Somatoform disorders are not only a frequent phenomenon but are also often accompanied by comorbid depression or anxiety disorders[35]. Thus, there is a necessity to substantiate an integrated multidisciplinary health care approach targeting persistent somatic symptoms, anxiety and depression at the same time[7].

The majority of current studies for collaborative and stepped care models for mental disorders do not fully address the needs of primary care in that they only treat one condition or a maximum of two conditions. For example, a systematic review on comorbidity in stepped care approaches found that of 39 studies only 5 studies addressed the comorbidity of mental disorders, and only one study included more than two mental disorders[36].

Thus far, research on collaborative and stepped care for mental disorders has been carried out predominantly in the United States (US)[12]. However, most health care systems outside the US are structured differently to the US, which is why US evidence for stepped and collaborative care might not be generalizable to other health care systems[37].

Taken together, the development of an overarching integrative collaborative and stepped treatment model is necessary for providing evidence and guideline-based treatment for the most common mental disorders (depression, anxiety, somatoform and alcohol use disorders) in primary care, taking into account the comorbidity between these disorders. This treatment approach needs to be examined

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with regard to effectiveness, cost-effectiveness as well as its barriers and facilitators for implementation into routine practice[9].

1.2 Objectives

The primary objective of the *Collaborative and Stepped Care in Mental Health by Overcoming Treatment Sector Barriers (COMET)-Study* is the effectiveness evaluation of a collaborative and stepped care model (CSC) for patients with depressive, anxiety, somatoform and/or alcohol use disorders. Secondary objectives are the assessment of cost-effectiveness and feasibility of the model. The collaborative and stepped care approach is expected to improve health care by optimizing the use of existing resources.

The primary hypothesis is that patients treated in CSC will exhibit a greater degree of improvement in mental health-related quality of life 6 months after baseline than patients with treatment as usual (TAU).

2 Methods and Analysis

2.1 Study design

The study is a cluster-randomized, prospective, parallel-group, superiority trial comparing the effectiveness of the CSC intervention and TAU with allocation ratio of 1:1 in a consecutive sample of primary care patients with depressive, anxiety, somatoform and/or alcohol use disorders. We selected treatment as usual as the control condition because the research question is to determine whether collaborative and stepped care is superior to usual care. Participants in the TAU-group will have unrestricted access to usual care for their mental health problems. General practitioners (GPs) in TAU will be instructed to continue treatment with affected patients in the same way as they would outside of the study. Clusters are defined as primary care practices. A cluster randomization design was chosen, because part of the intervention was an initial training for the GPs to improve their skills and practice visits from the study team to implement study procedures and instruments. We assume that GPs and primary care practices who have been trained and have access to the intervention would no longer be able to treat their patients under control conditions and thus the intervention and control conditions would be mixed. Patients will be assessed at baseline, at months 3 and 6 during treatment and at 12-month follow-up. The study started in February 2017 with a preparation phase. Recruitment and intervention were initiated in July 2018. The primary outcome will be available in February 2020.

2.2 Setting

Patients will be recruited in 38 primary care practices (19 TAU and 19 CSC practices) by GPs in Hamburg in Germany. Patients in CSC will be treated in the CSC network by GPs, psychotherapists, psychosomatic specialists and psychiatrists as well as inpatient clinics in Hamburg. The list of all participating care providers can be requested from the study coordinator (Daniela Heddaeus; d.heddaeus@uke.de).

2.3 Eligibility criteria

Cluster level (GP-practices): inclusion criteria for participation in the study will be to have the approval as a GP in an outpatient practice by the Association of Statutory Health Insurance Physicians of Hamburg. Psychotherapists, psychiatrists and inpatient institutions must have the approval of the Association of Statutory Health Insurance Physicians of Hamburg. All care providers have to sign a cooperation contract in order to participate in the study.

Individual level (patients): Inclusion criteria will be a minimum age of 18, informed consent and one or more of the following ICD-10-diagnoses, as determined by their GP: depressive episode (F32), recurrent depressive disorder (F33), dysthymia (F34.1), agoraphobia (F40.0), social phobia (F40.1),

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panic disorder (F41.0), generalized anxiety disorder (F41.1), mixed anxiety and depressive disorder (F41.2), somatoform disorders (F45), and/or mental and behavioral disorders due to use of alcohol (F10). Patients with insufficient knowledge of the German language or a health situation that does not allow questionnaire completion and the participation in telephone interviews as well as patients already receiving current in- or outpatient psychopharmacotherapy or psychotherapeutic care will be excluded. Neither somatic nor mental health comorbidities will be exclusion criteria.

2.4 Recruitment

Cluster level: Primary Care Practices

In order to recruit participating primary care practices, all State Health Insurance GPs of the city of Hamburg will be informed about the project by mail and invited to an information event where they will be informed about the concept of study, the research aims and study procedures but not given details concerning the intervention itself. Subsequently, they will be asked to participate in the study and to sign a cooperation contract. To increase their willingness to participate, GPs will also be contacted via telephone and, if desired, also receive a personal introduction to the study in their practices. All participating GPs will be visited by the study team to implement study procedures. They will receive detailed patient information materials, informed consent forms, in order to hand them out to the patients, and a tablet computer for the recruitment and screening procedure.

Individual level: Patients

Participating GP practices will determine certain days on which recruitment fits in well with their schedule and practice procedures. On these days each patient entering the practice will be informed about the study. After giving informed consent to participate in a computerized screening procedure, each patient will receive a tablet computer. In line with the recommendations of practice guidelines[31 38-40] the screening procedure consists of selected modules of the German version of the Patient Health Questionnaire (PHQ-D)(PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module), the Somatic Symptom Disorder-B Criteria Scale (SSD-12) and the Alcohol Use Disorders Identification Test (AUDIT). After the screening, the patient hands over the tablet computer to the GP who will discuss the results with the patient. The patient's screening scores are presented to the doctor, along with the relevance of the score and the cut-off of each test. Screening results may or may not be used by the physician for diagnostic purposes. Integrated ICD-10 diagnostic criteria checklists for the diagnoses under investigation (depressive, anxiety, somatoform and/or alcohol use disorders) support the GP in the selection of the diagnosis. In addition to the selection of the ICD-10-Code, the GP indicates the severity of the disorder by classifying it as mild, moderate or severe. If a patient receives one or more of the above mentioned ICD-10 diagnoses and gives their informed consent, the patient will be included in the study.

Further care providers for the CSC network: Psychotherapists, psychiatrists, psychosomatic specialists and inpatient institutions

All State Health Insurance psychotherapists, psychiatrists and inpatient institutions in Hamburg will be informed about the project by mail and invited to an informational event at which they will be informed about the study in detail. All psychotherapists, psychosomatic specialists and psychiatrists will receive detailed instruction on the study procedures by phone.

2.5 Participant timeline

Figure 1 shows the participant timeline.

2.6 Allocation of treatment and blinding

Cluster-randomization will be performed in order to control for potential bias and increase internal validity. In this study, a cluster-randomization will be performed at the level of GP practices, which will be randomly assigned to CSC and TAU in a ratio of 1:1 and a block length of 4 by a list of computer-generated random numbers without any stratification variables. The randomization list will be created

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by a research associate of the Department for Medical Biometry and Epidemiology of the University Medical Center Hamburg-Eppendorf, who is not involved in the implementation of the research project. With the aim to ensure recruiter blinding, the study coordinator, who will not be involved in the recruitment of GPs, will receive the computer-generated randomization list, preserve it in a place accessible only to her and carry out the allocation of participating GPs. Incoming cooperation contracts will be assigned to CSC vs. TAU according to the randomization list by the study coordinator. GPs will then be informed about their allocation status. Included patients will receive either CSC or TAU depending on their GP's allocation. This means that even though the allocation is determined by the ranking of the list designed for preventing bias, strictly speaking the allocation is not totally blinded. Blinding of randomization status cannot be granted for the study team, care providers or patients due to study implementation constraints. Nevertheless, the researchers who perform the statistical analysis will be blinded.

2.7 The CSC Intervention

The intervention will be a collaborative and stepped care program provided in the city of Hamburg, Germany by outpatient Statutory Health Insurance GPs, psychotherapists, psychiatrists, psychosomatic specialists and inpatient or day-care clinics embedded in the standard health care system in Germany. Number of sessions, treatment schedule and the intensity of care will be individually tailored to each patient. The intervention will contain the following elements:

Collaborative network

In contrast to an often-used approach which brings external care managers into GP practices, we will systematically integrate the resources and competencies of cooperating care providers (GPs, psychotherapists, psychiatrists, psychosomatic specialists, and inpatient facilities), which can more readily create the structures needed to provide a broad spectrum of interventions. Outpatient GPs, psychotherapists, psychosomatic specialists and psychiatrists as well as inpatient or day care facilities will be integrated into the CSC network to enhance the exchange of information about their work in general as well as individual cases of patients and facilitate immediate referral from GPs to specialized care providers. An existing online scheduling platform enables psychotherapists and psychiatrists to indicate available treatment resources and GPs of the network to book those resources. This tool has been developed and successfully implemented in a former project "Health network depression"[22]. At the beginning of the study, network participants will obtain initial training regarding the evidence-based guidelines of conditions in focus[31 38-40] and the planned care model. Additionally, further quality assessment and exchange will be provided in quarterly network meetings.

Computer-assisted and guideline-based diagnosis and treatment decisions

Following the diagnostic process (see 2.4), each GP will continue with the treatment selection. The algorithm of the program on the tablet computer will provide the GP with one or more treatment recommendations for the individual patient that will be based on guideline recommendations for the diagnosed disorder and its degree of severity[31 38-41]. While these recommendations will offer an orientation for therapeutic decisions, the actual treatment decision for one of the evidence-based treatment options will be carried out in cooperation with the patient by integrating individual preferences and needs, thus following the principles of patient-centered care and shared decision-making. Additionally, possible comorbidities and specific characteristics of each of the disorders are to be taken into account.

Collaborative and stepped care interventions

Within the CSC intervention, patients may be offered eight different interventions structured in three steps of varying intensity and setting (Table 1). The complex intervention will be delivered by different care providers and increase in intensity.

Table 1: Guideline-based treatments in the CSC intervention

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Step	Description		Responsible care provider	Setting
1a	Basic psychosocial care, psychoeducation	Establishment of a working alliance, the provision of psychoeducational materials, psychosocial counselling and treatment of possible comorbid somatic symptoms[31 38-40] including systematic monitoring	GP (or mental health specialist)	Outpatient
1b	Bibliotherapy	Disorder-specific cognitive-behavioral-therapy-oriented self-help books[42-47] accompanied by systematic monitoring	GP (or mental health specialist)	Outpatient
1c	Internet-based self-management	Internet-based self-help program with a cognitive-behavioral-therapy-oriented evaluated and certified computer program accompanied by systematic monitoring[48-50]	GP (or mental health specialist)	Outpatient
1d	Single brief interventions (for alcohol use disorders)	Up to five sessions of less than one hour, during which the patient receives individual feedback on alcohol consumption and advice as well as agreed upon goals[31]	GP	Outpatient
2a	Psychotherapy	Face-to face cognitive-behavioral therapy or psychodynamic psychotherapy either individually or in a group	Psychotherapist	Outpatient
2b	Pharmacotherapy	Medication according to guideline recommendations	GP or mental health specialist	Outpatient
3a	Pharmacotherapy plus psychotherapy	Intensified combination therapy of psychopharmacotherapy and face-to-face-psychotherapy	GP or mental health specialist and psychotherapist	Outpatient
3b	Intensified treatment	Intensified treatment carried out by a multi-professional treatment team	Multiprofessional team	Day hospital or inpatient facility

GP: General Practitioner

The materials for step 1 will be provided to the GP by the study team (i.e., psychoeducational materials, self-help books, licenses for the self-help internet programs). For step 1d, the single brief interventions for alcohol use disorders, GPs obtain special training in the context of one of the first network meetings. In case of referral to a specialized care provider in step 2 or 3, the GP will use the online scheduling platform to book free treatment capacity in the collaboration network. The patient will be instructed to call the booked care provider to confirm the appointment.

Patients will be monitored regularly by their responsible care provider(s) (see table 1) with monitoring forms in order to ensure that sufficient treatment response will be achieved and potential under- or oversupply will be corrected as quickly as possible. Completed monitoring forms will be sent to the study team.

Previous studies have shown that among patients with mental disorders, those with a high symptom severity in particular do not receive the treatment they need (e.g.,[51-53]). It is still unknown whether this is caused by barriers in the referral process, insufficient motivation on the part of the patient or other difficulties. In order to address this problem, case management will be implemented. Based on the digital diagnostic information assessed by the GP during the diagnostic process, a member of the study

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team will follow the treatment pathways of those patients who are diagnosed with a disorder of a high degree of severity. In those cases, the existing monitoring forms filled out by the care providers will be reviewed, and the responsible care provider will be informed if possible deficiencies in care are detected.

In order to improve the adherence of care providers to the intervention protocol, each provider will receive an initial three-hour training about the study procedures. Further trainings (also three hours each) will cover the guideline recommendation for the four relevant disorders. Additionally, there will be a network meeting for the CSC care providers each quarter. Furthermore all care providers will obtain detailed instruction manuals, prepared materials, and they will be visited in their practice at the beginning as well as in the event that any questions arise or problems occur.

Patients in CSC will be free to use any other additional care, as needed. Other care utilization will be recorded in data collection interviews (T2 and T3).

2.8 Outcomes

Primary outcome measure

Following the primary hypothesis that CSC patients will exhibit greater improvement in mental health-related quality of life at 6-month than TAU patients, the primary outcome parameter will be a change in mental health-related quality of life (Short Form Health Survey, SF-36 mental health score[54]) from baseline to 6 months.

Secondary outcome measures

Secondary outcome parameters will be the change in disorder-specific symptoms as measured using the German versions of the major depressive[55], generalized anxiety[56], panic and somatoform modules of the PHQ[57], the SSD-12[58-60] and the AUDIT[61]. We will analyze disorder-specific response (at least 50% symptom reduction at 6 months on the disorder-specific screening instruments) and remission (obtaining a value below the respective clinical cut-off value of the disorder-specific screening instruments at 6 months) for these outcome measures. Further secondary outcomes will be health-related quality of life assessed by the SF-36 physical health score, change in health-related quality of life according to the EQ-5D-5L and health care utilization. Table 2 gives an overview of the outcomes.

Table 2: Outcomes

Variable	Outcome Measure	Outcome	Baseline/ T0	T1	T2	T3
Primary Outcome						
Health-related quality of life mental health scale	SF-36 (36 Items)	change in mental health-related quality of life from baseline to 6 months	X	X	X	X
Secondary Outcome						
Disorder-specific symptoms	PHQ-9 (9 Items) GAD-7 (7 Items) PHQ-15 (15 Items) PHQ-Panic module (15 Items) SSD-12 (12 Items)	change in disorder-specific symptoms from baseline to 6 months	X	X	X	X
Response of diagnosed disorder(s)		at least 50% symptom reduction at 6 months on the disorder-specific screening instrument(s)	X	X	X	X

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Remission of diagnosed disorder(s)	AUDIT (10 Items)	obtaining a value below the respective clinical cut-off value of the disorder-specific screening instrument at 6 months	X	X	X	X
Health-related quality of life physical health scale	SF-36 (36 Items)	change in physical health-related quality of life from baseline to 6 months	X	X	X	X
Health care utilization	Questionnaire, CSSRI (26 Items)	Change in health care utilization at 6 and 12 months	X		X	X
Quality of life	EQ-5D-5L (5 Items)	Change in quality of Life at 6 and 12 months	X		X	X

SF: Short Form Health Survey; PHQ: Patient Health Questionnaire; GAD: generalized anxiety disorder; SSD: Somatic Symptom Disorder-B Scale; AUDIT: Alcohol Use Disorders Identification Test; CSSRI: Client Sociodemographic and Service Receipt Inventory

Economic evaluation

For the calculation of direct and indirect costs health care utilization, reduced productivity at work and work loss days will be measured by a modified version of the Client Sociodemographic and Service Receipt Inventory (CSSRI[62]). The utilization of inpatient care, outpatient physician services, outpatient non-physician services, medication, as well as formal and informal (long-term) care will be assessed. To assess health effects, quality-adjusted life years (QALYs) will be calculated based on utilities derived from the EQ-5D-5L questionnaire.

Process evaluation

Additionally, to allow for exploratory analyses, relevant process outcomes will be assessed: implementation, functionality, acceptability and sustainability of the network, including attributes of the health care model (e.g. relative advantage, compatibility, trialability), adoption/assimilation (e.g., needs, motivation, values, preferences, acceptance and skills of involved actors, including patients), communication and influence (diffusion and dissemination, including social networks, opinion leadership, change agents), the context (antecedents and readiness for innovation, incentives, reimbursement regulations), and the implementation process (support and advocacy of implementation process, feedback on progress). For the assessment semi-structured qualitative interviews will be conducted at the beginning and at the end of the study with patients, GPs, psychotherapists, psychosomatic specialists and psychiatrists of the CSC-group and the TAU-group. We will use semi-structured interview guides on implementation, functionality, acceptance and sustainability of the interventions of the CSC. The interview guides include questions regarding possible beneficial and impeding aspects referring to the implementation process, the care model, adoption/assimilation, communication/impact and context. Questions about the implementation of the study will be integrated in the patient interview at T2. For a separate evaluation of the care process, care providers will be asked at baseline and T3 using standardized short questionnaires. Moreover, process evaluation with care providers will be involved in the quarterly network meetings.

2.9 Sample size

We aim for a sample size that permits the detection of a small to moderate standardized mean difference (Cohen's d of 0.35); [63] between CSC and TAU for the primary outcome (change in the SF-36 mental health score after 6 months) with a statistical power of 0.80 at a type I error rate of 0.05 (two-sided). Assuming a correlation of 0.50 between baseline and follow-up measurements, this requires analyzable data from 95 patients per group (190 in total) for a linear model with the baseline measurement as covariate [64] if randomization takes place at the patient level. With an average cluster size (number of patients per practice) of 12 and an intra-cluster correlation (ICC) of 0.05, this sample size should be multiplied by a design effect of 1.55 [65], leading to 156 patients in 13 practices per group

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and 312 patients in 26 practices in total. As our experience suggests that up to 30% of the randomized practices and up to 20% of the recruited patients may drop out of the study, we aim to recruit 38 practices (19 per group) including 15 patients each, resulting in a target sample size of 570 recruited patients in total (285 per group).

2.10 Data collection methods

Data collection via tablet computer

Data on screening, diagnostics, severity of the disorder, indication and treatment decision as well as the baseline assessment of the primary outcome (SF-36) will be collected on a tablet computer using specially developed web-based screening and diagnostic software (for tests used for the screening see 2.4 Recruitment). The program will also ask for reasons for GP consultation, age, gender and whether the patient is already receiving psychotherapy or psychopharmacotherapy at baseline.

Telephone-based patient interviews

The telephone-based patient interviews will take place at four standard measurement points (baseline, 3, 6 and 12 months after baseline, see Fig. 1). All staff members conducting telephone interviews have undergone a special training for the Composite International Diagnostic Interview (CIDI[66]), which is part of the baseline interview, and received detailed guidelines and standard operating procedures for the interviews. In order to conduct the interview, the responsible staff member will call the patient to make an appointment for the interview. At the appointment the staff member will call the patient and carry out the interview. All contact attempts and contacts will be documented. Telephone interviews rather than written questionnaires were chosen to improve the response rate and the quality of the data collected.

The following questionnaires will be used for data assessment:

Short Form Health Survey (SF-36) (Primary Outcome): This questionnaire assesses the disease-unspecific, health-related subjective quality of life[54]. It comprises 8 dimensions (physical functioning, physical role functioning, physical pain, general health perception, vitality, social functioning, emotional role functioning and psychological well-being), which can be assigned to the two main scales "physical health" and "mental health". Answers are Likert scaled. They are weighted, added and transformed to the range 0 to 100. High values indicate a high health-related quality of life. It is an internationally used, test-theoretically validated instrument with a German reference population[67] The baseline assessment for this instrument is carried out via the tablet computer-based screening after study inclusion in the waiting room of the primary care practice, as described in 2.12.

Sociodemographic Questionnaire*:* Sociodemographic data will be collected only at baseline assessment and comprise date of birth, gender, country of origin, nationality, parental country of origin, marital status, postal code, educational level, occupation and professional status.

Composite International Diagnostic Interview (CIDI): This comprehensive interview procedure will be conducted at baseline and consists of 40 modules, which enables the standardized diagnosis of mental disorders (ICD-10, DSM-IV) for the entire lifetime (longitudinal section) or the last 12 months (cross-section). For this study only the sections for depressive, anxiety, somatoform and alcohol use disorders will be used with regard to the last 12 months[66].

PHQ-9, GAD-7, PHQ-15 and PHQ-Panic module from the Patient Health Questionnaire (PHQ-D): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the waiting room in the primary care practice, as described in 2.12. It is the German adaptation of the PHQ, a screening instrument based on the criteria of the DSM-IV, which covers various syndromes and is a practical and well validated instrument[57 68 69]. The following scales and subscales are used in this study:

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- The PHQ-9 (9 items) for the identification of depressive syndromes covers main and secondary symptoms of depression on a four-step scale according to their frequency[55]
- The GAD-7 (7 items) to detect generalized anxiety disorder[56] and the PHQ panic subscale (15 items) for panic disorder; The GAD-7 is measured on a four-step scale. On the PHQ panic subscale, each item corresponds to a DSM-IV panic disorder criterion and is answered with "Yes" or "No" [68].
- The PHQ-15 (15 items) identifies the somatoform syndrome measured on a three-step scale.

Somatic Symptom Disorder-B Scale (SSD-12): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the waiting room in the primary care practice, as described in 2.12. It measures the new psychological criteria of the Somatic Symptom Disorder (DSM-5) with 12 items that refer to three subscales to capture cognitive, affective and behavioral aspects. In a first validation study in an outpatient sample, the scale showed very good psychometric properties[60].

Alcohol Use Disorders Identification Test (AUDIT): The baseline assessment for this instrument is carried out via the tablet computer-based screening in the waiting room in the primary care practice, as described in 2.12. The AUDIT is an instrument developed by the World Health Organization to identify patients with problematic alcohol consumption in different settings. It is nationally and internationally recognized and includes 10 items related to alcohol consumption, dependence and abuse, with a choice of 3 to 5 alternatives[61 70].

Collaborate: This three-item scale will be assessed at baseline, T2 and T3 to evaluate the shared decision-making process. It measures the dimensions *explanation of the health issue*, e*licitation of patient preferences* and *integration of patient preferences* on a 0 to 9 scale. It evidences concurrent validity with other measures of SDM, good interrater reliability and sensitivity to change[71].

Quality of Life Questionnaire EQ-5D-5L: This generic health-related quality of life questionnaire consists of five items that measure current problems on the dimensions of mobility, self-care, usual activities, pain discomfort and anxiety/depression on five levels. It can be used as a simple health classification system to detect differences in the health status of population groups. Based on the 3,125 possible unique health states derived from the EQ-5D-5L, index scores can be assigned through a set of preference valuations of the general population regarding different health states[72]. It also contains a visual analogue scale for the general assessment of health-related quality of life, which allows easy comparisons with the general population.

Modified Client Sociodemographic and Service Receipt Inventory (CSSRI-D): This is the modified version of a questionnaire for measuring the utilization of services, which has been adapted to the specifics of the German health care system and serves to assess mental health care costs. It collects data about employment and income (employment status, occupation, days of incapacity to work, type and amount of social benefits), use of care services (inpatient, outpatient and complementary care) as well as medication (type and name of medication taken, dosage, number and size of medication packs collected from the pharmacy, price). The instrument has proven itself in practical use, as it allows conclusions to be drawn regarding direct and indirect costs, while providing information on the utilization and medication profiles of patients[62].

Illness Perception Questionnaire Brief (IPQ-B): This 9-Item tool for recording illness perceptions will be used at baseline. 8 items measure the dimensions of perceived consequences of disease, chronicity, perceived personal control and control over treatment, identity, concerns about specific disorders, coherence and emotional representation of said disorders on scales of 0-10. Higher scores reflect a stronger representation of this dimension. The last item serves to identify the three most subjectively

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relevant causes of the disease in question. The IPQ-B has predictive and discriminatory validity, and change sensitivity was confirmed in a systematic review [73].

Questionnaire on the intensity of the general practitioner commitment (F-HaBi): This questionnaire will be used at baseline, T2 and T3. It measures the utilization behavior of primary care patients. It distinguishes patients with close primary care coordination from those who access further care without prior contact to the GP. 9 items indicate whether the patient has a GP, how often the GP is consulted, how/whether the patient uses the GP as a coordinator, and patient satisfaction with the GP and the specialists. Answers are given on a five-point scale. Higher values indicate that the patient is more likely to perceive and use the GP as a coordinator.

Health care utilization and satisfaction with received treatments in the last 3 or 6 months: These items ask for the treatments received in the last 3 or 6 months on a "yes/no" scale and the patient's satisfaction with the received treatments on a five-point scale.

Questionnaire on satisfaction in outpatient care - focus on patient participation (ZAPA): This four-item questionnaire will be applied at T2 and T3 to measure patient satisfaction in outpatient medical care, taking into account the concept of patient participation. It has a one-dimensional structure. Its brevity makes it suitable for use in studies measuring patient satisfaction in outpatient care settings [74].

Process evaluation (quantitative): These four items will be asked at T2 to evaluate the implementation of the COMET study (information, acceptance, time expenditure, incentives). An open-ended question at the end will offer participants the opportunity to comment on their satisfaction with the study.

Monitoring forms

In CSC, care providers will be instructed to monitor their patients in regular time intervals. Time intervals will depend on the treatment conducted and will be at least once per quarter. The care provider will document the result of the monitoring on a standardized monitoring form that includes items on the frequency of consultations since the last visit, treatment decision at the last visit, realized treatment and reasons for deviations, symptom changes (deterioration, improvement), impairment due to symptoms, new diagnoses, remitted diagnoses, serious adverse events and future treatment plans.

Retention and Discontinuation

All care providers will receive financial incentives for those activities that are additional to their usual care. GPs receive expense allowances up to 120€ per patient, psychotherapists up to 290€ and psychiatrists up to 150€ per patient.

Patients will receive a voucher worth 10€ for each of the four conducted interviews. Patients will be contacted up to five times for each of the telephone interviews. If the patient is not available even after five attempts, the GP who included the patient in the study will be informed, and the patient will be called again at the next measurement point. Neither termination of the selected treatment nor termination of the relationship to the recruiting GP will be reasons for a subsequent exclusion from the study and participation in further interviews. Only if the patient explicitly wishes to terminate study participation and does not want to take part in interviews anymore, will they be excluded from the study. The data collected up until that time will only be deleted if the patient explicitly insists upon this. All drop-outs will be documented on a drop-out form that will include age, gender, drop-out date and reasons for drop-out.

2.11 Data management

Data collected with the web-based screening- and diagnostic tool on the tablet computer will be entered electronically by the patient and the GP and stored de-identified in an encrypted database on

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a server of the University Medical Center Hamburg-Eppendorf. The program will include range checks for data values. Data collected during the telephone interviews will be entered directly into a password-protected uniform data entry mask by the interviewing researcher. The data entry masks will be pre-programmed (with the program EpiData) to ensure valid values and prevent entry errors. Data collected via monitoring forms will be documented by the responsible care providers of the network and sent to the study team. A student assistant will enter the data into a digital data mask. All collected data will be stored in a database on the UKE internal server in a pseudonymous form. All participant files will be maintained in storage for a period of ten years after completion of the study. The principal investigators and the study team will have access to the cleaned and final data sets. All data sets will be cleared of any identifying participant information and password-protected.

2.12 Monitoring

The study will be monitored by an international advisory board that meets once a year to review the study progress. It consists of five international scientists with expertise in the field of health care services research in mental health and collaborative and stepped care models. Progress, challenges and possible adjustments will be presented by the study team and discussed with the advisory board. The board is independent from the sponsor. A data monitoring committee will not be established. Data will be monitored by the study coordinator, who has no competing interests.

2.13 Adverse events

We define adverse events as any adverse medical or psychological incident experienced by a patient. Adverse events will be documented by the care providers and the study team whenever they occur. Serious adverse events will be reported to the ethics committee and include suicidality, significant burden, severe or permanent disability, prolonged or unplanned hospitalization, functional impairment, significant hazard or life-threatening conditions. In order to address suicidality, a standard operating procedure was developed.

2.14 Statistical methods

The descriptive statistics will be presented by group and for the total sample. The primary analysis will be based on the intention-to-treat (ITT) population, which includes all practices and patients randomized and included in the study. A linear mixed model for the changes from baseline of SF-36 will be calculated with group (CSC / TAU) and time as fixed effects, practice and patients as random effects, and the baseline value of the SF-36 mental health score as a covariate. The time by group interaction will be tested, and if the interaction is not significant, the interaction will not be included in the model. The coefficient test, comparing the adjusted SF-36-values between the randomized groups, will be performed using the direct maximum likelihood as the statistical estimation procedure, which results in unbiased estimators under the missing-at-random-assumption. The contrast between both groups at the 6-month follow-up will be assessed in a confirmatory manner. The analysis will be repeated in the per protocol (PP) population. To investigate the effects of the missing values on the result of the primary analysis, sensitivity analyses will be carried out with different methods for missing value imputation (e.g., multiple imputation, last observation carried forward). The secondary endpoints will be examined in an exploratory manner. For the binary secondary endpoints, we will conduct a mixed logistic regression, and for the continuous secondary endpoints we will carry out a linear mixed model. The other model parameters will be set as in the primary endpoint analysis. The following subgroup analyses are planned: diagnosis, sex, age, socio-economic status and symptom severity. Adjusted means and odds ratios, respectively, with their 95% confidence intervals and p values were reported. The two-sided type I error will be set at .05. The safety endpoints will be determined using frequency tables and using mixed logistic regressions to compare the event frequencies, if possible. Interim analyses are not planned. A detailed statistical analysis plan will be prepared and finalized before the start of the analysis. Results will be reported according to the CONSORT statement extended for cluster randomized trials.

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Additional analysis

Direct and indirect costs will be calculated from the societal perspective based on health care utilization, reduced productivity at work and work loss days measured by a modified version the CSSRI [62]. For the monetary valuation of resources, German standard unit costs will be applied [75 76]. Indirect costs will be calculated based on the human capital approach by applying gross income plus nonwage labor costs [77]. For assessing health effects, QALYs will be calculated based on utilities (i.e., preference-based scores of health-related quality of life measured on a scale from 0=very bad health to 1=perfect health) derived from the EQ-5D-5L questionnaire. Costs and effects of CSC will be compared to standard care in incremental analyses. This will be done by calculating incremental cost-effectiveness ratios (ICERs)[78]. The ICER is defined as the ratio of the difference in cost and the difference in health effects between intervention and control group. As the ICER is a point estimate which neither considers statistical uncertainty in the data nor the effect of potential confounding variables, cost-effectiveness acceptability curves (CEACs) will be constructed by means of a series of net benefit regressions using different willingness-to-pay margins [79].

Process Evaluation: Data of the patient survey will be analyzed using descriptive statistics (i.e., frequencies, means, and standard deviations). The qualitative data will be analyzed using structuring content analysis, based on the above mentioned categories of facilitating and inhibiting factors of implementation and sustainability of CSC [80 81].The qualitative interviews will be transcribed and coded using a deductive category system (e.g., attributes of the health care concept, adoption/assimilation, communication/influence, context and implementation process), which will be further elaborated upon inductively.

Patient and Public Involvement

Research questions and outcome measures where not informed by patients' priorities, experience or preferences. Patients were not involved in the design of this study. Patients were not involved in the recruitment for and the conducting of the study. The results will be disseminated to the participating care providers by sending them reports about the study results. Patients will evaluate the impact of the intervention.

3 Ethics and Dissemination

The ethics committee of the Hamburg Medical Association approved the study design and intervention (PV5595) in September 2017, prior to commencing recruitment. We confirm that the study will be carried out in accordance with the principles of the Declaration of Helsinki. Any severe adverse events as well as any protocol changes will be reported to the ethical committee and the advisory board without delay. Written informed consent will be obtained from all patients by their GPs. There are no foreseeable risks for patients participating in the study. The study does not involve any restriction to standard care. The study has been registered at clinicaltrial.gov NCT03226743 in October 2017.

Personal information about participants

Personal information will be collected on the informed consent form, on which the patient provides their name and telephone number. This form also includes a unique patient code. The telephone number is needed to call the patient for the patient interviews. The GP sends the form via fax to the study coordinator. The study coordinator receives the fax digitally on her computer, extracts the patient code, the name of referring GP and the telephone number, sends this information to the study team and saves the fax as a password-protected file to which only the GP has access. The study team contacts the patient without knowing the patient´s name and conducts the interview. If the landline telephone number is given, the interviewer will ask for the person who is taking part in the COMET-study. At the end of the interview, the patient will be asked whether they are interested in an incentive in form of a 10€ gift coupon. If so, the patient will be asked for their postal address. The address will not be saved but will instead be eliminated immediately after the coupon is sent.

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Dissemination policy

The results and findings of the study will be published in peer-reviewed journals and presented at conferences and congresses. It will be disseminated also by mean of the multiple partnerships within the superordinate project Hamburg Network for Health Services Research (HAM-NET). Results will also be relayed to the participating health care providers. A completely anonymized data set will be delivered to an appropriate data archive for sharing purposes. No professional writers will be employed.

Conclusion

In line with the primary hypothesis, the intervention condition is expected to be superior to the control condition. This means that CSC is expected to provide more effective treatment than routine care in terms of improving health-related quality of life 6 months after treatment initiation. In addition, CSC is expected to outperform standard care in secondary outcomes, cost-effectiveness, and process variables. A significant contribution to the knowledge relating to whether it is possible and effective to treat a wide range of mental disorders (depression, anxiety, somatoform and alcohol-related disorders) within a collaborative and stepped care model based on evidence-based recommendations is expected. This is a challenge for the care providers and the whole network. Particular interest will be given to how the central issue of comorbidity is dealt with. As far as we know, this is the first randomized and controlled study dealing with complex co-morbidity patterns.

4 Authors' contributions

MH, BL, OvdK, MS, IS, HHK, KW and DH designed the study and obtained funding. MH, JD and DH are responsible for its conduct and overall supervision. HHK, CB, TG, KW and AD contributed to specific methodical and health economic issues. DH, JD, SP, KM, SW, AW, TZ, BS, MR and MH worked out study processes, treatment pathways and materials. DH coordinates the study with support from JD and MH. DH, SP, KM and SW organize the network and carry out the recruitment process, network meetings and data collection. DH is responsible for data management. DH, JD and MH wrote the manuscript. All authors contributed to, reviewed and approved the final manuscript.

5 Funding statement

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6 Competing interests

The authors declare that they have no competing interests.

7 Roles and responsibilities

7.1 Coordinating Center: Principal investigator and research team

- Designing and conducting of COMET
- Preparations of protocol and revisions
- Study planning
- Preparation of care provider brochure and case report forms
- Recruitment of general practitioners and further health care providers
- Organization of network meeting and trainings
- Network management
- Practice visits
- Publication of study reports
- Preparation of materials for participating health care providers and patients
- Development of the internet transferal platform and the eDiagnostic tool

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- Responsibility for trial master file
- Budget administration and contractual issues
- Randomization
- Data verification
- Maintenance of trial IT system and data entry

7.2 Steering committee/advisory board

- Approval of final protocol
- Study progress review and approval of changes to the protocol, as needed
- Consultation in clinical, methodological and content-related issues

8 Literature

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Legend: Figure 1: Participant timeline
GP: general practitioner; TAU: treatment as usual; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CIDI: Composite International Diagnostic Interview

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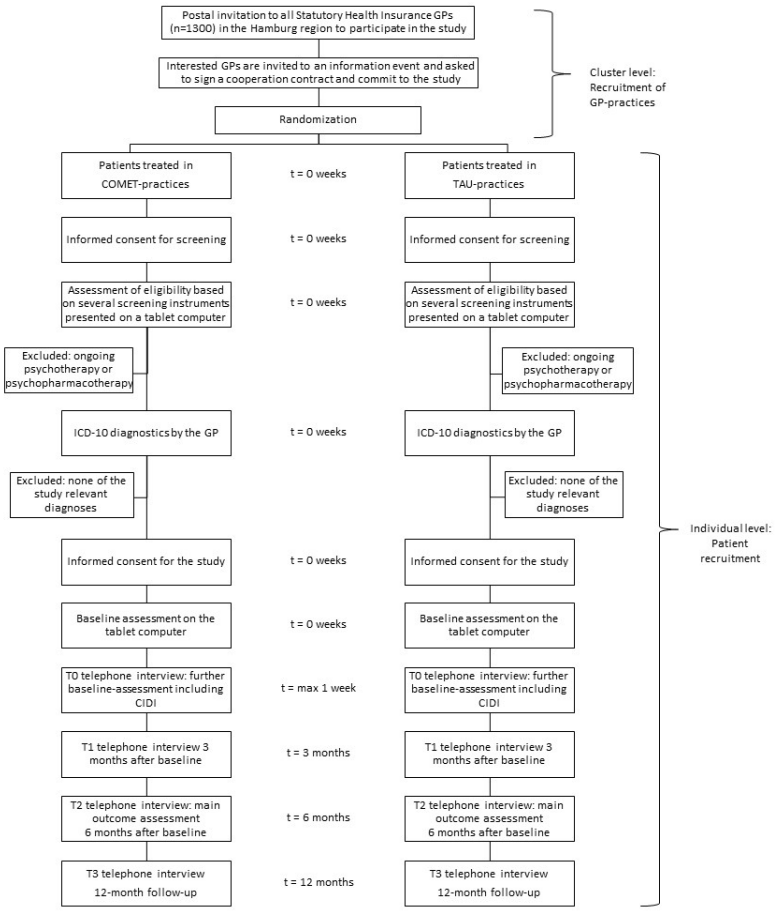

Figure 1: Participant timeline: GP: general practitioner; TAU: treatment as usual; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; CIDI: Composite International Diagnostic Interview

80x108mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 15

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 & 15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6

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Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8 & 12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6

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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

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Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

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Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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