



**Projekt Collabri Flex – The effect of a Danish model for collaborative care for people with anxiety and depression in general practice**

## **1. Introduction and background**

### **1.1 The patient population**

Depression and anxiety are common illnesses with a lifetime risk of 17-18 % and 14-29 % respectively (1,2). The human costs relating to these illnesses are great, but they also place a significant burden on the economy. It is estimated that the costs related to anxiety and depression are approximately DKK 20 billion per annum and an increasing number of people receive disability pension because of the illnesses (3).

### **1.2 Current treatment of anxiety and depression in general practice**

In Denmark the general practitioner (GP) is the main provider of primary, personal and continuous health care to individuals, families and vulnerable groups in Denmark. Common mental health disorders is a significant element in the general practitioner's workload, as the vast majority of the population of people with depression and anxiety is diagnosed and treated in primary care. It is agreed that the majority of these patients should continue to be treated here (4), but also that the effort must be optimised as studies show that many patients with anxiety and depression do not get the correct diagnosis and evidence based treatment in general practice (24-6).

Some of the obstacles in the current management and organisation of treatment of anxiety, depression and other non-psychotic mental health disorders in general are identified below:

- There is a lack of continuity in the management of anxiety, depression other non-psychotic mental health disorders, as there is no organised, coherent treatment regime between general practice and secondary care.
- There is a lack of treatment opportunities. There is currently no obligation for the GP to provide psychotherapy and it is estimated, that only around one third of GPs in Denmark are qualified to provide psychotherapy (7). However, the GP can refer the patient to a psychologist via "Psykologordningen". All adult patients with depression and patients with anxiety between 18-38 years can receive therapy from a psychologist; however, the patient has to contribute to the cost of the treatment.
- There is a shortage of practice psychiatrists and psychologists trained in Cognitive Behavioral Therapy (CBT) and other evidence based psychological methods. This can delay the specialised treatment of patients who have been referred from the GP.
- The compensation structure does not support the treatment guidelines. As an example, a GP only gets compensation for up to 7 sessions and although the GP has to document supervision he/she does not get compensated for this (8).
- There are no requirements for postgraduate education of GPs which can ensure the continuous professional development.

As mentioned, the vast majority of the population of people with depression is diagnosed and treated in general practice. Under-detection of depression in primary care has been extensively described and could lead to under-treatment (9). Also, over-detection could lead to over-treatment, but is less described in the literature. As referred to in a meta-analysis including 41 studies assessing the accuracy of unassisted diagnoses of depression in primary care, only about 50% of true cases are diagnosed and 15% treated. Conversely, the meta-

analysis concludes that about 80% of non-depressed individuals are correctly reassured (9). The findings of the meta-analysis suggest that for every 100 unselected cases seen in primary care, there are more false positives (n=15) than either missed (n=10) or identified cases (n=10) (9). Overall, although diagnosis seems to be modestly improved by the use of scales (screening instruments for depression), a positive effect on overall patient outcomes has not been shown. Only when screening is paired with organized systems of care can outcomes be improved (9). In a Danish observational study investigating high-risk screening with the MDI screening tool (Major Depression Inventory), screening with MDI on clinical indication on depression (called case-finding) and a combination of the two methods, investigators found that screening of patients in high risk groups had a limited effect in addition to the cheaper and less invasive method of case-finding (10). The general practitioners demonstrated a depression diagnostic sensitivity of 87% and a specificity of 67% using a case-finding strategy and the author concludes that a broad case-finding approach including a short validation test can help general practitioners when they identify depressed patients. Considering the potential harms of incorrect detection of depression in primary care, there is a need to further investigate the best way to correctly diagnose depression in primary care. Therefore, as part of the Collabri Flex study, a detection study will seek to clarify if a systematic use of the questionnaire MDI (Major Depression Inventory) in patients with suspected depression. This might give the general practitioner better means of detecting depression compared to their usual routine detection. The hypothesis is that systematic use of MDI will increase the probability of finding the patients who actually have a depression amongst patients that the general practitioner evaluate to have a depression (positive predictive value).

### **1.3 Evidence of Collaborative care**

There is national as well as international consensus that optimising anxiety and depression treatment in primary care should be done by introducing shared care interventions such as collaborative care programs (CC) (1,2). CC stems from the recognition that patients with depression in primary care may require changes in the organisation corresponding to the changes introduced through collaborative care for other chronic diseases (11) Thus, these ideals have now been transferred to the management of anxiety and depression. Health economy studies indicate that, in spite of there being a need for an investment when introducing CC, the cost tends to be recovered after 3-4 years, and in the long term there are substantial savings to be made because of the reduction in sick leave and people receiving disability pension (12).

A systematic review of the literature from 2009 has shown that CC has an effect on anxiety and depression (evidence level 1a for both diseases) (13). A Cochrane review from 2012 investigating the effects of CC on anxiety and depression concluded that CC is associated with significant improvements in treatment outcomes and for depression for up to 2 years compared with usual care. Thus, the authors conclude that CC represents a useful addition to clinical pathways for adult patients with anxiety and depression (14).

The literature on collaborative care for depression is therefore fairly robust. However, the evidence is primarily based on research conducted in the U.S.<sup>1</sup> and therefore based on an organisational framework not directly applicable to Danish context. Therefore it is not possible to know whether collaborative care for depression and anxiety will have the same effect in Denmark (15). Thus, there is a need to investigate a Danish model for collaborative care for depression and anxiety in Danish context. As the vast majority of the CC studies conducted so far are investigating CC for depression there is a need for further research in CC for anxiety (14).

Collaborative care models are complex interventions, and consist of a number of treatment modalities, therefore it is difficult to point out specific “active ingredients”. The term has evolved since the 90s, as treatment modalities have been continuously updated with the latest knowledge in the field. Four criteria for CC are listed in the Cochrane review (14):

- 1) A multi-professional approach to treatment
- 2) Scheduled monitoring and review
- 3) Enhanced inter-professional communication and
- 4) A structured treatment plan

A systematic review conducted by Eplov et al. (13) further indicates, that the following elements are essential to the intervention, which have also been integrated into the Collabri Flex model (a description of the model follows): Recruitment of staff with psychiatric experience, education of general practitioner and care manager, use of instruments for detection and follow-up, education and treatment of the patient, supervision from a psychiatric specialist and a stepped care approach to treatment where treatment is always commenced on the least invasive and least resource-demanding level.

#### **1.4 Evidence of consultation-liaison**

Before the development of Collaborative Care the consultant-liaison approach was used to optimising anxiety and depression treatment in primary care. Gask et al. (16) and Bower & Sibbald (17) describe four main criteria for a consultation-liaison model, these are:

- Regular face to face contact between psychiatrist and primary health care team
- Psychiatric referral only takes place after discussion at face-to-face meeting
- Some cases are managed by the primary health care team, after discussion
- When referral does take place there is feedback to the primary health care team and management by them

A review by Giles et al from 2015 (18) and Eplov et al. from 2009 (13) found only one study comparing Collaborative Care with Consultation-liaison, finding CC superior after 3 months on depression symptoms (19). However, the study is conducted in the U.S. and therefore based on an organisational framework not directly applicable to Danish context (15). Also, the study only included patients with depression, thus stressing the need for further research in comparing CC with consultaion-liaison for patients with anxiety.

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<sup>1</sup> Of 79 included studies 73 were from U.S, 2 were from Chile, 2 were from the UK, 1 was from Germany and 1 was from India.

## 1.5 Background for initiation of the Collabri Flex Project

In November 2014 we initiated four cluster-randomized controlled trials with cluster on general practitioner level after developing a Collaborative Care model called the Collabri model, examining the following:

- The effect of Collabri vs. Treatment as usual given to people with depression
- The effect of Collabri vs. Treatment as usual given to people with generalized anxiety
- The effect of Collabri vs. Treatment as usual given to people with panic disorder
- The effect of Collabri vs. Treatment as usual given to people with social phobia
- The effect of detection with case finding vs. standard detection in detecting people with depression in general practice.

Despite of several attempts to recruit the number required to conduct the four RCTs (see table below) we have realized that we cannot succeed, as we cannot get the general practitioners in the control arm to recruit enough patients despite of many efforts to achieve this.

	Social phobia	Panic anxiety	GAD	Depression	Total
Goal for inclusion	364	364	364	480	1572
Status for inclusion end of April 2016	38	98	149	296	581
- Control group	6	11	20	52	89
- Interventions group	32	87	129	244	492

In order to contribute to the good quality effect evaluation of an MTV (in English Health Technology Assessment), we will restructure the project in the following way:

- The collected data from Collabri will be used in before-after studies with follow-up at 6 and 15 months, supplemented with possible analysis on the not-finished RCTs
- We will initiate two new randomized controlled trials with randomization on individual level (patient level), where we compare the effect of Collaborative Care with Liaison-psychiatry given to people with depression and anxiety, respectively.
- Continue the detection-study as it is possible although we go from a cluster-randomization to randomization on an individual level.

At the same time we will update the Collabri model, as we have collected extensive information, giving us the possibility to examining the effect of a model more suitable for later implementation. Below, the Collabri Flex model and the consultation-liaison model which will be investigated in the Collabri Flex Project is described.

## 2. The Collabri Flex model

The Collabri Flex model for Collaborative Care takes point of departure in the Collabri model but is changed according to gathered information in the first study of the Collabri model in order to achieve a Danish Collaborative Care model easier to implement. Below it is described how the essential elements of collaborative care are addressed in the Collabri Flex model.

## **2.1 A multi-professional approach to treatment**

In the Collabri Flex model the following professionals will provide the treatment: Care managers (CM), general practitioners (GP) and psychiatrists/psychologists. Following recruitment they will all receive a short training. The specific roles and tasks are described in the following.

### ***The Care manager***

CM has a medium-long (approx. 3-4 years) health professional qualification e.g. as a nurse or occupational therapist, has experience of working in mental health services and an approved qualification in cognitive therapy. CM has the following responsibilities: Ensuring the diagnostic investigation made by the GP in close cooperation with the psychiatrist/psychologist, active follow-up (including assessment of disease progression and course), monitoring of adherence and side effects of medical treatment, cognitive behavioral therapy (CBT), supportive conversations, diagnostic specific treatment, psychoeducation, regular contact with social worker(s), conference with GP according to the individual agreement between the GP and the Collabri Flex project and conference with the psychiatrist/psychologist at supervision after reassessment or ad hoc at reassessment if the treatment plan is changed/should be changed and at reassessment at the end of the treatment course.

### ***The general practitioner***

The collaboration between the GP and the Collabri Flex team will be based upon an individual agreement between the GP and the Collabri Flex project. This agreement will specify the degree of involvement in the treatment and collaboration with the Collabri Flex team. The GP will maintain the overall treatment responsibility. The GP cannot refer the medical treatment to the Collabri Flex team. Also, the GP keeps the following roles: diagnostic procedure in collaboration with the Collabri Flex team, collaboration with CM at reassessment if the treatment plan is changed/should be changed and at reassessment at the end of the treatment course. Conference with psychiatrist ad hoc and possibility of shared consultation with psychiatrist at hoc. There is a possibility of regular supervision according to the individual agreement. The GP can choose whether treatment managed by care manager is to take place in the GPs practice. The GP can choose to keep or refer the following roles and functions to the Collabri Flex team: initiation of treatment - except for the medical treatment, other guidance of care manager that follow a treatment plan, collaboration with care manager on contact with social worker(s).

Requirements of the GPs will be:

- To undergo training in the Collabri Flex model
- To take part in a formalised collaboration with the psychiatrist/psychologist depending on the individual agreement between the GP and the Collabri Flex project
- To carry out assessments and provide treatment cf. the Collabri Flex model based on the individual agreement between the GP and the Collabri Flex project

### ***The Psychiatrist/psychologist***

The psychiatrists and psychologists have the following roles and responsibilities: Provide the diagnostic investigation in collaboration with the CM and GP, ensuring adherence to the Collabri Flex model, guiding and supervising the CM regularly and ad hoc. Guiding and supervising

ing the GP regularly and ad hoc as well as participate in shared consultation with GP according to the individual agreement between the GP and the Collabri Flex project.

## **2.2 Scheduled monitoring and review/reassessment**

Monitoring and reviews are essential in order to achieve the desired results of the treatment of depression or anxiety, including continued symptom relief and reduced risk of side effects or other risks associated with the illness or treatment.

In the Collabri Flex model, the patient is regularly monitored and reviewed at scheduled follow-up sessions. This is central to the model. All patients are discussed at regular supervision with the psychiatrist after reassessment or ad hoc at reassessment if the treatment plan is changed/should be changed and at reassessment at the end of the treatment course. Monitoring and review will consist of controls at intervals determined by the degree of illness – as a minimum monthly, and more frequently when needed. It includes:

- Ensuring compliance, pharmacological as well as non-pharmacological
- Assessment of symptom degree by MDI or ASS
- Assessment of suicide risk
- Assessment of side effects
- Evaluation of the need to control other parameters, such as weight, BT and heart rate, blood tests and other tests depending on necessity and comorbidity
- Consider step-up or referral to a psychiatric specialist, especially if deterioration is detected via MDI or ASS, suicidal or psychotic symptoms appear or increase, or other causes for concern

## **2.3 Enhanced inter-professional communication**

In the Danish reference programs for anxiety and depression, supervision of GPs has been highlighted (1,2). Reports recommend improved systematic collaboration between the primary and secondary system in order to improve the quality of care for patients with anxiety and depression in primary care (5). In the Collabri Flex model care manager and GP will preferably meet weekly. However, the amount of contact will be agreed upon in the individual agreement between the GP and the Collabri Flex project. The individual agreement will at least ensure contact at reassessment if the treatment plan is changed/should be changed and at reassessment at the end of the treatment course. Other communication depending on the individual agreement could be:

- Psychiatrist/psychologist supervises CM in groups twice monthly
- Psychiatrist/psychologist supervises CM individually ad hoc
- Psychiatrist/psychologist supervises GPs in groups monthly depending on the individual agreement between the GP and the Collabri Flex project
- Psychiatrist/psychologist supervises GP individually ad hoc.
- Psychiatrist/psychologist, GP and CM have joint consultations ad hoc.

The described communication can happen via video or telephone conferences if it is not possible to meet in person.

## 2.4 A structured treatment plan

The treatment of CC for anxiety and depression takes place according to treatment guidelines established on the basis of the Danish Health Board's Reference program for unipolar depression in adults, the Reference program for anxiety disorders in adults (1,2), the Danish College of General Practitioners clinical guidelines for unipolar depression and clinical guidelines for anxiety disorders (6,20), as well as the latest knowledge in the field regarding specific treatment modalities. Overall, a structured treatment plan based on the use of manuals is developed for each of the four illnesses (generalized anxiety, panic disorder, social phobia and depression) and contains the following elements: detection and diagnosis, general principles of treatment, stepped care and specific treatment modalities.

### *General principles of treatment*

In Collabri Flex the treatment is in line with a set of general treatment principles relevant for collaborative care interventions. Besides the four above mentioned criteria for CC, these are:

- **Detection.** Detection of anxiety in the Collabri Flex study will follow the guidelines for general practice recommending the use of the Anxiety Symptom Scale (ASS) in conjunction with ICD-10 criteria. Two methods for detection of depression will be examined in a randomized controlled design; the effect of standard detection vs. case finding with the use of Major Depression Inventory (MDI). Results from this study will create the basis for future detection of depression in the Collabri Flex model.
- **A stepped care approach to treatment as well as active and planned follow up.** The stepped care approach implies offering the most effective and least invasive treatment initially and upgrading and intensifying treatment after review. The English National Institute for Clinical Excellence (NICE) guidelines for anxiety and depression recommend the stepped care approach for the organisation of treatment (21,22), and the Danish reference programs for anxiety and depression identifies the stepped care approach as a good alternative to the current organisation (1,2). Treatment plans include a stepped care plan with the possibility of referral to secondary mental health services. According to illness and severity there will also be planned follow up contacts between the patient and the care manager.
- **Patient involvement in treatment.** In order to ensure informed decision making processes and dialogues about the development and implementation of treatment plans, a high level of information is provided to the patients about the illness, its progression, relapse prevention and treatment options. The care managers will be trained in the shared decision making model and encouraged to use it.
- **Involvement of relatives/carers.** All patients will be informed about the possibility of a relative/carer-consultation and the treatment plan will include involvement of relatives/carers if the patient consents. Relatives/carers will be provided with written information about the illness, its progression etc. and with relevant links and contact details for further information and advice.
- **Guided self-help.** All patients receive psychoeducational material in the form of the book "Lær at tackle angst og depression" and written information about their illness. The book is developed in connection to the training program "Lær at tackle angst og depression", which originates from the English Expert Patient Program. The goal of the program is that the patient attains tools in order to handle the symptoms of their illness and the difficulties it can present in everyday life, and is thus focused on active

self-help. . Patients also receive psychoeducation either independently or as integrated within the cognitive behavioral therapy. Relatives/carers will also receive written information about the illness.

### ***Detection in the Collabri Flex model (identification of persons with depression)***

Considering the potential harms of incorrect detection of depression in primary care and the literature concerning different methods of detecting depression in primary care, two methods for detection of depression will be examined in a randomized controlled design; the effect of standard detection vs. case finding coupled with collaborative care intervention. As in the Collabri project, half of the GPs in the Collabri Flex study on depression, will be selected randomly to perform standard detection and identifies patients with depression as usual. Use of a screening tool is optional in this group. The other half of the GPs performs case-finding detection. GPs in this group have to use the screening tool MDI if they suspect a depression. Results from this study will create the basis for future detection of depression in the Collabri Flex model.

### ***Specific treatment modalities***

#### *Medical Treatment*

The patient is offered medical treatment in accordance with treatment guidelines in Collabri Flex. These guidelines contain progressing algorithms. The treatment is initiated by the GP and will be monitored by the care manager.

#### *Psychotherapy*

The patients in the intervention group are offered cognitive behavioral therapy (CBT) by the care manager in accordance with treatment guidelines in Collabri Flex. If this treatment shows no or limited effect, patients may subsequently be referred to psychotherapeutic treatment by a psychologist based on the existing psychologist scheme (“Psykologordningen”)<sup>2</sup> or psychotherapy as a part of the secondary sector.

#### *Psychoeducation*

Patients are offered psychoeducation either as a part of CBT (when this is offered) or independently. All patients and relatives/carers are offered written psychoeducational material.

## **3. The consultaion liaison model**

Consultation liaison in the Collabri Flex study involves an ongoing educational relationship between the Collabri Flex team and the GP to enable the GP to care for individual patients based on regular contact between the GP, the CM and the psychiatrist.

## **4. Aims in the Collabri Flex study**

The aims of Project Collabri Flex are to:

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<sup>2</sup> If the GP has specialised training in CBT and normally offer CBT for anxiety and depression the GP can offer CBT on this level.

- Develop a flexible model for collaborative care (the Collabri Flex model) for patients with anxiety and depression.
- Study the effects of this Collabri Flex model against consultation liaison in a randomized design on selected outcomes.

## 5. The Collabri Flex study

### 5.1 Aim and hypotheses

As there will not be sufficient statistical power to conclude whether Collaborative Care is superior to Treatment as Usual (TAU), we will supplement the Collabri Study with the Collabri Flex study, where we compare collaborative care to consultation liaison in a trial randomized on individual level. We will not be able to compare collaborative care to Treatment as Usual in Collabri Flex, as we want to randomize at patient level instead of on general practitioner level. When we started the Collabri Study we chose to use a cluster randomization, as there would be contamination introduced if all general practitioners were offered collaboration with care manager and psychiatrist, as would be the case if the randomization were to be on an individual level. In the Collabri Flex study, where we are going to randomize on an individual level to make the study more doable, we compare collaborative care to consultation liaison, and thereby avoid contamination. Participants in Collabri Flex will be patients with generalized anxiety disorder (GAD), panic disorder (PD), social phobia (SP) or depression who is consulting their GP. The Collabri Flex study will consist of two sub-studies; one examining the effects of the Collabri Flex model on anxiety disorders (GAD, PD and SP) and one examining the effects on depression.

The aim of the Collabri Flex study is then to investigate the effects of collaborative care (CC) compared to consultation liaison in patients with anxiety disorder (generalized anxiety, panic disorder or social phobia) or depression consulting their GP in a randomized controlled trial.

The following hypotheses will be tested in the Collabri Flex depression studies:

- Patients receiving CC according to the Collabri Flex model, compared to patients receiving consultation liaison, will show a greater reduction in severity of depression 6 months after baseline (primary outcome investigation in Collabri Flex).
- Patients receiving CC according to the Collabri Flex model, compared to patients receiving consultation liaison, will show more progress in terms of functional level, psychological stress and anxiety symptoms (secondary outcome investigations in Collabri Flex).
- Case-finding increases the probability of finding the patients who actually have a depression among patients that the general practitioner evaluate to have a depression (positive predictive value) compared to current practice (primary outcome in Collabri detection study which was started in the Collabri project and continues in Collabri Flex).
- There is no difference in the effects of CC given to patients with depression and to patients with depression in combination with a personality disorder (explorative outcome investigation in Collabri Flex).

The following hypotheses will be tested in the Collabri Flex anxiety study:

- Patients with generalized anxiety, social phobia or panic disorder receiving CC according to the Collabri Flex model, compared to patients receiving consultation liaison, will show greater reduction in severity of anxiety 6 months after baseline (primary outcome investigation in Collabri Flex).
- Patients with generalized anxiety, social phobia or panic disorder receiving CC according to the Collabri Flex model, compared to patients receiving consultation liaison, will show more progress in terms of functional level, psychological stress and depression symptoms (secondary outcome investigations in Collabri Flex).
- There is no difference in the effects of CC according to the Collabri Flex model given to patients with generalized anxiety, social phobia or panic disorder and to patients with generalized anxiety, social phobia or panic disorder in combination with a personality disorder (explorative outcome investigation in Collabri Flex).

## **5.2 Design and methods**

### ***Design***

The Collabri Flex study is set up as a researcher-blinded individually randomized controlled trial with participation of an intervention group (treatment according to the Collabri Flex model) and a consultation liaison group. There will be conducted two RCTs examining the effects of collaborative care according to the Collabri Flex model for patients with anxiety (generalized anxiety, social phobia or panic disorder) or depression. See Figure 1-2 for the flow charts for the Collabri Flex depression study and the Collabri Flex anxiety study respectively.. To ensure internal and external validity, the study design takes its point of departure in the CONSORT-statement for randomized studies (23).

Figure 1: Flow-chart for the Collabri Flex anxiety study

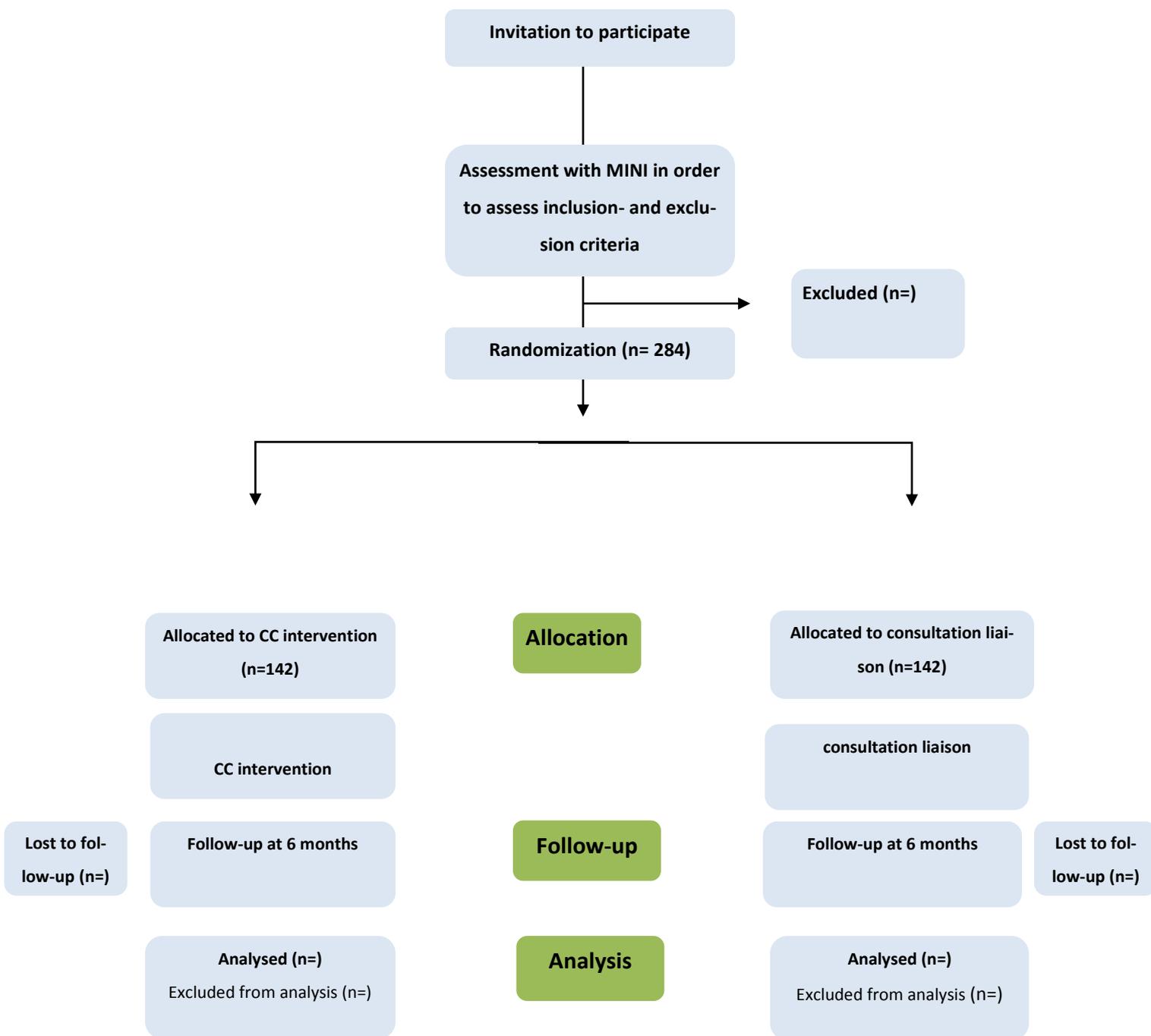
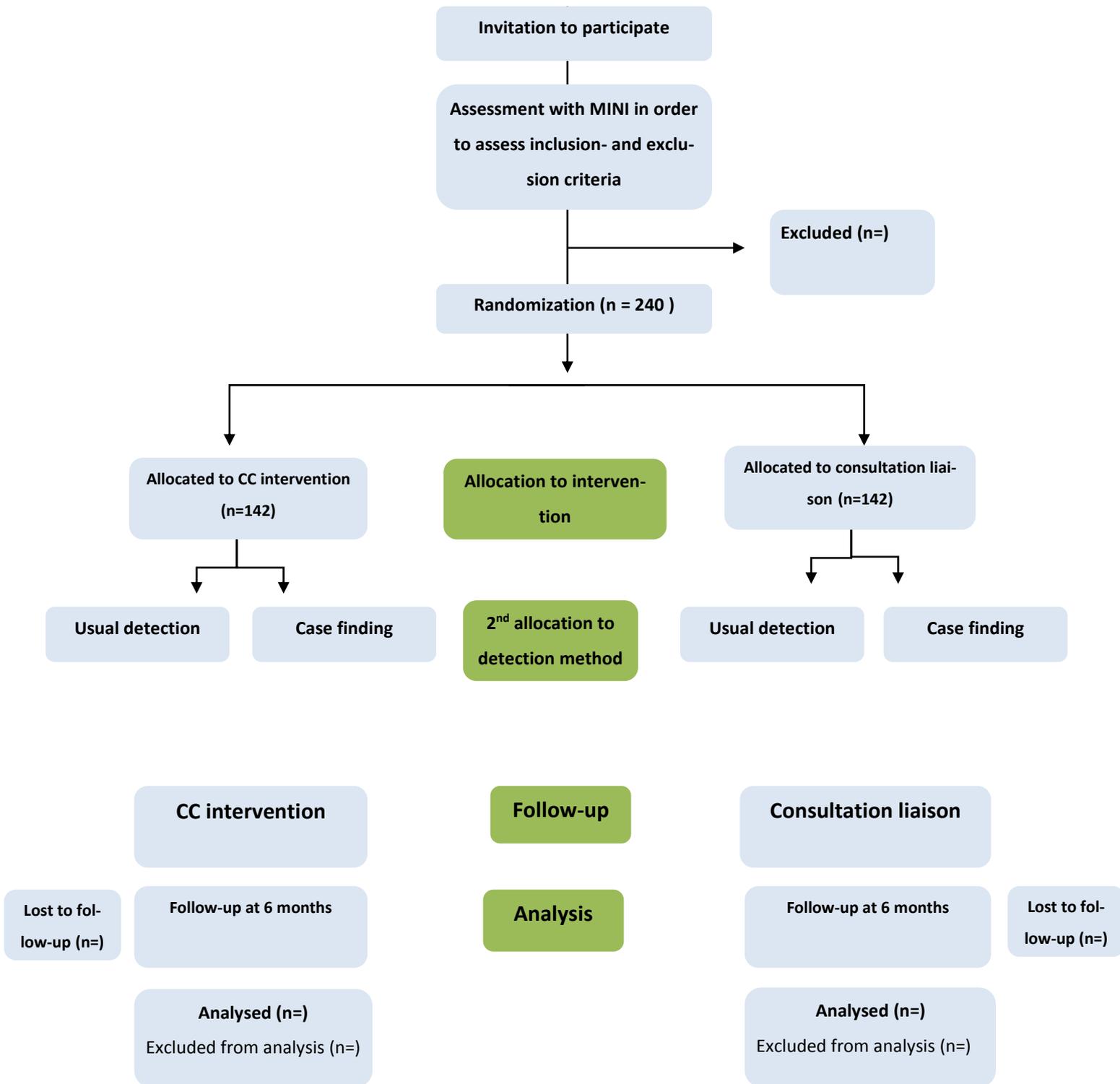


Figure 2: Flow-chart for the Collabri Flex depression study



**Description of study participants**

Patients will be eligible for the Collabri flex studies for depression and anxiety if their general practitioner is enrolled in the study and comply with the inclusion and exclusion criteria listed below upon presentation:

In the Collabri flex depression study the participants will be included in two different ways, through:

- Standard detection
- Detection with case-finding

For the standard detection group, patients will be eligible for the detection study if they meet the following inclusion criteria:

- Age: 18+ years
- Danish speaking
- The patient has given her/his written informed consent to participate in the trial at the described terms
- Referred by their GP with a depression diagnosis

For the detection with case-finding group, patients will be eligible for the detection study if they meet the following inclusion criteria:

- Age: 18+ years
- Danish speaking
- The patient has given her/his written informed consent to participate in the trial at the described terms
- Referred by their GP with a positive or negative MDI

The exclusion criteria are the same as for the below-mentioned depression study.

Study inclusion criteria for the Collabri Flex depression study:

- Age: 18+ years
- Danish speaking
- Diagnosis of current depression based on the Mini International Neuropsychiatric Interview (MINI) (24) by care managers that have been trained in using the MINI in close collaboration with the psychiatrist/psychologist. Patients can be referred from the GP on the basis of a panic disorder, generalized anxiety, social phobia or depression diagnoses
- The patient has given her/his written informed consent to participate in the trial at the described terms

Study exclusion criteria:

- High risk of suicide assessed in the MINI and/or by the GP
- Psychotic condition detected in the MINI and/or by the GP
- Pregnancy
- Patients with a diagnosis of dementia
- Alcohol, medicine or substance misuse that will hinder the person in participating in Collabri Flex treatment as assessed by the GP or care manager at inclusion interview

- Patients who indicate that they will not let treatment for anxiety or depression according to the Psychologist scheme be preceded by Collabri Flex treatment if they are randomly assigned to the group offered Collabri Flex treatment
- Patients currently receiving treatment for anxiety or depression according to the psychologist scheme who indicate that they will not opt out of treatment if they are randomly assigned to the group offered Collabri Flex treatment
- Patients who are already referred or after the inclusion interview is recommended referral to treatment in the secondary sector, that is mental health centres or psychiatrist in private practice
- Patients who are assessed by the GP as medically unstable making it impossible to adhere to treatment
- OCD, PTSD, bipolar affective disorder as assessed in the MINI and/or by the GP
- Patients included in the IBBIS Trial
- Patients included in the Collabri Trail who have not yet participated in 15 months follow up

Study inclusion criteria for the Collabri Flex anxiety study:

- Age: 18+ years
- Danish speaking
- Diagnosis of current anxiety in the form of panic disorder, generalized anxiety or social phobia based on the Mini International Neuropsychiatric Interview (MINI) (24) by researchers that have been trained in using MINI . Patients can be referred from the GP on the basis of panic disorder, generalized anxiety, social phobia or depression diagnosis
- The patient has given her/his written informed consent to participate in the trial at the described terms

Study exclusion criteria:

- High risk of suicide assessed in the MINI and/or by the GP
- Psychotic condition assessed in the MINI and/or by the GP
- Pregnancy
- Patients with a diagnosis of dementia
- Alcohol or substance misuse that will hinder the person's participation in Collabri Flex treatment assessed by the GP or care manager at inclusion interview
- Patients who indicate that they will not let treatment for anxiety or depression according to the Psychologist scheme be preceded by Collabri Flex treatment if they are randomly assigned to the group offered Collabri Flex treatment
- Patients currently receiving treatment for anxiety or depression according to the Psychologist scheme who indicate that they will not opt out of treatment if they are randomly assigned to the group offered Collabri Flex treatment
- Patients who are already referred or after the inclusion interview is recommended referral to treatment in the secondary sector, that is mental health centres or psychiatrist in private practice
- Patients who are assessed medically unstable assessed by the GP in a sense that makes it impossible for the patient to adhere to treatment
- OCD, PTSD, bipolar affective disorder assessed in the MINI and/or by the GP

- Patients included in the IBBIS Trial
- Patients included in the Collabri Trail who have not yet participated in 15 months follow up

### ***Randomization***

The Collabri Flex study will use individual randomization. As mentioned, by using this strategy there is a risk of contamination of the control group potentially affecting the outcome measures positively making it more difficult to detect an effect of CC. However, we assume that the individual randomization will enhance the GP's referrals to the project. Instead of comparing CC to TAU we will avoid contamination, by making the contamination an "add on" to the control group. Thus, the "add on" will consist of an offer to the GPs to consult the Collabri Flex team when needed (consultation liaison).

The randomization will take place after the participant has been assessed eligible to participate. The care manager, psychiatrist or an administrative staff member will contact Open Randomize, which is an external web based randomization provider who will perform the randomization. The randomization in both studies will be stratified for former treatment and in the anxiety study there will also be stratified for anxiety disorder. After randomization the care manager will contact the patient in order to tell which group they have been randomized to.

In the Collabri Flex study participating GPs are randomized according to detection method. This will be done in order to complete the depression detection study.

### ***Blinding***

In the Collabri Flex studies it is not possible to ensure blinding of the patient and GP. Researchers will be blinded to allocation if they collect data. If the blinding should be broken, the patient is referred to another researcher that will be blinded.

The intervention groups will be coded and anonymized (e.g. X and Y) so that researchers are blinded in the entire phase of analysis and when writing the conclusion.

Blinding of the patient diagnosis and possible MDI result will be maintained for the care manager during the MINI interview in order to ensure that the evaluation of diagnosis is not affected by the GPs referral diagnosis. This is especially relevant for the depression detection study. There is no technical solution available that can help ensure the blinding, but the care manager is instructed in not to activate a document with the diagnoses and MDI results until after the MINI diagnostic interview has been conducted.

### ***Outcome measures and other registration***

In Collabri Flex anxiety study the primary outcome will be Beck Anxiety Inventory BAI (25)

In Collabri Flex depression study the primary outcome will be Beck Depression Inventory BDI (26)

*Secondary outcomes for the Collabri Flex study on anxiety:*

- Self-reported degree of depression measured by the Beck Depression Inventory (BDI) (26) at 6 months.

- Self-reported psychological stress measured by the Symptom Checklist (SCL-92) (27) at 6 months.
- Self-reported functional impairment measured using the Sheehan Disability Scale (SDS) (28) at 6 months.

*Secondary outcomes for the Collabri Flex study on depression:*

- Self-reported degree of anxiety measured by the Beck Anxiety Inventory (BAI) (25) at 6 months.
- Self-reported psychological stress measured by the Symptom Checklist (SCL-92) (27) at 6 months.
- Self-reported functional impairment measured using the Sheehan Disability Scale (SDS) (28) at 6 months.

*Explorative outcomes for the Collabri Flex studies:*

- Self-reported quality of life measured by the WHO-5 (29) at 6 months.
- Self-reported side effects measured by PRISE (30) at 6 months.
- Sick leave obtained from the DREAM database at 6 months. If there is a follow-up at three years; early retirement due to anxiety or depression also obtained from the DREAM database.
- Self-reported self-efficacy measured with the IPQ-R scale (personal control) and two subscales from the Chronic Disease Self-Efficacy Scales (SECD-32); Obtain Help from Community, Family, Friends Scale and Control/Manage Depression Scale at 6 months.
- Self-reported health-related quality of life measured by the EQ-5D (31) at 6 months.

*Primary outcome for the depression detection study:*

- Positive predictive value of referral diagnosis in two different detection settings.

**Other registration**

*Safety measurements*

Safety measurements conducted through interviews will be collected at baseline. Register data will be collected at 6 months follow-up.

- Self-reported anxiety and depression symptoms measured by the BAI and BDI (25,26)
- Suicidal ideation measured by the questions concerning suicidality from the MINI interview (24). Obtained through structured interview with care manager
- Death (natural, accident, suicide, homicide/violence or unknown). Obtained from the Cause of Death Register
- Life threatening conditions for reasons other than suicide attempts. Obtained from the national patient register (LPR in Danish)
- Number of somatic outpatient services, admissions and inpatient days. Obtained from the national patient register (LPR)
- Number of psychiatric outpatient services, admissions and inpatient days. Obtained from the national patient register (LPR)

- Number of sick leave days. Obtained from the DREAM database

#### *Baseline registration*

At baseline the following will also be registered: Personality disorder measured by the Standardized Assessment of Personality: Abbreviated Scale (SAPAS) (32). ADHD-symptoms (Adult Self-Report Scale, ASRS v1.1) (44).

#### *6 months follow up*

##### *Recovery*

Patients will assess whether they felt supported in their recovery by their health care provider at 6 months. The INSPIRE questionnaire (33) will be used to assess this.

##### *Patient satisfaction*

Self-reported satisfaction with the treatment will be measured through the CSQ-8 questionnaire (34) together with project specific questions at 6 months.

##### *Depression detection study*

In the standard detection group: Positive and negative depression results from MDI carried out by the GP and MINI carried out by the research assistant in order to calculate the positive predictive value of diagnosis.

In the case-finding group: Positive and negative depression results from MDI and MINI in order to calculate the positive predictive value of diagnosis and the sensitivity, specificity and negative predictive value of diagnosis.

##### *Long term follow up*

If founding can be sourced or identified the patients will be contacted up to 10 years after treatment in order to participate in a long term follow-up assessment, or assessments will be made through registers.

#### ***Adherence to the Collabri Flex model***

To ensure the internal quality of the Collabri Flex intervention, an evaluation (fidelity measurement) will be carried out after 6 months with at least one more during the project. The fidelity measurement ensures that the intervention will be carried out according to the description of the Collabri Flex model. On the basis of the assessments, an action plan will be developed, if needed, in order to improve the implementation.

#### ***Data Collection***

The data for the Collabri Flex studies will consist of interviewer based data, register data and self-reported data (see the table below). Self-reported data will be completed electronically, but it is also possible for patients to get a paper version.

Services from the social- and health care system will be collected through databases as e.g. the DREAM database and the National Patient Register (in Danish LPR) as well as registers in chosen municipalities. Services in relation to collaborative care and consultation liaison will be registered by the care manager and psychiatrists/psychologists with psychiatric training and via the GPs.

## List of patient specific data to be collected

		Collabri Flex		
	Data collection method	Inclusion	Baseline	6 months
Collaborative care			↔	
Consultation liaison			↔	
MDI (screening tool for depression)	GP based	X		
MINI (according to DSM diagnoses + questions allowing to also access according to ICD10)	Interviewer based	X		
Self-efficacy	Self-reported		X	X
ASRS	Interviewer based	X		
SAPAS	Interviewer based	X		
SDS	Self-reported		X	X
BDI/BAI	Self-reported		X	X
WHO-5	Self-reported		X	X
PRISE	Self-reported		X	X
EQ-5D-3L	Self-reported		X	X
SCL-92	Self-reported		X	X
CSQ-8 (client satisfaction) + project developed questionnaire and LUP-questions	Self-reported			X
Suicidality obtained through the questions from the MINI interview	Interviewer based	X		
INSPIRE	Self-reported			X
Death	Register			X
Life-threatening conditions	Register			X

Somatic outpatient services, admissions and inpatient days	Register			X
Psychiatric outpatient services, admissions and inpatient days	Register			X
Number of sick leave days	Register			X
Use of social services and home services from chosen municipalities	Register			X
Medicine use	Register			X
Former treatment	Register/self-reported	X		X
Employment	Register			X
Educational level	Register			X
Marital status, sex and age	Register			X
Somatic co-morbidity	Register			X

### ***Procedure for visitation of participants to the project***

The procedure for visitation in the Collabri Flex study is described below. This will also describe the procedure for collecting informed consent.

1. The GP enrolled in the study detect the patient according to randomization allocation (see figure 2):
  - Patients who meet the inclusion- and exclusion criteria and have been detected with depression through standard detection will be offered to participate in the Collabri Flex study for depression with the embedded detection study.
  - Patients who meet the inclusion- and exclusion criteria and have been detected with depression through case-finding (GPs assess they have a depression using MDI to guide them, but both patients with MDI positive and MDI negative scores can be referred) will be offered to participate in the Collabri Flex study for depression with the embedded detection study.
  - Patients who meet the inclusion- and exclusion criteria and at case-finding have a MDI negative score which the GP rely on (the patient will not be given a depression diagnosis) will be offered to participate in the detection study only. If the MINI is positive, and confirmed by a psychiatrist, the patient will be offered to participate in the Collabri Flex study for depression or anxiety. However, the GP must agree on a depression or anxiety diagnosis in order for the patient to participate.

- Patients with anxiety who meet the inclusion- and exclusion criteria will be offered to participate in the Collabri Flex study for anxiety.
2. According to the above mentioned characteristics the patients will be asked to participate in a. the depression detection study, b. the Collabri Flex depression study with the embedded detection study or c. the Collabri flex anxiety study.
    - At a consultation, written information about the study is given to the patient by the GP or by a Collabri Flex staff member and oral information about the project is provided on basis of the written material. Patients who are only offered to participate in the depression detection study will only receive information about this and will not be randomized according to intervention.
    - If the information is given by the Collabri Flex staff, the GP obtains oral consent from the patient that a Collabri Flex staff member can make contact by telephone or in person in order to provide information.
    - The GP or the Collabri Flex staff member providing information will make sure that the information can be given without interruptions and that there is time for the patient to ask questions. The possibility for the patient to bring a person (e.g. friend or family) for personal support at the information meeting will be stressed to the patient. The possibility of time for reflection of at least 24 hours will also be stressed to the patient as well as the possibility of discussing the project with a family member or friend before the patient decides to participate.
    - If the patient would like an assessor to sit in on the information meeting, a project assistant who has a substantial knowledge about the project can provide information by telephone or in person.
    - The patient is also provided with a number to call to get additional information about the study.
  3. If the patient shows interest in the project (either the depression detection study or the Collabri Flex studies, the person providing information obtains oral consent from the patient that a care manager can make contact in order to conduct a diagnostic interview (MINI interview).
  4. The GP initiates relevant treatment.
  5. The care manager contacts the possible participant and schedules a time for conducting a MINI interview. The patient will be asked to fill out the online baseline questionnaire before the interview.
    - The care manager makes sure that the interview can proceed without interruptions, and emphasizes to the patients that they cannot tell which diagnosis their GP has given them (because of the detection study).
    - If the patient meets the inclusion criteria and not the exclusion criteria, a consent form (including a copy to be obtained by the patient) is signed by the patient.
    - In the expected few cases where the detection study reveals a depression based on the MINI interview even though the MDI was negative, a psychiatrist in the project will contact the GP in order to discuss the diagnosis. If there is

still discrepancy between diagnoses the patient will be informed and advised to make an appointment with the GP again. At the new consultation the patient will be asked to participate in the one of the Collabri Flex studies if the inclusion- and exclusion criteria are met.

- If the MINI diagnosis is inconsistent with the GP diagnosis, the research assistant consults a psychiatrist in the Collabri Flex team, who contacts the GP to ensure the diagnosis is correct. The patient will be informed of the outcome.
- The GPs will be informed about the MINI result

6. If the patient meets the inclusion criteria and not the exclusion criteria and has filled out the baseline questionnaire, the randomization will take place. The care manager will contact the patient in order to inform the patient about the result.

*Patients who have been diagnosed with depression:*

- Will be asked to participate in the Collabri Flex study for depression with the embedded detection study and will receive information and a consent form about this.

*Patients who have been screened with the MDI tool but have not been diagnosed with depression:*

- Will be asked to participate in the depression detection study and will receive information and a consent form about this.

*Patients who have been diagnosed with one of the three anxiety diagnoses:*

- Will be asked to participate in the Collabri Flex study on anxiety and will receive information and a consent form about this.

### **5.3 Statistical considerations**

#### ***Sample size calculation***

*The Collabri Flex depression study*

A recent Cochrane review on consultation liaison in primary care for people with mental disorders reported no change in depression symptoms, although it found an improvement in mental health with consultation liaison (18). The quality of the findings was low. Thus, we use the same figures to calculate the sample size as in the Collabri study.

The primary outcome will be Beck Depression Inventory (BDI) (26). Clinical relevant treatment response at group level is defined as a difference in degree of depression measured by BDI of 4 points (35,36). There are no surveys carried out in Denmark, which can contribute to the estimation of the standard deviation (SD) for BDI. However, according to international surveys the SD for BDI can be set at 11 (35,37-39).

A sample-size calculation based on the above figures shows that 240 participants should be included for depression in order to be able to reject the null-hypothesis that the intervention group and the consultation liaison group have improved similarly in terms of symptoms with a power of 0.8 and a significance level of 0.05.

### *The depression detection study*

On the basis of a study carried out by Michell et al. (9) it is estimated that the positive predictive value with standard detection is 45 %. A clinical meaningful and possible increase in the number is estimated to be 60 % (10). On this basis, the material size calculation shows that 480 individuals should be included in order to be able to reject the nul-hypothesis that the intervention group and the control group improve similarly in terms of symptoms, with a power of 0.8 and a significance level of 0.05. We want to perform the following comparison: standard identification vs. case-finding. Using case-finding, it is conservatively estimated that only 60 % of those who are screened has a depression (10). Thus, up to 400 individuals should be screened in order to include 240 persons (480/2).

As of primo April 2016, 290 patients have been included in the detection study in Collabri. By including an additional 240 patients in the Collabri Flex study, up to 530 patients will be included in the detection study.

### *The Collabri Flex anxiety study*

There is as far as we know, no studies investigating consultation liaison for anxiety disorders specifically, however a recent Cochrane review on consultation liaison in primary care for people with mental disorders reported no change in depression symptoms, although it found an improvement in mental health with consultation liaison (18). The quality of the findings was low. Thus, we use the same figures to calculate the sample size as in the Collabri study.

The primary outcome will be Beck Anxiety Inventory (BAI) (25). Clinical relevant treatment response at group level is defined as a difference in degree of anxiety measured by the Beck Anxiety Inventory (BAI) of 4 points. There are no surveys carried out in Denmark, which can contribute to the estimation of the standard deviation (SD) for BAI. However, according to international surveys the SD for BAI can be set at 12 (40-43).

Based on the above figures for anxiety, the sample-size-calculation shows that 284 individuals should be included in the Collabri anxiety study in order to reject the nul-hypothesis that the intervention group and the consultation liaison have improved similarly in terms of anxiety symptoms with a power of 0.8 and a significance level of 0.05.

### ***Dimensioning***

We have used numbers from the Collabri Study in order to dimensioning the Collabri Flex study. So far 80 % of the referrals have been included in the study. This means that we need 300 referrals with depression and 355 with anxiety, in total 655 patients should be referred in order to include 524 patients that we need in the Collabri Flex studies. Eight care managers can give treatment to maximum 750 patients per year. In the Collabri study 46 GPs are participating. We need to recruit 40 GPs to the Collabri Flex studies if they all refer 1.5 participants per month, and that is possible based on the figures in the Collabri studies. Thus it will take  $655/(40 \times 1,5) = 11$  months to include 524 patients.

### ***Statistical methods***

The Collabri Flex studies will be conducted according to the statistical principle "intention-to-treat", which means that once a person is included in the project, he/she stays in the study

population to be followed, regardless of whether the person later meets the exclusion criteria.

The primary outcome measure for the Collabri Flex study on anxiety is the continuous measurement BAI after 6 months and for depression it is BDI after 6 months. The analysis of differences between groups will be conducted using t-tests and variance analysis. Repeated measures techniques may also be applied. Missing data is a potential source of bias and therefore the operation of multiple imputations can be used to address the issue of missing values.

In the depression detection study the positive predictive value will be calculated for both groups and compared.

## **6. Organization in Project Collabri Flex**

### ***Treatment***

The patient treatment will preferably be carried out in general practitioner clinics or in local community settings such as local authority health centers. However, this will also depend on the individual agreement made with the GP. The care manager will be working in the clinic or in the local community but employed and managed by the secondary care system. In the Capital Region of Denmark 8 care managers will be employed as well as 1 1/2 psychiatrists or psychologists specialized in psychiatry. The psychiatrists/psychologists and care managers will be based at the Psychiatric Centers in Copenhagen and will work jointly with the GPs in the project.

### ***Research and publications***

The Collabri Flex study protocols for anxiety and depression will be published at ClinicalTrials.gov. Results from the 6 months follow up will be published in international journals as well as in 1-2 Ph.d. studies. Positive, negative and inconclusive results will be published. Also, a Health Technology Assessment (in Danish MTV) with data from the Collabri and Collabri Flex studies will be published. A short resumé of the results will be made for interested to read, including participants in the project.

### ***Management***

The project is led by a steering group. The aim of the steering group is to ensure the progress of the research project as a whole and in the respective organisations. In the Capital Region of Denmark a lead project manager (Rikke Vinding) will ensure the general management of the project together with a project manager in charge of implementation of the intervention (Nicole Rosenberg) and a project manager in charge of the research project (Lene Falgaard Epløv). To ensure the administration of the project, 1-2 staff members will support the project managers.

## 7. Ethical considerations

The trials will be conducted in compliance with this protocol, the Helsinki Declaration in its latest version, good clinical practice guidelines and follow the rules for informed consent. No substantial deviation from the protocol will be implemented without the prior review and approval of the regulatory authorities.

Personally identifiable information collected in the study will be treated according to the Danish law "Lov om behandling af personoplysninger" and the upcoming (May 2018) "Persondataforordningen". Potential other collected data (in the form of paper, recorded interviews, transcriptions, observation notes and video recordings etc.) will be stored as confidential in a secure cupboard. Data that is stored electronically will be secured according to the relevant regulations for data storage. The project will also be carried out in accordance with the applicable guidelines for social science research ethics. When communicating the results, the participating persons and clinics will be made anonymous.

Prior to commencement the project will be evaluated by the scientific ethics committee in the Capital Region of Denmark, and it has been approved by the regional Data Protection Agency (Datatilsynet). . The project will be registered on the web site ClinicalTrials.gov.

. .The participants' consent has to be voluntary and informed, and given both verbally and written. Written declarations of consent will be dated and signed and stored electronically. The participants will receive the original form On the consent form, there is no option for the patient to choose to be informed if any significant information about the patient's health condition is revealed. This is not considered relevant, as the data collected at baseline and follow up will be self-reported, and thus known to the patient. The participants will be informed of their rights to exit the study at any point if they wish and without consequences for their future treatment.

Previous international experience does not indicate that the intervention provided by the Collabri Flex model is associated with any disadvantages or side effects for the patients. In order to minimize the possible risks of discomfort, the research interview will be conducted in a flexible manner and interspersed with breaks if necessary. The extent of the interview is estimated to take 1-2 hours and questionnaires will take a maximum of an hour to complete. It will be possible to fill out questionnaires in stages. If the participants experience the interview as stressful or uncomfortable, the interview can be conducted in stages or they can without further ado step out of the trial, without it affecting their ability to receive current or future treatment.

The care managers in Collabri Flex all have experience of working in mental health services. The GPs or care managers that inform the patients about the trial will be given sufficient information to enable them to inform patients adequately. This is provided via a training program before commencement of the project and distribution of written information material.

The results of the Collabri Flex studies can contribute to improving the care and treatment for patients with anxiety and depression in primary care.

### ***Participant discontinuation and withdrawal***

If participants wish to exit the trial, there are two options:

- The participant no longer wants to participate in the intervention, but would like to participate in the research including follow up at 6 months. All information that describes the patient at the time of inclusion, interviews and questionnaires will be used in analyses.
- The participant no longer wants to participate in the intervention, but would like to participate in the research. However, the participant does not want to fill out questionnaires after 6 months. All information that describes the patient at the time of inclusion, interviews and questionnaires will be used in analyses.

There are currently no known circumstances that can lead to exclusion from further participation in the study once a participant is included. If such circumstances that conditions exclusion comes to our knowledge, the participant will be notified. It should be noted that referral to the secondary care system (i.e. because of a deterioration of depression, increased risk of suicide or psychotic condition) is a part of the model that is being tested, which means that participants who are being referred are still included in the study and followed up unless they choose to exit the project.

### ***Detection considerations***

Considering the potential harms of incorrect detection of depression in primary care, a quality randomized controlled trial investigating the effect of a potentially better detection of depression is important. In the study, we try to minimize the risk and potential harm of a false positive result by using a diagnostic test (MINI) after a positive MDI screening result. Also, if the GP suspects depression although the screening with MDI is negative, the GP can still refer the patient to the study.

## **8. Financial support**

Project Collabri Flex is part of a larger study called Collabri which is financed by a grant from the Danish Ministry of Health "Pulje til styrket samarbejde mellem behandlingspsykiatrien og almen praksis (shared care)". The amount granted for the Capital Region of Denmark is 30.046.409 Dkr. If further financial support is received the Scientific Committee will be notified and the participant information will be updated.

The general practitioners that participate in the project will receive remuneration according to a local agreement between the Capital Region of Denmark and the Organisation of General Practitioners in Denmark (in Danish PLO). Project manager in charge of the research project, Lene Falgaard Eplov, who is employed in The Mental health services in the Capital Region of Denmark and attached to the Mental Health Center Copenhagen, has together with an expert group taken initiative to the project.

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