Optimising treatment for patients with depressive episodes in General Practice through algorithm-based treatment

A Randomised open-label Controlled Trial

Study Protocol

Psychiatry

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Introduction

Depression is a widespread mental health disorder estimated to affect around 3.8% of the global, adult population to various degrees (1). In Denmark, data suggest an overall prevalence of depression of 4.1% with moderate to severe depression comprising 3% (2).

Major depression is linked to various negative health outcomes such as diminished quality of life and medical morbidity and mortality (3, 4). In 2014, depression was ranked by The World Health Organization (WHO) as the fourth leading cause of disability worldwide, and it was, at the time, estimated that by 2020, depression would be the second leading cause of disability globally (3). This was later supported by a large study in 2021, The Global Burden of Diseases, Injuries, and Risk Factors Study 2021(GBD 2021) (3, 5). The study aimed to quantify health loss and the burden of disease across places and over time, and the analysis estimated "years lived with disability" (YLDs) for 371 diseases and injuries in 204 countries from 1990 to 2021. Among the top three causes of YLDs (across all ages and sexes combined), depressive disorders were the second leading cause with approximately 56 million YLDs (5). They observed the largest increase in age-standardised YLD rates, between 2010 and 2021, in depressive disorders, as well as diabetes, anxiety disorders, drug use disorders and neonatal disorders (5).

Furthermore, it is well established that depression can lead to symptoms that impact the individual's ability to perform in the workplace, such as lack of concentration, fatigue, decreased motivation and job performance, but also diminished sense of self-worth and confidence (6). The cost of depression is not only on the level of the individual, but also on a societal level (7). It has been estimated that, in the United States alone, the total economic cost of depression in 2000 was over US$83 billion, with workplace costs (i.e., absenteeism and presenteeism) accounting for US$51.5 billion of the total (6). By 2017, the total cost of depression in the USA had risen to an estimated US$210 billion (8). From both an economic and an ethical point of view, the need for optimised and effective treatment approaches for depression is crucial.

In Denmark, treatment for depression most often consists of medication, psychotherapy, or a combination of both, and the treatment is facilitated through four main settings: general practitioners, psychologists, psychiatrists in private practice, or hospital-based psychiatry.

General practitioners act as gatekeepers to hospital-based psychiatry, meaning that a large proportion of individuals experiencing a depressive episode are primarily seen and treated in general practice.

Studies from general practice have shown that, on average, about 10% of all contacts with general practitioners can be attributed to depressive disorders, and that depression is highly underdiagnosed in general practice, with fewer than half of the cases being identified (9).

Treatment of depressive disorder is challenging, with up to 40% of patients not responding to the initial medication prescribed, and often several trials of different treatments are required to achieve symptomatic remission (7, 10-12). Remission often occurs within four to six weeks after treatment has been initiated. However, there is often a delay between recognising that a treatment is ineffective and making changes to the treatment strategy, thereby prolonging the overall time to remission and resulting in longer duration of depressive symptoms for the patient (7). These findings stress the importance of accurate and timely diagnosis and treatment of individuals with depression.

Algorithm-based treatment offers a means of reducing this impediment, resulting in more efficient treatment for depression. Several studies have shown that algorithm-based treatment of depressive episodes is more effective than treatment as usual (TAU), by reducing time to remission, entailing fewer changes in medication and producing better outcomes as well as a greater reduction in symptoms (4, 7, 10, 12-14).

Results from the *Randomized Controlled Multicentre German Algorithm Project3 Trial* (GAP3) showed a significantly reduced time to remission for patients with depression in the group randomised to algorithm-based treatment, compared with the group randomised to treatment as usual (TAU) (10). Additionally, a structured algorithm-guided treatment was associated with fewer medication changes to achieve remission compared to the TAU group (10).

The Texas Medication Algorithm Project (TMAP) found that an algorithm-based approach to the treatment of major depressive disorder (MDD) was associated with a statistically and clinically better outcome for participants, in terms of the primary and most of the secondary efficacy assessments, compared with patients in the TAU group (15).

An Algorithm-based treatment approach consists of key elements, such as strategies and treatment steps, that determine which treatments to use, when to use them, how to implement

them and in which order. Another essential element is the use of critical decision points (CDPs), at which time the response to the current treatment is assessed. This assessment leads to specific, predefined adjustments to the current treatment (e.g. to continue the current treatment or change treatment choice according to a predetermined plan) applying preset "if-then-rules", meaning that "if X happens, then Y will happen" (13). Most often, measurement-based care is implemented to assess treatment effects, meaning that a symptom, outcome, or process measure is administered routinely, e.g. a rating scale (16, 17). The structured treatment plan will also define the interval between the critical decision points, thereby determining how long a specific treatment is maintained and when to revise it.
A systematic approach to treatment of depression could enhance patient outcomes and improve the quality of care, while also ensuring personalised care and accommodating individual differences among patients, potentially leading to a decrease in the costs of health care (14).

As previously mentioned, treatment for depression is most often based on either pharmacological treatment, psychotherapy — often facilitated by a psychologist — or a combination of both. Medication plays a crucial role in treating depression, and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressants that have demonstrated efficacy in alleviating depressive symptoms and are generally well tolerated (8). These are often prescribed by general practitioners as a first-line treatment for depression.
Collaboration between general practitioners and psychologists is essential in providing comprehensive care for individuals with depression. In general practice, patients can be referred to a psychologist for psychotherapy to address underlying psychological factors and to develop coping strategies.
One of the most well-documented types of psychological interventions is cognitive behavioural therapy (CBT), which is recommended in most treatment guidelines (18). Previous studies have shown a significant efficacy when it comes to psychological interventions such as cognitive behavioural therapy (CBT) in the treatment of depression. However, a recent meta-analysis including 409 trials with over 52.000 patients, examined the effect and efficacy of CBT compared with other psychotherapies and pharmacotherapies (18). They concluded that the

efficacy of CBT for depression is documented across different formats, age groups, target groups, and settings, but that the superiority of CBT over other psychotherapies for depression did not emerge clearly from the analysis. On the other hand, the findings suggested that CBT was as effective as pharmacotherapy in the short term and more effective in the long term.
Another meta-analysis investigated the relative efficacy of psychotherapy against combined therapy (i.e. psychotherapy with pharmacotherapy) (19). Combined therapy was more efficacious than psychotherapy alone, however, the results depended on the severity and chronicity of the depressive disorder. No differences in the outcome were observed when comparing mild and moderate non-chronic depressive episodes, indicating that psychotherapy alone had the equivalent efficacy as psychotherapy and pharmacotherapy combined in these patients.

Studies on algorithm-based treatment and its efficacy have primarily focused on either hospitalised patients (inpatients) or those receiving treatment in an outpatient clinic (outpatients). In Denmark, most individuals with depressive episodes are treated in general practice and not as in- or outpatients.
Since studies show a significantly better outcome compared to treatment as usual, it is plausible to think that this also applies to patients treated for depression in general practice. If proven to be true, the results of this study could potentially lead to changes in the management and treatment of patients with depressive disorder in general practice, resulting in a more efficient treatment strategy with several benefits — both for the individual patient and from a societal perspective — including improved quality of life, reduced morbidity and mortality, and lower economic costs for society in general.
Additionally, the study aims to identify, through direct comparison, whether treatment provided by a general practitioner, both TAU and algorithm-based, is superior to treatment as usual (psychotherapy in the form of CBT) provided by a psychologist.
To our knowledge, no such study has been conducted to date.

Aim of the study

The purpose of this study is to investigate the effectiveness of three different treatment pathways for moderate depressive episodes as part of unipolar depressive disorder, through a three-armed, open-label randomised controlled study. Participants will be allocated to one of the three groups in a 1:1:1 ratio.

The three treatment pathways will be as following:

1. Treatment as usual by a general practitioner (TAU-GP).
2. Treatment as usual by a psychologist (TAU-P).
3. An algorithm-based pharmacological treatment by a general practitioner (ALGO).

The primary outcome of the study is to examine whether there is a difference between the three groups. It will be measured by using a F-test from baseline to end of study at 12 weeks, using the Hamilton Depression Scale, 6 item version (HAM-D6).

Additionally, several secondary outcomes will be explored, e.g. the difference in differences (DID) between TAU-GP vs. ALGO, TAU-GP vs. TAU-P and TAU-P vs. ALGO.

The hypothesis is that a tailored algorithm-based treatment regarding patients with depression, treated in general practice, is more effective than treatment as usual (TAU), whether provided by general practitioners (GPs) or psychologists.

Furthermore, a qualitative study will be conducted to investigate the impact of the assigned treatment pathway from the participant's perspectives.

Methods and Material

Study design

To address the aim of the study, an open-label, randomised controlled trial (RCT) will be conducted, as well as a qualitative interview.

Participants will be allocated in a 1:1:1 ratio to either: treatment as usual by a general practitioner (TAU-GP), treatment as usual by a psychologist (TAU-P) in the form of cognitive

behavioural therapy (CBT), or an algorithm-based medical treatment by a general practitioner (ALGO). The duration of the study is up to 14 weeks, with 12 weeks of treatment and up to 2 weeks between screening and baseline. Participants will be evaluated at baseline, 4 weeks, 8 weeks and 12 weeks after baseline, respectively. For all 3 arms, an external rater will carry out the Hamilton Depression Rating Scale (HAM-D) screening.

The study design and duration are illustrated in Figure 1.

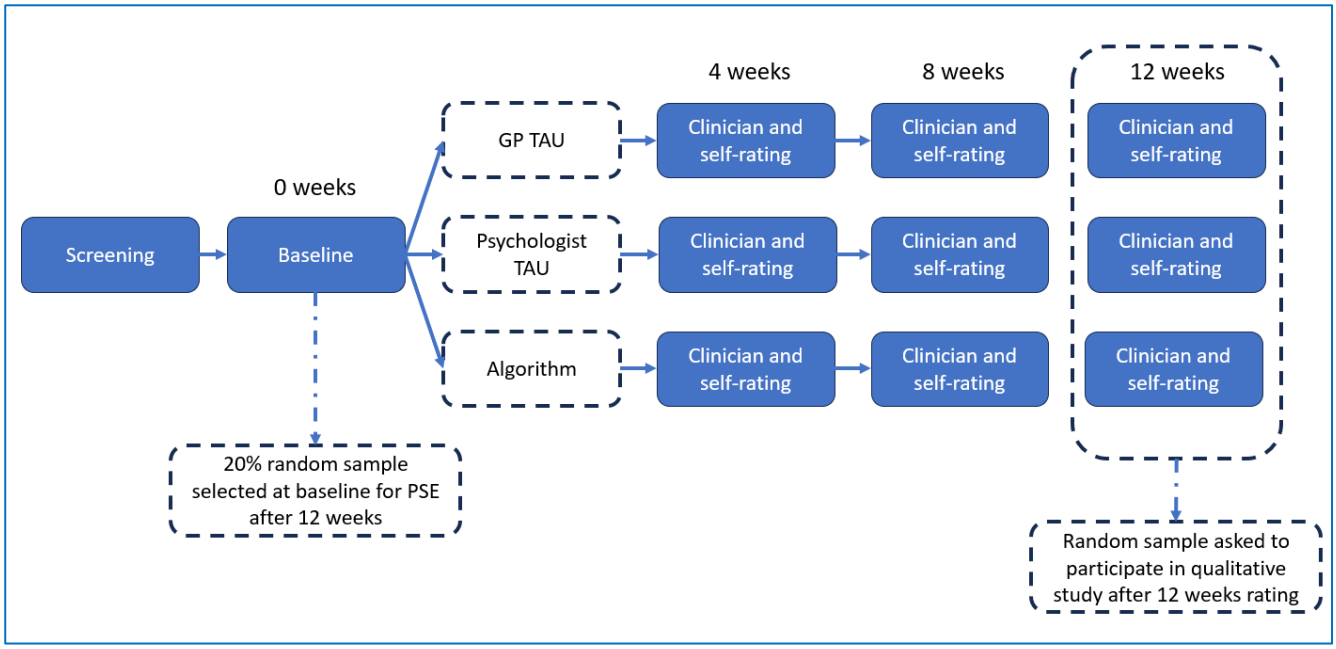

Figure 1: Study Design (GP: General practitioner. TAU: Treatment as usual. PSE: Present State Examination).

Study intervention

In the two treatment as usual arms (TAU-GP and TAU-P), the choice of treatment and the frequency of patient consultations are at the discretion of the general practitioner (GP) and the psychologist. However, the psychologist will utilize cognitive behavioural therapy (CBT) as part of the treatment approach.

In the TAU-GP arm, the GP's can refer patients for psychotherapy, if deemed necessary, after initiation of medication. In the TAU-P arm, the psychologist may request initiation of medication through the general practitioner after psychotherapy, in the form of cognitive behavioural therapy (CBT), has been initiated.

For the algorithm-based treatment arm (ALGO), the GP drafts an individual, algorithm-guided stepped-care plan that merges measurement-based care with pre-set critical decision points (see figure 2). Every 2–4 weeks, validated symptom scores and side-effects are reviewed against evidence-based thresholds. Symptom scale score results are conveyed as “if-then” rules, triggering the next action, e.g. dose optimisation, switch, augmentation, or psychologist referral, as defined at baseline. These structured checkpoints prevent therapeutic drift and ensure the treatment keeps advancing until meaningful improvement is achieved, while still leaving room for clinical judgement and patient preference. The plan is based on the patient’s symptoms, previous treatment history, current clinical guidelines, possible side effects to antidepressants and the general practitioner’s clinical assessment.

The choice of treatment will follow predetermined steps, and the algorithm will include critical decision points (CDPs) at weeks 4, 8 and 12, where treatment efficacy is assessed. This assessment will lead to specific and predetermined adjustments regarding the current treatment (e.g. to continue current treatment or to change choice of treatment from the predefined plan) and in relation to preset “if-then” rules.

As a result of lack of tolerability to the current treatment, an earlier switch to an alternative treatment will be possible. In such cases, the algorithm will continue from that point, with a new HAM-D6 measurement conducted four weeks later.

Figure 2 illustrates the baseline measurement of HAM-D6, followed by initial treatment, and subsequent HAM-D6 measurements and treatment decisions at weeks 4 and 8.

Figure 3 illustrates the patient’s course in the ALGO group, including consultations in general practice, where the GP follows the algorithm-based treatment strategy, and study visits with the investigator or study staff during which ratings are conducted.

Supportive consultations with the participant’s general practitioner will continue as part of the usual care and are available to participants in all three treatment arms. The protocol exclusively evaluates the defined pharmacological strategies; other clinical interventions, including supportive consultations in accordance with current guidelines, are not restricted by the study.

Additionally, following randomisation, a random sample of 20% of the participants from each of the three treatment arms will be invited to a semi-structured diagnostic interview using Present State Examination (PSE) to elucidate the diagnostic accuracy of the diagnosis of depression made by the GPs and to investigate further comorbidities. The participants will be selected at baseline, but the diagnostic interview will be carried out after end of study week 12. In figure 1, the selection of 20% of the participants is illustrated with a dashed box beneath baseline, including that the diagnostic interview (PSE) will be carried out after 12 weeks.

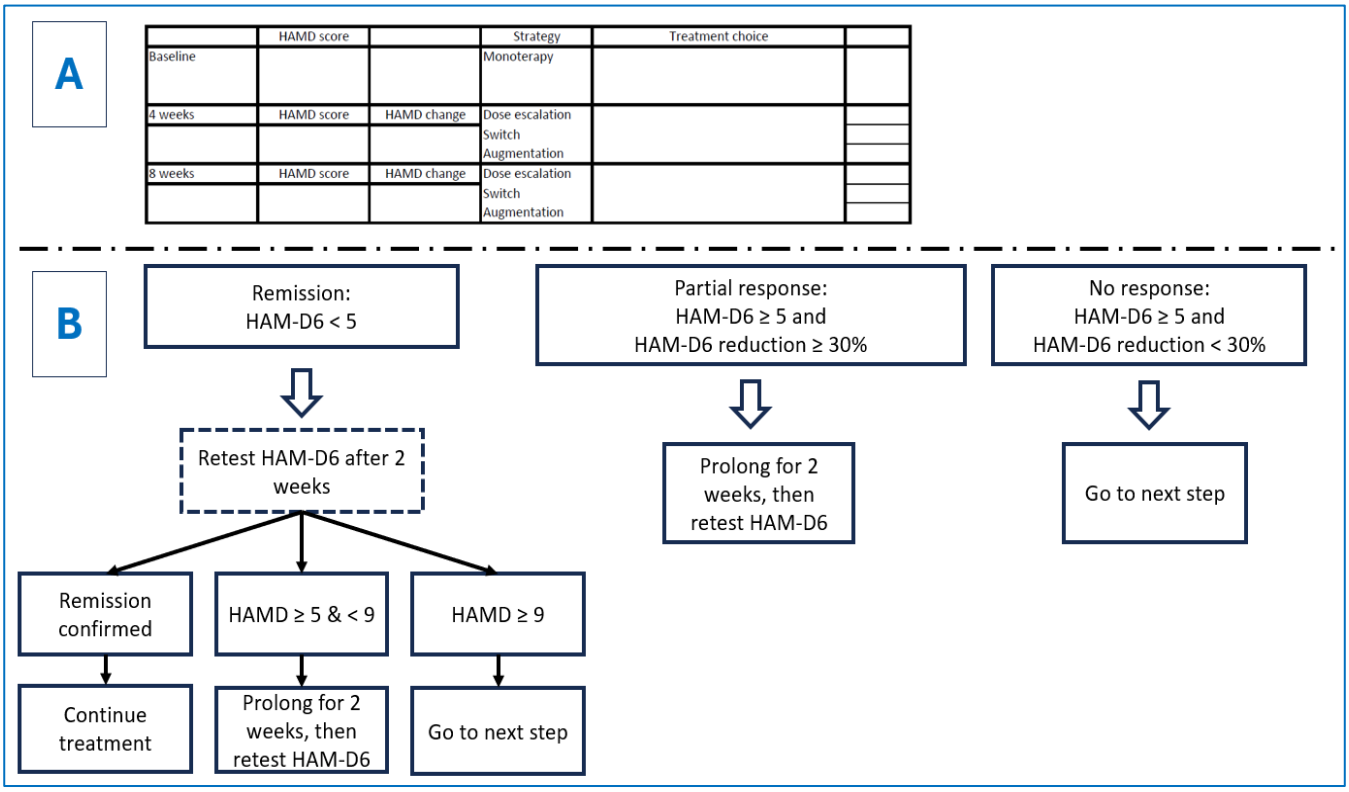

Figure 2: Treatment algorithm: A) Illustrates the measurements, treatment strategies, and critical decisions points. B) Visualises the steps used for each measured HAM-D6 score after baseline.

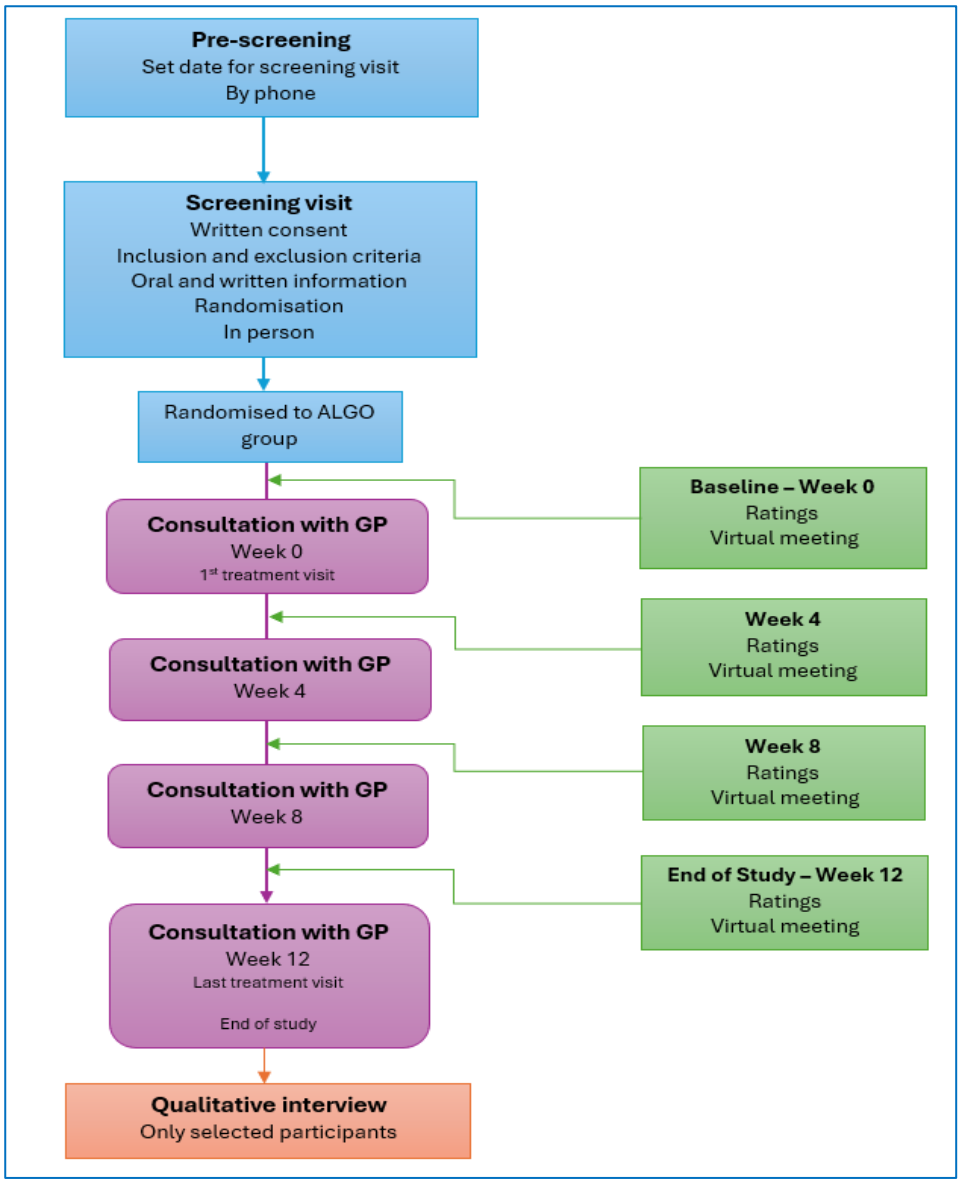

Figure 3: Patient's course in the ALGO group.

Randomisation

Patients will be allocated to one of the three arms by randomisation in a 1:1:1 ratio. At least 57 patients are required in each group, including an estimated dropout of 20%, to detect a clinically relevant difference as outlined in the Statistics section.

The randomisation sequence is coded by a single programmer with random block sizes of 3, 6 and 9 participants and with the randomisation sequence stored in REDCap (Research

Electronic Data Capture, Vanderbilt University), thus ensuring inaccessibility to all clinicians using the REDCap module for the randomisation of patients.

Measures and Outcomes

Modified intention-to-treat (mITT) population and Per Protocol (PP) populations

The modified intention-to-Treat (mITT) population encompasses all randomised participants with at least one post-baseline HAM-D6 rating. The endpoint of the study is 12 weeks.
For participants with premature endpoints, the latest endpoint available will be used with last-observation-carried-forward (LOCF).
The Per Protocol (PP) populations are defined as completers at week 4 (PP4), at week 8 (PP8), or at week 12 (PP12).

Primary outcome measure

The primary outcome measure is the Hamilton Rating Scale for Depression, 6 item version (HAM-D6), used as a continuous variable (20).
For all 3 arms an external rater will carry out the HAM-D6 screening.

Secondary outcome measures

The following instruments will be used to assess the treatment course:

- The Columbia-Suicide Severity Rating Scale (C-SSRS) (21).
- The Major Depression Inventory (MDI) (22).
- The Personal and Social Performance Scale (PSP) (23).
- The Danish Adult Reading Test (DART) (24).
- The Brief INSPIRE-O (25).

Primary outcome

The primary outcome of the study is the difference in HAM-D6 score from baseline to end of study at 12 weeks. It will be based on the mITT population.

Secondary outcomes

All secondary outcomes are based on the mITT population unless otherwise specified. The following secondary outcomes will be explored:

- The difference in differences (DID) in HAM-D6 score, from baseline to end of study, between participants in:
    1. TAU-GP and ALGO
    2. TAU-GP-and TAU-P
    3. TAU-P and ALGO
- The DID in C-SSRS score, from baseline to end of study, between participants in:
    1. TAU-GP and ALGO
    2. TAU-GP-and TAU-P
    3. TAU-P and ALGO
- The DID in MDI score, from baseline to end of study, between participants in:
    1. TAU-GP and ALGO
    2. TAU-GP-and TAU-P
    3. TAU-P and ALGO
- The DID in PSP score, from baseline to end of study, between participants in:
    1. TAU-GP and ALGO
    2. TAU-GP-and TAU-P
    3. TAU-P and ALGO
- The impact of the assigned treatment pathway from the participant's point of view and the participant's personal experience of recovery through a self-rating scale (Brief INSPIRE-O). This will also be done using the DID, from baseline to end of study, between participants in:
    1. TAU-GP and ALGO

2. TAU-GP-and TAU-P
3. TAU-P and ALGO

- The concordance between MDI and HAM-D6.
- Duration of sick leave after baseline (indicated in days) within the current depressive episode.
- A Per Protocol analysis at week 12 (PP12) will also be completed for all continuous secondary outcomes.
- A Per Protocol analysis at week 12 (PP12) will also be completed for the primary outcome.
- Between-group difference for adverse events and serious adverse events.
- Between-group difference for the ITT population in reasons for premature discontinuation, time to all-cause discontinuation

Demographic data

Several individual markers of treatment response will also be explored in the study.
The following areas will be assessed through direct questioning of the study participants:

- Age, sex and educational status.
- Duration of untreated depression.
- Age at first depressive episode.
- Psychiatric comorbidities (i.e. anxiety disorders, PTSD, OCD and personality disorders).
- Familial disposition for psychiatric disorders among first-degree relatives.
- Physical comorbidities (i.e. pain, cardiovascular disorders, diabetes and neurological disorders).
- Treatment history of depression.
- DART score at baseline.

Furthermore, individual characteristics of the participants will be examined. Specific patient traits could potentially guide future treatment decisions leading to enhanced treatment

outcomes, minimised side effects, and hopefully a reduction in the trial-and-error process, which is associated with finding the right treatment.

To explore the clinical utility of these individual characteristics, we aim to analyse how they are associated with treatment outcome in the context of the RCT, i.e. all three arms of the study.

Patient Population

Study population

Participants will include patients from general practice diagnosed with unipolar depressive disorder by a general practitioner, in which there is clinical uncertainty as to which of the initial treatments (medication or psychotherapy) would be most beneficial. Patients will be aged 18 to 65 at baseline.

Participants will be recruited from multiple general practices in the North Denmark Region by their general practitioner. 171 participants will be included with an expected dropout rate of 20%.

Symptomatic remission (i.e. remitters) is evaluated using the Hamilton Rating Scale for Depression, 6 item version (HAM-D6) and is defined as a score ≤ 5 (20). Symptomatic response (i.e. responders) is also evaluated using the HAM-D6 and if defined as a 50% reduction in the HAM-D6 score. For further details, see figure 2.

Inclusion criteria

1. The participant must be referred to the study with a diagnosis of unipolar depressive disorder, as judge by the GP.
2. Severity of the depressive episode corresponding to moderate depression, as judged by the GP.
3. Clinical uncertainty regarding which of the treatments, medication or psychotherapy, would be the better choice in the case concerned.
4. Age criteria: Participants must be at least 18 years old and no more than 65 years old at the time of randomisation.

5. The participant must be a patient in general practice.
6. Participants must be able to participate in virtual meetings (e.g. by phone or computer) and have e-Boks.
7. The participant must be willing to receive psychotherapy by a psychologist and/or medication.
8. Must have signed the document of informed consent.

Exclusion criteria

1. Misuse of substances that might influence the study, as judged by the investigator.
2. Difficulty in understanding the Danish language, as judged by the investigator.
3. A diagnosis of dementia.
4. Medical conditions that might interfere with the study outcome or safety, judged so by the investigator.
5. Pregnancy.
6. High risk of non-adherence at the investigator's discretion.
7. Suicidality: according to C-SSRS with a positive response to question 4 or 5 within the last three months or upon investigator's discretion.
8. No current medical or psychotherapy treatment initiated within the last 4 weeks prior to screening.

Discontinuation criteria

- Suicidality according to C-SSRS with a positive score to question 4 or 5 or upon the investigator's discretion.
- Severe somatic illness, as judged by the investigator.
- The patient wishes to stop participation and/or withdraws consent.
- The patient is unable to follow the treatment in one of the arms.
- Treatment will be terminated if the subject does not show up for two virtual meetings with the study staff or two meetings with the GP/psychologist, without cancelling, and

the study personnel are unable to get in contact with the participant. Attempts of contact are documented in the CRF.

Withdrawal and dropout

Withdrawal from the study will occur at the time when any of the discontinuation criterion are fulfilled, as judged by the investigator.

If possible, data regarding all outcome measures will be collected immediately or as soon as possible after the time of withdrawal. The primary outcome measure (HAM-D6) will have the highest priority. The primary reason for discontinuation will be recorded as well as the time of discontinuation. Subjects who have withdrawn will not be replaced.

If a study participant wishes to dropout, an interview regarding the reasons for dropping out will be offered to the patient concerned. The planned next rating session will be executed as soon as possible hereafter.

It is recommended that study participants discuss further treatment with the treating general practitioner responsible for their care.

Completers

Study participants will be defined as completers following the final visit at week 12 after baseline.

Recruitment and Information

Recruitment of study participants

Recruitment will solely take place from general practices in the North Denmark Region by general practitioners, and participants will be recruited from among their patients.

All eligible patients will be informed that participation in the study is voluntary and a refusal to participate will not affect their treatment in any way. Further, they are informed that, if choosing

to participate, they can withdraw their consent at any given time during the trial. This information will be given by the investigator.

When a general practitioner has found a patient eligible for inclusion into the study, the GP can refer the willing, potential participant to the investigator or study staff for further information regarding the study and for possible participation. An oral acceptance is obtained by the GP, permitting the investigator to contact the potential participant through telephone (pre-screening) to set up a time for the screening visit. The written information about the study will be sent prior to the screening visit but will be discussed during the visit regardless. Inclusion and screening are carried out by the investigator during a physical meeting (screening visit) with the participant. When informed consent has been acquired, baseline interview and ratings can commence. During the screening visit, the participants will receive both the informed consent form as well as oral and written information about the study.

Screening visits for eligibility in the trial as well as virtual meetings can be delegated to a research assistant if deemed competent by the investigator.

Oral information

The participants will receive oral information about the study in a personal meeting (screening visit) with the investigator or study staff. The oral information will be based on the written information and will be given in a language and level that is comprehensive for the participant. The meeting will be scheduled in a quiet office and the information will be delivered in an uninterrupted and calm environment. The participants will be able to ask questions regarding the study and participation.

Several matters concerning the study will be discussed, such as the study purpose and design, treatment options including the algorithm-based treatment, and advantages and disadvantages for the participants. Further, study discontinuation will be explained, and it will be emphasised that participation in the study is voluntary.

Participants are encouraged to bring a friend or next of kin to the information meeting.

If participants wish, they will be informed by letter about the results of the study, when analysed.

Consent declaration

Study participants will need to sign a consent form at the screening visit and before the first treatment visit. The declaration is in accordance with the recommendations of the Danish National Committee on Health Research Ethics (NVK).

The consent letter will be presented to the possible participant at the screening visit, and it will be up to the individual participant if the consent letter is signed immediately, or if the participant needs time to consider entering the study. The period of consideration will be at least 24 hours and no more than a week.

The consent declaration can be sent in advance before the screening visit, but the letter of consent will be discussed in a personal meeting with the investigator at screening.

Flowchart of Participant's Course

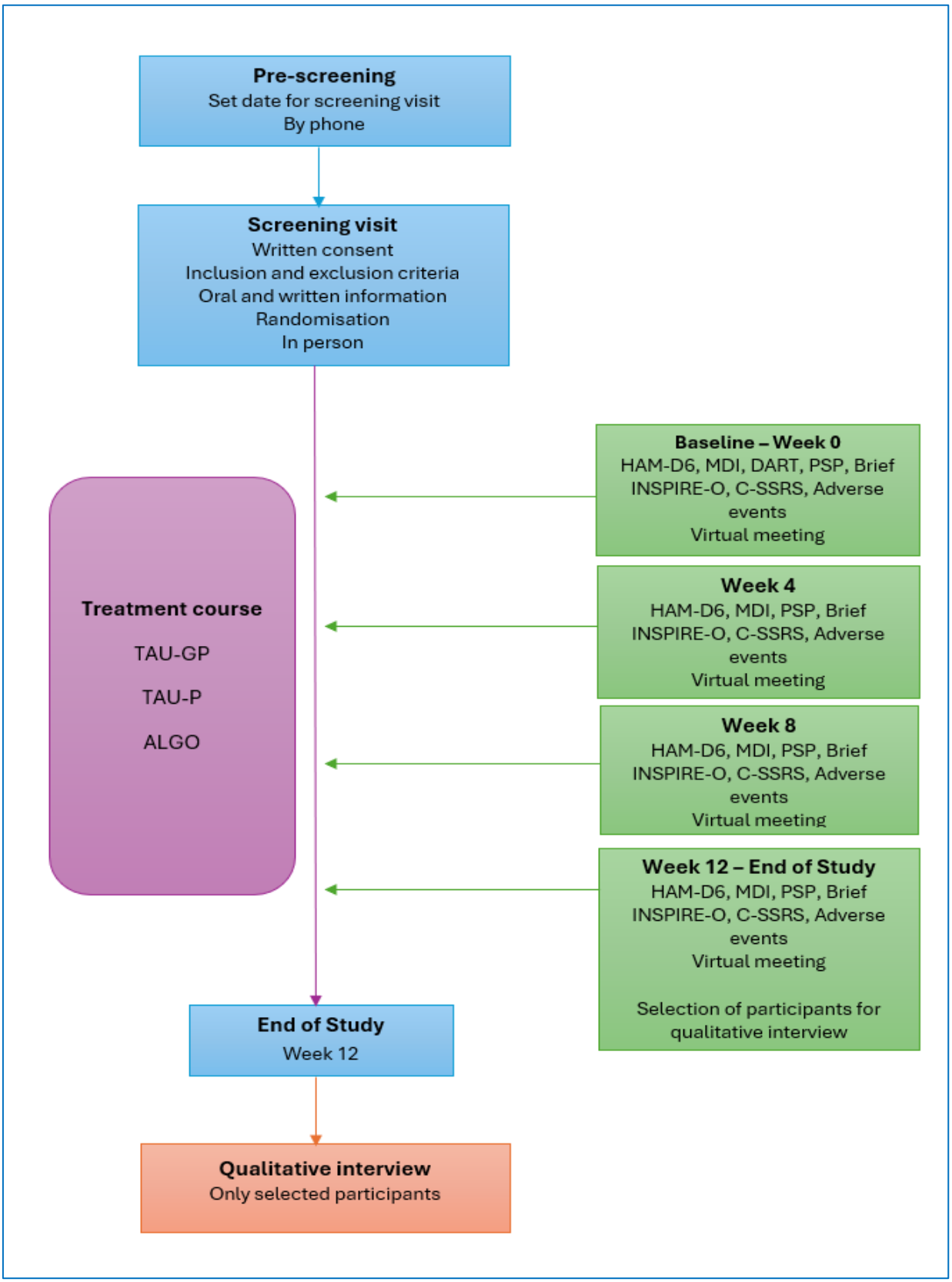

Table of Measurements

Week	**-2 to -1 Screening**	**0 Baseline**	**4**	**8**	**12 End of Study**	**Un-scheduled visit**
Meeting form	**In person**	**Virtual meeting**	**Virtual meeting**	**Virtual meeting**	**Virtual meeting**	**Virtual meeting**
Signed Consent Form	X					
Inclusion and exclusion criteria	X					
Oral + written information	X					
Randomisation	X					
Adverse events		X	X	X	X	X
Demographic data	X					
Rating Scales						
HAM-D6		X	X	X	X	X
C-SSRS	X	X	X	X	X	X
PSP		X	X	X	X	
DART		X				
PSE					X*	
Self-report forms						
MDI		X	X	X	X	
Brief INSPIRE-O		X	X	X	X	

HAM-D6: The Hamilton Depression Scale, item 6.

C-SSRS: The Columbia-Suicide Severity Rating Scale.

PSE: Present State Examination.

MDI: Major Depression Inventory.

PSP: The Personal and Social Performance Scale.

DART: The Danish Adult Reading Test.

*In person

All visits and phone calls are scheduled within the defined time frame +/- 3 days. Pre-screening is conducted by a phone call by the investigator or study staff. The written study information will be sent in advance of the screening visit, and if the patient prefers, the letter of consent will also be sent prior to screening. The screening visit is a physical meeting where oral and written information is presented, and written consent can be obtained. Should the patient wish to, they can have at least 24 hours and no more than a week to consider the consent form. A follow-up meeting will be scheduled.

If, during the screening visit, the patient is found to meet all criteria for trial participation, the first treatment visit (baseline visit) will be scheduled within 14 days of the screening. The patient is randomised to treatment at screening.

A virtual baseline meeting is scheduled with the investigator or a competent research assistant. Study visits (virtual meetings) at 4, 8 and 12 weeks, as well as potential telephone calls, are scheduled with the investigator or study staff. Both screening and baseline visits are study related.

Table 1 further visualises the duration of time of each rating scale and interview as well as type of the rating scale, along with the duration of time and type for the different kinds of visits.

	Duration	Type
C-SSRS	1. visit 20 minutes (hereafter 5 minutes)	Rating scale - Interview
PSP	15 minutes	Rating scale - Interview
DART	5 minutes	Rating scale - Interview
HAM-D6	15 minutes	Rating scale - Interview
PSE	60-90 minutes	Semi-structured interview
Brief-INSPIRE-O	2 minutes	Questionnaire – Self-reporting
MDI	2 minutes	Questionnaire – Self-reporting
Screening visit	60 minutes	In person meeting
Baseline meeting	60 minutes	Virtual meeting
Other/un-scheduled visits	30-45 minutes	Virtual meeting

Table 1: Illustrates the duration and type of rating scales and meetings.

The Qualitative Interview Study

An individual qualitative interview study will be conducted as part of the overall project.

The aim of the interview study is to explore participants' experiences of the impact of the assigned treatment pathway on their everyday life. From each assigned treatment pathway, 10-12 participants will be interviewed by a research assistant using an interview guide. Participants will be sampled randomly.

Participants will be asked to take part in the interview, when the course of their specific treatment is finalised at week 12, by the clinician overseeing the final rating. If a participant accepts, a follow-up meeting with a research assistant will be scheduled, where the qualitative interview will be conducted.

Both the qualitative interview as well as selection and recruitment of participants will be carried out at end of study week 12, i.e. not when the overall RCT is finalised, to ensure that there will be no interference with the quantitative outcomes of the RCT-study, and to minimise recall bias among participants.

All interviews will be transcribed by a student helper, and the qualitative data will be analysed using reflexive thematic analysis (26).

Figure 1 illustrates the overall study design with the qualitative interview after week 12.

Statistics and Power Calculation

Statistics

The difference in HAM-D6 score between baseline and follow up will be compared between the three groups. A F-test will be used to assess if there is a significant difference among the groups. The analysis will be applied to the mITT population using last-observation-carried-forward (LOCF).

The three different treatment groups will be directly compared to each other, i.e. TAU-GP against ALGO, TAU-GP against TAU-P and TAU-P against ALGO. The groups will be compared based on the change in HAM-D6 scores from baseline to endpoint using a two-sided t-test (difference-in-differences [DID] analysis), along with other relevant secondary outcomes.

The DID-analysis will be applied to the mITT population at 12 weeks using LOCF, and the PP12 population.

In secondary analysis, differences between treatment groups regarding changes during the study period for each of the HAM-D6, MDI, PSP, C-SSRS, and Brief INSPIRE-O scores, will be analysed in separate mixed effects models. The models will be analysed with the relevant outcome as dependent variable, and time, treatment, and their interaction as fixed effects as well as patient and centre as random effects, also using the mITT and PP12 populations.

The proportion of responders (defined as a 50% reduction of HAM-D6 score) or remitters (defined as a HAM-D6 score ≤ 5) will be compared between the three groups, using chi-square tests for association and/or Poisson regression with a robust estimation of the standard error. The same will be applied to the remaining categorical variables. The analyses will be performed by using the mITT population. A similar analysis will be carried out for the categorical variable reasons for treatment discontinuation in the ITT population.

Further, risk of adverse events and serious adverse events is compared by applying Poisson regression with a robust estimation of the standard error in the mITT population.

To investigate the differences in time to all-cause discontinuation and duration of sick leave after baseline between the three groups, compared two and two, the time in the study will be compared by applying a two-sided t-test. Analysis of sick leave days is carried out on the mITT population and time to all-cause discontinuation will be performed on the ITT population.

Concordance between HAM-D6 and MDI will be analysed visually.

Exploratory analyses will extend the primary linear mixed-effects model by adding baseline variables (age, sex, educational level, baseline HAM-D6, duration of untreated depression, age at first episode, psychiatric/physical comorbidity, prior treatment history and DART score). If deemed feasible, non-linear dynamics as the interaction with treatment arm or an estimation using splines will be included. Relevant effects will be reported as regression coefficients or odds ratios with 95 % CIs and visualised in stratified plots where relevant.

All model assumptions are checked visually and sensitivity analyses, using bootstrap to estimate standard errors, are conducted in case of any violations.

All secondary outcomes will be analysed regardless of the significance of the primary outcome.

The statistical analyses will be performed by a statistician at the Department of Psychiatric Research, Aalborg University Hospital, Psychiatry, using Stata 19.

Power calculation

To detect a clinically relevant difference of at least 2.25 points of HAM-D6, with a power of 0.80 and a significance level of 0.05 (two-sided), 45 patients are required in each of the three groups (27, 28). To further account for an estimated dropout of 20%, a total of 57 patients are needed in each group.

The standard deviation of the difference in HAM-D6 between baseline and 12 weeks of treatment is assumed to be equal to 3.9 in all three groups (29).

Handling and Storage of Data

All trial data will be registered in the electronic Case Report Form (eCRF) and source data on paper (e.g. notes, diagnostic interviews, etc.) will be stored in a room at the site, secured under a two-lock system.

The eCRF will be divided to differentiate material from baseline, week 4, week 8, and week 12, as well as material from the qualitative study.

Source data will be preserved for a minimum of 5 years after completion of the study, and all electronic data are preserved for 15 years, after which the data will be given to the Danish Data Archive.

All data will be registered online in a database, REDCap, centrally administered by North Denmark Region, with central personal registry numbers. Registration will happen on the site and data will be entered directly into REDCap. The database (REDCap) is approved by the Data Protection Agency and is used in other research projects.

Study participants will be given an identification number relating to the eCRF. The identification number will follow the participant throughout the period of the trial. The numbers are used for export of anonymous data and all identifiable data are treated confidentially. Further, the identification list is registered in the site file.

The information in the database and in the eCRF are kept together with personal registry numbers.

Data Protection

The study complies with the General Data Protection Regulation (GDPR) and is a part of North Denmark Region's record of processing activities (under §30).
Both the sponsor and the principal investigator will be responsible for the upholding of data protection regulations regarding the processing of personal data within the study.
The study will also be registered in the *Psychiatry of North Denmark Region's List of Research Projects,* according to internal rules.

Risk and Side Effects

All treatments used in the study, medications and cognitive behavioural therapy (CBT), are approved treatment options in Denmark and have been used in the treatment of depression.
Regarding medication, trial participants will primarily receive treatment with antidepressants.
All medication is administered by the individual patient's general practitioner.
Common side effects of antidepressants include nausea, headaches, sleet disturbances i.e. insomnia or excessive sleepiness, weight changes and sexual dysfunction (30).
Information about the different medication will be provided by the general practitioner in question, as well as follow up regarding the medication and potential side effects.

Biological Material

In this research project, no biological material will be required. If a general practitioner finds that there is indication for, e.g., blood samples, it will be at the discretion of the respective GP to administer, interpret, store, and act upon such initiatives.

The results of blood tests will be accessible for the study staff through the participant's medical record.

Information from Patient Medical Record

All study participants are recruited from general practice, and their medical records are stored in the respective clinics' systems. These medical records are not directly accessible to the study staff or investigator, however, during the participant's treatment course, the investigator will be granted permission to access the patient's current list of medications through Fælles Medicinkort (FMK).

Further, a medical record for each of the participants will be created in the official medical record system, Elektronisk Patient Journal (EPJ), related to Aalborg University Hospital. The records will occur under the Department of Psychiatric Research.

Through EPJ, it will be possible to communicate with general practitioners through correspondence letters regarding a specific patient and to obtain relevant information about the participant and their treatment course. Throughout the trial period, the study staff will be granted access to information about participants.

After the participants sign the written letter of consent, all information concerning their treatment and medical history will be used in the study, including previous diagnoses and medications, as well as adverse events, hospital, and outpatient visits. This is necessary to create the most accurate and safe treatment plan for the patient, which is central to the study's purpose.

The declaration of consent will grant the sponsor-principal investigator and the sponsor's representatives, including relevant regulatory authorities, direct access to retrieve relevant information from the participants' medical records and electronic health records.

This access is granted to allow review of relevant information on the study participant's health status, as it is necessary for the execution of the project and for oversight purposes.

This includes internal audits, quality control, and monitoring.

Funding and Financing Budget

The study is initiated by René Ernst Nielsen, M.D., PhD., professor and Chief Physician from Aalborg University Hospital, Department of Psychiatry.

Funding is partially achieved through the *Independent Research Fund Denmark* (DFF). The remaining part will be financed through external funds, with a deficit guarantee from the Department of Psychiatry South, Aalborg University Hospital.

The estimated total budget for this project is 4.1 million DKK.

Budget overview

The budget figures are collected from the uploaded spreadsheet file

	DFF-financing	Co-financing	Other sources	Total (DKK)
Applicant		648.420		648.420
Scientific/academic staff excluding postdocs and PhD students		59.880		59.880
Postdoc(s)				
PhD-student(s)	1.700.634	600.000		2.300.634
Total scientific/academic	1.700.634	1.308.300		3.008.934
Technical/administrative staff	219.361	374.863		594.224
Equipment expenses				
Operating expenses	279.876	236.000	27.360	543.236
Total - excl. overhead	2.199.871	1.919.163	27.360	4.146.394
Overheads	68.196	*n/a*	*n/a*	68.196
Total (DKK)	**2.268.067**	**1.919.163**	**27.360**	**4.214.590**

Table 2: Illustrates the total budget amount.

Amount for scientific/academic salaries:	1.700.634 kr.
Amount for technical/administrative salaries:	219.361 kr.
Amount for equipment:	0 kr.
Amount for operating expenses:	279.876 kr.
Amount applied for excl. overhead/administration expenses:	2.199.871 kr.
Amount for overhead/administration expenses:	68.196 kr.
Amount applied for incl. overhead/administration expenses:	2.268.067 kr.

Table 3: Illustrates the funding from the Independent Research Fund Denmark (DFF).

Publication of Results

All findings, whether positive, negative, or inconclusive, will be published.

Publication will take place in scientific journals, on www.clinicaltrials.gov, or www.clinicaltrialsregister.eu, and the results will also be presented at an international scientific conference.

Currently, three publications are planned concerning this study:

1. A publication of the study protocol
2. A publication on the primary outcome of the study
3. A publication on the secondary outcomes of the study

The authors of the primary publications are expected to be Sarah Christiane Bloch as first author and René Ernst Nielsen as last author. Other co-authorships will be assigned and offered in accordance with the ICMJE criteria.

Scientific Ethics and Significance

Ethics

Participation and treatment in the study do not involve greater risk for the participants than that associated with the average clinical practice, and all medications used for treatment in the study are approved pharmaceuticals by the Danish health authorities and are commonly used in the treatment of depression.

All three of the study models (TAU-GP, TAU-P, and ALGO) are acknowledged as efficient treatment choices for depression and supported scientifically in the literature as well as in clinical practice.

The participants will help improve the current knowledge about treatment for depression in general practice and potentially help to elucidate which treatment path is most beneficial for future patients with depressive episodes.

If the participants have accepted to receive a letter with the results of the study, such will be sent to them after the completion of the entire study.

Potential significance

The insights gained from this study could significantly enhance the understanding of specific patient traits and their relation to treatment for depression, but also potentially alter the approach currently used in general practice regarding treatment of depression.

Successfully identifying individual characteristics in relation to depression holds great promise in the field of depression treatment. Specific patient traits could perhaps guide future treatment decisions. By understanding the unique psychological profile of individuals with depression, clinicians can optimise medication selection, dosage, and treatment modalities. This approach may enhance treatment outcomes by minimising side effects and reducing the trial-and-error process associated with finding the right treatment.

It could ultimately lead to improved treatment for depression in general practice and enhanced patient outcomes.

The results of the study could potentially impact which form of treatment should be used in the future, when treating patients with moderate depression in general practice, and hopefully lead to optimised treatment and possibly reducing direct as well as indirect healthcare costs.

Patient Insurance and Compensation

All participants in the study are covered consistent with the law on patient insurance and the law on patient compensation.

Participants will not receive any renumeration or reimbursement for taking part in the trial.

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