STUDY PROTOCOL

The DEXA-PSYCH Study: Dexamethasone Repurposing for Moderate to Severe Depression - A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Trial

Sponsor Institution:
Mental Health Services in the Capital Region of Denmark ("Region Hovedstadens Psykiatri")

Sponsor:
Prof. Michael Eriksen Benros, MD/PhD
Mental Health Center Copenhagen,
Mental Health Services in the Capital Region of Denmark,
Copenhagen University Hospital,
Gentofte Hospitalsvej 15, 2900 Gentofte

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EU-Trial Registration Number: 2022-501428-45-00
ClinicalTrials.gov identifier: NCTXX(To be added upon registration)
WHO Universal Trial Identifier: U1111-1280-7614

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Summary

Background

Depression is a severe, psychiatric condition associated with increased morbidity and mortality. Globally, 1 in 20 people will be diagnosed with depression every year, making depression the second leading cause of years lived with disability worldwide.

Even though current anti-depressants show some effect in treating depression, most antidepressants take three to six weeks to show effect and 30 % of patients do not achieve remission even after long-term treatment. New, effective, and fast-acting treatments are therefore needed.

Both epidemiological, clinical, and experimental studies have linked depression with immunopathological mechanisms. Our recent meta-analysis of all placebo-controlled randomized controlled trials (RCTs) measuring effects of anti-inflammatory compounds on depressive symptoms showed that glucocorticoids – although the current evidence is weak – displayed the largest effect size of the drugs tested, equivalent to more than double the effect sizes of current anti-depressants, in as little as 1-14 days after treatment initiation.

Glucocorticoids are low-cost, off-patent drugs with well-known side effects and established dosing regimens. However, prior studies on glucocorticoids in depression included only a limited number of patients (n_{Total}=59) and did not investigate if inflammatory biomarkers moderate treatment response. In previous studies, DeBattista and colleagues found a significant reduction in the score on the 21-item Hamilton Depression Rating Scale (HAM-D) the day after administration of 15 mg intravenous hydrocortisone (n=22). Likewise, Arana and colleagues administered 4 mg/day of oral dexamethasone for 4 days and detected a significant reduction on HAM-D score 14 days after treatment initiation (n=37). However, further evidence is needed before glucocorticoids can be established as a viable treatment regimen in the acute phases of depression.

Objectives

To investigate the acute effect and safety of oral dexamethasone compared to placebo as augmentation in treatment of moderate to severe depression.

Design

Investigator-initiated, double-blind, parallel-group, superiority, randomized, placebo-controlled clinical trial.

Inclusion and exclusion criteria

We will include adult patients from 18 to 64 years of age who a) are diagnosed with non-psychotic, recurrent or single episode moderate to severe depression according to ICD-10 criteria and b) are receiving pharmacological treatment for depression. We will exclude patients who are hypersensitive to glucocorticoids, who are pregnant, diagnosed with a psychotic disorder, personality disorder, intellectual disability, eating disorder, bipolar disorder (or have a family history thereof) or disorders that are relative contraindications for treatment with glucocorticoids, including diabetes. In addition, patients with prolonged QTc-intervals, increased alanine aminotransferase (ALAT) levels, suicidal plans or patients undergoing electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or treatment with medications interacting with glucocorticoids will be excluded.

Experimental intervention
Orally administered dexamethasone at 4 mg/day for 4 days and subsequently 2 mg/day for 3 days as add-on to treatment as usual (TAU).

Control intervention
Placebo mimicking dexamethasone as add-on to TAU.

Outcomes
The primary outcome is change from baseline (day 0) on the Montgomery-Asberg Depression Rating Scale ($MADRS_{10}$) at day 7.

Key secondary outcomes include effects on remission rates, quality of life, suicidal ideation and psychiatric hospitalizations as well as suicide attempts. Safety outcomes and all-cause discontinuation will also be reported. Exploratory outcomes include long-term effects on the primary and secondary outcomes as well as additional measures of labor market affiliation and all-cause mortality. In addition, it will be investigated if biomarker levels are associated with treatment response.

Statistics
The primary outcome will be analyzed through a Mixed Model for Repeated Measurements (MMRM) in an intention-to-treat analysis. Secondary outcomes will be analyzed using either logistic regression models or Cox proportional hazard models. We will consider two-tailored *p*-values below 0.05 significant. For secondary outcomes, *p*-values will be reported both crude and after adjustment for multiple testing.

Trial size and strategy
300 participants will be randomized in a 1:1 ratio without stratification. We will recruit and screen in- and out-patients from the Mental Health Services in the Capital Region of Denmark (MHSC). Patients, investigators, outcome assessors and data analysts will all be blinded to patient allocation status.

Estimated timeline

October 2022:	Authority approval, recruitment initiated
November 2022:	First patient randomized
May 2025:	Last patient, last 28-day visit. Breaking of randomization code and database lock (excluding data from 6-month follow-up). Outcome assessors will remain blinded.
September 2025:	Submission of paper based on outcomes up until 28 days
November 2025:	Last 6-month follow-up
February 2026:	Submission of paper based on outcomes up until 6-months

1 Administrative information

1.1. Sponsor Institution

Mental Health Services in the Capital Region of Denmark (MHSC) ("Region Hovedstadens Psykiatri")
Mental Health Center Copenhagen (MHCC)
Kildegårdsvej 28, Entrance 15, 4th floor
DK-2900 Hellerup
Denmark

Sponsor and Principal Investigator:
Michael Eriksen Benros, MD/PhD
Professor, Chief Physician, MD, PhD
Board Certified Consultant in Psychiatry
Biological and Precision Psychiatry
Copenhagen Research Center for Mental Health
Gentofte Hospitalsvej 15, Entrance 3, 4th floor
DK-2900 Hellerup
Denmark
Tel: +45 26 25 52 39
Michael.Eriksen.Benros@regionh.dk

1.2. Research group

Michael Eriksen Benros, MD/PhD (Sponsor/Principal Investigator)
Professor, Chief Physician, MD, PhD
Board Certified Consultant in Psychiatry
Biological and Precision Psychiatry
Copenhagen Research Center for Mental Health
Gentofte Hospitalsvej 15, Entrance 3, 4th floor
DK-2900 Hellerup
Denmark
Tel: +45 26 25 52 39
Michael.Eriksen.Benros@regionh.dk

Troels Boldt Rømer (Sub-Investigator)
Medical Doctor (MD), PhD-Student
Biological and Precision Psychiatry
Copenhagen Research Center for Mental Health
Gentofte Hospitalsvej 15, Entrance 3, 4th floor
DK-2900 Hellerup
Denmark
Tel: +45 31 47 43 45
Troels.Boldt.Roemer.03@regionh.dk

Rune Haubo Bojesen Christensen, PhD (Statistician)
Senior statistician
Biological and Precision Psychiatry
Copenhagen Research Center for Mental Health
Gentofte Hospitalsvej 15, Entrance 3, 4th floor
DK-2900 Hellerup

Denmark
Tel: +45 30 26 45 54
Rune.Haubo.Christensen@regionh.dk

1.3. Clinical trial site

Participants will be recruited from the sponsor institution, The Mental Health Services in the Capital Region of Denmark (MHSC), and through advertisement within and outside MHSC (for example to patient organizations).

The participants will be interviewed, enrolled and followed at Copenhagen Research Center for Mental Health (CORE). If a participant is hospitalized at MHSC and is not able to be physically present at the research office, the participant will be enrolled in the trial from the given inpatient department at MHSC, by members of the PI's team. Thus, all participants in the trial will be included in the study by medical doctors under the supervision and responsibility of the sponsor/PI:

Prof. Michael Eriksen Benros, MD/PHD, Chief Physician, Specialist in Psychiatry
Mental Health Services in the Capital Region of Denmark (MHSC),
Mental Health Center Copenhagen (MHCC)
Copenhagen Research Center for Mental Health
Biological and Precision Psychiatry
Gentofte Hospitalsvej 15, Entrance 3, 4th floor
DK-2900 Hellerup
Denmark

1.4. Trial medication

Trial medication will be delivered by The Hospital Pharmacy of The Capital Region of Denmark. In charge of trial medication is Pharmacist Laila Rabbani (telephone: +45 44 57 78 03; email: laila.rabbani@regionh.dk).

1.5. Laboratory analyses

Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital. Blegdamsvej 9, 2100 Copenhagen. In charge of the departments research services is Professor Ruth Frikke-Schmidt (email: ruth.frikke-schmidt@regionh.dk)

1.6. GCP monitoring

The DEXA-PSYCH RCT will be continuously monitored by the Good Clinical Practice (GCP) unit of Copenhagen University Hospital, Frederiksberg Hospital, Nordre Fasanvej 57, Skadestuevej 1, parterre, 2000 Frederiksberg.

1.7. Sponsor/Principal Investigator signature

I hereby take responsibility for the content in the protocol at hand, affirm that the content is true to the best of my beliefs and take responsibility for the conduct of the trial according to the standards listed in this protocol (version 1.1, September 19th 2022):

_____ *Place and date:*

Michael Eriksen Benros, Sponsor/Principal Investigator

2 List of abbreviations

- AE = Adverse Event
- AR = Adverse Reaction
- ALAT = Alanine aminotransferase
- BACS = Brief Assessment of Cognition in Schizophrenia
- CBT = Cognitive Behavioral Therapy
- CI = Confidence Interval
- C-SSRR = Columbia-Suicide Severity Rating Scale
- CSF = Cerebrospinal Fluid
- CTIS = Clinical Trials Information System
- DSM-5 = Diagnostic and Statistical Manual version 5
- DST = Statistics Denmark
- ECT = Electroconvulsive Therapy
- EHR = Electronic Health Record
- FAS = Full Analysis Set
- GCP = Good Clinical Practice
- GDPR = General Data Protection Regulation
- GTI = Glucocorticoid Toxicity Index
- ICD-10 = International Classification of Diseases version 10
- ICH = International Clinical Harmonization
- ICMJE = International Committee for Medical Journal Editors
- ITT = Intention-to-treat
- HAM-D = Hamilton Depression Rating Scale
- MADRS = Montgomery-Asberg Depression Rating Scale
- MCID = Minimum Clinically Important Differences
- MD = Medical Doctor
- MDD = Major Depressive Disorder (DSM-5 definition equivalent to ICD-10 diagnosis of moderate to severe depression)
- MMRM = Mixed Model for Repeated Measurements
- RCT = Randomized Control Trial
- RR = Risk Ratio
- SAE = Serious Adverse Event
- SAP = Statistical Analysis Plan
- SAR = Serious Adverse Reaction
- SAS = Safety Analysis Set
- SMD = Standardized Mean Differences
- SNRI = Selective Noradrenaline and Serotonin Reuptake Inhibitors
- SSRI = Selective Serotonin Reuptake Inhibitors
- SUSAR = Serious and Unsuspected Adverse Reaction
- TAU = Treatment As Usual
- TCA = Tricyclic Antidepressants
- TMS = Transcranial Magnetic Stimulation

3 Introduction and Background

3.1. Depression

Globally, 1 in 20 people is diagnosed with depression every year, making depression the second leading cause of years lived with disability worldwide.[1,2] Depression is associated with a marked reduction in quality of life and life expectancy as well as a substantially increased risk of suicide.[3,4]

In Denmark, depression is diagnosed according to the criteria stipulated in the International Classification of Diseases, 10th edition (ICD-10). Core symptoms consist of a reduced capacity for enjoyment, interest and concentration and marked tiredness even after minimal effort. There is usually disturbance of sleep, reduced appetite, self-esteem, and self-confidence as well as a feeling of worthlessness. The lowered mood varies little from day to day and is, crucially, unresponsive to circumstances. "Somatic" symptoms such as early awakening, worsening of the depression in the morning, marked psychomotor retardation, agitation, weight loss and loss of libido often occur.

Depression is subdivided into mild (at least 2 of the depressive core symptoms and at least 2 additional depressive symptoms), moderate (at least 2 of the depressive core symptoms and at least 4 additional depressive symptoms with great difficulty in continuing ordinary activities) and severe depression (at least 3 of the depressive core symptoms and at least 5 of the additional depressive symptoms with a severe reduction in functioning).

3.2. Treatment options

Current treatment options include a) pharmacological therapy using anti-depressants, which is recommended for moderate to severe depression in Danish and international guidelines and b) psychotherapy for mild to severe depression, of which cognitive behavioral therapy (CBT) has the strongest evidence-base.

The current state-of-the-art within pharmacological therapy of moderate to severe depression is the use of anti-depressants, primarily of the selective serotonin reuptake inhibitor (SSRI) class or the selective noradrenaline reuptake inhibitor (SNRI) class. A recent, large meta-analysis concluded that anti-depressants show up to moderate effect in treating depression, with the most effective antidepressants being those of the tricyclic anti-depressants (TCAs) class yielding a maximum standardized mean difference (SMD) of 0.43 compared to placebo.[5] However, clinical effects are often delayed until three to six weeks after treatment initiation, meanwhile leaving the patients at increased risk of e.g. suicide.[6] In addition, one-third of patients do not achieve remission at all after long-term treatment with at least two of the currently used anti-depressant drugs.[7,8] Furthermore, antidepressants have non-neglectable side-effects, including weight gain, sexual dysfunction, sleep disturbances, fatigue and cognitive impairment.[9] Notably, even among the patients who achieve remission upon treatment with anti-depressants, patients on average still face a substantially lower quality of life than the general population.[10]

Non-pharmacological treatment strategies, such as psychological interventions, show some effect; however, a recent meta-analysis reported that only a third of patients undergoing psychotherapy achieved remission whereas more than half of the patients had no response at all.[11] Electroconvulsive Treatment (ECT), an alternative non-pharmacological treatment for severe depression, show better remission rates of 50 to 60 %, but is considered an invasive procedure with limited accessibility.[12] Despite these unsatisfactory clinical outcomes, there has been a shortage of new treatment options for people affected by depression, with the recent approval of esketamine being the only introduction of an anti-depressive drug with a new

mode of action for several decades.[13] New, effective and fast-acting treatment options are therefore needed.

3.3. Glucocorticoids

Glucocorticoids are steroid hormones that are naturally produced by the zona fasiculata of the adrenal gland and are regulated in a circadian and stress-associated manner. Glucocorticoid signaling is an integral part of the hypothalamic-pituitary-adrenal (HPA) axis of which disturbances have been detected in depression.[14] Glucocorticoids assert their pleiotropic effects primarily through the glucocorticoid receptor, of which there are several isoforms with both genomic and non-genomic downstream effects.

Synthetic glucocorticoids are drugs that resemble natural glucocorticoids, of which different types have been used clinically for over 7 decades.[15] Dexamethasone is a widely used synthetic glucocorticoid and an off-patent and easily accessible drug with well-known dosing regiments and potential side-effects. Dexamethasone and other glucocorticoids are used in the treatment of a range of disorders, primarily rheumatological diseases, where their anti-inflammatory properties are harnessed.[16] In addition, glucocorticoids are used in the palliative care setting, specifically for the treatment of "low mood",[17] and can be used to treat fatigue among oncological patients.[18] Furthermore, dexamethasone has recently been successfully repurposed in the treatment of COVID-19 and thereby shown its potential for repurposing in a clinical setting.[19]

3.4. Depression, inflammation and anti-inflammatory treatments

Both epidemiological, clinical and experimental studies have linked immunopathological mechanisms to psychiatric disorders in general and depression specifically.[20] Epidemiological research has shown that infections[21] as well as auto-immune disorders[22] increase the risk of depression and that inflammatory markers such as interleukin-6 are elevated in the cerebrospinal fluid (CSF) of patients with depression.[23] A recent meta-analysis of the effect of anti-inflammatory agents in the treatment of depression[24] demonstrated that anti-inflammatory agents show larger effect sizes (SMD = 0.64) than anti-depressants (SMD = 0.43), while also improving response (rate ratio (RR) = 1.76) and remission rates (RR = 2.14) compared to placebo. Of all anti-inflammatory agents investigated, glucocorticoids displayed the largest effect sizes, exceeding the effect sizes in reduction of depressive symptoms of the currently most effective anti-depressives by more than 2-fold (SMD = 0.90; 95 % CI: 0.36 to 1.44). The effect on depressive symptoms was rapid and occurred in as little as 1 to 14 days.[25,26]

However, the two studies on the effect of glucocorticoids included in the meta-analysis had notable shortcomings. First, they only included a limited number of patients (n_{Total} = 59) of which 25 received glucocorticoid treatment and followed the patients for only a short time-period. Second, no studies investigated if subgroups of patients with increased inflammatory markers showed improved response to glucocorticoid therapy. And third, they investigated two different glucocorticoids: hydrocortisone administered intravenously and dexamethasone administered orally. Finally, reporting of adverse reactions and events in the previous studies was inadequate, detailing only that no participants were eliminated from the studies due to side effects or toxicity. Further evidence is therefore needed before glucocorticoids can be considered as a viable, evidence-based treatment option in the acute phase of depression.

According to EudraCT and Clinicaltrials.gov, no currently active trials are investigating the effect of glucocorticoids in the treatment of depression.

3.5. Hypothesis

The trial is based upon the hypothesis that dexamethasone as add-on to treatment as usual (TAU) is superior to placebo as add-on to TAU in reducing depression symptoms amongst patients with moderate to severe depression.

3.6. Considerations of the type and dose of glucocorticoids

As stated, dexamethasone has shown large effect sizes in reduction of depressive symptoms in a small study and is the only glucocorticoid drug that has been investigated in the treatment of depression in an orally administered form.[25] It is therefore chosen as the drug of intervention in this trial, as oral administration is compatible with treatment in an out-patient setting and generally increase adherence to therapy compared to intravenous administration.

According to Danish guidelines, orally administered dexamethasone can be used in short-term treatment (up to 1 week) at doses of 1 mg/day to 4 mg/day (with the possibility of increasing dosage to 8 mg/day or above under special circumstances) for anti-inflammatory purposes.[27] Furthermore, guidelines recommend that dosing should be tapered by 1-2 mg every 3 days before treatment stop. As 4 mg/day of dexamethasone has been trialed previously for depression, we will use this dose in the experimental group for 4 days with a subsequent tapering of 2 mg/day for the last 3 days of treatment in accordance with Danish guidelines.

3.7. Considerations on the choice of primary outcome

The primary outcome of the trial will be change from baseline (day 0) on the 10-item Montgomery-Asberg Depression Rating Scale ($MADRS_{10}$) at day 7.

The primary aim of the trial is to investigate if dexamethasone can cause a rapid improvement in symptoms and thus "bridge" the effect until conventional anti-depressants have effect, which is why the primary outcome on treatment effect is evaluated already after 7 days of treatment.

Additionally, previous studies of glucocorticoids in depression have not evaluated treatment effect later than 14 days after treatment initiation, which is why we have also included long-term follow-up assessments.

When evaluating the clinical efficacy of anti-depressant agents or psychotherapeutic interventions, it is standard practice to use a psychometric rating scale. The most widely used rating scales are MADRS and the Hamilton Depression Rating Scale (HAM-D). Current international guidelines are based on state-of-the-art meta-analyses that exclusively includes studies measuring outcomes on MADRS or HAM-D.[5] Both scales can be used to graduate the severity of depression and follow treatment response; however, they cannot be used as diagnostic tools, where interviews according to diagnostic criteria should be used.

Both rating scales exist in 6-item versions ($HAM\text{-}D_6$ and $MARDS_6$), primarily rating the core symptoms of depression, and in extended versions consisting of 17 or 28 items for the HAM-D ($HAM\text{-}D_{17}$ and $HAM\text{-}D_{28}$) and 10 items for MADRS ($MADRS_{10}$). $HAM\text{-}D_{28}$ is rarely used, and $HAM\text{-}D_6$ has been found to "outperform" $HAM\text{-}D_{17}$ in anti-depressant trials, as the 6-item scale captures the core depressive symptoms, whereas the 17-item scale also encompasses anxiety symptoms and sleep disturbances not specific to depression and only partially responsive to anti-depressive treatment.[28] Both MADRS and HAM-D are interview-based, but reliable self-reporting versions of the scales have been developed.[29]

The MADRS scale was developed specifically to measure the short-term effects of anti-depressant treatment, which is why is has been chosen for the DEXA-PSYCH trial.[30] $MADRS_{10}$ has a theoretical span of

0-60, with remission defined as a score of 11 or below (equivalent to a score of 7 on the HAM-D_{17} and 4 on the HAM-D_6).[31] Mild depression is defined as a $MADRS_{10}$ score of 18-21, moderate depression as a score of 22-29 and severe depression as a score of 30 or above. Each item on $MADRS_{10}$ is scored from 0-6, with only the scores 0, 2, 4 and 6 being used for each item. Psychometric testing using Rasch-analysis methodology has shown that $MADRS_{10}$ is multidimensional (i.e. measuring more than one underlying phenomenon), whereas MADRS-6 is considered unidimensional (i.e. only measures depressive features).[32,33]

The Monsenso app will be used to supplement the observer-based rating of depression with a patient-reported depression rating, enabling us to follow longitudinal, day-to-day changes in depressive symptoms without observer-bias, as well as collecting data on physical and social activity reflecting general functioning.

3.8. Ethical justification and trial rationale

The rationale and ethical justification of the trial relies on the following assumptions, all of which has been accounted for in the above:

a) Moderate to severe depression is a severe mental disorder with high costs to the individual and society; however,
b) Current treatment options show only small to moderate effects, which are often delayed by three to six weeks after treatment initiation, and they only relieve symptoms in a subset of patients.
c) Inflammatory pathophysiological processes have been associated with depression and
d) Anti-inflammatory treatments have been shown to have effects against depression in meta-analyses, with the largest effect sizes detected for glucocorticoid drugs; however,
e) The current evidence on glucocorticoid treatment in depression is not strong enough to guide clinical practice.

If the trial demonstrates superiority of glucocorticoid treatment as add-on to TAU compared to placebo, this could pave the way for a new class of potentially fast-acting antidepressants that could alleviate symptoms in days rather than weeks. This could improve disease trajectories in depression, where the first weeks of treatment represent a crucial window.[6]

The repurposing of existing medicine, in this case dexamethasone, can have a fast, positive impact on outcomes for patients.[34] However, this potential, clinical benefit can only be achieved if a large, high-quality randomized clinical trial (RCT) can provide sufficient evidence to warrant a change of guidelines. The potential benefit is, on a global scale, vast – especially since dexamethasone is a cheap, off-patent drug that can be readily employed for treatment in both low- and high-income countries.

If glucocorticoids, with their potent anti-inflammatory effects, indeed alleviate depressive symptoms, this could furthermore be an important, conceptual advance in our understanding of the etiology of depression. In addition, the trial will enable investigation of how specific biomarkers might enable prediction of treatment response. This will deepen our understanding of the underlying factors influencing the trajectories in depression treatment while potentially giving us the possibility of tailoring anti-inflammatory treatment to the patients exhibiting depressive symptoms with an inflammatory component and introduce a more personalized, biologically based treatment approach in psychiatry.

The trial will be the first clinical trial in 20 years to test glucocorticoids for treatment of depression and the, to date, largest trial of its kind globally. The trial will be conducted to the highest methodological standards with appropriate surveillance of adverse reactions. The placebo-controlled, double-blind nature of the trial will provide causal evidence at the highest level of the evidence hierarchy, justifying the execution of the

trial both medically and ethically. The trial is investigator-initiated and no parties with commercial interests in dexamethasone or treatment of depression are involved in the trial.

3.9. Trial conduct

The DEXA-Psych trial will comply with the published trial protocol, the Helsinki Declaration in its latest version,[27] the International Conference on Harmonization on Good-Clinical-Practice (GCP) guidelines,[35] the EU General Data Protection Regulation (GDPR)[36] and national, Danish laws. The Sponsor/PI and the research group of the trial will oversee the conduct of the trial. The protocol is written in accordance with the SPIRIT Statement[37] and the trial will be reported in accordance with the CONSORT guidelines.[38] The trial will be registered through the Clinical Trials Information System (CTIS) (EU) and ClinicalTrials.gov (USA). The design of the trial has been conducted to achieve the lowest risk of bias possible in accordance with the Cochrane risk-of-bias assessment tool (RoB 2).[39]

Recruitment, screening and enrollment will commence after approval from the Danish Medicines Agency, relevant Ethics Committees and the Capital Region Knowledge Center for Data Compliance. After inclusion of the first 10-20 participants, the trial design will be evaluated, and protocol amendments will be submitted to the authorities as appropriate.

4 Trial objectives

The objective of the DEXA-PSYCH trial is to test the efficacy and safety of dexamethasone, a well-tolerated glucocorticoid, as add-on to TAU in treatment of moderate to severe depression. For hypothesis, see section 3.5. For details on outcomes, see section 8.

5 Trial design

The DEXA-PSYCH trial is an investigator-initiated, double-blind, parallel-group, superiority, randomized, placebo-controlled, clinical trial. For trial design chart, see appendix 1. For CONSORT flow chart, see appendix 2.

5.1. Randomization

Participants meeting inclusion criteria (see section 6.1.), meeting no exclusion criteria (see section 6.2.) and providing written informed consent will be randomized.

The randomization will be an individual level randomization with an allocation ratio of 1:1 to dexamethasone or placebo. Randomization will occur in blocks of randomly selected sizes of 6, 8, 10 or 12 participants to reduce the risk of unblinding.[40] The randomization process will not be stratified.

The Hospital Pharmacy of The Capital Region of Denmark (Marielundvej 25, 2730 Herlev) will coordinate the randomization process and allocation concealment. The randomization will be based on a computer-generated random-number allocation sequence stored at the pharmacy. The randomization sequence will not be available to staff involved in data management, analysis, report writing or patient care until breaking of randomization code.

Trial medication or placebo will be prepared in sealed pill containers (see section 5.2.1.) and further packaged in opaque envelopes with tamper-proof seals, numbered with a randomization number linking the envelope to the randomization sequence. The participants will be randomly assigned to the intervention or control group through the hand-out of these opaque envelopes upon trial enrollment and their individual randomization number will be recorded in their respective electronic Case Report Form (eCRF).

5.2. Blinding

Trial participants, investigators, outcome assessors, trial staff and data analysts are all blinded to the allocation. The quality of the blinding will be tested by having the sub-investigators and the participant independently reporting which allocation group they think the individual patient belong to on day 7 (date of assessment of primary outcome).

5.2.1. Preparation of trial medication and sealed envelopes

Envelopes will be sequentially numbered, opaque and closed with tamper-proof seals and will be prepared by adequately trained staff at the pharmacy certified in handling of medicine and un-blinded to the allocation sequence, but not involved in participant contact, data management or data analysis during the trial.

Dexamethasone tablets are available on the Danish market in 1 mg or 4 mg formulations. The pharmacy will encapsulate either two 1 mg Dexamethasone tablet, one 4 mg Dexamethasone tablet or placebo in a gelatin capsule to ensure blinding (see enclosed IMDP). The gelatin capsule will be dissolved within minutes from digestion and does not affect the absorption of the medicine. The dexamethasone tablets will be bought from the manufacture Abcur.

Each envelope will contain encapsulated dexamethasone or placebo in a plastic pill strip with pills dispensed and stamped with time and date of administration. Four of the compartments will contain two capsules of 1 x 4 mg dexamethasone tablet each (for the first 4 days of the intervention) and three compartments will contain one capsule of 2 x 1 mg dexamethasone (for the last 3 days).

For the placebo group, pill strips will contain encapsulated placebo tablets mimicking the dexamethasone containing capsules exactly in the ratio described for dexamethasone tablets.

Labels for trial medication are enclosed in appendix 10.

5.2.1.1. Shipping

The pharmacy is responsible for delivery of trial medication to the clinical trial site. Date and time will be arranged after agreement with the research nurse or sub-investigator. Upon receipt, the medicine will be checked and immediately stored in accordance with regulations.

The encapsulation will reduce the shelf life to 12 months, implicating that trial drugs will be ordered from the pharmacy on an ongoing basis with an initial production and delivery time of six weeks and subsequently four weeks for new orders.

Envelopes containing trial medication will be handed out at inclusion in the study on day 0.

5.2.1.2. Storage

There are no strict temperature requirements for storage of dexamethasone. Trial medication will be stored (until use) in the medicine storage room of the Mental Health Center Copenhagen at the Mental Health Services in the Capital Region of Denmark in a locked compartment, separated from medicine used at the department and under strict temperature control.

5.2.1.3. Accounting

Accounting for the trial medicine will be done on an ongoing basis. The arrival of trial medication from the pharmacy, hand-out of trial medication to participants and return of trial medication from participants to the trial staff will be documented by the trial staff in a centralized medicine accounting document.

Medication batch number will be registered by the pharmacy and linked to participants randomization numbers.

5.2.1.4. Destruction

The pharmacy is responsible for the destruction of any excess medication. The research nurse and/or sub-investigator is responsible for collecting and shipping excess medication to the pharmacy.

5.2.2. Blinded data analysis

Pre-specified analyses, tables and figures will be programmed with a fake group-ID before unblinding to ensure blinding in the analyses. Primary analyses will furthermore be conducted using independent parallel programming by at least two separate statisticians/analysts.

5.3. Unblinding

5.3.1. Unblinding of the intervention for an individual patient

For a specific individual, the intervention may be unblinded if deemed necessary by the sub-investigator or the sponsor/PI for safety reasons.

The sponsor/PI or the sub-investigator will break the blind for a participant if there is clinical suspicion of an unexpected serious adverse reaction (SUSAR) and judge the 'expectedness' of this according to the product information (see "Safety" section for additional information).

It will be noted in the participant's electronic health record (accessible to all hospital staff) that the patient participates in the trial and therefore might have been allocated to glucocorticoid treatment and that telephonic contact should be made to the sub-investigator or sponsor/principal investigator if treating clinicians consider unblinding needed.

Codes for unblinding of individual participants will be stored at the pharmacy. In case unblinding of an individual patient is needed, the sponsor/PI or sub-investigator will be able to access the unblinding code for the individual participant through telephonic contact to the pharmacy at any hour of the day. Unblinding will be recorded in the eCRF and reported in the final trial report.

5.3.2. Unblinding of the entire trial

Participant allocation will be unblinding to the sponsor/PI, statistician and sub-investigator after the last patient has completed the 28-day follow-up visit and blinded data analysis has been completed. The primary publication reporting on the primary outcome of the trial will be completed based on data recorded up-until day 28. To record outcomes at 6-month follow-up in a blinded fashion (exploratory outcomes), outcome assessors (who are not sub-investigators) and participants will continuously be blinded to participant allocation. Unblinding of outcome assessors and participants will occur after the last 6-month follow-up visit has been completed.

5.4. Participant timeline and trial phases

Participants will be recruited from the Mental Health Services in the Capital Region of Denmark (MHSC), a secondary level care psychiatric hospital.

Prospective participants will be asked by their treating physician at MHSC if they are interested in participating in the DEXA-PSYCH trial. If the participant consents, the sub-investigator will contact the participant by phone to arrange an information meeting (section 10.3.). The participant will be offered 24 hours reflection time from the information meeting until written consent will be obtained (section 10.4.).

Inclusion of participants will be conducted by medical doctors (sub-investigators) from the PIs group under the responsibility of the PI.

Upon obtained written consent, participants will be screened and enrolled (day 0). Participants will be randomized as soon as they fulfil inclusion criteria, and it is ensured they do not meet exclusion criteria (day 0). The allocated intervention will be continued so that participants in total receives 7 days of the intervention (day 1-7). Thus, no participant will receive glucocorticoids for more than 7 consecutive days.

Depressive symptoms will be scored daily using the Monsenso app on day 1-28, through telephonic contact on day 4, 14 and 28, and during a physical visit on day 7. Patients will receive additional calls on day 2 to encourage adherence (see section 5.11) and at day 8 for safety reasons (see section 9.3.). In addition, trial staff will follow-up on participants by phone in the close-out phase at 6-months.

We will allow -/+ 2-day variability on visits at day 2, 4, 7, 8, 14 and 28 and -/+ 2-week variability on 6-month follow-up.

For an example for a patient timeline, see appendix 6. For Schedule of Activities, see appendix 5.

5.4.1. End of trial

The trial will end when the last patient enrolled has completed 6-month follow up (last-patient last-visit). We will report the end-of-trial no later than 90 days after the last-patient last-visit to the Danish Medicines Agency and Ethics Committee through CTIS.

5.4.1.1. Clinical trial termination criteria

The trial can be terminated prior to the pre-defined end of trial if the sponsor/PI finds that:

a) Other, currently unpublished trials produce evidence that dexamethasone is either highly beneficial or harmful to patients suffering from depression
b) An unexpectedly high number of SARs occur in the trial
c) It is not feasible to reach the planned recruitment target

5.5. Study intervention and treatment responsibility

The intervention is a period of 7 days (days 1-7) from randomization (day 0) and will consist of add-on treatment with dexamethasone or placebo in addition to treatment as usual (TAU) for moderate to severe depression.

Participants will be instructed to administer trial medication at 9 AM every morning, as circadian rhythms influence endogenous glucocorticoid production. Maximum plasma half-life of dexamethasone according to the Danish product resume is 4.5 hours and the wash-out period (defined as minimum three times plasma half-life) will thus be considered as day 8.[41]

The trial staff (sponsor/PI and sub-investigator) will be responsible for any trial related procedures. Concomitant anti-depressant treatment will be managed by the participants treating clinician (GP or physician at in- or out-patient clinic, depending on where the patient is currently undergoing clinical follow-up and treatment for depression).

Considerations on the trial length: Due to the potential, long-term side effects of persistent dexamethasone treatment, the intervention will not be extended past the initial 7-day phase.

5.6. Experimental intervention

The intervention group will receive encapsulated, orally administered dexamethasone at 4 mg/day for 4 days and 2 mg/day for 3 days before discontinuation as add-on treatment to TAU. Dexamethasone is approved by the Danish Medicines Agency for clinical use in humans for anti-inflammatory purposes.

Considerations on the experimental intervention: The gradual dose decrease is consistent with Danish guidelines, which recommend that dexamethasone administration should be tapered by 1-2 mg/day over the course of 3 days before discontinuation.[41]

5.7. Control intervention

The control group will receive encapsulated placebo tablets mimicking dexamethasone as add-on treatment to TAU.

Considerations on the control condition: As there is currently no add-on treatment recommended for initial treatment of moderate to severe depression, we consider placebo the most relevant comparator.

5.8. Co-interventions

Participants are required to receive pharmacological treatment for depression at the onset of the intervention. This could include anti-depressive medication (e.g. SSRIs, SNRIs and TCAs) as well as treatment with antipsychotics (e.g. quetiapine and aripiprazole) and lithium for anti-depressive purposes. However, patients who have received ECT or TMS therapy or have been treated with MAO-inhibitors within the last 2 weeks are not eligible for participation. Other interventions administered in accordance with Danish guidelines as implemented at the MHSC will be allowed, including psychotherapy.

Any current or previous anti-depressive treatment will be registered in the eCRF of the individual patient.

We will recommend against the use of additional glucocorticoids and other anti-inflammatory agents in all trial participants during the study intervention (day 1-7) and wash-out period (day 8). This will be stated explicitly to the patient upon enrollment and be noted in the electronic health record of the participants.

5.9. Monitoring of participants

Participants will be monitored closely during the intervention phase and in the weeks following withdrawal of the intervention as described in this section and in the "Safety" section.

5.9.1. Physiological and psychometric measures

Before treatment initiation, electrocardiograms (ECGs) and blood samples will be taken at day 0. Additional ECGs and blood samples will be drawn at day 7 (+/- 2 days variability allowed). Blood samples (5-10 mL) will be drawn according to standard procedures between 9-10 AM and analyzed immediately at the Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, by technicians blinded to the randomization status of the participants. The samples will be analyzed for hemoglobin, erythrocytes, leukocytes, lymphocytes, thrombocytes, blood glucose, HbA1c, sodium, potassium, creatinine, cholesterol, triglycerides, high density lipoprotein (HDL), low-density lipoprotein (LDL), ALAT, phosphatase, thyroid stimulating hormone (TSH), human chorionic gonadotropin (HCG) and C-reactive protein (CRP).

In case of suspected reduced liver function (ALAT >45 U/l for women and >70 U/l for men), diabetes mellitus (HbA1c >45 mmol/mol) or pregnancy (positive blood HCG), the prospective participant will be excluded from the trial and the sub-investigator will immediately contact the participant to inform him/her about the exclusion.

In case of suspected active infection (CRP > 10 mg/L), participants will be diagnostically evaluated to exclude active tuberculosis infection and systemic fungal infections prior to treatment initiation. If blood samples raise suspension of hematological malignancies, the Department of Hematology at the University Hospital of Copenhagen will be contacted, and participants will be evaluated to exclude any malignancies. In addition, any lab test results will be reviewed by the including medical doctor (sub-investigator) and will be acted upon if the abnormalities are considered as being of clinical importance. If blood tests result in further diagnostic procedures and/or acute/sub-acute treatment, the enrollment of the participant will be deferred until deemed appropriate by the sub-investigator and the participant will then be invited for a new day 0 visit (including new blood tests and baseline assessments).

During the trial, depressive symptoms will be scored on day 0, 4 and day 7 by the sub-investigator using $MADRS_{10}$ and suicidal ideation will be evaluated by the Columbia Suicide Severity Rating Scale (C-SSRS) on day 0 and 7. Glucocorticoid toxicity will be evaluated using a modified version of the Glucocorticoid Toxicity Index on day 7 not including a bone density scan.[42] For additional rating scales used and variables recorded, please refer to section 8 and 11. Following discontinuation of the intervention, the sub-investigator will access symptoms of glucocorticoid withdrawal and adrenal gland insufficiency on day 8. Depressive symptoms and suicidal ideation will furthermore be monitored by a research nurse or medical student through phone on day 14 and 28 in the close-out phase.

If a participant fails to show for the visit on day 7, the sub-investigator will contact the participant to encourage adherence to the visit and evaluate if acute medical and/or psychiatric care is needed (for additional details, see “Safety” section).

5.10. Criteria for modification of interventions for a given trial participant

The sponsor/principal investigator, sub-investigator or clinical staff caring for the patient outside the clinical trial setting may at any time violate the protocol if they find it to be in the best interest of the participant.

We will have a trial hotline to enable discussion between clinicians caring for trial participants and the DEXA-PSYCH sub-investigator regarding protocol related issues. Contact information for the trial hotline will be registered in the electronic health record of the participant. Protocol violations will be registered in the eCRF for the individual patient and reported by the sub-investigator to the sponsor/PI without unnecessary delay. Repeated and/or serious protocol violations will be reported to the Danish Medicines Agency and Ethics Committee through CTIS no later than 7 days after protocol violation. Violations will furthermore be documented in the final reporting of the trial.

5.11. Assessment of participant adherence

Adherence will be encouraged during the first trial visit (day 0) and telephonic contact on day 2 and 4. Adherence will be monitored through daily app-based reporting using the Monsenso app on day 1-7. This enables the sub-investigator to contact the participant by phone if non-adherence should be reported on the Monsenso app and encourage adherence. Adherence will furthermore be monitored through tablet return on day 7.

5.12. Intervention accountability

The trial intervention medication is routinely used for both in- and out-hospital treatment of patients. We will use off-the-shelf-medication from the pharmacy in accordance with the product resume and Danish clinical guidelines. Packaging of trial medication will be handled by trained staff at the pharmacy.

5.12.1. Trial medications

5.12.1.1. Experimental intervention

Active medication: dexamethasone, tablets, 1 mg or 4 mg per tablet, ATC code: H02AB02. Procured from the manufacture Abcur.

Other ingrediencies: lactose monohydrate, gelatin encapsulation.

5.12.1.2. Control intervention

Placebo pills containing lactose monohydrate, starch, gelatine, talc and magnesium stearate in a gelatin encapsulation.

6 Selection of participants

6.1. Inclusion criteria

Participants are eligible for the trial if they:

a) Are diagnosed with non-psychotic, moderate to severe depressive disorder (single episode or recurrent) by a medical doctor according to ICD-10 criteria (ICD-10 codes: F32.1, F32.2, F33.1, F33.2) as operationalized in the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), Section 6 AND
b) Score 22 or above on the $MADRS_{10}$ scale at day 0 AND
c) Are currently receiving pharmacological treatment for depression
d) Are between 18 and 64 years of age (both included) at the date of enrollment AND
e) Are habile (i.e. able to give informed consent) AND
f) Speak Danish fluently

6.2. Exclusion criteria

Participants are not eligible for the trial if they:

a) Have a known hypersensitivity to glucocorticoid treatment (including any drug in the glucocorticoid class) either explicitly stated in the patient journal or known to the patient from prior glucocorticoid treatment
b) Are undergoing or have undergone systemic (oral or intravenous) treatment with any drug in the glucocorticoid class within the last 14 days
c) Have previously been diagnosed with a psychotic disorder (including depression with psychotic symptoms), personality disorder, eating disorder or bipolar disorder
d) Have suicidal plans
e) Have undergone electroconvulsive treatment (ECT) or transcranial magnetic stimulation (TMS) within the last 2 weeks
f) Have experienced or are experiencing manic and/or hypomanic episodes as uncovered according to section 10 of the SCAN assessment
g) Have a known 1st-2nd degree family history of bipolar disorder (i.e. among parents, siblings, children, grandchildren, grandparents or siblings of parents)
h) Are diagnosed with disorders that are listed as contra-indications for glucocorticoid treatment in Danish guidelines including immunodeficiencies, systemic fungal infections, active tuberculosis, hematological malignancies, epilepsy, myasthenia gravis, ocular herpes simplex, pheochromocytoma, systemic sclerosis or acute coronary syndrome (within the last 6 months)
i) Have prolonged QTc-interval (>480 ms)

j) Have reduced liver function as measured by increased ALAT levels (men >70 U/l, women >45 U/l)
k) Have diagnosed diabetes mellitus or suspected diabetes mellitus (as measured by HbA1c of >45 mmol/mol)
l) Have been vaccinated within 14 days before intervention initiation or is planning on being vaccinated during the intervention or within 14 days after the vaccination
m) Are currently undergoing treatment with potassium-depleting diuretics.
n) Are currently undergoing immunosuppressive treatments or treatments affecting the CYP3A4 system (i.e. erythromycin, itraconazole, ritonavir, lopinavir, phenobarbital, phenytoin, rifampicin)
o) Have undergone treatment with monoamine oxidase (MAO) inhibitors in the last 14 days
p) Are pregnant (i.e. fertile woman below 60 with a positive urine or plasma human gonadotropin test), currently breast-feeding or not adherent to a sufficient anticontraceptive plan

We will not exclude participants enrolled in other interventional trials, but co-enrollment will be registered in the participant eCRF.

6.3. Participant discontinuation and withdrawal

The procedure for handling withdrawal of consent from a participant will follow national regulations.

A participant who no longer wishes to participate in the trial can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment, by contacting the sub-investigator. To limit the amount of missing data, we will collect as much data as possible from each participant. Therefore, the sub-investigator will ask the participant if they – despite discontinuation – will allow continued data registration through electronic health records and national registers as well as physical follow-up at day 7 and close-out follow-up at day 14, 28 and 6-months.

The sponsor/PI and/or sub-investigator may stop the intervention at any time for an individual participant, if:

- The participant experiences intolerable adverse reactions or events (Suspected Unexpected Serious Adverse Reactions (SUSARs)) related to the trial intervention, including psychotic symptoms, severe infections and organ failure.
- Any clinician (medical doctor) involved in the care of the participant in conjunction with the investigators decide that it is in the best interest of the participant.

Participants discontinued on the intervention by the sponsor/PI or the sub-investigator will be included in the intention-to-treat analysis and the collection of data will continue, including follow-up visits and calls as well as close-out data collection in national registers and electronic health records (given that participants do not withdraw their consent).

Pill strips containing the trial medication should be returned to the sub-investigator or research nurse by participants and destroyed accordingly upon discontinuation or withdrawal.

7 Trial site and personnel

Patients will be recruited from The Mental Health Services in the Capital Region of Denmark (MHSC) and through advertisement. Patients will be included in the study by medical doctors (sub-investigators) under the responsibility of the sponsor/PI.

7.1. Trial site and setting

After pre-screening of out-patients, all trial-related physical meetings, participant interviews and treatment visits will be conducted at the MHSC-affiliated research unit: Biological and Precision Psychiatry Unit, Copenhagen Research Center for Mental Health (CORE), Mental Health Center Copenhagen (MHCC), Gentofte Hospitalsvej 15, 2900 Hellerup.

For in-patients, for whom it is not feasible to leave their in-patient facility, trial-related physical meetings, participant interviews and treatment visits can also be conducted at the psychiatric department at which they are admitted, but the investigations related to the trial will still be performed by relevant trial personal under the responsibility of the PI. After the participant is discharged, all subsequent visits will be conducted at the Biological and Precision Psychiatry Unit, Copenhagen Research Center for Mental Health (CORE).

The principal investigator is employed as a professor and chief consultant at MHSC and the sub-investigator(s) will be employed as medical doctors and PhD-students in the PIs group.

The MHSC is a public, free-of-charge hospital and outpatient service, covering secondary- and tertiary-level psychiatric care in The Capital Region of Denmark.

7.2. Recruitment site

Participants will primarily be recruited through in- and out-patient services the Mental Health Services in the Capital Region of Denmark (MHSC), where it is expected that the majority will be included from the out-patient diagnostic center (Center for Visitation and Diagnostics – CVD) and the out-patient clinics at Mental Health Center Copenhagen (MHCC), all part of MHSC.

Patients are referred to CVD mainly by general practitioners (GPs) for evaluation regarding diagnosis and if treatment at MHSC is indicated. Every year, more than 2000 patients are referred to MHSC through CVD from GPs due to depressive symptoms, providing a large patient flow for the trial.

In addition, participants will be recruited from in- and out-patient clinics at MHSC responsible for the treatment of depression that cannot be managed in the primary care setting.

Treating physicians will be informed of the trial through advertisement and through a pre-programmed pop-up box in the EPIC electronic health journal system (see section 10.1.) and will not be involved in trial-related procedures.

7.3. Trial personnel

The primary trial staff will be constituted by a dedicated research group consisting of the sponsor/PI (MEB, professor, chief physician and specialist in psychiatry), two sub-investigators (TBR and one additional medical doctor/PhD-student), one statistician/data analyst (RHBC, senior statistician), a research nurse, medical students and a project secretary. The research group will be based at MHCC and meet at least once a week.

All personnel will be adequately trained in trial-related procedures as appropriate to their tasks, including use of rating scales, assessment of adverse events and reactions as well as relevant interview. The sponsor/PI will be responsible for the content of the training. In addition, participant interviews and psychometric testing will be video recorded in order for the PI to vet the ratings of the sub-investigators and outcome assessors.

The sponsor/PI will oversee the conduct of the trial and be responsible for the adherence to the protocol, Danish law and Good Clinical Practice (GCP) of the trial. The sponsor/PI will be responsible for reporting

SARs and SUSARs to the authorities. The sponsor/PI will be responsible for the education and supervision of the trial personnel in all trial-related procedures.

The sub-investigators will be responsible for pre-screening, screening, inclusion and enrollment of participants, database management as well as outcome assessment up until day 10 and reporting of SARs and SUSARs to the sponsor/PI. The sub-investigators will be supervised by the PI and any day-to-day trial and/or treatment related questions will be discussed between the sub-investigators and the PI on a daily, ad-hoc basis and through regular supervisor-meetings. For a visual example of the timeline/schedule for the sub-investigator, see appendix 7.

Research nurses and medical students will assist the sub-investigators in ECG measurements and blood draws during the trial. Furthermore, they will conduct follow-up outcome assessments after completed wash-out (day 14, 28 and at 6 months follow-up) including extraction of data from electronic health records.

The statistician will be responsible for analyzing the trial data.

The project secretary will be responsible for booking patient appointments, including follow-up calls.

The sub-investigators, sponsor/PI and statistician will be responsible for drafting the scientific articles based on the findings of the trial.

8 Outcome measures

The table below lists outcomes in the DEXA-Psych study. Primary outcomes, secondary outcomes and safety outcomes will be reported in the primary publication of the trial results. Exploratory outcomes will be reported on in follow-up publications on the trial.

Objective	**Endpoint/outcome**
Efficacy	
Primary	
• To assess the efficacy of dexamethasone as add-on therapy to TAU compared to placebo in improving depressive symptoms	1. Change from baseline (day 0) on the Montgomery-Asberg Depression Rating Scale ($MADRS_{10}$) at day 7. Assessment will be done in accordance with the SIGMA structured interview guide.[43]
Secondary	
To assess the efficacy of dexamethasone as add-on therapy to TAU compared to placebo on:	
• Remission rates	1. Number of participants with remission ($MADRS_{10}$ score less than or equal to 11) before day 28 (“time-to-event”)
• Quality of life	2. Change in quality of life as measured by change from baseline (day 0) on the EQ-5D-5L on day 7.
• Suicidal ideation	3. Change in suicidal ideation as measured by change from baseline (day 0) on the Columbia-Suicide Severity Rating Scale (C-SSRS) on day 7.
• Anxiety	4. Change in anxiety symptoms as measured by change from baseline (day 0) on the

	Hamilton Anxiety Rating Scale (HAM-A) on day 7.
• Functioning	5. Change in functioning as measured by change from baseline (day 0) on the Global Assessment of Functioning (GAF) scale on day 7.
• Psychiatric hospitalization	6. Number of participants with admissions due to psychiatric illness before day 28.
• Suicide attempts	7. Number of participants with suicide attempts (attempted and completed) before day 28.
Safety outcomes	
• To assess the safety and tolerability of dexamethasone as add-on therapy to TAU compared to placebo	1. ARs (including SARs) occurring on or before day 10. 2. All-cause discontinuation of the intervention. 3. Vital signs. 4. Laboratory tests and electrocardiograms (ECG). 5. Score on the Glucocorticoid Toxicity Index (GTI) on day 7. 6. Score on UKU-SSRI on day 7. 7. Change in positive psychotic symptoms as measured by change from baseline (day 0) the Scale for Assessment of Positive Symptoms (SAPS) on day 7. 8. Change in manic symptoms as measured by change from baseline (day 0) on the Young Mania Rating Scale (YMRS) on day 7. 9. Relative risk of admissions due to somatic illness before day 28. 10. All-cause mortality before day 28.
Exploratory	
To assess the efficacy of dexamethasone as add-on therapy to TAU compared to placebo on:	
• Long-term depressive symptoms	1. Change from baseline (day 0) on the $MADRS_{10}$ and $MADRS_6$ at day 28 and at 6-months follow up.
• Depressive symptoms measured on the HAM-D scale	2. Change from baseline (day 0) on the Hamilton Depression Rating Scale ($HAM\text{-}D_6$ and $HAM\text{-}D_{17}$) on day 7 and 28 and at 6-months follow-up.
• Depressive symptoms measured on the MDI scale	3. Change from baseline (day 0) on MDI on day 7 and 28 and at 6-months follow-up.
• Long-term quality of life	4. Change in quality of life as measured by change from baseline (day 0) on the EQ-5D-5L on day 28 and at 6-months follow-up.
• Long-term suicidal ideation	5. Change in suicidal ideation as measured by change from baseline (day 0) on the

	Columbia-Suicide Severity Rating Scale (C-SSRS) on day 28 and at 6-months follow-up.
• Long term anxiety symptoms	6. Change in suicidal ideation as measured by change from baseline (day 0) on the Hamilton Anxiety Rating Scale (HAM-A) on day 28 and at 6-months follow-up.
• Long-term functioning	7. Change in suicidal ideation as measured by change from baseline (day 0) on the Global Assessment of Functioning (GAF) on day 28 and at 6-months follow-up.
• Physical and social activity	8. General level of physical and social activity as measured in the Monsenso app day 1-28
• Long-term remission rates	9. Number of participants with remission of Major Depressive Disorder ($MADRS_{10}$ score less than or equal to 11) at 6-months follow-up.
• Labor market affiliation	10. Relative risk of being unemployed or on full time sick leave at day 7, day 28 and at 6-months follow-up (as assessed through patient interviews) as well as beyond (as assessed through national Danish registers).
• Long-term risk of psychiatric admission	11. Relative risk of admissions due to psychiatric illness before 6-months follow-up (as assessed through patient interview and electronic health records) as well as beyond (as assessed through national Danish registers).
• Long-term risk of suicide attempts	12. Relative risk of suicide attempts before 6-months follow-up (as assessed through patient interview and electronic health records) as well as beyond (as assessed through national Danish registers).
• Long-term mortality	13. All-cause mortality at 2-months and 6-months (as assessed through electronic health records) as well as beyond (as assessed through national Danish registers).
Additional exploratory outcomes	
• To access if baseline levels of inflammatory biomarkers predicts or moderates change in depressive symptoms following dexamethasone treatment	14. Baseline levels of CRP and leucocytes in responders and non-responders

8.1. Minimum Clinically Important Difference

A systemic review on minimum clinically important differences (MCIDs) for depression scales found one study investigating MCID for the MADRS.[44] The study used a distribution-based method and data from clinical trials of patients between 18-65 years of age with MADRS scores above 22 (i.e., corresponding to the population in the DEXA-PSYCH trial) to determine a MCID of between 1.6 to 1.9.[45] In the DEXA-PSYCH trial, we will therefore define the MCID for the primary outcome as a change from baseline in MADRS score of minimum 1.9.

9 Safety

9.1. Well-known reactions to dexamethasone

9.1.1. Short-term

Adverse reactions to dexamethasone treatment are both dose- and time-dependent. Short-term use of dexamethasone is both well-tolerated and widely used clinically. In the present study, the drug will furthermore be used in a low-risk population. The most common serious adverse events reported for systemic glucocorticoid treatment includes sepsis, venous thrombosis, fractures, gastro-intestinal bleedings, psychotic symptoms and heart failure.[46]

9.1.2. Long-term

Long-term use of systemic glucocorticoids is a significant predictor for adverse events including fractures, sepsis, gastrointestinal bleedings, organ failure, weight gain, hypertension, adrenal insufficiency and cataract.[42,46] The most common adverse events associated with glucocorticoid therapy has been collected in the Glucocorticoid Toxicity Index (GTI) – a consensus-based metrics for estimating toxic effects of glucocorticoid exposure.[42]

9.2. Definitions

In the DEXA-PSYCH trial, we will use the definitions below:

Adverse event (AE)

Any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR)

Any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial. The ARs are identified in the Danish Summary of Products Characteristics (SmPC) for dexamethasone and listed for reference in Appendix 8.

Serious adverse event (SAE)

Any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious adverse reaction (SAR)

Any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. A list of ARs from the SmPC that will be considered SARs is provided in Appendix 9.

Suspected unexpected serious adverse reaction (SUSAR)

Any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with SmPC for dexamethasone).

9.3. Risk and safety issues

Glucocorticoid use has been associated with increased risk of psychosis, which might cause harm to patients undergoing treatment for depression; however, recent epidemiological studies have shown that psychosis is a very rare adverse event in treatment with glucocorticoids and that symptoms remit after drug discontinuation.[47]

A primary concern is the development of adrenal gland insufficiency after withdrawal of treatment with synthetic glucocorticoids. However, adrenal insufficiency is considered improbable after <3 weeks of glucocorticoid treatment.[48] Any signs of adrenal insufficiency will be accessed by the sub-investigator on day 8 (see section 5.6.)

In addition, manic symptoms have been associated with use of glucocorticoids and patients with a diagnosis of bipolar disorder, a family history of bipolar disorder or a history of manic or hypomanic symptoms will therefore be excluded from the trial.

Furthermore, patients suffering from depression are at increased risk of suicide. The trial personnel will therefore be instructed in screening of suicidal risk in the trial population, including during the interviews on day 2 and 4 shortly after the initiation of the intervention. According to the Danish SmPC for dexamethasone, acute overdosing with even very high doses does not result in clinical symptoms and does not warrant medical management/hospitalization. Participants with active, suicidal plans are excluded from the trial on grounds of safety.

If the patient at any time during the trial intervention, the wash-out phase or the close-out phase requires hospitalization due to suicidal ideation, psychotic symptoms or other acute psychiatric issues, the trial staff will refer the patient to assessment at the local acute psychiatric admission center. All trial staff with participant contact will be instructed to inform the sub-investigator and/or principal investigator if there are doubts about whether patients require hospitalized. The sub-investigator and/or principal investigator will, if needed, instigate involuntary hospitalization of trial participants.

9.4. Assessment of adverse events

9.4.1. Registration and timing

AEs and ARs will be registered from day 1 to day 10, i.e. during the intervention itself (day 1-7), in the wash-out phase (day 8) and in the days following withdrawal (day 9-10) where there is a risk of developing adrenal gland insufficiency due to the reduction in exogenous glucocorticoid stimulation. Should participants experience one or more AE/AR on day 10, the sub-investigator will be responsible for monitoring, treating and registering the AE/AR beyond the day 10 window.

For all participants, we will actively register the presence or absence of AEs and ARs through physical contact on day 7 and telephonic contact on day 2, 4 and 8 (wash-out phase). In addition, participants will be able and encouraged to report AEs and ARs through the trial hotline. For in-patients participating in the trial, we will additionally record AEs and ARs from electronic health records.

We will register ARs and SARs according to the Danish SmPC for dexamethasone (appendix 8). Furthermore, structured assessment of glucocorticoid toxicity, psychotic symptoms, antidepressant side-

effects and general side effects of psychotropic medications will be conducted on day 7 using the Glucocorticoid Toxicity Index (GTI)[42], the Structed Assessment of Psychotic Symptoms (SAPS) and the UKU-SSRI checklist,[49] respectively (see section 5.6). For this purpose, the GTI will be modified to not include bone density, as the trial participants will not undergo a DEXA-/bone density-scan.

9.4.2. Classification of an event

We will register the occurrence of any ARs, AEs, SARs, SAEs and SUSARs in the groups and report them in the final report according to the definition given above.

9.4.3. Reporting

Any SAEs, SARs or SUSARs will be reported by the sub-investigator to the sponsor/PI without unnecessary delay and latest after 24 hours. If deemed a SUSAR by the sponsor/PI, he will report it to the Danish authorities without further delay and latest after 7 days if fatal and after 15 days if non-fatal. SUSARs will be reported to the EudraVigilance database.

Once a year, the sponsor/PI will submit a safety report, including details on SARs and SUSARs, in accordance with EU legislation through CTIS and thereby to the Danish Medicines Agency and National Ethics Committee. In addition, we will report all SARs as outcome measures and all SUSARs in the final trial report.

10 Recruitment, information and consent

10.1. Recruitment

Treating clinicians at the recruitment site (see section 7.2.) will be informed of the trial through regular information about the project, through presentations at clinical conferences, by posters describing the trial and recruitment procedures, and trough the trial as well as hospital website.

If inclusion criteria appear to be met, the treating clinician is encouraged to inform the patient of the possibility to participate in the DEXA-PSYCH trial. If the potential participants consent, the treating physician will inform the sub-investigator about the participant and hand over his/her contact information to the sub-investigator. Consent from the participant will grant the sub-investigator allowance to contact the participant and access his/her electronic health record for pre-screening purposes.

10.1.1. Recruitment through EPIC

In selected departments of the MHSC – including, but not limited to, the Center for Visitation and Diagnostics – a pre-programmed pop-up message informing the treating clinician on eligibility of the patient to participate in the trial will appear in the EPIC electronic health journal system, which is used throughout the MHSC. Physicians at these departments will be informed about the pop-up messages and the DEXA-PSYCH trial prior to the implementation of the messages.

If a patient a) is between 18 and 64 years of age and b) is diagnosed with depression (excluding mild depression) or have depression listed as referral diagnosis, the pop-up box in the electronic health record will inform the clinician about the potential eligibility of the patient in the context of an out-patient consultation. If the patient consent to be contacted about the trial, the physician can tick a box in the pop-up window and the contact info of the potential participant will be send automatically to the “In-Basket” (inbox) of the sub-investigator in the EPIC system. If the patient or the treating physician choose the “No consent” option, the pop-up box will not re-appear. If the pop-up box is closed without any decision being made, it will re-appear at the next consultation with the patient.

10.2. Pre-screening

After consenting to be contacted in the recruitment process, the participant will be contacted by the sub-investigator informing him/her about the objective of the trial, the intervention (including known adverse effects) and the time commitment required to undertake the study. In addition, the sub-investigator will pre-screen the patient by phone to evaluate if inclusion criteria appear to be met and ensure that no exclusion criteria are obviously met. If the patient is still interested in participating, an information meeting will be scheduled thereafter. The patient will be offered written information prior to the information meeting (appendix 4).

10.3. Information meeting

The patient will, prior to the meeting, be informed about the agenda, and that he/she are free to bring an assessor or a relative.

At the information meeting, detailed oral information about all relevant aspects of the study will be given by the sub-investigator. This will be done in a confidential and calm setting. The potential participant will be given amble time to ask questions. Written information will also be provided if this was not received in advance (appendix 4).

The voluntary nature of the participation in the trial, and that the participant may withdraw his/hers consent at any time without giving a reason and without treatment consequences, will be carefully emphasized. The leaflet "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt" will be handed out to the patient and, if present, to the assessor/relative.

10.4. Reflection time and informed consent

The potential participant will be offered 24 hours reflection time from the information meeting to written consent will be obtained, but more if the patient wishes so. If the patient decides to participate, he/she will be invited for a screening, enrollment and randomization consultation (day 0) conducted by the sub-investigator. Here, the patient will sign The National Committee on Health Research Ethics' statement of consent ("Den Videnskabsetiske Komités Samtykkeerklæring"). The informed consent will also be signed by the sub-investigator and scanned into the patient eCRF.

Informed consent can be withdrawn at any time during the trial.

10.5. Screening, enrollment and randomization (day 0)

Upon provision of informed consent, the patient will be screened to ensure that the patient meets all inclusion criteria and does not meet one or more exclusion criteria. This will be done using the SCAN interview and a structured questionnaire corresponding to the in- and exclusion criteria programmed in the eCRF. The interview will be conducted by the sub-investigator.

If the patient is found eligible for the trial, the patient will be enrolled, baseline variables will be recorded as described in section 11.1.4 and the participant will be randomized.

11 Collection and storage of data and biological material

11.1. Patient data

All participant data will be handled according to the General Data Protection Regulation (GDPR), the Data Protection Act (Databeskyttelsesloven) and the Health Act (Sundhedsloven).

The data will be saved until 25 years after the end of the trials. If the participant withdraws consent to data storage during the trial, the data recorded will be deleted within 72 hours, but the participant randomization ID will be kept in the REDCap database for monitoring and reporting purposes.

11.1.1. eCRF and database (REDCap)

All participant data collected at trial visits – whether physically or by phone – will be entered into the eCRF using either a computer interface or an iPad (as approved by the Capital Region of Denmark Center for IT, Medico and Telefoni (CIMT)) during the interviews. The eCRF will be programmed in REDCap, a secure survey database approved by CIMT. The REDCap project database will contain all trial related data (except national register data) and any changes in the database will be logged automatically.

Prior to initiation of any data analysis on actual trial data, we will conduct a database lock ensuring that data cannot be changed.

The database will be regularly managed, including routine range checks, data validation and data extraction.

11.1.2. Source data

Data sources will be participant interviews (during which the sub-investigator or outcome accessor writes notes and/or scores directly into the eCRF), participant electronic health records (EHRs), Danish national registers, ECG strips, psychometric scoring sheets, the Monsenso app and laboratory test results as depicted in the electronic health record/EPIC.

Access to patient electronic health records will be granted to the sponsor/PI and his delegates until the last follow up visit has been completed (6 months after initiation of the intervention, +/- 14 days).

The research group already holds a broad approval for register-based studies related to psychiatric illness. The registers will be used to follow participants beyond the 6-months visit for outcomes coded in the registers, e.g. admissions, mortality, suicide attempts and labor-market affiliation. The research group manages a project-database at Statistics Denmark (DST) containing most of the nationwide registers. In this secured DST project-database, a subfolder for the DEXA-PSYCH study participants with linkage to their register data will be made.

The Monsenso product is a CE marked, Class I, Medical Device, and is thus approved for use in the treatment of patients and ISO 13485 certified according to the requirements of medical devices. Furthermore, Monsenso is approved by the Capital Region of Denmark Center for IT, Medico and Telefoni (CIMT). Patients will be instructed in the installation and use of the app at baseline. If the patient a) does not have a smartphone compatible with the app and/or b) do not which to use the app, the patient will still be eligible for the study. Participants will be able to call the sub-investigator if they face any issues using the app and the sub-investigator will contact the patients if adherence is not reported in the app in order to a) encourage adhesion and secure that registration of data in the app is done in accordance with the protocol.

11.1.3. Data access

Only the sponsor/PI, statistician and sub-investigators will have access to the entire database. Other trial personnel (outcome assessors, i.e. nurses and medical students) will have limited access to the individual eCRF in order to input data.

Data will be pseudonymized, such that patient names and CPR numbers are not included in the database. Instead, the patient randomization ID/trial ID will be used to identify the patient. This ID will also be used to mark blood samples and relevant source document pertaining to the participant. A participant identity log

containing the trial ID, inclusion and randomization date, participant name and CPR-number will be store in the Trial Master File as well as in a password protected folder on The Capital Region of Denmark network, which is protected in accordance with GDPR regulations. Only the sponsor/PI and sub-investigators will have access to the identify log.

The sponsor/PI will allow direct access to the database and any source data/documents (including patient electronic health records) for monitoring, auditing and/or inspection purpose from the GCP units, the Danish Medicines Agency (LMST) and the Danish Data Protection Agency (Datatilsynet), respectively.

11.1.4. Variables, data collection and procedures

The following variables/data points will be recorded at the designated visits during the trial. All data will be entered into the eCRF (REDCap). In addition, text boxes for comments that do not fit under the listed variables will be made available at each trial visit.

Furthermore, if the trial staff is informed about suicidal attempts, hospitalization, death, SARs, SAEs or SUSARs through other means than the participant visits (e.g. participant EHRs or calls to the trial hotline), this will be recorded in the eCRF.

11.1.4.1. Day 0: Screening, enrollment and randomization

The interview and data recording will be conducted by the sub-investigator during the interview on day 0. Participant electronic health records will be used to validate data from the interview and collect data on variables not covered during the interview. All interviews will start at 9 AM (a variability of +/- 2 hours will be allowed).

Trial identification data

Data	**Source**
Patient randomization ID/trial ID	Randomization envelope containing trial medication
Date of enrollment	Patient interview/eCRF
Date of birth	Patient interview/eCRF and EHR
Sex	Patient interview/eCRF

Screening data

Data	**Source**
• SCAN, section 6 items (see SCAN manual for detailed description of rating items)	Digital questionnaire in eCRF completed during patient interview
• SCAN, section 10 (see SCAN manual for detailed description of rating items)	Digital questionnaire in eCRF completed during patient interview
• Diagnosis and diagnostic code (based on SCAN interview)	Reported in eCRF based in SCAN interview at the discretion of the sub-investigator
• Diagnosis and diagnostic code (as noted in patient journal)	Patient electronic health record (EHR)
• Date of onset of current depressive episode	Patient interview/eCRF and EHR
• In- or out-patient status	Patient electronic health record (EHR)
• Is the patient a fluent Danish and/or English speaker? (yes/no)	Patient interview/eCRF

• Is the patient habile to give informed consent? (yes/no)	Patient interview/eCRF and EHR
• Does the participant have a known hypersensitivity to glucocorticoids? (yes/no)	Patient interview/eCRF and EHR
• Medication currently and previously taken (including dosage and time of treatment initiation) o Is the patient undergoing treatment with immunosuppressive treatments? o Is the patient undergoing treatment with drugs affecting the CYP3A4 system? o Has the patient undergone systemic glucocorticoid treatment in the last 14 days? (yes/no) o Has the patient undergone treatment with monoamine oxidase inhibitors in the last 14 days? (yes/no) o Has the patient been vaccinated within the last 14 days or planning on being vaccinated in the up-coming 21 days? (yes/no)	Patient interview/eCRF and EHR
• History of somatic and psychiatric illness (including date of onset and remission for each illness), as well as prior depressive episodes (if relevant), age of onset of depression and o Psychiatric admissions ▪ Date ▪ Length o Prior suicide attempts ▪ Date ▪ Method o Alcohol use ▪ Units ▪ Harmful use ICD-10 10.1. (yes/no) ▪ Dependence ICD-10 10.2. (yes/no) • Specific questions covering: o Psychotic disorder (yes/no) o Personality disorder (yes/no) o Bipolar disorder (yes/no) o Immunodeficiency (yes/no) o Systemic fungal infection (yes/no) o Tuberculosis (yes/no) o Hematological malignancy (yes/no) o Epilepsy (yes/no) o Myasthenia gravis (yes/no) o Ocular herpes simplex (yes/no) o Pheochromocytoma (yes/no) o Systemic sclerosis (yes/no) o Acute coronary syndrome within the last 6 months (yes/no)	Patient interview/eCRF and EHR

○ Diabetes (yes/no)	
• Family history of somatic and psychiatric illness including diagnostic code and family relation and specific questions covering: ○ Bipolar disorder (yes/no)	Patient interview/eCRF and EHR
• ECG ○ QTc interval (in ms)	ECG scanned into eCRF from physical ECG strip. QTc calculated on ECG machine and manually typed in eCRF
• Blood tests: ○ Hemoglobin ○ Erythrocytes ○ Leukocytes ○ Lymphocytes ○ Thrombocytes ○ Blood glucose ○ HbA1c ○ Sodium ○ Potassium ○ Creatinine ○ Cholesterol (LDL, HDL) ○ Triglycerides ○ ALAT ○ Phosphatase ○ TSH ○ hCG ○ CRP	Laboratory test results transferred from patient EHR to eCRF.

Baseline data

Data	**Source**
• Employment status (employed full-time, employed part-time, on sick-leave, unemployed)	Patient interview/eCRF, EHR and Danish national registers
• Highest obtained education qualification (primary school, vocational training, upper-secondary school, bachelor level, masters level oherr PhD level)	Patient interview/eCRF, EHR and Danish national registers
• Ethnicity (asian, african, latino, caucasian)	Patient interview/eCRF
• Annual income	Patient interview/eCRF
• Smoking status (current smoker, previous smoker, non-smoker)	Patient interview/eCRF and EHR
• Height (recorded in centimeters to the nearest millimeter)	Patient interview/eCRF
• Weight (recorded in kilogram to the nearest 0.1 kg)	Patient interview/eCRF
• Blood pressure, heartrate, temperature, respiratory frequency	Patient interview/eCRF

Clinical ratings and interviews

Data	Source
• $MADRS_{10}$ (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-D_{17} (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• MDI (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-A (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• GAF (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• YMRS(see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• C-SSRS (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• EQ-5D-5L (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• SAPS (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• BACS (see manual for individual rating items)	Physical questionnaire completed during patient interview and recorded in eCRF

11.1.4.2. Day 2: Safety assessment

The sub-investigator will contact the participant by phone to encourage adherence and assess ARs or AEs.

Data	Source
• Symptoms of AR and SARs (appendix 8 and 9)	Digital questionnaire in eCRF completed during patient interview

11.1.4.3. Day 4: Mid-term assessment

The sub-investigator will contact the participant by phone to encourage adherence, assess MADRS-10 score and any ARs or AEs.

Data	Source
• $MADRS_{10}$ (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• Symptoms of AR and SARs (appendix 8 and 9)	Digital questionnaire in eCRF completed during patient interview

11.1.4.4. Day 1-28: Variables scored daily through the Monsenso app

The following variables will be recorded through the Monsenso app daily during day 1-28 of the trial. The patients will be instructed to report their data at the same time every day (preferable at 12 PM).

Participant reported data

Data	Source
• Modified, self-reported $MADRS_{10}$ score, asking participants to evaluate symptoms within the	Recorded in Monsenso app and transferred to eCRF

last 24 hours as opposed to 3 days (see manual for individual rating items) ○ Time and date of scoring will be recorded	
• Have you taken the pill from the study today? (yes/no) ○ If no, why? Please describe.	Recorded in Monsenso app and transferred to eCRF

Automatically recorded data

Data	Source
• Physical activity as measured by movement	Recorded in Monsenso app and transferred to eCRF
• Social activity as measured by outgoing and incoming calls.	Recorded in Monsenso app and transferred to eCRF

11.1.4.5. Day 7: Physical visit and intervention termination

The interview and data recording will be conducted by the sub-investigator during the interview on day 7. Participant electronic health records will be used to validate data from the interview and collect data on variables not covered during the interview. All interviews will start at 9 AM (a variability of +/- 2 hours will be allowed).

Adherence

- Has the participant been adherent to the trial intervention (self-reported)? If no, why?

Clinical ratings and interviews

Data	Source
• $MADRS_{10}$ (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-D_{17} (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• MDI (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-A (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• GAF (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• YMRS(see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• C-SSRS (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• EQ-5D-5L (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• SAPS (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview

Side-effects

Data	Source

• UKU-SSRI (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• GTI (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• Symptoms of AR and SARs (appendix 8 and 9)	Digital questionnaire in eCRF completed during patient interview

Physiological measures

Data	**Source**
• ECG, including QTc interval (in ms)	ECG scanned into eCRF from physical ECG strip. QTc calculated on ECG machine and manually typed in eCRF
• Blood tests (levels): o Hemoglobin o Erythrocytes o Leukocytes o Lymphocytes o Thrombocytes o Blood glucose o HbA1c o Sodium o Potassium o Creatinine o Cholesterol (LDL, HDL) o Triglycerides o ALAT o Phosphatase o TSH o HCG o CRP	Laboratory test results transferred from patient EHR to eCRF.
• Height (recorded in centimeters to the nearest millimeter)	Patient interview/eCRF
• Weight (recorded in kilogram to the nearest 0.1 kg)	Patient interview/eCRF
• Blood pressure, heart rate, temperature, respiratory frequency	Patient interview/eCRF

Event measures

Data	Source
• Employment status (employed full-time, employed part-time, on sick-leave, unemployed)	Patient interview/eCRF, EHR and Danish national registers
• Patient-reported AEs and ARs	Patient interview /eCRF
• Admission due to psychiatric illness during the last 7 days. If yes, time of admission will be specified.	Patient interview/eCRF, EHR and Danish national registers
• Suicide attempts due to psychiatric illness that last 7 days. If yes, time of attempt will be specified.	Patient interview/eCRF, EHR and Danish national registers

• All-cause mortality.	Patient interview/eCRF, EHR and Danish national registers

Test of blinding

Data	Source
• (Should be recorded at the end of the interview and before asking the patient) Do you think the patient received the active drug of placebo? (placebo/active drug)	Sub-investigators evaluation/eCRF
• Does the patient think he/she is in the active drug or placebo group? (placebo/active drug)	Patient interview/eCRF

11.1.4.2. Day 8: Interview by phone in wash-out phase

The sub-investigator will contact the participant by phone to assess adverse events including symptoms of glucocorticoid withdrawal.

Adverse events and side-effects

Data	Source
• Symptoms of AR and SARs (appendix 8 and 9)	Digital questionnaire in eCRF completed during patient interview

Day 14: Interviews by phone in the close-out phase

The interview and data recording will be conducted by phone by a trained research nurse or medical student. The assessor will inform the sub-investigator in case of suicidal ideation or adverse events with no further delay. Patient electronic health records will be used to validate data from the interview and collect data on variables not covered during the interview.

Clinical ratings and interviews

Data	Source
• $MADRS_{10}$ (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview

Events

Data	Source
• Admission due to psychiatric illness that last 7 days. If yes, time of admission will be specified.	Patient interview/eCRF, EHR and Danish national registers
• Suicide attempts due to psychiatric illness that last 7 days. If yes, time of attempt will be specified.	Patient interview/eCRF, EHR and Danish national registers

11.1.4.6. Day 28 and 6-months: Interviews by phone in the close-out phase

The interview and data recording will be conducted by phone by a trained research nurse or medical student. The assessor will inform the sub-investigator in case of suicidal ideation with no further delay. Patient electronic health records will be used to validate data from the interview and collect data on variables not covered during the interview.

Clinical ratings and interviews

Data	Source
• $MADRS_{10}$ (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-D_{17} (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• MDI (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• HAM-A (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• GAF (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• C-SSRS (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview
• EQ-5D-5L (see manual for individual rating items)	Digital questionnaire in eCRF completed during patient interview

Event measures

Data	Source
• Employment status (employed full-time, employed part-time, on sick-leave, unemployed)	Patient interview/eCRF, EHR and Danish national registers
• Admission due to psychiatric illness since last contact. If yes, time of admission will be specified.	Patient interview/eCRF, EHR and Danish national registers
• Suicide attempts due to psychiatric illness since last contact. If yes, time of attempt will be specified.	Patient interview/eCRF, EHR and Danish national registers
• All-cause mortality.	EHR and Danish national registers

11.2. Biobank

Upon enrollment, the participants will be asked if they wish to contribute biological material to an already established biobank at the Copenhagen Research Center for Mental Health. The biological material will be defined as "extra" material in the DEXA-PSYCH project, in accordance with the definitions stipulated by the National Center for Ethics (https://nationaltcenterforetik.dk/anmeld-forsoeg/vejledninger/biobanker#5).

The biobank is established under the PSYCH-FLAME project and covered by a separate protocol under which the research group holds approval for collection, storage and future analysis on immune-related biomarkers in patients with depression, psychotic disorders and healthy controls. The prospective participants will be presented with a separate subject information letter and consent form detailing the conditions under which the contribute to the PSYCH-FLAME biobank. If the participants do not consent to contribution of extra biological material, they can still participate in the DEXA-PSYCH study.

12 Statistical plan and data analysis

The analyses will be done according to the principles stipulated in International Clinical Harmonization (ICH-GCP) guidelines. The protocol and detailed statistical analysis plan will be published online at the trial website and in a peer-reviewed journal prior to analysis.

12.1. Sample size and power calculations

Two studies have previously compared glucocorticoids to placebo for treatment of depression. DeBattista et al.[26] compared 6 subjects treated with glucocorticoids to 10 subjects treated with placebo observing a mean difference of 7.8 favoring glucocorticoids on the HAM-D_{21} scale after 1 day of treatment with a pooled standard deviation of 4.8. Arana et al.[25] compared 19 subjects treated with glucocorticoids for four days to 18 subjects treated with placebo for four days observing a mean difference of 6.2 favoring glucocorticoids on the HAM-D_{21} scale 14 days after treatment initiation with a pooled standard deviation of 6.3. Based on these results, the required sample sizes to detect the observed differences are 10 and 23 subjects in each treatment arm with a power of 90% and 5% significance level.

However, the previous studies were rather limited in sample size and have not been replicated. We therefore assume that the effect in this larger and much more thorough trial will be substantially smaller. Our meta-analysis based on the previous studies yielded an SMD of 0.93 for dexamethasone. If the DEXA-PSYCH study finds an effect size half or that (SMD = 0.42), this would make dexamethasone comparable to the effect sizes of the most effective current antidepressants, the TCAs (SMD = 0.43). We find this assumption reasonable, as it both takes the larger effect sizes of the previous studies into account, while considering that more thoroughly tested anti-depressants have not been shown to yield greater effects than approximately 0.4.Our ongoing PSYCH-FLAME study includes subjects with new onset depression from the same geographical area in a case-control study. Here the mean (standard deviation) HAM-D_{17} score among 106 of the first subjects was 20.6(6.3). Conservatively assuming 20% drop-out of patients the following table illustrates the relation between power and the mean difference ("delta") that a trial with 150 subjects randomized to each treatment arm that can be detected. The standardized mean difference (SMD) is the detectable difference (delta) divided by the standard deviation:

Power	**delta**	**SMD**
80%	2.29	0.36
85%	2.45	0.39
90%	2.65	0.42
95%	2.94	0.47
99%	3.50	0.56

Assuming an effect size for dexamethasone of 0.42, this would yield a power of 90 % for a study with a total of 300 participants. For this reason, we are aiming to include 300 participants in the trial, with 150 in the intervention arm and 150 in the control arm.

12.2. Definition of analysis sets

Two analysis sets will be used for analyses of trial data:

- The full analysis set (FAS) includes all randomized subjects with at least one post-baseline measurement of the outcome. Subjects contribute to the analyses "as randomized" following the intention-to-treat (ITT) principle.

- The safety analysis set (SAS) includes all randomized subjects who took at least one dose of randomized treatment. Subjects contribute to evaluation "as treated."

Observe that the number of subjects in the FAS may differ across outcomes.

12.3. Statistical analyses

If necessary, a statistical analysis plan (SAP) will be written and finalized before unblinding of the trial. The SAP may contain further details on the statistical analyses, models, and methods. Any deviations from the published SAP will be documented in the final trial report.

Outcomes pertaining to the effect of dexamethasone will be analyzed using the FAS. Outcomes pertaining to the safety of dexamethasone will be analyzed using the SAS.

Baseline values are obtained at the baseline visit. If baseline values are missing the last available measurement before randomization is used. If no such measurements exist, missing baseline values are imputed (single imputation) with the mean baseline value of all subjects with non-missing baseline values.

Effect endpoints will be reported with an effect estimate, a 95% two-sided confidence interval (CI) and two-sided *p*-values. Superiority of the primary endpoint can be claimed if the effect favors dexamethasone and the p-value is less than 0.05.

12.4. Estimands

The primary estimand is an *efficacy estimand* aiming to quantify the average treatment effect of dexamethasone as compared to placebo if taken according to the schedule described in the protocol.

12.5. Primary analysis

The primary statistical analysis of the primary outcome will address the primary estimand.

The primary endpoint is the change in $MADRS_{10}$ score (the primary outcome) from baseline to the day 7 visit.

The intermediate assessments used in the primary analysis are the assessments of the primary outcome at the day 4 visit.

Assessments are considered *on-treatment* if randomized treatment was taken on the day, or the day before, the assessment is made.

The primary analysis model is a Mixed Model for Repeated Measurements (MMRM) for the post-baseline assessments of the primary outcome variable. The model includes the covariates treatment arm and baseline assessment of the outcome variable all nested in visit. Other covariates may be included as appropriate. An unstructured variance-covariance for measurements within the same subject will be used. The MMRM will all use on-treatment assessments; assessments from subjects who are not on-treatment will not contribute to the model. Subjects who have no on-treatment post-baseline assessments will not contribute to the model.

If the measurements of all subjects who contribute to the MMRM are all on-treatment and non-missing, the MMRM mathematically reduce to an analysis of covariance (ANCOVA) for the primary outcome with treatment arm and baseline assessment of the outcome variable as a covariates.

The MMRM handles missing values of the primary outcome variable under *missing at random* (MAR) assumptions.

12.5.1. Subgroup analyses

Pre-specified subgroup variables:

- Age: <40 year vs. >=40 years of age (might be changed within a span of +/- 10 years when we defined the content of the SAP, depending on age distribution in the participant groups)
- Severity of depression: moderate ($MADRS_{10}$ score 22-29) vs. severe depression ($MADRS_{10}$ score 30 or above)
- Sex: male vs. female

Subgroup analyses are performed using primary analysis model but also includes the subgroup variables as covariates and the interaction between the subgroup variable both nested within visit (if present). The *p*-value for the interaction at the primary endpoint quantifies the evidence of effect modification by the subgroup variable.

12.6. Analyses of secondary outcomes

All continuous outcomes measured as concentrations or ratios will be log-transformed prior to analysis and estimated effects, means and confidence intervals will be back-transformed and presented on the original scale.

Binary outcomes will be analyzed using logistic regression models.

Time-to-event outcomes will be analyzed using Cox proportional hazard models.

For secondary outcomes, *p*-values will be reported both crude and after adjustment for multiple testing.

13 Quality control and assurance

13.1. Monitoring

The DEXA-PSYCH RCT will be continuously monitored by the Good Clinical Practice (GCP) unit of Copenhagen University Hospital, Frederiksberg Hospital, Nordre Fasanvej 57, Skadestuevej 1, parterre, 2000 Frederiksberg.

After consent is obtained, investigators will have access to the participants electronic health records for quality control and monitoring. The sponsor/PI will allow direct access to source data and database data for monitoring purposes as described in section 11.1.

13.2. Drug traceability measures

The registration of the batch numbers and the expiry dates of the dexamethasone will be done at the pharmacy and matched to randomization numbers as described in section 5.2.1.3. These data will not be registered in the trial documents but can be obtained by the sponsor/PI or the authorities if needed.

14 Legal and organization aspects

14.1. Finance

The trial is funded by unrestricted grants to the PI from the Novo Nordisk Foundation (DKK 8.869.996) and by the MHSC. The grant will be paid according to the grant agreement between the funding body and the sponsor/PI. The Novo Nordisk Foundation has not been or will not be involved in the design, conduct, analyses, or reporting of the trial nor will it have ownership of the data. The sponsor/principal investigator, sub-investigators and other trial staff have no financial affiliations to the Novo Nordisk Foundation.

14.1.1. Compensation

Participant expenses, including transport to and from the trial site and food during the physical visits, will be covered by the trial budget.

14.2. Insurance

Study participants are covered by the Patient Compensation Association.

15 Plan for publication, dissemination and organization

The full protocol will be assessable to the public and the protocol will be published. Participant level, anonymized datasets will be accessible through the Zenodo repository (CERN) after the termination of the trial, as requested by the Novo Nordisk Foundation. Moreover, results will be disseminated through conferences, patient organizations and through Danish and International media.

The trial will be registered on CTIS and trial reporting on the register will be conducted in accordance with applicable European regulations (i.e. within one year of trial completion) as well as on ClinicalTrials.gov.

15.1. Articles and authorship

The results of the trial will be published in a high-ranking international, peer-reviewed journal in accordance with the CONSORT Statement and irrespective of whether the results are positive, negative or inconclusive.

Authorship will be granted according to the guidelines from the International Committee for Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). The listing of authors will be as follows on the primary publication: T.B. Rømer will be first author, R.H.B. Christensen will be second author and M.E. Benros the last and corresponding author. The PI may grant additional authorships depending on personal input as per the Vancouver definitions.

The funding sources will be acknowledged, but they will have no influence on the data handling or analyses, the writing of the manuscript or the decision to publish.

15.2. Sub-studies

Sub-studies will be encouraged if they do not hamper the completion of the main protocol and can be conducted after approval of the specific protocol by the sponsor/principal investigator and the authorities. Thus, specific protocols for any sub-studies will be submitted to and approved by the relevant authorities and ethic committees before the commencement of such studies.

15.3. Intellectual property rights

The MHCC owns the trial data.

15.4. Organizational framework

The trial will take place and be managed from the Biological and Precision Psychiatry group at the Copenhagen Research Center for Mental Health, Mental Health Centre Copenhagen (MHCC), Mental Health Services in the Capital Region of Denmark (MHSC). The sponsor/principal investigator and the research center have extensive expertise within clinical studies, randomized controlled studies and register-based and biobank-based research. The Copenhagen Research Centre for Mental Health is a leading Danish psychiatric research institution, which has twice been awarded with the “Global Excellence in Health” prize.

It consists of 65 researchers, including 10 senior researchers, 27 PhD students, a data manager, two senior statistician, three scholarship students and many research assistants.

The day-to-day organization of the trial will be the responsibility the sub-investigators (2 medical doctors hired as PhD students) under the supervision of the principal investigator (MEB) and will be carried out by a research group consisting of the sponsor/PI, two sub-investigators (TBR and one additional medical doctor), one senior statistician/data analysts (RHBC), one research nurse, one project secretary and one or more medical students (see section 7.3. for additional information). The research group will be based at MHCC and meet at least once a week.

For trial GANNT chart, see appendix 3.

16 References

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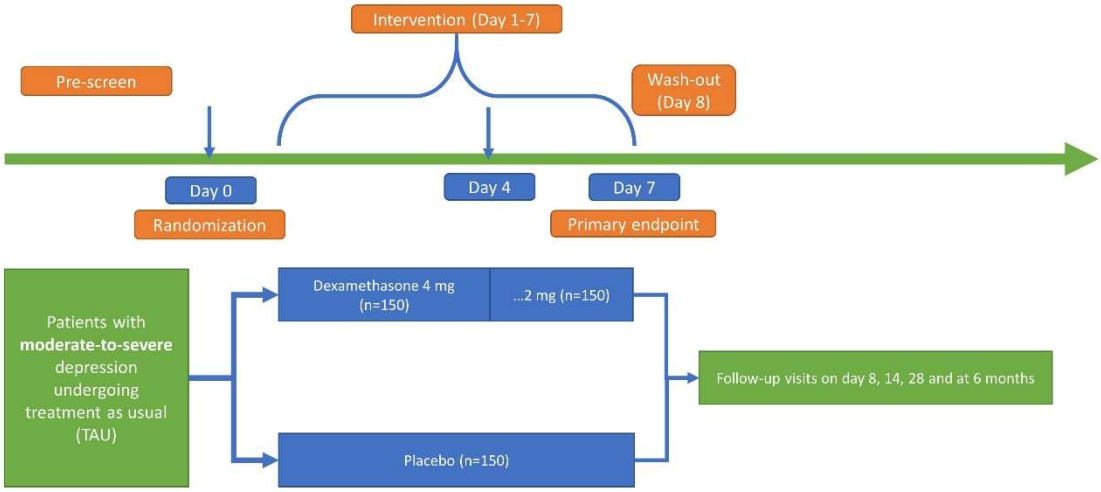
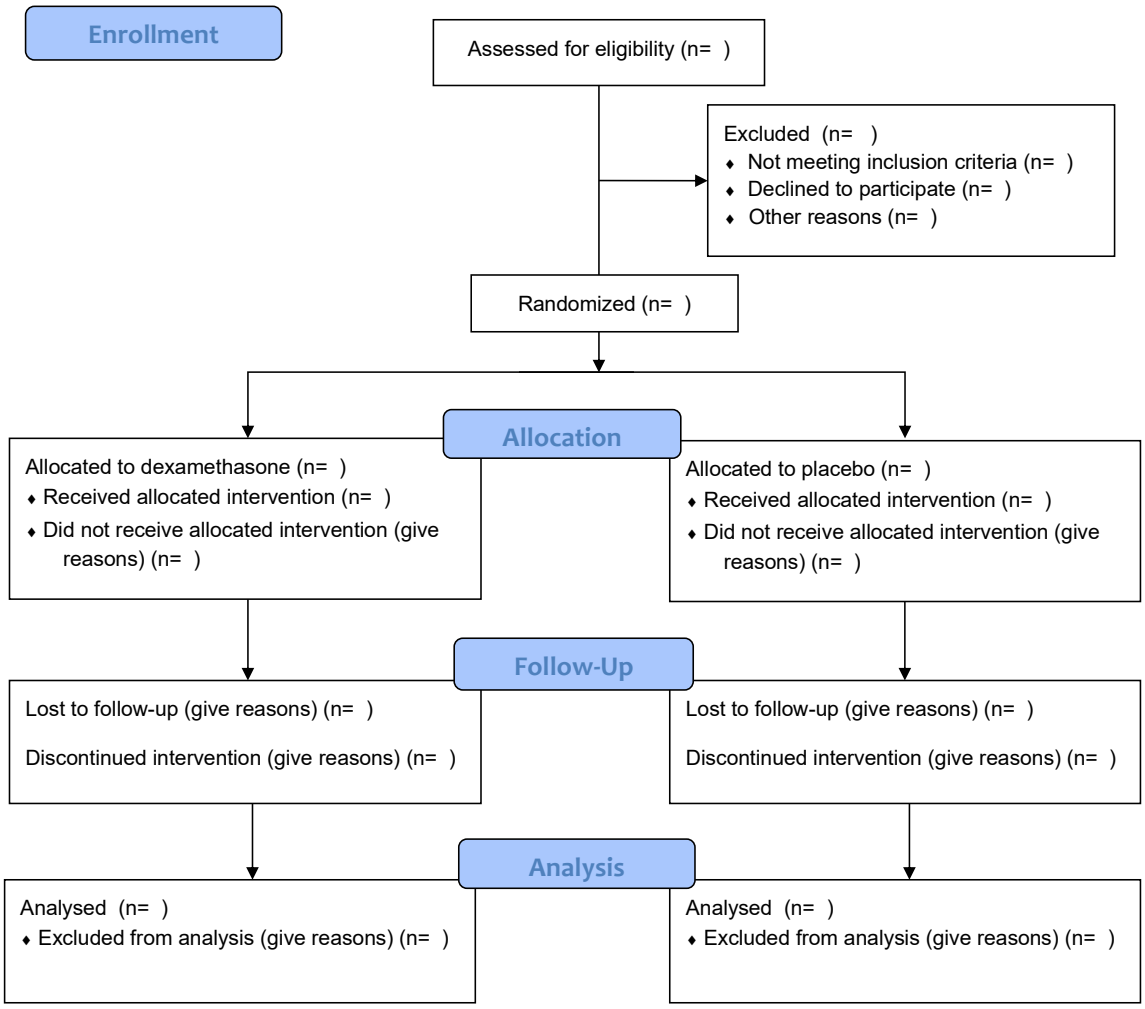
Appendix 1: Trial design

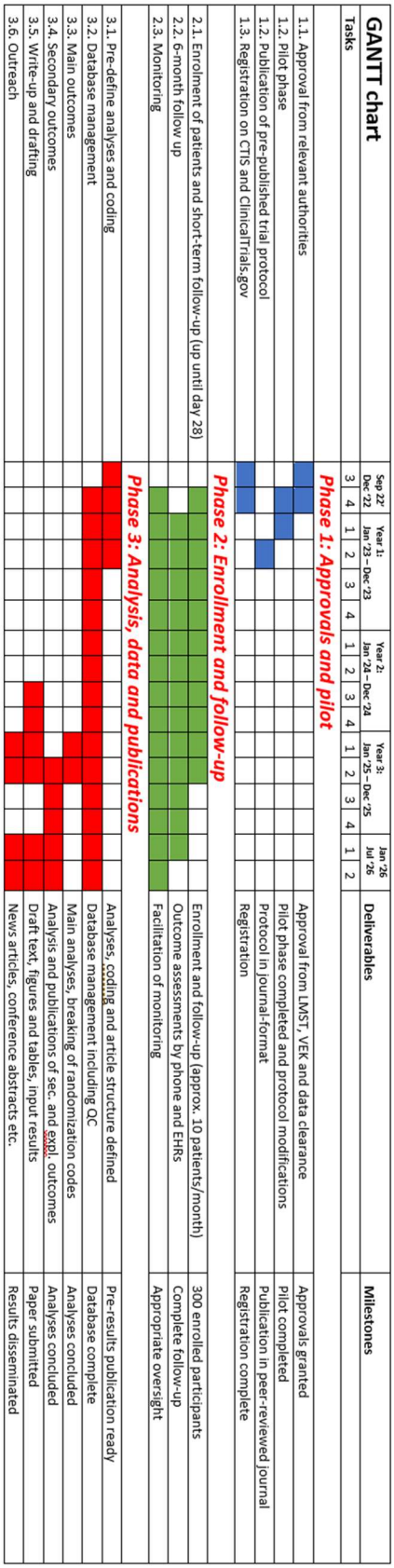


All participants will undergo treatment as usual (TAU) throughout the entire study.
Dexamethasone dose in the intervention group will be reduced from 4 mg to 2 mg on day 4.
Physical visits will occur on day 0 and 7. Telephonic visit will occur on day 4, 8, 14, 28 and at 6 months.
Primary endpoint is $MADRS_{10}$ score assessed at a physical visit.
Patients will rate their depressive symptoms daily on the self-reported $MADRS_{10}$ scale daily from day 1-28.

Appendix 2: Trial CONSORT flow chart



Appendix 3: GANNT chart



Appendix 4: Participant information (Danish)

Information om deltagelse i et videnskabeligt forsøg for patienter med moderat til svær depression

Vi vil spørge, om du vil deltage i et videnskabeligt forsøg om behandling af patienter med depression. Forsøgets titel er *"DEXA-PSYCH studiet: Dexamethason til behandling af moderat-til-svær depression"*. Studiet er et offentligt forskningsprojekt som professor og overlæge Michael Eriksen Benros har taget initiativ til at starte.

Før du beslutter, om du vil deltage i forsøget, skal du fuldt ud forstå, hvad forsøget går ud på, og hvorfor vi gennemfører forsøget. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Det er frivilligt at deltage i forsøget. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Deltager du ikke i forsøget, eller vælger du at trække dig fra forsøget, vil du fortsat modtage tilbud om behandling af depression efter gældende, danske retningslinjer.

Hvad er formålet med studiet? Og hvorfor udfører vi det?

Lægemidlet dexamethason har været afprøvet i mindre studier til behandling af depression og disse studier tyder på, at dexamethason har en hurtig og lindrende effekt på depressionssymptomer. Vi ønsker derfor at undersøge effekten i et stort, velgennemført studie, der kan afgøre om lægemidlet kan forbedre den nuværende behandling af depression.

Dexamethason er et stof, der ligner et hormon, som mennesket producerer i vores binyrer (hormonet kaldes kortisol). Hormonet kortisol har en række virkninger på kroppen og reducerer blandt andet inflammation, der er en "betændelsestilstand". Meget forskning peger på, at netop en øget grad af inflammation kan øge risikoen for depression. Ideen bag studiet er, at dexamethason kan være med til at dæmpe betændelsestilstande, der kan medvirke til depressionssymptomer.

Dexamethason er et lægemiddel, der har været anvendt i årtier. Stoffet er særligt anvendt til behandling af sygdomme, hvor aktivering af immunsystemet er involveret, men er aktuelt ikke godkendt til behandling af depression. Dexamethason er et velafprøvet lægemiddel med en velkendt virknings- og bivirkningsprofil.

Hvis du siger "ja" til at deltage i studiet, vil du i syv dage skulle tage en pille klokken 9 om morgenen. Pillen vil enten indeholde det aktive lægemiddel (dexamethason) eller være en kalkpille, som ikke indeholder aktive lægemidler (også kaldet "placebo"). Hverken du eller vi ved hvad pillen indeholder – og på den måde kan vi undersøge, om den effekt, du måtte opleve af behandlingen, faktisk skyldes medicinen eller måske nærmere har noget af gøre med dine og vores forventninger til forsøget. Samtidigt med, at du deltager i forsøget, vil den vanlige behandling af din depression (eksempelvis antidepressiv medicin eller psykologsamtaler) fortsætte uændret. Alt i alt vil 300 personer deltage i forsøget.

Hvad får du ud af det?
Vi håber på, at medicinen vil kunne hjælpe dig til hurtigere at få det bedre. Tidligere forskning har som nævnt vist, at dexamethason kan reducere depressive symptomer meget hurtigt og efter kun kortvarig behandling. Samtidigt vil du med din deltagelse hjælpe med at fremme videnskaben og forbedre den behandling, som vi har i psykiatrien. Hvis studiet viser, at dexamethason virker, vil fremtidige patienter kunne få gavn af behandlingen, der er både billig og sikker. Det vil være muligt for dig at få at vide, om du har fået medicinen eller kalktabletten, og hvad studiet overordnet har vist, når hele studiet er færdigt og den sidste deltager har været til den sidste kontrol. Vi regner med, at dette sker senest i 2026.

Hvad sker der i studiet?
Før du deltager i studiet, vil du blive inviteret til et informationsmøde med den læge, som vil stå for studiet og som du vil have kontakt med. Her har du mulighed for at høre mere om studiet og stille spørgsmål. Du er velkommen til at tage et familiemedlem, en ven eller en bekendt med til samtalen. Hvis du beslutter dig for at deltage i studiet, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til betænkningstid, før du beslutter, om du vil underskrive samtykkeerklæringen.

Hvis du vælger at deltage i studiet, vil du blive inviteret til en ny samtale, hvor du – sammen med lægen – vil tale om dine symptomer, dit helbred og udføre en række mindre undersøgelser, der har til formål at måle eksempelvis depressive symptomer. Vi vil også tage en blodprøve og et elektrokardiogram (EKG), der er en simpel måling af dit hjertes aktivitet. Det hele vil tage 3-4 timer.

Blodprøverne og EKG'et tages primært for at sikre, at du ikke lider af sygdomme, som vil betyde, at du har forøget risiko for bivirkninger ved behandling med dexametason. Vi vil desuden anvende de immunologiske markører i blodprøven til at undersøge sammenhænge mellem behandlingsrespons og underliggende immunologisk aktivitet. For at vurdere dette foretaget vi en række standardundersøgelser af dit blod. Blodprøvesvarene vil blandet andet kunne give mistanke om diabetes (sukkersyge), stofskiftesygdomme, infektioner, eller problemer med din saltbalance samt kunne udelukke udelukke graviditet. Skulle vi få mistanke om noget af dette, vil vi informere dig om det (medmindre du frabeder dig dette) samt hjælpe dig videre til den rette udredning og behandling.

Dagen efter undersøgelserne er gennemført, kan du begynde at tage medicinen. Lægen vil herefter kontakte dig telefonisk i løbet af den uge, hvor du tager medicinen, for at følge op på, hvordan du har det. Derudover vil du også selv kunne kontakte lægen telefonisk i løbet af ugen. Vi vil derudover spørger dig, om du vil bruge en app på din telefon, der kan hjælpe med at registrere dit humør, dit aktivitetsniveau og hvornår du tager medicinen. Hvis du ikke ejer en smartphone eller ikke ønsker at bruge app'en, kan du alligevel deltage i forsøget.[1]

[1] App'en hedder "Monsenso" og du vil blive instrueret i brugen af den af den læge, der vil følge dig, mens du får medicin. Det vil ske, når du kommer til dit første undersøgelsesbesøg. App'en overholder dansk lovgivning og EU's persondataforordning – se https://www.monsenso.com/wp-content/uploads/2022/03/Data-management-data-security-%E2%80%A2-Monsenso.pdf. Projektets dataanvendelse er godkendt af Region Hovedstadens Videnscenter for Dataanmeldelse.

Efter en uge er behandlingen slut. Herefter vil du mødes med lægen igen og tale om hvordan det er gået. Derudover vil vi udføre mange af de samme test (inklusiv blodprøver og EKG-målingen) som vi gennemførte dagen før du startede på medicinen. Både ved det første og andet undersøgelsesbesøg vil du – uanset om du gennemfører hele dagens program eller ej – få betalt frokost på dagen samt få tilbud om transport i taxa til og fra Gentofte Hospital (hvor undersøgelserne foregår, såfremt du ikke er indlagt). Transporten med taxa (såfremt dette er nødvendigt) vil blive bestilt og betalt af forskningsprojektet, og er således ikke skattepligtig indkomst.

Når forsøget er færdigt efter en uge, vil du fortsætte med din vanlige, antidepressive behandling – ligesom du har gjort under forsøget. Det vil ikke være muligt at fortsætte behandlingen med forsøgsmedicinen udover de syv dage, som forsøget tager.

Efter du er stoppet med at tage medicinen, vil vi ringe til dig en gang imellem. Her vil vi stille en række spørgsmål til hvordan du har det. Første opringning kommer fra lægen dagen efter behandlingsugen er slut. Herefter vil vi ringe til dig igen efter en uge og efter 3 uger. Det sidste opkald vil du få fra os et halvt år efter du er færdig med at tage medicinen.

Alt i alt vil du have følgende kontakter med os:

Fysiske møder	• Dagen før du starter med at tage medicinen (dag 0) • Dagen, hvor du tager medicinen sidste gang (dag 7)
Telefoniske opringninger	• Dagen efter du starter på medicinen (dag 2) • Fire dage efter du er startet med medicinen (dag 4) • Dagen efter du er stoppet med medicinen (dag 8) • Et par gange i ugerne efter du er færdig med medicinen (dag 14 og 28) • 6 måneder efter du er begyndt på medicinen

Hvad kræver det af mig?

For at kunne deltage i forsøget skal du have lyst til at afprøve den nye medicin og deltage i de to fysiske møder i begyndelsen og slutningen af behandlingsugen. Møderne bliver afholdt om formiddagen, så det kan være du skal tage fri fra arbejde eller uddannelse i de timer for at deltage i forsøget. Deltagelse i forsøget har ikke konsekvenser for din øvrige behandling. Har du planlagt udlandsrejser indenfor 2 uger efter start i forsøget vil vi anbefale, at du drøfter rejse med din rejseforsikring inden afrejse.

Der er en række sygdomme, som du desværre ikke må have af sikkerhedsgrunde, hvis du skal være med i forsøget. Det vil du snakke med lægen om inden forsøget starter. Er du kvinde, må du

ligeledes ikke være gravid eller ammende og du skal følge en relevant, graviditets-præventiv rutine.

Derudover skal du have lyst til at prøve den nye medicin. Samtidigt skal du også give adgang til, at vi (den forsøgsansvarlige og dennes repræsentanter) må følge med i din journal fra hospitalet både under og efter studiet og indhente relevante helbredsoplysninger derfra og fra registrene for at kunne gennemføre, monitorere og kontrollere studiet. Vores adgangen til din journal bortfalder, når du har deltaget i den sidste, opfølgende telefonsamtale, som afholdes et halvt år efter dagen, hvor du starter med at afprøve medicinen.

Derudover vil du give adgang til, at de myndigheder, der overvåger studiet (herunder Lægemiddelstyrelsen og GCP-enheden i Region Hovedstaden), også må se i din elektroniske journal, såfremt der skulle opstå et behov for dette. Alle personoplysninger vil blive behandlet fortroligt efter gælden lovgivning. Det data, vi henter fra din journal, vil blandt andet omhandle diagnoser, indlæggelser og lægers vurdering af din tilstand og skal bruges til vi løbende kan følge med i, hvordan behandlingen virker på dig, og om du måtte opleve bivirkninger ved medicinen, som vi skal hjælpe dig med.

Er der farligt at deltage?
Dexamethason er en meget sikker form for medicin, der bruges af læger verden over til at behandle en lang række sygdomme. De fleste bivirkninger til dexamethason afhænger af hvor høje doser man tager og hvor længe man tager medicinen. Da du kun vil skulle tage medicinen en uge er risikoen for bivirkninger ikke særlig stor. Selvom man kun tager medicinen i kort tid, kan der dog opstå bivirkninger, herunder at ens egen produktion af hormonet kortisol undertrykkes.
Derudover er der i sjældne tilfælde rapporteret om infektioner, blodpropper i benet, knoglebrud, mave-tarm problemer, hjerteproblemer og psykotiske symptomer hos patienter, der tager medicinen i kort tid. Vi tilbyder tæt monitorering, mens du tager medicinen, og du vil kunne få fat på os hurtigt, hvis du skulle opleve nogle bivirkninger.
Skulle der ske noget uventet under forsøget er du dækket af Region Hovedstadens patientforsikring og har ret til at klage som patient – ligesom du ville i andre sammenhænge, hvor du fik behandling, men ikke var en del af et videnskabeligt studie.

Hvad sker der med min data?
Alle indsamlede oplysninger vil blive behandlet fortroligt. Da der er tale om personoplysninger overholder vi selvfølgeligt også databeskyttelsesloven og EU's persondataforordning (GDPR). Din identitet og al information vedrørende dig, såsom helbredstilstand og resultaterne af helbredsvurderinger, vil altså blive behandlet anonymt, som loven foreskriver det. Du har som alle andre forsøgspersoner ret til aktindsigt. Resultaterne fra forsøget vil blive præsenteret i videnskabelige tidsskrifter eller på videnskabelige møder, men data vedrørende din identitet vil forblive anonyme. Resultaterne vil også offentliggøres på den offentlige hjemmeside euclinicaltrials.eu sammen med et let forståeligt resume. Samtykket omfatter adgang til videregivelse og behandling af nødvendige oplysninger om dine helbredsforhold, øvrige rent private forhold og andre fortrolige oplysninger som led i relevante myndigheders tilsyn med projektet.

Ved informationsmødet vil vi derudover spørger dig om, hvorvidt du har lyst til at bidrage med ekstra prøver til et andet forskningsprojekt. Hvis du ikke har lyst til dette, vil det ikke have nogen konsekvenser for din mulighed for at deltage i forsøget med dexamethason.

Kan jeg ombestemme mig?
Dit tilsagn om at deltage i projektet kan trækkes tilbage når som helst uden begrundelse herfor og uden at det får betydning for din fremtidige behandling. Såfremt du trækker dit samtykke tilbage, vil det dog ikke påvirke resultatet af forsøgsaktiviteter, der allerede er udført, eller data, der er indsamlet før tilbagetrækningen af samtykket. Vi opfordrer dig til at læse de udleverede pjecer "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt" og "Før du beslutter dig".

Kan forsøget blive afbrudt? Og hvad sker der så?
Såfremt en læge vurderer, at du mod forventning oplever alvorlige bivirkninger til forsøgsmedicinen, kan lægen beslutte af afbryde forsøget – også imod din vilje. Hvis dette sker, vil du fortsat kunne modtage anden behandling som normalt. Derudover vil vi fortsat invitere dig til de fysiske og telefoniske samtaler, som er beskrevet ovenfor, samt indsamle data fra din journal. Dette sker selvfølgeligt kun, hvis du ikke trækker dit samtykke tilbage.

Oplysninger om økonomiske forhold
Projektet indgår som en del af den videnskabelige forskning ved Psykiatrisk Center København, Region Hovedstadens Psykiatri, Københavns Universitetshospital, ledet af professor, overlæge, ph.d. Michael Eriksen Benros. Projektet er finansieret af Region Hovedstadens Psykiatri og Novo Nordisk Fonden (8.869.996 kr.), og vil desuden blive finansieret af yderligere endnu ikke navngivne fonde. Støtten indgår i en forskningsfond, som er underlagt offentlig revision. Der er ikke private økonomiske interesser fra initiativtagers side forbundet med projektets gennemførelse og du vil, såfremt du ønsker det, modtage information omkring yderligere opnået støtte fra forskningsfonde til undersøgelsen.

Kontaktinformationer
Hvis du har spørgsmål eller vil have mere information er du meget velkommen til at kontakte

Troels Boldt Rømer, læge og PhD-studerende
31 47 43 45
troels.boldt.roemer.03@regionh.dk
Gentofte Hospitalsvej 15, 2900 Hellerup

Du kan også læse mere om studiet på vores hjemmeside.
Vi glæder os til at se dig!

Med venlig hilsen,

Hele holdet bag DEXA-PSYCH
Psykiatrisk Center København (Gentofte)
Region Hovedstadens Psykiatri

Appendix 5: Schedule of Activities (SoA)

Phase	Pre-screening	Information meeting	Informed consent, screening, enrolment and randomization	Intervention							Wash-out	Follow-up		
Study day	-30 to -9	-9 to -1	0	1	2	3	4	5	6	7	8	14	28	
Study month	-1	-1	1	1	1	1	1	1	1	1	1	1	1	6
Visit (bold = physical)		**1**	**2**		3		4			**5**	6	7	9	11
Visit window[2]					+/- 2		+/- 2			+/- 2	+/- 2	+/- 2	+/- 2	+/- 14
Trial procedures														
Randomization			X											
Study drug hand-out			X											
Intervention				X	X	X	X	X	X	X				
Pill return										X				
Adherence				X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X				
Assessment of blinding										X				
Screening/administrative data														
Demographic data			X											
In- and exclusion criteria			X											
Medical history			X											
Psychiatric history			X											
Family medical and psychiatric history			X											
Current- and pre-study therapy			X											
Employment status			X							X			X	X
Educational qualifications			X											
Smoking status			X											
Monsenso[3]				X	X	X	X	X	X	X	X	X	X	
Psychopathological assessment, psychometric testing and social activity														
SCAN			X											
MADRS (ex. Monsenso)			X				X			X		X	X	X
MDI			X							X			X	X
HAM-D			X							X			X	X
HAM-A			X							X			X	X
C-SSRS			X							X			X	X
EQ-5D-5L			X							X			X	X

[2] Visit window allowed as measured in days

[3] Data will be registered continously in the Monsenso app from day 1-28 (both days included). Through the app, data will be registered on adherence (day 1-7), MADRS (day 1-28) as well as physical and social activity (day 1-28). The self-rated MADRS score is modified, such that participants are asked to evaluate symptoms within the last 24 hours as opposed to 3 days in order to facilitate day-to-day scoring.

GAF			X							X			X	X
YMRS			X							X				
SAPS			X							X				
BACS			X											
UKU-SSRI										X				
GTI										X				
Social activity[a]				X	X	X	X	X	X	X	X	X	X	
Physiological measurements														
Physical examination			X							X				
ECG			X							X				
Blood tests[4]			X							X				
Vital signs			X							X				
Height			X							X				
Weight			X							X				
Physical activity[a]				X	X	X	X	X	X	X	X	X	X	
Safety measures														
SAR and AR				X	X	X	X	X	X	X	X[b]			
SAE and AE				X	X	X	X	X	X	X	X[b]			
SUSAR				X	X	X	X	X	X	X	X[b]			
Admissions to somatic care										X				
Admissions to psychiatric care										X		X	X	X
Suicide-attempts										X		X	X	X

AE = Adverse Event, AR = Adverse Reaction, BACS = Brief Assessment of Cognition in Schizophrenia, C-SSRR = Columbia-Suicide Severity Rating Scale, ECG = Electrocardiogram, GAF = Global Assessment of Functioning, GTI = Glucocorticoid Toxicity Index, HAM-A = Hamilton Anxiety Rating Scale, HAM-D = Hamilton Depression Rating Scale , MADRS = Montgomery-Asberg Depression Rating Scale, MDI = Major Depression Inventory, SAE = Serious Adverse Event, SAR = Serious Adverse Reaction, SCAN = Schedule for Assessment in Neuropsychiatry, SUSAR = Serious and Unsuspected Adverse Reaction, YMRS = Young Mania Rating Scale

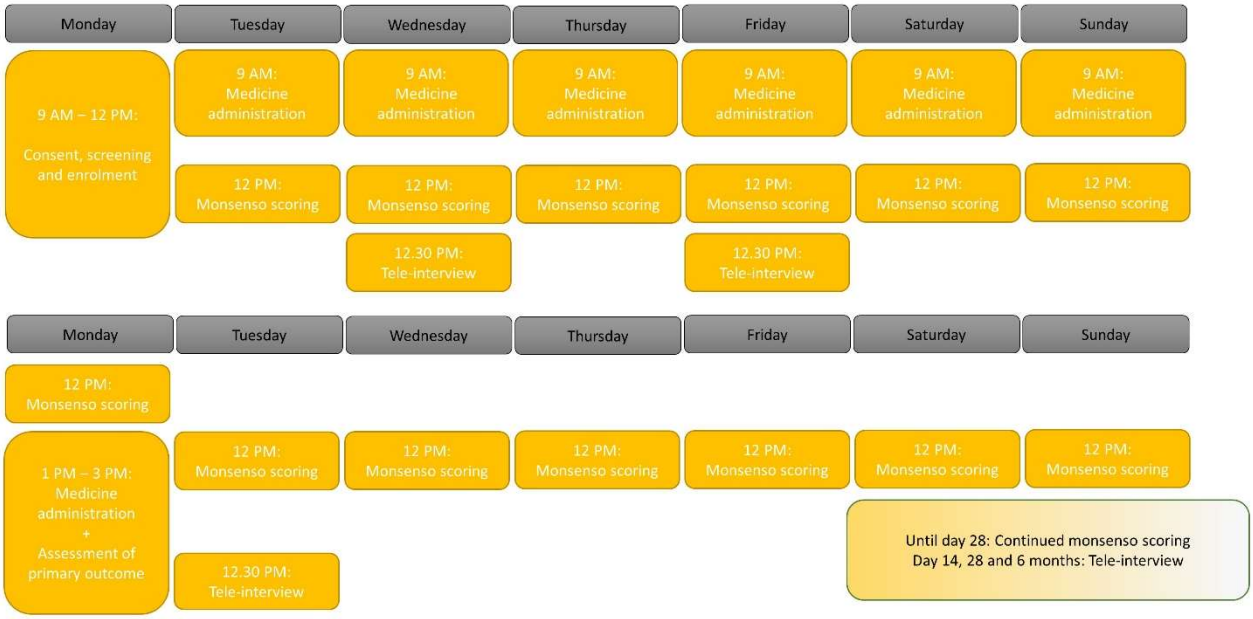
[a] = Monitored through the Monsenso app

[b] = SAR, AR, SAE, AE and SUSARs will be registered until day 10 as to be able to identify events related to discontinuation of glucocorticoid treatment, such as symptoms of adrenal gland insufficiency.

[4] For details on biochemical parameters analyzed in the blood samples, please refer to section 5.9.1. and 11 of the trial protocol

Appendix 6: Participant timeline (example)

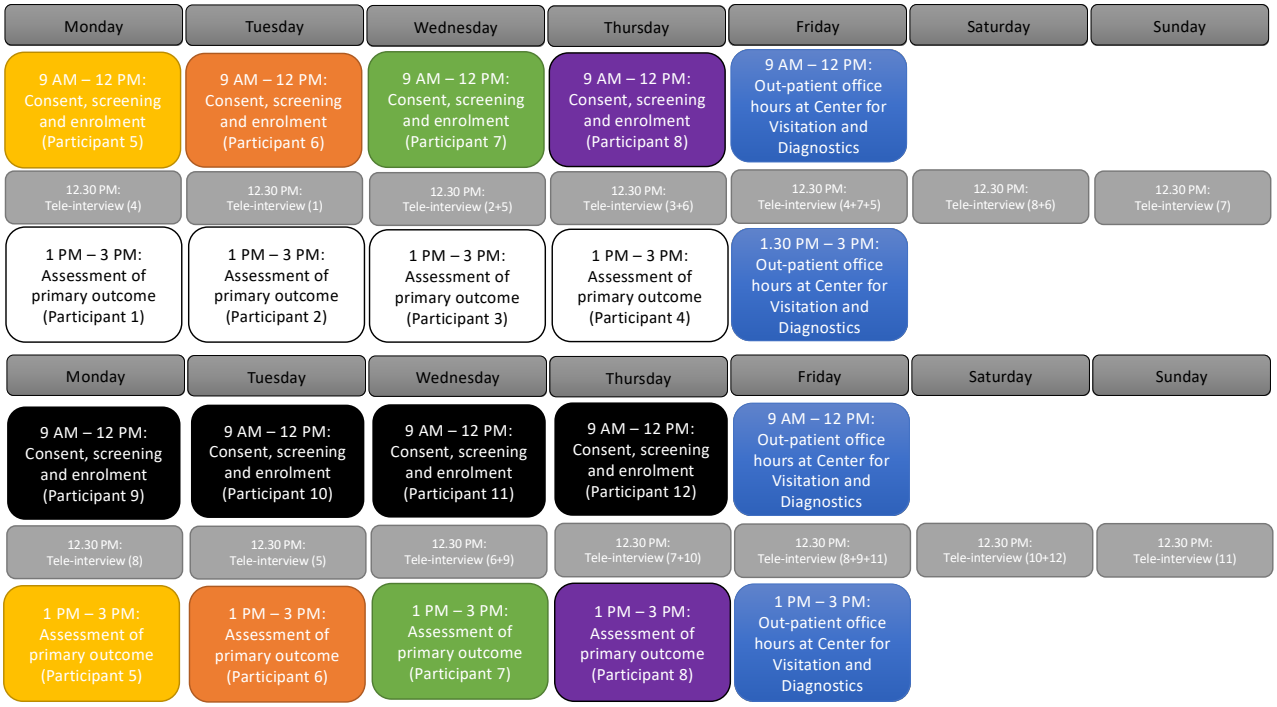
Participant timeline - Example



Appendix 7: Sub-investigator timeline

Sub-investigator timeline – Example

Participants 1+2+3+4 are enrolled the prior week – participants 9+10+11+12 are outcome assessed the next week



Appendix 8: Adverse reactions to dexamethasone

The following are the listed adverse reactions in the Danish Summary of Product Characteristics (SmPC) for dexamethasone. The text is reproduced in its original format and is therefore in Danish. The original SmPC is submitted along this protocol for authority approval.

Systemorganklasse	
Infektioner og parasitære sygdomme	
Almindelig:	Øget modtagelighed for infektioner
Immunsystemet	
Ikke almindelig:	Hypersensitivitetsreaktion
Endokrine sygdomme	
Almindelig:	Binyresuppression, Cushing-lignende symptomer retarderet vækst hos børn, diabetes mellitus
Metabolisme og ernæring	
Ikke almindelig:	Hypokaliæmi, natriumretention
Ikke kendt:	Væskeretention, hypokalæmisk alkalose,
Psykiske lidelser	
Ikke almindelig:	Psykiatriske tilstande, der spænder fra eufori, søvnløshed, humørsvingninger og depression til psykose
Nervesystemet	
Sjælden:	Forhøjet intrakranielt tryk
Ikke kendt:	Svimmelhed, hovedpine
Øjne	
Ikke almindelig:	Forhøjet intraokulært tryk, glaukom, posterior katarakt, exophthalmus
Ikke kendt	Chorioretinopati, sløret syn
Hjerte	
Ikke almindelig:	Kardial dekompensation
Ikke kendt:	Myokardieruptur efter nyligt myokardieinfarkt
Vaskulære sygdomme	
Ikke almindelig:	Trombose, hypertension

Systemorganklasse	
Ikke kendt:	Emboli
Mave-tarm-kanalen	
Ikke almindelig:	Gastrointestinale lidelser såsom kvalme, ulcus pepticum
Ikke kendt:	Hæmoragisk tarmperforation, ulcerøs esofagatis, pankreatitis, abdominal distension
Hud og subkutane væv	
Almindelig:	Acne, hirsutisme
Ikke almindelig:	Hudatrofi, nedsat såhelingsevne, suppression af hudtest, hudreaktioner såsom allergisk dermatitis, urticaria, angioneurotisk ødem
Ikke kendt:	Petekkier, erytem, ekkymoser, hyperhidrose
Muskuloskeletale system og bindevæv	
Almindelig:	Muskelatrofi, osteoporose
Sjælden:	Aseptisk knoglenekrose, seneruptur
Ikke kendt:	Proksimal myopati, frakturer af vertebrae og rørknogler, muskelspasme
Det reproduktive system og mammae	
Ikke kendt:	Menstruationsforstyrrelser
Almene symptomer og reaktioner på administrationsstedet	
Ikke almindelig:	Ødem, øget appetit
Ikke kendt:	Utilpashed
Undersøgelser	
Almindelig:	Negativ kvælstofbalance
Ikke almindelig:	Vægtøgning
Ikke kendt:	Nedsat kulhydrattolerance

Appendix 9: Serious adverse reactions

The following reactions selected from the SmPC will be considered SARs according to the definitions given in the "Safety" section of this protocol and reported/monitored accordingly:

Psychiatric	○ Psychotic symptoms
Endocrine	○ Glucose intolerance or manifestation of latens diabetes mellitus ○ Cushing's syndrome (moon-face, buffalo neck, truncal obesity) ○ Acute adrenal insufficiency (fewer, myalgia, arthralgia, rhinitis, conjunctivitis, dermal nodules, weight loss, hypertension and risk of death)
Metabolic	○ Severe hypokalemia, including hypokalemic alkalosis ○ Severe hypernatremia ○ Severe calcium imbalance
Neurological	○ Epileptic seizures
Ophthalmological	○ Any subconjunctival eye infection ○ Visual impairment due to increased intraocular pressure
Infections	○ Systemic infections, including: ○ Bacterial septicemia ○ Systemic fungal infections ○ Tuberculosis (including clinical manifestation/activation of latent tuberculosis) ○ Chicken pox (varicella zoster infection) ○ Measles
Gastrointestinal	○ Gastrointestinal bleedings ○ Acute pancreatitis ○ Ulcerative esophagitis
Hematological	○ Leukocytosis ○ Lymphopenia ○ Eosinophilia ○ Polycythemia
Immunological	○ Hypersensitivity reactions, including anaphylaxis
Cardiovascular	○ Acute coronary syndrome ○ Thromboembolic events ○ Heart arrythmias ○ Heart failure ○ Vasculitis
Bone	○ Fractures of the spinal cord ○ Aseptic bone necrosis

Appendix 10: Medication labels

Etiket forslag

Til klinisk forsøg: "The DEXA-PSYCH Study": Dexamethasone Repurposing for Moderate to Severe Depression - A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Trial.

EU CT number: 2022-501428-45-00

Dexametason 2 mg (Abcur) eller placebo 3 kapsler

(Indeholder: kapsler med 2 mg Dexametason "Abcur" eller placebo)

Dosering: følge lægens anvisning

Til oral anvendelse, kapsler synkes hele

Patient nr. XXX

Lot: xxxxxxx **Anv. inden: xx-xx-xxxx**

Forsøgsansvarlig læge

Prof. Michael Eriksen Benros, MD/PhD
Mental Health Services in the Capital Region of Denmark,
Copenhagen University Hospital,
Gentofte Hospitalsvej 15, 2900 Gentofte
Tel: (+45) 26255239

Opbevares ved temperaturer under 30 °C. Opbevares utilgængeligt for børn

Opbevares i beholderen for at beskytte mod lys

Regionhovedstadens Apotek (logo)

Etiket forslag
Til klinisk forsøg: "The DEXA-PSYCH Study": Dexamethasone Repurposing for Moderate to Severe Depression - A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Trial.

EU CT number: 2022-501428-45-00

Dexametason 4mg (Abcur) eller placebo 4 kapsler

(Indeholder: kapsler med 4 mg Dexametason " Abcur " eller placebo)

Dosering: følge lægens anvisning

Til oral anvendelse, kapsler synkes hele

Patient nr. XXX

Lot: xxxxxxx **Anv.inden: xx-xx-xxxx**

Forsøgsansvarlig læge

Prof. Michael Eriksen Benros, MD/PhD
Mental Health Services in the Capital Region of Denmark,
Copenhagen University Hospital,
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Tel: (+45) 26255239

Opbevares ved temperaturer under 30 °C. Opbevares utilgængeligt for børn

Opbevares i beholderen for at beskytte mod lys

Regionhovedstadens Apotek (logo)