Effects of structured skills training group in treatment of Attention Deficit Hyperactivity Disorder in adults: a controlled multicentre study

PROTOCOL VERSION - 29.10.15

Ethics approval:

Regional Committees for Medical Research Ethics - South East Norway, 29/10/2015, ref: 2015/1523 A

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PROTOCOL SYNOPSIS

Effects of structured skills training group in treatment of Attention Deficit Hyperactivity Disorder in adults

A growing number of adults are diagnosed with Attention-Deficit Hyperactivity Disorder, or ADHD. People with ADHD can have problems in paying attention, feeling restless or hyperactive and behaving impulsively. Pharmacological (drug) treatments are well established, but a significant number of patients does not respond well or experience adverse effects, which results in stopping the treatment. Furthermore many patients request for psychological treatment to help them with symptoms that are not resolved by simply taking drugs.

Structured group therapy has shown improvement of symptoms among patients with other psychiatric conditions. Although still inconclusive, some studies have indicated that structured skills training groups are beneficial for adult patients with ADHD in outpatient psychiatric units, reducing ADHD symptoms in people who remained stable regarding their medication status.

This study aim to investigate the potential effects of structured skills training groups in a clinically relevant but still controlled setting, and whether they help alleviate symptoms and improve quality of life for adult ADHD patients. This trial examines effects of Dialectical Behavioral Therapy-based group treatment (DBT-bGT) on the broader and clinically relevant executive functioning and emotional regulation in adults with ADHD

By use of a controlled design, adult patients with ADHD will be randomly assigned to receive either weekly DBT-bGT or treatment as usual (TAU) during 14 weeks therapy period. Subsequently, participants receiving TAU will also be offered the supplementary DBT-bGT. All participants will bed reassessed at a follow-up visit six months after ended DBT-bGT.

Primary outcomes are the Behavior Rating Inventory of Executive Function (BRIEF-A) and the Difficulties in Emotion Regulation Scale (DERS). Secondary outcomes include self-reported ADHD-symptoms, depressive and anxiety symptoms, and quality of life assessments.

Investigational treatment method:	Manualized Dialectical Behavioral Therapy-based group treatment (DBT-bGT) for ADHD in adults
Centres:	Regional Resource Center for Autism, AD/HD, Tourettes Syndrome and Narcolepsy, Western Norway Regional Health Authority, Haukeland University Hospital, 5021 Bergen, Norway Regional Resource Centre for Autism, AD/HD, Tourettes Syndrome and Narcolepsy, South-Eastern Norway Regional Health Authority, Oslo University Hospital, 0424 Oslo, Norway Department of Clinical Medicine, University of Bergen, 5020 Bergen, Norway

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Study Period:	Recruitment start date December 2015 Estimated recruitment end date 31/12/2016 Anticipated study period: 2 years Estimated date of last patient completed: 31/12/2017
Treatment Duration:	Participants will be offered a 14 week manualized Dialectical Behavioral Therapy-based group treatment (DBT-bGT) or treatment as usual (TAU). After 14 weeks participants of the TAU group will be offered DBT-bGT as well.
Objectives:	The main objective for this trial is to investigate the potential effects of structured skills training groups in a clinically relevant but still controlled setting on broader outcomes including both symptomatic, functional and health related quality of life measures. • Describing the effect of treatment by DBT-bGT on outcomes of the Behavior Rating Inventory of Executive Function (BRIEF-A) and the Difficulties in Emotion Regulation Scale (DERS) compared to treatment as usual • Describing the effect of treatment by DBT-bGT on core symptoms of ADHD • Describing the effect of treatment by DBT-bGT on other psychiatric symptoms and quality of life measurements
Study Design:	A multicentre Randomized-Controlled Trial, with a parallel group design; active treatment by a manualized Dialectical Behavioral Therapy-based group treatment (DBT-bGT) versus treatment as usual (TAU). Participants of the TAU groups eventually gets DBT and all participants are followed up 6 months after ended active treatment.
Main Inclusion and Exclusion Criteria:	– Diagnosis of ADHD assessed by a trained specialist clinician according to the Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV) persisting in adulthood – Unmedicated or stably medicated with any ADHD-medication. – Between 18 and 60 years of age (all groups). – Exclusion criteria are any ongoing psychiatric disorders and/or

psychosocial factors considered to clearly interfere with the patients' ability to participate in the group, i.e., ongoing substance or alcohol abuse, psychotic disorder, major depressive or manic episode, and suicidal behavior; organic brain damage, neurological diseases causing mental handicap, intellectual disability (IQ ≤ 70), and pervasive developmental disorder.

Sample Size:	Estimated 120 patients
Efficacy Criteria:	Measures of changes in the defined outcome measures between groups and pre-post individually at follow-up.
Safety Criteria:	In case of SAE (severe adverse events), patient will be considered for exclusion and indicated treatment will be administered immediately.

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INTRODUCTION

1.1.Background

Hyperkinetic disorder or attention-deficit hyperactivity disorder (ADHD) is the most common neurobiological developmental disorder in children and adolescents (Remschmidt, 2005). The incidence in Norway is assumed to be between 3-5% (Hdir, 2005). Studies estimate the prevalence of ADHD in the adult population to be about 2% (Philipsen, et al, 2010). Research shows that of those diagnosed as children, about 2/3 will have persistent functional difficulties in adulthood (Kooji et al., 2010). ADHD in adulthood has many serious consequences and is a risk factor for unfavorable socio-economic conditions, disease burden and intoxication, to name a few. Disabilities have been found to persist into old age. Up to 75% of the adult population with ADHD has also been shown to have other additional difficulties such as depression, abuse, difficulty sleeping, anxiety and low self-esteem. Studies show that a large number of patients, up to 50% of the adult population, do not benefit optimally from medication, and need other treatment instead or in addition to medication to cope with residual symptoms or comorbid conditions of their ADHD (Safren et al., 2005; Raman et al. 2015, Fredriksen et al., 2014).

Questions about ADHD currently make up a large proportion of referrals to child and adolescent psychiatry, and significant quality-improving work has been carried out within the health services with assessment, diagnosis and treatment of children and young people with ADHD. However, the mental health care for adults has not had a similar focus on ADHD. It is mainly the district psychiatric centers (DPS) that are responsible for the assessment and treatment of adults with ADHD. The contact with clinical environments and the user organization shows that the treatment options for adults with ADHD have their main focus on offering drug treatment. At the same time, there are studies that document that between 25 - 50% have a lack of continuity in their medication use after about one year (Aanonsen et al., 2005, Bejerot et al., 2010). In addition to drug treatment, there is little systematic knowledge about treatment options offered to this patient group in Norway.

1.2.Non-pharmacological treatment for ADHD in adults

A literature search in relation to non-drug treatment of adults with ADHD has revealed two relevant manuals; «Treatment that works; Managing your adult ADHD »(Safren et al., 2005) and« Psychotherapy for adults with ADHD »(Hesslinger et al.,2004; Hirvikoski et al., 2010). The former manual is based on cognitive-behavioral therapy, while "Psychotherapy for adults with ADHD" is a manual established over dialectical behavioral therapy (DBT). The manuals offer a method for dealing with symptoms (residual symptoms) where additional problems have been established, or where it is felt that drug treatment alone is not sufficient, - multimodal treatment (combination of drug and non-drug treatment). Both manuals have an introduction to psychoeducation. Such an approach is in accordance with, among other things, the national guide for the assessment and diagnosis of ADHD (IS-2062/2014), where psychoeducation is emphasized as an important element in treatment and follow-up. A recent user survey among adult patients with ADHD at four DPS in the Bergen area, showed that the most important predictor of satisfaction with the follow-up was whether the patients were satisfied with the information they had received about ADHD. Offering non-drug treatment was the single factor that most patients missed (Solberg et al., 2015, in press). This is also in accordance with the assignment document 2015, which emphasizes the importance of health trusts being able to offer both drug and non-drug treatment, where this is considered prudent.

1.3. Psychotherapy for adults with ADHD / Structured skills training group therapy

The selected manual in this project is "Psychotherapy for adults with ADHD" (Hirvikoski, et al., 2010). The manual is based on DBT, which was originally developed for the treatment of personality disorders, but which has later come in a version adapted to the patient group of adults with ADHD. A basic principle in DBT is the balance between acceptance of the symptoms of ADHD and change (how to live best with the symptoms). In terms of content, the treatment consists of various components such as; psychoeducation, behavioral analysis, homework / skills training and mindfulness (exercises in mindful presence). The form of therapy has been developed to also take into account the emotional regulation difficulties and the effect they have on interpersonal relationships. According to the literature, this can be considered a core symptom of ADHD (Retz et al., 2012).

This manual has been developed with group treatment in mind (group of 7-9 participants). Experience from relatives' groups and contact with the patient association (ADHD Norway) indicates that follow-up in a group is preferable for several adults with ADHD, as you meet people in the same situation and can benefit from each other's experiences, while it can reduce perceived stigma related to the diagnosis. The treatment is given once a week, lasting 1-2 hours. There will be 14 treatment meetings, with homework between treatments in this structured skills training group therapy. Each group is led by 2 therapists.

2. STUDY OBJECTIVES

The study wants to investigate the treatment effect of "Psychotherapy for adults with ADHD" given in groups, a manual made over DBT.

2.1. The hypotheses:

- Adult patients with ADHD gain increased knowledge about ADHD
- Adult patients with ADHD experience increased coping ability in relation to their own condition and symptom regulation
- Adult patients with ADHD experience improvement in relation to self-reported additional symptoms / difficulties: emotional dysregulation, organizational difficulties, sleep, anxiety / depressive symptoms
- Adult patients experience improvement in relation to self-reported functional goals and quality of life

2.2. Endpoints

Treatment effect will be investigated through mapping of symptoms of ADHD, anxiety and depression, as well as measures of functioning and quality of life before and after treatment. Registrations must be carried out before start-up (baseline) and after treatment (immediately and after 6 months) with the aim of evaluating the treatment effect.

- Behaviour Rating Inventory of Executive Functions (BRIEF)
  Change in executive function impairments

- Difficulties in Emotion Regulation Scale (DERS)
  Change in emotional regulation
- Adult ADHD Quality of Life Scale (AAQoL)
  Change in quality of life
- Adult ADHD self-report scale (ASRSv1.1), 18 items version
  Change in ADHD symptoms
- Beck Depression Inventory (BDI)
  Change in depressive symptoms
- Beck Anxiety Inventory (BAI)
  Change in anxiety symptoms
- Weiss Functional Impairment Rating Scale, self-report (WIFRS)
  Change in functional impairments
- Global Assessment of functioning (GAF)
  Change in global symptoms and functioning

3. STUDY POPULATION

3.1. Selection of study population

Participants with ADHD diagnosis (according to DSM-IV criteria) will be recruited from the psychiatric specialist health services, mainly District Psychiatric Centres but also from privately practicing specialists in psychiatry / clinical psychology in the region of the centres taking part. Participation in the study is voluntary and consent-based. Information about the study will be announced to clinicians in the specialist health service and private practitioners via email and through the hospitals' websites, as well as distributed to relevant sections and professionals in the relevant hospitals in Helse Vest and Helse Sør-Øst.

3.2. Number of participants and intervention

Inclusion will progress until about 120 participants are enrolled into this trial. The participants who will be randomized into two groups; and allocated to either:

1. Group 1 (G1) with start of weekly treatment in active structured skills training group therapy lasting for 14 weeks, following the Norwegian translation of the Swedish version of the ADHD skills training manual/workbook (Hirvikoski 2011; Morgensterns 2015) based on an adaption of Marsha Linehan's dialectical behavior therapy (DBT) for borderline personality disorder. The groups embrace 7 - 10 participants, and two group leaders trained in group therapy, cognitive behavioral treatment or DBT. Each session contains an initial short repetition and feedback on the previous session, followed by review of the homework during the first hour. After a break, a new topic with exercises and homework for the following week is introduced.

2. Group 2 (G2) with treatment as usual/clinical management for the first 14 weeks, followed by delayed admission to the active intervention of structured skills training group therapy (partial cross-over).

3.2.1. All participants

For eligibility the prospective participants at screening prior to receiving the study intervention must meet all of the following conditions:

- Clinically diagnosed with ADHD according to DSM-IV. Diagnostic assessment is part of standard diagnostic procedures at the clinics, which include confirmatory assessment by a specialist in psychiatry or psychology
- On stable treatment with ADHD medication or off medication.
- Must be between the ages of 18 and 60.
- Signed informed consent and expected cooperation of the patients for the intervention and the questionnaires must be obtained and documented according to International Conference on Harmonization, Good Clinical Practice and national/local regulations.

3.3. Exclusion criteria

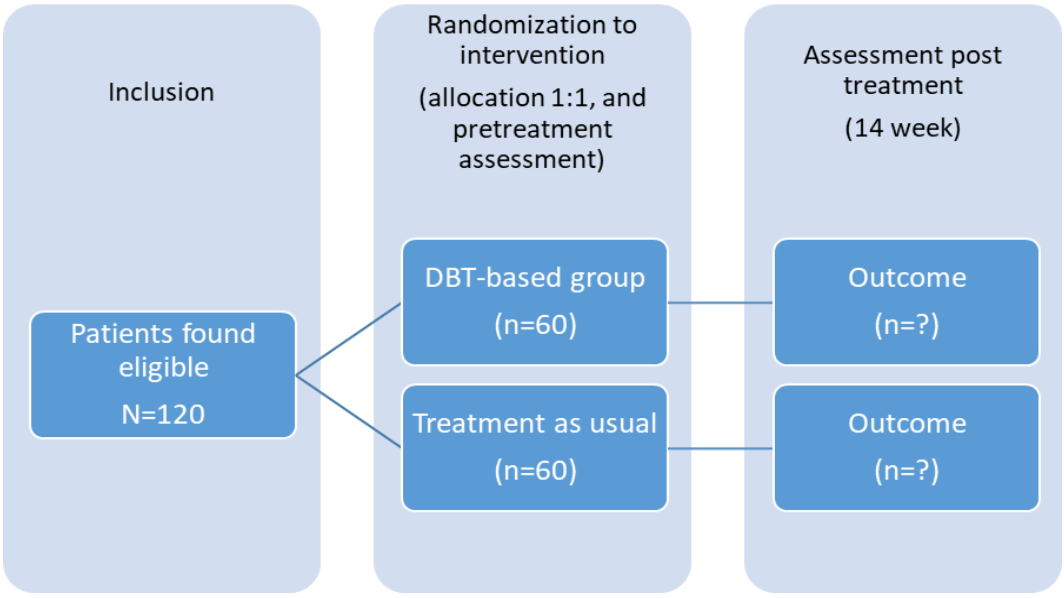
Any participant (from either of the three groups) will be excluded from the study if ongoing psychiatric disorders and/or psychosocial factors are considered to clearly interfere with the patients' motivation or ability to participate in the group therapy, and if they meet any of the following criteria:

- Any psychotic disorder
- Recently suicidal behaviour
- Substance or alcohol abuse or dependence within three months prior to screening for inclusion
- Pervasive developmental disorder
- Intellectual disability
- Seizures or any neurological diseases causing mental handicap

4. OVERALL STUDY DESIGN

The study is a parallel group multicenter randomized controlled trial (RCT), comparing the effects of a 'DBT-based group therapy' (DBT-bGT) /structured skills training group treatment with 'Treatment as usual' (TAU) for adults with ADHD.

Fig. 1 Trial flow-chart



In an uncontrolled extension phase of the initial 14 week trial, participants initially receiving TAU will be offered the DBT-based group treatment. All participants will be re-assessed at follow-up 6-months after ended DBT-bGT.

Study Period:	Estimated date of first patient enrolled: December 2015 Anticipated recruitment period: 1 years Estimated date of recruitment end: 31/12/2016 Estimated date of last patient completed follow-up: 15.05.2017
Treatment Duration:	The DBT-based group therapy (DBT-bGT) /structured skills training group treatment lasts for 14 weeks, and thereafter participants will be re-assessed at follow-up 6-months after. Those of the participants receiving initial TAU conditions will have an additional duration of 3 months representing the duration of treatment as usual.

5. INVESTIGATIONAL INTERVENTION

5.1. Elements of the DBT-based group therapy

The structured skills group treatment uses elements from DBT such as psychoeducation, acceptance, mindfulness, and functional behavioral analysis, such targeting symptoms and functional problems common in ADHD. It consists of 14 weekly group sessions, each lasting two hours separated by a 15-minute break. Each group includes 7-9 patients with ADHD and two therapists. Group sessions follow a structure with manualized instruction for the therapists and workbook for the patients.

A typical session begins with introducing a new mindfulness exercise performed together in the group. The first part of the session then focuses on feedback on last week's homework of skill training, while the second part introduces a new topic and related homework for the next week. The topics for the different sessions include psychoeducation, mindfulness, functional behavioral analyses, and how to understand and manage different symptoms and aspects of ADHD, e.g. impulsivity, addiction, emotional

regulation, self-esteem, and relation to others. Interaction between the participants is important, and the therapists should encourage and balance their feedback and discussion during the session. After each group session, patients will receive 15-20 minutes of individual coaching with one of the therapists. This is an add-on element according to a Swedish adaptation of the program. The coaching focuses on adherence to homework related to each participant's situation and pre-defined goals.

5.2. The arm of treatment as usual condition

The control condition of treatment as usual (TAU) was not standardized but rather defined as the clinical management/ treatment that the patient would have received if not included in the project. Some patients will be able to receive drug treatment, while others receive psychoeducation alone or in combination with medication. It could thus vary between both individuals and clinics. A survey will be made of what the patients have received from "treatment as usual" before they enter the psychotherapeutic group treatment.

5.3. Concomitant medication

Treatment with the following groups of pharmacological agents will be recorded in the case report form (CRF), but is not considered as any exclusion criteria for participation. It is however recommended that the dose be kept stable during participation in the study, and for inclusion it must have been at least 6 weeks after the last dose change of drug treatment.

- ADHD medication (centralstimulants or non-stimulants)
- Other psychopharmaca

Alcohol or substance abuse will be screened for alcohol- and substance-problems; The Alcohol Use Disorder Identification Test (AUDIT) and The Drug Use Disorder Identification Test (DUDIT).

6. PROJECT PHASES

6.1. Steps with deadlines

Assignment	Deadline
Establish the project	Spring 2015
Design research protocol	Summer 2015
Application to the Regional Ethics Committee deadline	Deadline 16. August
Clarify participation from therapists in the project	Before the deadline REK application
Arrange teaching days, with introduction to the use of the manual	October/november 2015
Carry out treatment based on the manual	Start-up in November 2015 - March 2016
Analyze data and write report	2016 - 2017
Make adjustments and adapt the Norwegian version of the manual	2016 - 2017
Publication and feedback	2017

6.2. Phases

Phase 1:
1.2 Clarify roles and responsibilities between participating bodies
1.3 Clarify the procedure for translating the manual into Norwegian.
1.4 Design and secure consensus in connection with research protocols
1.4 Apply for REK approval

Phase 2:
2.1 Recruitment of patients
2.2 Obtain information from therapists and from patients.

Phase 3:
3.1 Arrange a seminar with a lecturer who has participated in the work on the Swedish manual

3.2 Start-up treatment, based on the Norwegian version of the manual "Psychotherapy for adults with ADHD"
3.3 Guidance for therapists along the way
3.4 Arrange a gathering for therapists midway through the treatment process

Phase 4:
4.1 Summary of results and feedback to participating units
4.2 Publishing dissemination and making available knowledge and experiences from the project
4.3 Give recommendations to relevant units on effective measures
4.4 Regional follow-up in relation to the dissemination of knowledge and competence.

6.3.Enrollment of patients

Treating clinicians will ask patients whether they are interested in participation as they meet for regular appointment. Project therapists will evaluate patient eligibility and be responsible for acquiring informed consent (for either DBT, or TAU). Patients will then be given oral and written information, and asked to give permission for one of the contributing researchers to contact them.

6.4. Criteria for patient discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator.
- Incorrect enrollment (i.e. the patient does not meet the required inclusion/exclusion criteria for the study)
- Related Serious Adverse Event

6.4.1 Procedures for discontinuation

Patients who withdraw or are withdrawn from the study will continue clinical treatment as determined by their physician. Any reasons for withdrawing from the study will not impact the patient’s clinical treatment.

Reason for discontinuation shall be recorded if reason is disclosed. The investigator is obliged to follow up any significant adverse events until the outcome is resolved.

7. EFFICACY ASSESSMENTS

7.1. Assessment of efficacy response

The main aims of this study is to examine the efficacy of a manualized DBT-based group treatment compared to treatment delivered as usual for adults with ADHD on self-reported executive

functioning and emotional regulation, and secondly on core symptoms of ADHD, symptoms of depression and anxiety, and quality of life. Participants will be assessed pretreatment, after ended group-treatment or at 14-week og treatment as usual and at 6 month follow-up.

Primary Outcome(s)
1.Change in executive function impairments (total and separate dimensional scores) assessed by the self/informant-reports of adults aged Behavior Rating Inventory of Executive Function (BRIEF-A) at end of 14-weeks group treatment, and after 6 months post-treatment, compared to baseline and treatment as usual as control treatment strategy
2. Change in emotional regulation (total and separate dimensional scores) assessed by the self/informant-reports Difficulties in Emotion Regulation Scale (DERS) at end of 14-weeks group treatment, and after 6 months post-treatment, compared to baseline and treatment as usual as control treatment strategy

Secondary Outcome(s)
1. Adult ADHD self-report scale (ASRS), the 18 items version
2. Beck Depression Inventory (BDI)
3. Beck Anxiety Inventory (BAI)
4. Alcohol Use Disorder Identification Test (AUDIT)
5. Drug Use Disorder Identification Test (DUDIT)
6. Weiss Functional Impairment Rating Scale, self-report (WIFRS)
7. Adult ADHD Quality of Life Scale (AAQoL)
8. Global Assessment of functioning (GAF)

The following parameters of *clinical treatment* recorded from patient journal:

- Type of medication, dosage, intervals, efficacy and duration.
- Diagnosis (subtype and comorbidities).

8. SAFETY ASSESSMENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. Included patient participants will already have been evaluated by treating clinicians. The methods for collection of safety data are described below.

8.1.Definitions

8.1.1. Adverse Event (AE)

An adverse event (AE) can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

This study does not delay nor administer medication as part of the study. However any untoward medical occurrence that results in any of the following will be reported:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

8.2. Procedure

8.2.1. AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF.

The investigator must report SAEs to the sponsor, within 24 hours after the site has gained knowledge of the SAE. The investigator must document every SAE on the CRF. The Serious Adverse Event Report Form must be completed, signed and sent to sponsor 1. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor 1 keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

8.2.2. Clinical Study Report

The unexpected adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

9. RECORDING OF DATA AND SOURCE VERIFICATION

9.1. Case Report Forms (CRFs)

Case report forms (CRF) will be provided for the recording of all data. Data will be recorded directly and legibly onto the record forms, in blue/black ink. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections if applicable, should be made legibly, dated and initialled. Correction fluid is not allowed. There are three CRFs in total for each participant in this study, except for stimulant-naïve participant later included in the drug-group, who will have four CRFs.

9.2. Source data

The medical records for each patient should contain information that is important for the patient's safety and continued care and to fulfil the requirement that critical study data should be verifiable. To achieve this, the medical records of each patient should clearly describe at least:

- Dates for tests in relation to the study and scores on ASRS
- Date of, and reason for, withdrawal from study

9.3. Archiving and storage of study documents

Patient files shall be kept for the maximum period of time permitted by each hospital. The code list for patient identification and the study documentation (CRFs, Site File etc.) shall be retained and stored according to instructions from the Regional Ethics Committee. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

10. STATISTICAL CONSIDERATIONS

10.1. Determination of sample size

To assess the required number of participants, a power analysis was calculated on the basis of literature indicating the similar DBT-group intervention in a smaller study showed a significant reduction in ADHD measures in the skills training group (n=19) compared to the control group (n=18) (Hirvikoski et al 2011). To address the hypothesis of superiority of the DBT-based group treatment on different outcome measures and an assumed difference in at least 10% between means (and SD 15%) of the two independent groups, we estimated a need of sample size of about 50 participants in each group (alpha = .05, power = .9) (https://clincalc.com/stats/samplesize.aspx). To account for dropouts up to 20%, more patients are needed, resulting in a total of 120 participants.

10.2. Randomisation

Participants are randomly allocated (ratio 1:1) to either the active DBT-bGT or the control TAU condition by a blinded lottery procedure at each site. This manual procedure of randomization method is suitable to randomize participants into groups that result in equal sample sizes, and is used to ensure a balance in sample size across groups over time.

At each site, clinicians are recruiting patients for the study. Patients who concent to participate are assigned a unique number by the study administrator at the site, entering it to a key code list. When the list is fully subscribed with a sufficient number of participants to form two groups, all the numbers are written on a folded piece of paper, and placed in a container. Then, under supervision and by a lottery procedure, one number at a time is drawn by an independent person every second time to the DBTgroup and the TAU-goup respectively. The draw takes place blindly for the participant and the person who draws and the monitor. Afterwards, when all the numbers have been drawn and assigned to their group, are the numbers with corresponding name and group announced so that the participants get to know which group they shall belong to in the study.

10.3. Statistical analysis

Collected data will be analyzed with SPSS (PASW statistics). Descriptive statistics is used for testing potential differences between the groups at baseline (chi-square tests for categorical variables, independent samples t-tests for continuous variables). We use independent samples t- tests to compare the mean difference of change from pre- to post-treatment between the two treatment groups, and analyses of covariance (ANCOVA) to compare these differences while adjusting for variables that differed between the groups at baseline as covariates. For the non-controlled extension part of the study, we use paired sample t-tests to assess change from baseline to 6-months follow-up, and analyses of variance (ANOVA) for repeated measures to assess change in symptom scores from baseline to post-treatment from the RCT and at 6 months follow-up after group treatment for all participants.
We will estimate standardized effect sizes (ES) of the treatment by dividing the mean difference in symptom scores from pre-to post treatment with the pooled standard deviation (SD) of the respective measure, reporting as Cohen's d. The significance threshold is set at 5% (two-tailed) and we use two-sided 95% confidence intervals (CI). Analyses are restricted to participants with actual responses on each of the respective questionnaires, i.e., will exclude participants with missing values analysis-by-analysis.

11. STUDY MANAGEMENT

11.1. Investigator delegation procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of the staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2. Study amendments

If changes are found to be necessary, the amendment and/or a new version of the study protocol (Amended Protocol) will be submitted to the Competent Authorities and the Ethics Committee for approval according to EU and national regulations.

11.3. Audit and inspections

Authorised representatives of a regulatory authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the centre to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12. ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1. Ethics Committee approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the Regional Ethics Committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2. Other regulatory approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be preregistered in www.clinicaltrials.gov.

12.3. Informed consent

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator File binder.

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient numbers, full names and last known addresses.

The patients will be identified in the CRFs by patient ID and date of birth.

13. TRIAL SPONSORSHIP AND FINANCING

The trial will be financially supported by the Regional Resource Centers for Autism, AD/HD, Tourettes Syndrome and Narcolepsy in Western and South- Eastern Norway Regional Health Authorities . Representatives from the latter are included in the board responsible for conducting the practical part of the study and covered costs for training of clinicians and translation of the manual to Norwegian.

14. TRIAL INSURANCE

Participants are patients receiving treatment as part of their ordinary helath service, and is such covered by Norwegian patient injury compensation.

15. PUBLICATION POLICY

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

16. REFERENCES

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