

Four-day Intensive Treatment Versus Standard Cognitive Behavioral Therapy for Adults with Obsessive-compulsive Disorder: a Single-blind, Randomized Controlled Non-inferiority Trial

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Abstract

Introduction

Obsessive-compulsive disorder (OCD) is a persistent and disabling psychiatric disorder. Individual cognitive behavioral therapy (CBT) with exposure and response prevention (ERP) is an effective treatment for OCD and is recommended as a first-line intervention. However, patients need to remain in treatment for several months and around 50% remain symptomatic after treatment. In response, a condensed version of CBT (Bergen 4-Day Treatment, B4DT) has been developed. B4DT has shown promising results in several uncontrolled trials and one randomized controlled trial with inactive control; however it has yet to be directly compared to gold standard CBT.

Methods and analysis

This single blind, randomized controlled trial including 120 patients (60 per arm) will compare B4DT to individual CBT. The primary outcome is the blind assessor-rated Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). We hypothesize that B4DT will be non-inferior to gold- standard CBT 14 weeks after treatment start. The non-inferiority margin is set at 4 points on the Y-BOCS. Secondary outcomes are time to response, cost effectiveness, response and remission rates, dropout rates, and negative effects.

Ethics and dissemination

This study has been approved by the Swedish Ethical Review Authority (EPM 2022-01713-01) and Helse Bergen HF (no. 490097). Hypotheses were specified and the analysis code was published before data collection started. Results from all analyses will be reported in accordance with the Consolidated Standards of Reporting Trials statement for non-pharmacological trials (CONSORT) and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) irrespective of outcome. The study will be published open access and results will be disseminated to patient organizations.

Trial registration number

Clinicaltrials.gov (XYZ), Open Science Framework (<https://osf.io/w5bfp/>).

Keywords: Obsessive-compulsive disorder, cognitive behavior therapy, intensive treatment

Introduction

Obsessive-compulsive disorder (OCD) is a disabling psychiatric disorder characterized by recurrent uncontrollable and unwanted thoughts (obsessions), and repetitive behaviors in response to those obsessions (compulsions). The lifetime prevalence of OCD is 2-3% [1], and the time-consuming symptoms often interfere with all aspects of daily life. Moreover, population-based studies have shown that OCD is associated with academic underachievement across the lifespan [2] and with substantial labor market marginalization, including higher risk of receiving disability pension, being on long-term sickness absence, and long-term unemployment [3].

One of the recommended first-line treatments for OCD is individual cognitive behavioral therapy (CBT) that includes exposure and response prevention (ERP). In CBT, patients are exposed to situations that trigger obsessions while actively refraining from performing compulsions. Although it is an effective treatment with 65% of participants responding to treatment [4], CBT typically requires weekly sessions during at least 3 months [5]. This extensive time-frame requires significant effort and persistence from patients and increases the risk of dropout. Moreover, a substantial proportion of patients remain impaired even among those who complete the treatment.

In response to this, several condensed formats of CBT have been developed in various countries. Amongst them is the Bergen 4-Day Treatment (B4DT), developed in Norway. In this treatment, patients receive intensive CBT at the clinic for 4 consecutive days. B4DT has been shown to achieve response rates over 90% when delivered in regular care in several uncontrolled treatment trials, and one randomized controlled trial (RCT) that used waitlist and self-help as controls [6]. However, it has yet to be compared to the gold standard CBT.

In this non-inferiority RCT, we will test the efficacy of B4DT compared to gold standard CBT. If B4DT turns out to be non-inferior to traditional CBT, the range of evidence-based options will be broadened and patients may be able to achieve clinically meaningful improvements within a shorter period of time.

Research questions

The overall approach of this study is to directly compare the intensive Bergen 4-day treatment (B4DT) to gold-standard individual cognitive behavior therapy (CBT) for adults with OCD.

Primary outcome

The primary outcome is OCD severity as assessed by the blind rater-administered Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Specifically, we will test whether B4DT is non-inferior to

standard CBT 14 weeks after treatment start. The non inferiority margin is set to 4 points on the Y-BOCS.

Non-inferiority designs test whether a novel treatment is not unacceptably less efficacious (in this case, 4 points) than another treatment whose efficacy has already been established. However, a non-inferiority study may also be used to test for superiority without inflating the false-positive rate [7]. We will therefore sequentially test 1) whether B4DT is non-inferior to gold standard CBT , and 2) whether B4DT is superior to gold standard CBT.

Secondary outcomes

Our secondary objectives are to compare B4DT and gold standard CBT with regards to:

- 1) Time to response. We hypothesize that B4DT, due to its intensive design, will provide a faster response than gold- standard CBT. A comparison of the proportion of treatment responders at week 4 and week 7 will be used to test this hypothesis.
- 2) Rates of response and remission. The proportion of participants in response and remission will be compared 14 weeks after treatment start. For these outcomes, we have no directed hypotheses.
- 3) Dropout rate. We will test whether the proportion of patients that discontinue treatment prematurely (i.e., complete less than 50% of the treatment) differs between the B4DT and the gold standard CBT arm. For this outcome, we have no directed hypothesis.
- 4) Cost-effectiveness. Health economic data will be collected using clinic data on therapist usage and the Treatment Inventory of Costs in Psychiatric Patients [11]. Between-group costs will be calculated and compared 14 weeks after treatment start. The emphasis will be on cost-effectiveness analyses using responder status as outcome and health-care provider as the cost perspective. For this outcome, we have no directed hypothesis.
- 5) Negative effects. The total score of the Negative Effects Questionnaire will be compared 14 weeks after treatment start, as well as the prevalence of severe adverse events. For this outcome, we do not have a directed hypothesis.

This study was designed to have high power to test the primary hypothesis, that B4DT is non-inferior to gold standard CBT using a 4-point margin on the Y-BOCS. However, this study is not sufficiently powered to make confirmatory claims based on the results of the secondary analyses. This means that the results will be interpreted as explanatory (despite the fact that 95% confidence intervals of group differences will be reported to follow common practice in the field).

Methods

Study Design

We will conduct a single-blind (blinded outcome assessors), randomized (1:1), controlled non-inferiority trial comparing intensive 4-day CBT and gold-standard individual CBT for adults with OCD. The total number of participants will be 120 (60 per group). Participants will be assessed before treatment start, at week 4 and 7, 14 weeks after treatment start (primary end-point), and 7- and 16-months after treatment start (follow-ups). The Consolidated Standards of Reporting Trials (CONSORT) flow chart of the trial is shown in Figure 1. The study is pre-registered at XYZ (no. 123). Hypotheses were specified in advance. This process included determining outcome scales, statistical models and cut-offs, time-points of evaluation, and publishing analysis scripts before the beginning of data collection. During the trial, we will follow Good Clinical Practice (GCP) and all quality- and safety aspects will be regularly monitored by an external party, the Karolinska Trial Alliance (i.e. case by case monitoring of informed consent, inclusion/exclusion criteria, source data quality, and adverse events). The study has been approved by the Swedish Ethical Review Authority (EPM 2022-01713-01) and Helse Bergen HF (no. 490097).

CONSORT 2010 Flow Diagram

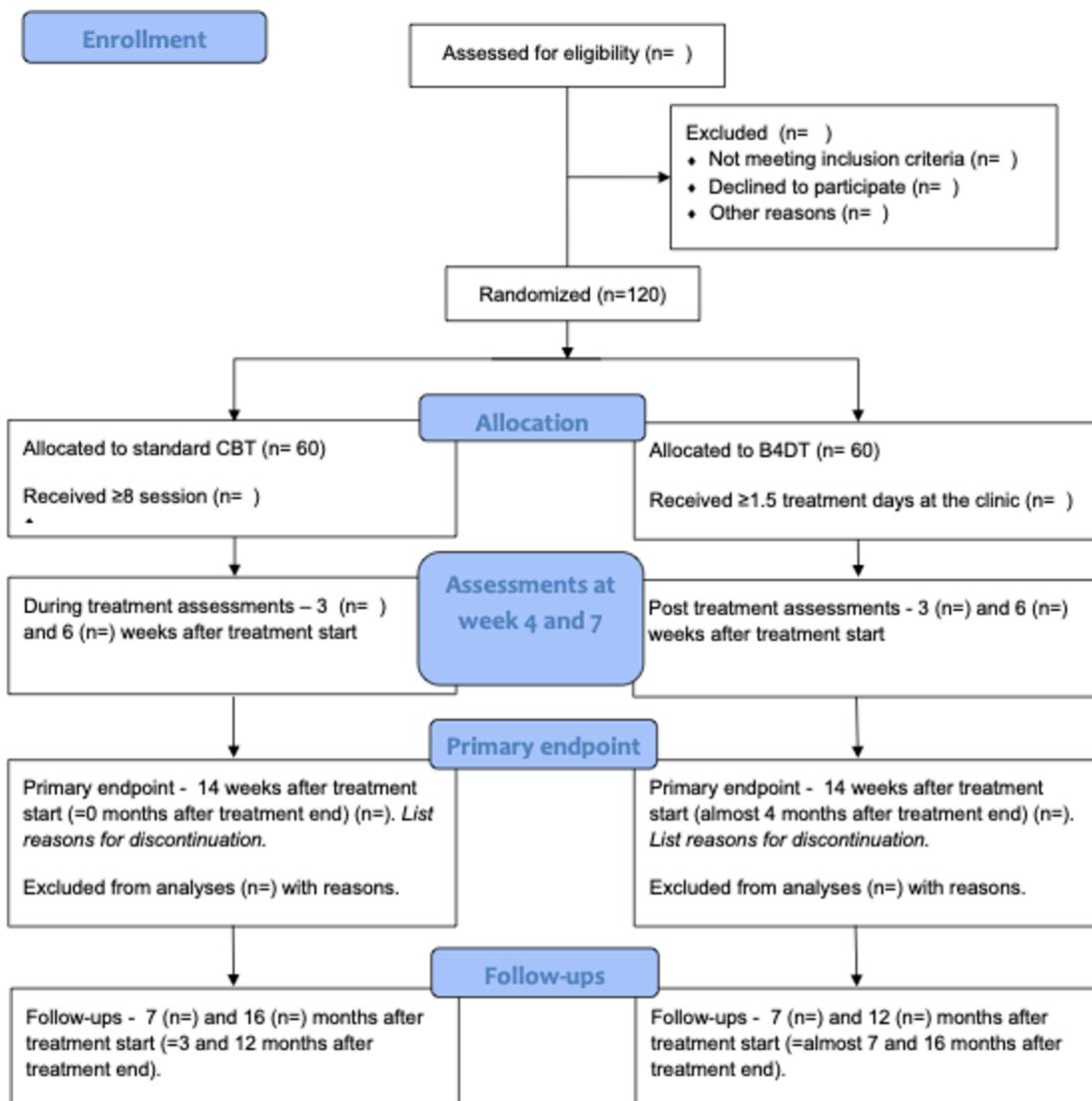


Figure 1. CONSORT-flow diagram. Abbreviations: B4DT, Bergen 4-day treatment; CBT, cognitive behavior therapy.

Participants

Patients referred to one of the two involved OCD specialist clinics in Stockholm and self-referred patients will be assessed for eligibility by a staff clinician during a full psychiatric assessment. Candidates that live within approximately one hour of both clinics and match the inclusion/exclusion criteria (see Table 1) will be offered participation in the study and asked to provide informed consent.

Table 1. Overview of inclusion and exclusion criteria

Inclusion criteria	≥ 18 years of age.
	Primary diagnosis of OCD according to DSM-5.
	Clinician-rated Y-BOCS score of ≥ 16
	Written informed consent.
	To be willing and able to attend treatment at any one of the two treatment clinics, regardless of the clinic where the initial assessment took place (the two clinics are located at different locations in Stockholm, about 20 Km apart).
	Be fluent in Swedish.
Exclusion criteria	Other psychological treatment for OCD planned during trial period.
	Completed CBT with exposure and response prevention (ERP) for OCD in the last 12 months.
	Changes in psychotropic medication within the last 2 months.
	Bipolar disorder.
	Psychosis.
	Alcohol or substance dependence.
	Organic brain disorder.
	Hoarding disorder or OCD with primary hoarding symptoms.
	Suicidal ideation that would warrant close monitoring.

Abbreviations: CBT, cognitive behavior therapy; DSM-5, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

Randomization and concealment

A block randomization method will be applied where included participants are randomized to receive either B4DT (delivered at Ångestenheten, Psykiatri Nordväst), or gold standard CBT (delivered at OCD-programmet, Psykiatri Sydväst), regardless of their clinic of origin in blocks of 4 or 6. Block size will vary randomly. This approach was chosen to achieve balance in the allocation of participants to treatment arms and to prevent selection bias. It entails that patients assessed in one clinic may have to travel to the other clinic to receive treatment. A third party, the Karolinska Trial Alliance, will generate the randomization sequence. Participants will receive their randomization number based on order of inclusion.

Assessors will be blind to the study objectives as well as group assignment up to the last follow-up. To ensure that the blinding is maintained, assessors will be asked to guess the intervention received at each assessment after randomization, and to indicate whether the blinding has been broken (for example, the participant revealing details about the treatment). If blinding is broken, the participant will be assigned another assessor at subsequent follow-ups. The proportion of correct guesses will be estimated, and blinding is adequate if the proportion of correct guesses does not differ significantly from what would have been achieved by guessing treatment allocation by chance.

Interventions

Bergen 4-day treatment (B4DT)

Patients in this arm will receive an intensive treatment delivered mostly in group format, the Bergen 4-day treatment (B4DT) [6]. The group sizes will be 3-6 participants with a 1:1 patient to therapist ratio. In the week leading up to the intensive part of the treatment, participants will have two scheduled phone/video calls with a therapist to assess readiness and encourage participants to prepare relevant exposure tasks. Day 1 of the intensive treatment includes psychoeducation about the rationale for exposure with response prevention (ERP), and deciding on exposure tasks. Days 2 and 3 focus on individually tailored and therapist-assisted ERP in as many relevant settings as possible (up to 7 hours of ERP per day). In the evenings, patients should continue with self-guided ERP and may receive therapist support via text messages or phone calls on demand. In the afternoon of day 3, patients can invite relatives and friends to a psychoeducation session. Day 4 of the intensive treatment focuses on treatment summary and relapse prevention, as well as planning self-guided ERP for the upcoming 3 weeks. After 14 weeks, participants have individual follow-up sessions at the clinic where they summarize their experiences after completing treatment. There is no ERP during this session.

All groups will be led by a therapist with expertise in B4DT. All therapists will have participated in the Norwegian OCD-training program [12] or have documented equivalent training. Prior to participation, all therapists will have participated in at least two B4DT groups.

Individual CBT

Patients will receive 16 90-minute sessions of individual CBT for OCD with an emphasis on ERP, delivered over a time period of 14 weeks according to a validated protocol [10]. Sessions will be held twice weekly at a specialist clinic during the first 2 weeks and once a week for the remaining 12 weeks. Sessions 1-2 contain psychoeducation about OCD and CBT, goal setting, and planning of ERP exercises. Sessions 3-14 include therapist-guided ERP (at the clinic, in the patients' homes or elsewhere as needed) with planned self-practice ERP between sessions. Sessions 15-16 contain a summary of the treatment and lessons learned, as well as relapse prevention and planning of continued self-practice ERP.

Therapist competence and adherence

Therapists in both arms will be licensed clinical psychologists or psychologists under supervision employed at the two specialist OCD clinics. All sessions in both treatments will be audiotaped for the purpose of rating competence and adherence. Such ratings will be conducted on 20% of audiotaped sessions (randomly selected) by two independent psychologists not otherwise involved in the study specialized in B4DT, and two independent psychologists specialized in individual CBT treatment for OCD. Adherence to protocol in the B4DT arm will be checked using a treatment checklist, and therapist adherence in the individual CBT arm will be checked using the session checklist in the treatment manual. Therapist competence in both treatment arms will be rated using the Cognitive Therapist Scale-Revised (CTS-R) [22].

Sample size calculation

A power calculation has been conducted in order to determine the number of participants needed to test the primary hypothesis; that B4DT will be non-inferior compared to gold standard CBT at the pre-specified margin of 4 points on the Y-BOCS. Clinical outcome data from a recent randomized controlled trial (individual CBT) and regular clinical practice (B4DT) were obtained to simulate study data. The following parameters were used: A pre-treatment mean of 22.6 (SD = 3.78) for both arms, and a post-treatment mean of 12.9 (SD = 4.07) for the gold standard CBT arm. Statistical power was then assessed by simulating 10000 datasets assuming different true group differences. An ANCOVA was then conducted on each dataset to test for between-group differences at post-treatment accounting for pre-treatment scores. With 60 participants per arm, no difference in efficacy between the treatments, and 10% missing values,

this test has >95% power to demonstrate non-inferiority. Details on this calculation, including analysis code, is provided in the online pre-registration (<https://osf.io/w5bfp/>).

Measurements

Table 2 lists clinician-rated and self-rated assessments at the different time points.

The primary outcome measure is the blind assessor-rated Y-BOCS, which will be administered at pre-treatment, at weeks 4 and 7 during treatment, 14 weeks after treatment start (primary endpoint), and at the 7- and 16-month follow-ups [21]. Blinded assessors will undergo training prior to conducting clinician-rated assessment and practice on videos of OCD case examples. In order to be allowed to conduct assessments for the project, the assessors will have to deviate no more than 1 point on single items, no more than 2 points on the obsessions subscale and the compulsions subscale and no more than 4 points on the Y-BOCS total score compared to expert raters at the two clinics. Inter-rater reliability on the Y-BOCS will be reported.

Secondary clinician-administered outcome measures are the Clinical Global Impression – Severity and Improvement (CGI-S, CGI-I), the Patient Exposure/Response Prevention Adherence Scale (PEAS), the Structured Clinical Interview for DSM-5 for OCD and related disorders (SCID-5) and the Mini International Neuropsychiatric Interview. SCID-5 and MINI will be administered at pre-treatment to confirm the OCD-diagnosis and assess comorbidities

Secondary self-rated outcome measures are the Obsessive-Compulsive Inventory-Revised (OCI-R), self-rated Y-BOCS, Montgomery-Åsberg Depression Rating Scale—Self-Rated (MADRS-S), Work and Social Adjustment Scale (WSAS), Assessing Quality of Life 6 Dimensions (AQoL-6D) (for economic evaluation), Credibility/Expectancy Questionnaire (CEQ), Working Alliance Inventory—Short Form Revised (WAI-SR), the TIC-P resource use questionnaire (for economic evaluation), and the Negative Effects Questionnaire (NEQ). Participants will also rate their treatment preference measured on a 7-point Likert-type scale (pre-treatment and post-treatment).

Table 2. Assessments of secondary outcomes at different time points

	Pre-treatment	Week 4	Week 7	Week 15 (primary end-point)	7-month follow-up	16-month follow-up
Clinician-rated instruments						
SCID-5 (OCD)	X					
MINI	X					
Y-BOCS	X	X	X	X	X	X

CGI-S	X	X	X	X	X	X
CGI-I		X	X	X	X	X
PEAS*		X	X	x		
Self-rated instruments						
YBOCS-SR	X			X	X	X
OCI-R	X			X	X	X
MADRS-S	X			X	X	X
WSAS	X			X	X	X
AQoL-6D	X			X	X	X
TIC-P	X			X	X	X
NEQ				X	X	X
Other adverse events		X	X	X	X	X
CEQ**		X				
WAI-SR**		X				
Treatment preference	X			X		

Abbreviations: AQoL-6D, Assessing Quality of Life 6 Dimensions; CEQ, Credibility/Expectancy Questionnaire; CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; MADRS-S; Montgomery–Åsberg Depression Rating Scale–Self-Rated; MINI, Mini International Neuropsychiatric Interview; NEQ, Negative Effects Questionnaire; OCI-R, Obsessive–Compulsive Inventory–Revised; PEAS, Patient Exposure/Response Prevention Adherence Scale; SCID-5, Structured Clinical Interview for DSM-5 Disorders; TIC-P, Treatment Inventory of Costs in Psychiatric Patients; WAI-SR, Working Alliance Inventory–Short Form Revised; WSAS, Work and Social Adjustment Scale; Y-BOCS, Yale–Brown Obsessive Compulsive Scale; Y-BOCS-SR, Yale–Brown Obsessive Compulsive Scale–Self-Rated; Other adverse events, semi-structured questions about potential severe adverse events and psychiatric care outside the study

* PEAS rated once at the last day of B4DT treatment

** CEQ and WAI-SR rated by participants at the last day of B4DT treatment and week 2 in individual CBT

Treatment-response will be defined as a $\geq 35\%$ reduction on the Y-BOCS and a Clinical Global Impression–Improvement (CGI-I) score of 1 ("very much improved") or 2 ("much improved"). Remission will be defined as a score of ≤ 12 on the Y-BOCS and a Clinical Global Impression–

Severity (CGI-S) rating of 1 ("normal, not at all ill") or 2 ("borderline mentally ill"). Recovery will be defined as a sustained remission status at the long-term follow-ups[8].

Safety and adverse events

Data on adverse events including suicidal ideation, and initiation of additional psychiatric care, will be collected at each assessment following inclusion, as well as through the regular contact between participants and therapists during treatment. A standardized self-rated questionnaire (Negative effects questionnaire, NEQ; [9]) containing 32 questions about incidents and negative effects will be used at the primary endpoint and follow-ups.

If a participant expresses suicidal ideation during treatment or at subsequent assessments, assessors will initiate a structured suicide risk assessment in accordance with routines at the clinic. If there is an urgent need for psychiatric care, a trial psychiatrist will contact participants to schedule an appointment as soon as possible. Serious adverse events (e.g., urgent psychiatric care or discontinued treatment due to a worsening of psychiatric symptoms) will be described in detail on a case-by-case basis.

Statistical analysis

All analysis scripts have been uploaded to a public repository with the analysis strategies described in detail using simulated data (<https://osf.io/w5bfp/>).

Primary outcome

Y-BOCS

The primary non-inferiority hypothesis on the clinician-rated Y-BOCS will be evaluated using ANCOVA of group differences at post-treatment with pre-treatment score as covariate. It will be based on participants that have received at least 50% of the treatment (i.e., attended at least 8 sessions of individual CBT or 1.5 days of B4DT) and completed the post treatment assessment 14 weeks after treatment start. This per protocol approach is chosen to avoid potential problems related to study design that can bias the results towards the alternative hypothesis of non-inferiority (the opposite is true in superiority trials). No data imputation will be conducted at this stage. A 95% confidence interval will be used to model the gold standard CBT-B4DT effect. Non-inferiority will be considered supported if the upper bound is less than 4 (the non-inferiority margin) and superiority will be considered supported if the upper bound is less than 0. This testing procedure has the Type I error rate controlled at the 2.5% level for both comparisons.

For sensitivity assessment, the same ANCOVA model will be used again but with an intention to treat approach. Missing data will then be estimated using maximum likelihood after which the models are refitted. The aim of these steps is to address the potential influence of non-random missing data in the primary per protocol analysis.

Non-inferiority margin

Although there are no strict guidelines regarding the selection of non-inferiority margins, half the placebo-controlled effect of gold-standard treatment is often recommended as adequate [23]. The proposed non-inferiority margin of 4 is smaller than half of the 10-point effect for ERP on the Y-BOCS [4], and would therefore be a stringent non-inferiority margin. Moreover, a non-inferiority margin of 4 points gives similar precision compared to previous non-inferiority trials for OCD in adults that have used 5 points [19] or 3 points [20], and a previous non-inferiority trial in pediatric OCD that used a margin of 4 points [30]. From a clinical point of view, a 4-point margin on the Y-BOCS is considered a small but observable difference in OCD symptoms.

Secondary outcomes

While this study was designed to have high power to assess the primary hypothesis, we do not have sufficient power to robustly compare the secondary outcomes between the treatment arms without inflating the false positive rate. This means that the results from these analyses should be interpreted with caution. On secondary outcomes, our approach will be to compute 95% confidence intervals of group differences without comparing the bounds to any predefined margin. Because the non-inferiority testing procedure will not apply, the secondary outcomes will be analyzed using an intent to treat approach including all randomized participants.

Moreover, we do not plan to collect data continuously throughout the treatments since our focus is on the pre-post comparisons. This decreases the usefulness of statistical methods that make imputations based on past observations. Therefore, unless the proportion of missing data exceeds 10%, no data imputation methods will be used as default (unless stated otherwise). However, if the proportion of missing data exceeds 10%, we will perform maximum likelihood imputations based on demographics and the scores from the pre-treatment assessment to complement the complete case analyses. The implications of these analyses on the reliability of the results will be discussed.

Time to response

To explore whether B4DT leads to a faster treatment response than individual CBT, the proportion of responders in the two treatments will be compared 4 weeks after treatment start. The 95% confidence intervals of the odds ratio of response will be calculated for this purpose. Because the B4DT-group will have received their full treatment dose at the point of assessment while the gold standard CBT-group will have received only about 25%, there are strong reasons to believe that, from this perspective, B4DT will lead to faster symptom relief. An identical analysis will be conducted at 7 weeks to evaluate whether there is a difference between the treatments when participants in the individual CBT group have received 50% of the treatment.

Rates of response and remission

The proportion of participants in response and remission will be compared 14 weeks after treatment start. Response is defined as a reduction of 35% or more on the Y-BOCS and a CGI-I score of 1 or 2. Remission is defined as a Y-BOCS score of 12 or less and a CGI-S score of 1 or 2. Proportions will be compared using a two-sided two-proportions z-test.

Dropout rate

To explore whether the groups differ in terms of treatment completion, we will compare whether the proportion of patients that discontinue treatment prematurely differs between B4DT and gold standard CBT. A dropout will be defined as a patient in the B4DT arm that participates in less than 1.5 full days at the clinic, or a patient in the gold standard CBT arm that participates in less than 8 CBT sessions. Proportions will be compared using a two-sided two-proportions z-test.

Negative effects

To describe negative treatment effects, a two-sample t-test will be used to compare the total NEQ-scores at the primary endpoint (scores on the subscales will be presented in the supplement). The additional semi-structured questions about suicidal behaviors and thoughts, hospitalization, deterioration of psychiatric symptoms, and psychiatric care outside the study, will be reported in a frequency table.

Cost effectiveness

Health economic data will be collected using the self-rated Treatment Inventory of Costs in Psychiatric Patients (TIC-P) questionnaire [11]. The TIC-P records costs for the past month

(pretreatment) or the past 14 weeks (post-treatment and follow-up), and costs will be extrapolated to cover the entire period between assessments when needed. Costs from third party payer (including only intervention costs), healthcare, and societal perspectives will be analyzed in relation to clinical efficacy (responder status; cost-effectiveness analysis) and quality-adjusted life-years on the AQoL-6D (QALYs; cost utility analysis). Additional cost-effectiveness analyses will use remitter status as outcome. The economic analysis will be conducted using multiple imputation of missing values. Cost data and QALYs will be analyzed using generalized linear models (GLM) to allow for the consideration of other distributions and functional forms to fit the cost and outcome data [24]. Total costs will be analyzed while controlling for baseline costs. Total QALYs will be analyzed while controlling for baseline AQoL-6D utility values [25].

A micro costing framework will be used to estimate the cost of delivering the interventions prospectively. Intervention costs will include the therapists' time to deliver sessions, as well as any training needed. Healthcare resource use will be costed using national pricelists, and medication costs using market prices, and estimated by multiplying frequencies of resources used by unit costs. Unit costs for resources related to social support and assistance will be sourced from published sources or based on authors' own estimates. Productivity losses will be estimated using the human capital approach [26]. Productivity losses due to absenteeism from paid work will be the product of the number of days off from work by individuals due to mental illness by the average hourly salary rate in Sweden [27] including social fees. Losses due to absenteeism from unpaid work will be the product of the number of days not performing unpaid work by the estimated hourly cost of leisure time [28]. Productivity losses related to reduced efficiency at work will be estimated in the same fashion as productivity losses due to absenteeism, but additionally multiplied by a weighed score representing how the illness impacted the participants' productivity [29].

Additional outcomes used for quality assessment

Therapist competence and adherence

Therapist competence will be scored using the Cognitive Therapist Scale-Revised (CTS-R) by independent raters not otherwise involved in the study. Descriptive information (average total score and standard deviation) for the two treatments will be presented.

Therapist adherence will also be presented using descriptive information (average adherence to protocol) as well as inter-rater reliability between independent assessors. For individual CBT, a session-by-session checklist of prescribed techniques will be used [5]. In B4DT, a checklist based on the content for each day in therapy, as well as adherence to B4DT-specific techniques, will be used.

Treatment preference, credibility and working alliance

Responses to the question about treatment preference will be presented descriptively at pre-treatment and the 4-month follow-up, respectively (means and standard deviations). In addition, an exploratory analysis will evaluate whether the degree of agreement between pre-treatment preference and treatment received moderates the main Y-BOCS outcome.

Treatment credibility and working alliance will be rated by participants at week 2 in treatment, and the total score means with standard deviations will be presented for both treatments.

Discussion

This study is the first trial to directly compare an intensive treatment for OCD, the Bergen 4-day treatment (B4DT) with traditional individual CBT delivered over 14 weeks. It will address the non-inferiority of B4DT, early rates of response for both treatments, as well as quality aspects including attrition and negative effects. By comparing the cost-effectiveness of both treatments, the study will be informative for decision makers in health care who strive for efficient use of resources. The study will also include follow-up until 16 months to evaluate the long-term effects of the treatments.

Limitations

First, the clinics in this study are located in different parts of Stockholm. This means that some participants might prefer to be randomized to the clinic closest to their home, which could pose a risk of selection bias. In addition to highlighting the importance of only agreeing to participate if the location of both clinics are acceptable to the patient, we will continuously monitor the dropout rate in both arms and assess whether the distance to the clinic has caused dropouts. After data collection, we will evaluate the potential importance of travel distance on the risk of dropout and explore if and how this threatens the validity of the results.

Second, this study does not have sufficient statistical power to robustly assess the secondary outcomes. Hence, results from the secondary analyses will be interpreted as exploratory and need to be confirmed in independent datasets before firm conclusions can be drawn.

Last, blinding is always a problem in psychotherapy trials. In this study, while therapists and patients will be aware of which treatment arm they belong to, we aim to keep the outcome assessors, statisticians, and other investigators blinded. After each assessment, the outcome assessor will be asked to guess which treatment the participant has received and to indicate whether blinding has been broken. Sensitivity analyses will then be conducted to evaluate the potential effect of this type of blinding problem on the results.

Patient and public involvement

Patient representatives have not been involved in the design of the current study. The Swedish OCD Foundation (OCD-förbundet) supports the study by providing information about the project to their members and the public through their various channels. Results from the study will be reported to the public and relevant patient organizations (e.g., OCD-förbundet) through open access publishing and lectures.

Ethics and dissemination

Patient safety

All patients will get either gold standard CBT or B4DT delivered by clinicians who are specialized in each of these forms of treatment delivery. Gold standard CBT is already the firsthand choice for this patient group, and its efficacy and safety has been demonstrated by several studies of high quality [4]. While B4DT has not yet been evaluated in an RCT with an active control group, it is an intensive face-to-face treatment built on ERP. Moreover, uncontrolled studies have suggested that the effect is similar or improved compared to gold standard CBT [6]. We therefore consider the additional risks associated with participating in the B4DT-arm to be small. All participants will be monitored closely during the study and additional treatment will be provided in case of severe deterioration. Such decisions will be made on a case-by-case basis by the clinicians. This means that if a patient becomes significantly worse during treatment, he/she will be handled in the same way as the regular patients at the clinic.

The requirement to travel to another specialist clinic within Stockholm may put a strain on some participants who have financial or mobility difficulties or simply do not wish to travel. Participants referred to the clinics by other health-care services and who decline participation in the trial or turn out not to be eligible, will have an equal chance to receive specialist treatment at the clinic they were assessed. Excluded self-referred participants will be guided to adequate care.

Maximizing knowledge gain and minimizing risk of bias

Systematic evaluations of clinical trials have in recent years highlighted limitations in current practice that bias the scientific literature [14, 15, 16, 17]. As researchers and other stakeholders have begun to acknowledge the need to better control different sources of bias, the interest in issues related to replicability, transparency, and error control have grown substantially in

clinical fields [16]. Minimizing the influence of bias is an ethical as much as a technical concern and will be a top priority in this study. We will adopt practices that are known to increase the trustworthiness of scientific research such as preregistering all hypotheses and analysis plans, adhering to gold standard outcome reporting, controlling the risk of false positive results by interpreting the secondary (uncorrected) results with caution, and sharing materials that are needed to evaluate our results including the analysis code, the protocol, and a detailed description of the dataset (raw data will be saved in a searchable database, SND, as recommended by KI) [18].

Current trial status

Inclusion is expected to start in November 2022 and end in August 2024. The last follow-up appointment is expected to take place in August 2025. Data analysis and reporting of results will begin once the primary endpoint has been reached.

Conclusion

Current treatment options for OCD include individual CBT delivered over several months. The proposed project will evaluate the Bergen 4 day treatment (B4DT) compared to gold-standard individual CBT. The study is well powered to test whether B4DT is non-inferior to gold standard CBT in terms of symptom reduction with a 4 point non-inferiority margin. If the two treatments are comparable in terms of clinical efficacy, B4DT should be considered a candidate for implementation in regular care. While we lack power to conclusively compare the secondary outcomes between the groups, data from this trial on speed of response, attrition rate, negative effects, response, remission and recovery status, and cost-effectiveness will provide a first step towards comparing gold standard CBT to B4DT more broadly.

Intensive treatments such as the B4DT have the potential to profoundly change how psychotherapy is delivered and could minimize treatment time and the risk of dropouts. Increasing the availability of evidence-based treatments that provide rapid recovery for individuals with OCD has the potential to decrease their suffering and strengthen their capability to actively take part in all aspects of society.

References

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