DET SAMFUNDSVIDENSKABELIGE FAKULTET
KØBENHAVNS UNIVERSITET

PHD THESIS
SOPHIE MERRILD JUUL

WHICH LENGTH FOR WHOM?

A systematic review, meta-analysis, and a randomised clinical trial of short-term versus long-term psychotherapy for adult psychiatric disorders

Which length for whom? A systematic review, meta-analysis, and a randomised clinical trial of short-term versus long-term psychotherapy for adult psychiatric disorders

PhD thesis

Sophie Merrild Juul

Author: Sophie Merrild Juul, M.Sc.

Departments: Department of Psychology, University of Copenhagen and
Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark

Academic advisors:

Primary PhD supervisor: Susanne Lunn, associate professor, Department of Psychology, University of Copenhagen, Denmark

Secondary PhD supervisor: Stig Poulsen, PhD, associate professor, Department of Psychology, University of Copenhagen, Denmark

Project supervisor Sebastian Simonsen, PhD, senior researcher, Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark

Submitted: January 2021

This research is funded by the Research Fund of the Mental Health Services in the Capital Region of Denmark with DKK 1.590.000 and by Trygfonden A/S with DKK 2.670.000 (Grant no. 123488)

ISBN:
Printed by:

Content

LIST OF ABBREVIATIONS AND DEFINITIONS

BDI	Beck Depression Inventory
Chi^2	Chi square heterogeneity index
CI	Confidence Interval
CONSORT	Consolidated Standard of Reporting Trials
DBT	Dialectical Behavior Therapy
Df	Degrees of freedom
ERGT	Emotion Regulation Group Therapy
g	Hedges *g*
GAF	Global Assessment of Functioning scale
GRADE	Grading Recommendations, Assessment, Development and Evaluation
HDRS	Hamilton Depression Rating Scale
I^2	I square heterogeneity index
ICD-11	International Classification of Diseases 11th Revision
ICH-GCP	International Conference on Harmonization- Good Clinical Practice
ITT	The intention-to-treat principle
IQ	Intelligence Quotient
M	Mean
MBT	Mentalization-Based Therapy
MBT-I	Introduction to Mentalization-Based Therapy
MBT-G	Mentalization-Based Group Therapy
MCID	Minimal Clinically Important Difference
NICE	UK National Institute for Health and Care Excellence guidelines
p	*p*-value
PCS	Stolpegaard Psychotherapy Centre

PICO	Participants, Interventions, Comparators, and Outcomes
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis Guideline
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guideline
RCT	Randomised Clinical Trial
ROB	Risk of Bias
RR	Relative Risk
SCL-90	Symptom Checklist 90
SD	Standard Deviation
SF-36	Short-Form Health Survey 36
SMD	Standardized Mean Difference
STEPPS	Systems Training for Emotional Predictability and Problem Solving
TIDieR	The template for intervention description and replication checklist and guide
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder
WSAS	Work and Social Adjustment Scale

PREFACE

This PhD was carried out at Stolpegaard Psychotherapy Centre, an outpatient psychiatric facility for non-psychotic disorders within the Mental Health Services in the Capital Region of Denmark. The randomised clinical trial (RCT) was implemented at the Outpatient Clinic for Personality Disorders. The study was carried out in a close collaboration with the Department of Psychology at University of Copenhagen, where I was formally enrolled as a PhD fellow, and with Copenhagen Trial Unit, Centre for Clinical Intervention Research at Rigshospitalet, Copenhagen University Hospital, where I was also part-time employed as a methodologist through the last part of my PhD.

The primary objective of this study was to systematically review the evidence-base for short-term compared with long-term psychotherapy for all adult psychiatric disorders, and to synthesize the evidence in a meta-analysis including Trial Sequential Analysis. The second objective of this study was to develop a short-term mentalization-based treatment approach for outpatients with borderline personality disorder and to plan and conduct a randomised clinical trial comparing its efficacy to the standard long-term mentalization-based treatment approach. Both beneficial and harmful treatment effects would be evaluated blind to treatment allocation at 8, 16, and 24 months after randomization. The third objective was to discuss the clinical challenges related to the termination phase of mentalization-based therapy for patients suffering from borderline personality disorder.

ACKNOWLEDGEMENTS

This thesis would not have been possible to write without the hard work and dedication of many other people.

I am deeply grateful to my project supervisor and the sponsor-investigator of the randomised clinical trial, Dr. Sebastian Simonsen, who has shown me epistemic trust from the very beginning, when this project was merely on the sketching board. Without his trust, admirable expertise in the field of personality disorders, and good-enough-mentoring, this study would simply not have been possible to conduct. I also want to thank my supervisors at University of Copenhagen, Susanne Lunn, for containing all my joys and frustrations and for continuously helping me develop as a scientist, and Dr. Stig Poulsen for enlightening me with his great expertise in psychotherapy research. I am also deeply grateful to Dr. Janus Christian Jakobsen from Copenhagen Trial Unit for teaching me everything I know so far about clinical research methodology. Janus has made me realize that psychologists can also become researchers in evidence-based medicine. For that I am forever grateful.

Many people at Stolpegaard Psychotherapy Centre supported me in this work. I owe the biggest thank you to my talented and extraordinarily well-organized research assistants: Amanda Ark Søndergaard, Caroline Kamp Jørgensen, Marie Zerafine Rishede, Emilie Hestbæk, Mathilde Hasselby-Andersen, Laura Alsing Juul, and Anders Sonne Munch. I am also deeply grateful to the professional and dedicated staff at the Outpatient Clinic for Personality Disorders for their good cooperation throughout the project. I want to especially thank the secretaries Johanne Rentzmann and Marie-Louise Hemicke for always helping me keeping track of everything (and everybody), Mehrak Salimi for her dedicated and tireless efforts in implementing short-term mentalization-based therapy, Ann Bøckel, Trine Schaltz, Dr. Torben Heinskou, and Dr. Catherine Wohlert for the close and openminded collaboration with the clinic, and Dr. Per Sørensen for his continuous organizational and personal support in our efforts to integrate research into clinical practice.

I owe the deepest thank you to my family, my parents Charlotte and Søren, my sister Laura, and my husband Simon for moral support. Particularly Simon. Writing a PhD thesis and conducting a randomised clinical trial is no easy job but, somehow, he managed to witness the process everyday with great understanding and care. Thank you.

Above all, I would like to thank the participants for teaching me about these painful borderline conditions. Without them, this project would just have been theoretical speculations.

Sophie Merrild Juul
Gentofte, January 2021

LIST OF PAPERS

This thesis is based on results reported in the following papers, which will be referred to in the text by their Roman numerals.

Paper I

Juul, S., Poulsen, S., Lunn, S., Sørensen, P., Jakobsen, J. C., & Simonsen, S. (2019). Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis. *Systematic Reviews*. *8*(1):169. [1]

Paper II

Juul, S., Jakobsen, J. C., Jørgensen, C. K., Poulsen, S, Sørensen, P., & Simonsen, S. (submitted to *British Journal of Psychiatry*). Short-term versus long-term psychotherapy for adult psychiatric disorders: a systematic review with meta-analysis. [2]

Paper III

Juul, S., Lunn, S., Poulsen, S., Sørensen, P., Salimi, M., Jakobsen, J. C., ... & Simonsen, S. (2019). Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomised clinical trial. *Trials*. 20(1):196. [3]

Paper IV

Juul, S. Simonsen, S., Poulsen, S., Lunn, S., Sørensen, P., Bateman, A., Jakobsen, J. C. (submitted to *Trials*). Detailed statistical analysis plan for the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder randomised clinical trial (MBT-RCT). [4]

Paper V

Juul, S., Simonsen, S., & Bateman, A. (2020). The capacity to end: termination of mentalization-based therapy for borderline personality disorder. *Journal of Contemporary Psychotherapy*. 50:331-8. [5]

All papers are available in the appendices.

ABSTRACT

English abstract

Background

According to the World Health Organization (WHO), psychiatric disorders are one of the leading causes of disability worldwide. Many psychiatric disorders can be effectively treated at relatively low costs, but the gap between people needing care and those with access to care remains substantial. Psychotherapy is often used to treat adults with psychiatric disorders either alone, or in combination with psychopharmacology. The effects of specific psychotherapy approaches for psychiatric disorders (e.g. psychodynamic psychotherapy, cognitive-behavioural therapy) have been previously assessed. However, the optimal duration of psychotherapy for adults with psychiatric disorders still remains unclear.

Methods

We assessed the effects of short-term versus long-term psychotherapy for adult psychiatric disorders in a systematic review according to Cochrane methodology including meta-analysis, and we planned to perform Trial Sequential Analyses. We developed a comprehensive trial protocol and a detailed statistical analysis plan for a randomised clinical trial with low risk of systematic errors (bias) and low risk of random errors (play of chance) to assess the beneficial and harmful effects of short-term (5 months) versus long-term (14 months) mentalization-based therapy for outpatients with borderline personality disorder. We discussed the clinical challenges related to the termination phase of mentalization-based therapy, often caused by shortening the existing treatment for patients with borderline personality disorder.

Results

In our systematic review, we included 16 trials randomizing 2,651 participants to a short-term or a long-term version of the same psychotherapy type. All trials and outcomes were at high risk of bias. It was only possible to conduct two pre-planned meta-analyses. Meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms at end of treatment (SMD: 0.08; 95% CI: -0.47 to 0.63; p = 0.77; I^2 = 73%; four trials; very low certainty) or at maximum-follow-up (SMD: -0.17; 95% CI: -0.74 to 0.41; p = 0.57; I^2 = 75%; four trials; very low certainty). Meta-

analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy for mood- and anxiety disorders on level of functioning at end of treatment (SMD -0.13; 95% CI -0.42 to 0.15; p = 0.37; I^2= 44%; two trials; very low certainty). It was not possible to perform other pre-planned meta-analyses, Trial Sequential Analysis, or tests for publication bias due to sparse data.

We successfully designed and implemented a randomised clinical trial assessing the effects of short-term versus long-term mentalization-based therapy for outpatients with subthreshold or a diagnosed borderline personality disorder. We reached the target sample size of 166 randomised participants, and the outcome assessments are still underway. We discussed the clinical challenges of delivering time-limited mentalization-based therapy for outpatients with borderline personality disorder. We categorized termination challenges in three overall categories: patient factors, therapist factors, and therapeutic relationship factors.

Conclusions

In our systematic review with meta-analysis of different durations of psychotherapy for psychiatric disorders, we found no evidence of a difference between short-term and long-term psychotherapy for mood- and anxiety disorders. However, the evidence was sparse or even absent, of very low certainty, and with insufficient information sizes to allow us to confirm or reject realistic intervention effects. Furthermore, psychiatric patients are clinically heterogeneous, which may challenge the interpretation of randomised clinical trials and meta-analyses due to the sparse data currently available. Borderline personality disorder is one psychiatric condition, which historically has been treated with long-term psychotherapy. We successfully implemented a randomised clinical trial assessing short-term versus long-term mentalization-based therapy for borderline personality disorder, and the trial is still ongoing. The termination phase of mentalization-based therapy is a continuous clinical challenge for clinicians and patients, particularly when changing from a long-term to a short-term treatment format. To aid this process, we propose to extend the case formulation with the use of a "termination formulation" in which patients' outcomes and future goals are recapitulated in the termination phase of mentalization-based therapy. Evidence regarding the beneficial and harmful effects of short-term compared with long-term psychotherapy for psychiatric disorders remains inconclusive.

Dansk resumé

Baggrund

Psykiatriske lidelser er en af de hyppigst forekomne diagnosegrupper i verden. Mange psykiatriske lidelser kan behandles effektivt, men der er en diskrepans imellem hvor mange mennesker, som har brug for behandling og hvor mange mennesker, der har let adgang til denne behandling. Psykoterapi bruges ofte til at behandle voksne med psykiatriske lidelser enten som et enkeltstående tilbud eller i kombination med psykofarmakologi. Effekten af forskellige psykoterapeutiske retninger (eksempelvis psykodynamisk psykoterapi og kognitiv adfærdsterapi) er tidligere blevet testet. Den optimale længde af psykoterapi til voksne med psykiatriske lidelser er endnu uklar.

Metoder

Vi undersøgte effekten af forskellige længder af psykoterapi i en systematisk litteraturgennemgang udført efter Cochrane samarbejdets anbefalinger inklusiv metaanalyse, og vi planlagde sekventielle analyser. Vi udarbejdede en udførlig forsøgsprotokol og en detaljeret statistisk analyseplan til et randomiseret klinisk forsøg med lav risiko for systematiske fejl (hildethed) og lav risiko for tilfældige fejl (tilfældighedernes spil) for at sammenligne effekten af kort (5 måneder) versus lang (14 måneder) mentaliseringsbaseret terapi til ambulante patienter med subtærskel eller diagnosticeret borderline personlighedsforstyrrelse. Vi diskuterede de kliniske udfordringer, som kan afstedkommes af at afslutte behandlingen af patienter med borderline personlighedsforstyrrelse.

Resultater

I vores systematiske litteraturgennemgang inkluderede vi 16 forsøg, som randomiserede 2.651 deltagere til en kort eller en lang udgave af den samme psykoterapeutiske retning. Alle forsøg og effektmål var i høj risiko for systematiske fejl. Det var kun muligt at gennemføre tre planlagte metaanalyser. De første to metaanalyser viste ingen forskel mellem kort og lang kognitiv adfærdsterapi til patienter med angstlidelser ved behandlingens afslutning (SMD: 0.08; 95% CI: -0.47 to 0.63; p = 0.77; I^2 = 73%; fire forsøg; meget lav sikkerhed) eller ved det maksimale opfølgningstidspunkt (SMD: -0.17; 95% CI: -0.74 to 0.41; p = 0.57; I^2 = 75%; fire forsøg; meget lav sikkerhed). Den tredje metaanalyse viste ingen forskel mellem kort og lang psykodynamisk psykoterapi til angst- og affektive lidelser ved behandlingens afslutning (SMD

-0.13; 95% CI -0.42 to 0.15; $p = 0.37$; $I^2 = 44\%$; to forsøg; meget lav sikkerhed). Det var ikke muligt at udføre andre planlagte metaanalyser, sekventielle analyser, eller tests for publikationsbias på grund af sparsom data.

Vi designede og implementerede et randomiseret klinisk forsøg, som undersøger effekten af kort versus lang mentaliseringsbaseret terapi til ambulante patienter med borderline personlighedsforstyrrelse. Vi har nået vores planlagte deltagerantal på 166 deltagere, og dataindsamlingen efter 8, 16 og 24 måneder er fortsat i gang. Vi diskuterede de kliniske udfordringer, som kan afstedkommes af at udføre mentaliserings-baseret terapi med en forhåndsbestemt tidsafgrænsning til patienter med borderline personlighedsforstyrrelse, som ofte præsenterer vanskelige psykopatologiske udfordringer, også (og måske særligt) ved behandlingens afslutning. Vi kategoriserede de kliniske udfordringer forbundet med afslutning i tre overordnede kategorier: patientfaktorer, terapeutfaktorer og faktorer relateret til den terapeutiske relation.

Konklusioner

I vores systematiske litteraturgennemgang med metaanalyse af forskellige længder af psykoterapi til voksne patienter med psykiatriske lidelser fandt vi ingen forskel mellem kort og lang psykoterapi til patienter med angst- og affektive lidelser. Evidensen var dog enten sparsom eller manglende, af meget lav sikkerhed, og med utilstrækkelige informationsstørrelser. Patienter med psykiatriske lidelser er klinisk heterogene. Denne heterogenitet i populationen kan vanskeliggøre tolkningen af randomiserede kliniske forsøg og metaanalyser, da det ikke var muligt at lave subgruppeanalyser af patienter med eksempelvis forskellige psykiatriske sværhedsgrader. Borderline personlighedsforstyrrelse er en psykiatrisk lidelse, som historisk er blevet behandlet med langvarig psykoterapi. Vi implementerede et randomiseret klinisk forsøg, som sammenligner kort og lang mentaliseringsbaseret terapi til patienter med subtærskel eller diagnosticeret borderline personlighedsforstyrrelse. Forsøgets dataindsamling er stadig i gang. Afslutningsfasen i mentaliseringsbaseret terapi er en kontinuerlig klinisk udfordring for klinikere og patienter. For at hjælpe denne proces foreslår vi at udvide caseformuleringen med en ”afslutningsformulering”, hvor patientens mål kan rekapituleres i behandlingens afslutningsfase. Evidensen for de gavnlige og skadelige effekter af kort sammenlignet med lang psykoterapi for psykiatriske patienter er fortsat inkonklusiv.

BACKGROUND

Which length for whom?

Since the earliest days of modern psychotherapy, clinicians and researchers have aimed to tailor the treatment to the individual patient by seeking to answer the question: *what works for whom?* [6]. The quest for the most effective psychotherapy approach for the individual patient still continues today, causing what Bruce Wampold entitled "*the great psychotherapy debate"* [7]. While this debate still remains largely empirically unsettled, another one arises: *which length for whom?* This is likewise an empirical question. When it comes to the duration of psychotherapy, the question of optimal dosing remains open. While some patients benefit from short-term treatments, long- term treatments may be required for others [8]. Knowing which patients require short-term psychotherapy and which patients require longer-term psychotherapy could benefit both patients, their relatives, and professionals in the mental health care services. Furthermore, most patients may prefer to be alleviated by their symptoms as quickly as possible with no or minimal side-effects. Nevertheless, it is a common struggle for many mental health professionals to make the difficult judgement of when to terminate and when to extend the treatment for their patients, who sometimes present with treatment demanding psychopathology, also (and sometimes particularly) at the end. The aim of this thesis is to theoretically discuss, and empirically assess the efficacy and safety of different lengths of psychotherapy for adults with psychiatric disorders with special attention to outpatients with borderline personality disorder. But first, I will briefly present a historical overview of the theoretical and empirical evidence regarding time and efficacy in psychotherapy.

A historical overview

The concept of psychotherapy as a "*talking cure*" can be traced back to various forms of religious healing procedures in ancient Greece and Rome such as the practice of incubation, where the sufferer would sleep near the temples in order to receive healing and guidance from a God mediated by priests [9]. In the Catholic church, the central notion of the confessional, where the confession of one's sins either directly to God or to a priest followed by repenting and seeking forgiveness, can be seen as an early form of a therapeutic practice [9]. In these religious practices, the "therapeutic" relationship with the priest was often long-term and by definition open-ended. Throughout the 18th century, staff members at the asylums were

responsible for walking with, listening to, and talking to patients, with the purpose of freeing them from their mental problems [10]. However, the foundation of modern talking cures most notably stems from Sigmund Freud's psychoanalysis at the end of the 19th century [10]. Inspired by the works of Josef Breuer and Jean-Martin Charcot, Freud's first treatment attempts were carried out using hypnosis [9]. However, Freud later abandoned hypnosis in favor of the treatment method we now know as psychoanalysis, believing that the key to therapeutic success is the uncovering of previously repressed personality material through the analysis of free associations [11]. Working with unconscious processes within a therapeutic relationship was, and still is, seen as a time-consuming task. However, while Freud argued that psychoanalysis should last a minimum of three days a week in order for the analysist to keep up with the pace of the patient's life, he did not propose a fixed day of termination. In the essay *On Beginning of Treatment* published in 1913 [12], Freud writes:

> *"An unwelcome question which the patient asks the doctor at the outset is: 'How long will the treatment take?' 'How much time will you need to relieve me of my trouble?' If one has proposed a trial treatment period of a few weeks, one can avoid giving a direct answer to this question by promising to make more reliable pronouncement at the end of the trial period. Our answer is like the answer given by the Philosopher to the Wayfarer in Aesop's fable. When the Wayfarer asked how long a journey lay ahead, the Philosopher merely answered: "Walk!" and afterwards explained his apparently unhelpful reply on the ground that that he must know the length of the Wayfarer's stride before he could tell how long his journey should take. This expedient helps one over the first difficulties; but the comparison is not a good one, for the neurotic can easily alter his pace and may at times make only very slow progress. In point of fact, the question as to the probable duration of a treatment is almost unanswerable."* [12]

Freud was not particularly keen on advising the optimal treatment duration for his patients. The optimal time for effective psychotherapy has, nevertheless, been a matter of discussion and controversy for a number of years [13]. Although Freud tended to be somewhat defensive about the necessary length of time required for psychoanalysis, some of his early psychoanalytical followers even experimented with attempts at reducing the time required for therapy [14].

However, such attempts were not viewed upon too favorably by most psychoanalysts. As psychoanalysis became more available worldwide, the length of time required appeared to increase, amounting sometimes up to 5, 10, and 15 years [13]. One could speculate, that the earlier dominance of psychoanalytic and related psychodynamic views concerning psychotherapy led to the expectation that effective therapy had to be of long duration. Since the psychological problems of the patient supposedly developed over a period of many years, it was believed that a reasonably long period of time was required in order for a significant improvement to be obtained. Furthermore, accompanying this view was the belief that only by gaining insight into the unconscious conflicts causing the patient's difficulties could he or she be helped. Such therapeutic insight would require sophisticated therapeutic techniques, such as working with the transference, which would be seen as a long-term process. According to some psychoanalysts, too quick an attempt at uncovering repressed material might also lead to the shattering of the patient's defenses and to possible disintegration of the personality [13]. Furthermore, if one did not get to the source of the neurotic difficulty and concentrated only on treating the symptoms, the result would be the eventual appearance of substitute symptoms. In short, effective therapy had to be intensive, reconstructive, and take plenty of time. Brief therapies, on the other hand, were usually referred to as supportive or directive therapies and tended to be viewed as less effective. From a psychoanalytical point of view, the effects of such therapies were thought to be mainly palliative [13].

As the need for psychological services became more apparent and acceptable in the post-World War II period, attempts were made to modify and streamline mental health services in order to better meet the needs of large segments of society who had been underserved previously. In a report of the international Joint Commission on Mental Illness and Health (1961) [15] for example, inadequacies and limitations in the mental health facilities and personnel were highlighted. Psychoanalysis was singled out particularly because the lengthy education required to practice it, and the length of time required for treatment, which greatly limited its potential to meet the nation's rising needs. The report pointed to a need to train additional personnel to staff the developing community mental health centers and to develop more effective methods of treatment [15].

Now, the availability of psychotherapy has been internationally expanded, and psychotherapy as a treatment for various psychiatric disorders has undergone a great development since Freud's work and the later psychoanalytical and psychodynamic tradition. Today, different schools of psychotherapy exist, which have been empirically tested for different durations. The largest schools of psychotherapy are *psychodynamic therapies, cognitive and behavioural therapies, humanistic therapies,* and *systemic therapies* [10]. For a more detailed description of each of the largest schools of psychotherapy, please see **Paper I**.

Current clinical guideline recommendations for the duration of psychotherapy

Today, different recommendations for the duration of psychotherapy exists for various adult psychiatric disorders. **Table 1** presents and overview of the clinical guideline recommendations for the duration of psychological interventions presented in the UK National Institute for Health and Care Excellence (NICE) guidelines [16-30]. It must be noted, however, that clinical guideline recommendations across a wide range of healthcare topics have been assessed to be of low to very low quality [31]. Nevertheless, they still serve as recommendations for current clinical practice.

Table 1. Recommendations for the duration of psychological interventions in the NICE Clinical Guidelines for Mental Health and Behavioural Disorders

DIAGNOSIS		**TREATMENT DURATION**
ADDICITION AND DRUG/SUBSTANCE USE DISORDERS		
ADDICTION		Not specified
ALCOHOL USE DISORDER		
	Preventive strategies	First line: Structured brief advice. Second line: Extended brief interventions consisting of more than one session, including motivational interviewing programs, such as: • 'Drinker's check-up', 1 assessment -, feedback - and counseling session • 'Motivational Enhancement Therapy', 3-4 sessions

	High-risk drinking and mild alcohol dependence	A psychological intervention, such as: • CBT and behavioural therapies, weekly 1-hour sessions over 12 weeks • Social network and environment-based therapies, eight 50-minute sessions over 12 weeks • Behavioural couples' therapy, a 60-minute session per week over 12 weeks
DRUG MISUSE		
	People with limited or no contact with drugs services	An opportunistic brief intervention, consisting of 2 sessions of 10–45 minutes.
	People in contact with drugs services or other healthcare centers	A range of psychosocial interventions are effective, including contingency management and behavioural couples' therapy, and other evidence-based interventions such as CBT. Duration not specified.
	People with a stimulant or opioid misuse, in close contact with a non-drug misusing partner	Behavioural couples' therapy, at least 12 weekly sessions. Duration not otherwise specified.
ANXIETY DISORDERS		
BODY DYSMORPHIC DISORDER		
	Mild functional impairment	CBT (including ERP) in individual or group format. Duration not specified.
	Moderate functional impairment	Intensive individual CBT (including ERP). Duration not specified.
	Severe functional impairment	Combined treatment with SSRI and CBT (including ERP). Duration not specified.
GENERALISED ANXIETY DISORDER		
	People with no improvement after education and active monitoring	A low-intensity psychological intervention: • Individual non-facilitated self-help. Duration not specified • Individual guided self-help. Duration not specified • Psychoeducational groups based on CBT, 2 hours sessions over 6 weeks The choice of the treatment should be guided by the patient's preference.
	Severe cases; patients with marked functional impairment; persons who did not respond to	A high-intensity psychological intervention: • CBT, 12-15 weekly sessions. Duration not otherwise specified • Applied relaxation, 1-hour sessions over 12–15 weeks. Duration may be adjusted: fewer if the person recovers sooner; more if clinically required Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment is better.

	first-line interventions	
OBSESSIVE COMPULSIVE DISORDER		
	Mild functional impairment	A low intensity psychological intervention*: • Brief individual CBT (including ERP) using structured self-help materials, up to 10 therapist hours per patient • Brief individual CBT (including ERP) by telephone. Up to 10 therapist hours per patient • Group CBT (including ERP). Note, that patients may be receiving more than 10 hours of therapy in this format
	Moderate functional impairment	High intensity CBT (including ERP) consisting of more than 10 therapist hours per patient. Duration not otherwise specified.
PANIC DISORDER		
	Moderate to severe (with and without agoraphobia)	CBT, 7-14 hours in total. • For most people, CBT should be delivered weekly with sessions of 1-2 hours, and completed within a maximum of 4 months • Otherwise, briefer CBT. 7 hours in total • For a few people, more intensive CBT over a very short period might be appropriate. Duration not specified
SOCIAL ANXIETY DISORDER		Individual CBT, based on one of the following : • The Clark and Wells model, up to 14 sessions of 90 minutes, over approximately 4 months • The Heimberg model, 15 sessions of 60 minutes, and 1 session of 90 minutes for exposure, over approximately 4 months If patients decline CBT, offer CBT-based supported self-help consisting of up to 9 sessions over 3-4 months. A total of 3 hours additional support should be delivered either face to face or by telephone. If patients decline the above-mentioned interventions, offer short term psychodynamic psychotherapy consisting of up to 25−30 sessions of 50 minutes over 6−8 months.
ATTENTION DEFICIT DISORDERS		Not specified
AUTISM SPECTRUM DISORDER		Not specified
COEXISTING SEVERE MENTAL ILLNESS AND SUBSTANCE MISUE		Not specified
EATING DISORDERS		
ANOREXIA NERVOSA		One of the following psychological interventions: • Individual CBT-ED, up to 40 sessions over 40 weeks, with twice-weekly sessions in the first 2 or 3 weeks • Maudsley Anorexia Nervosa Treatment for Adults (MANTRA), 20 sessions with weekly sessions the first 10

		weeks. Patients with complex problems should be offered up to 10 extra sessions • Specialist supportive clinical management (SSCM), 20 or more weekly sessions depending on severity • FPT, up to 40 sessions over 40 weeks
BINGE EATING DISORDER		Group CBT-ED, 16 weekly 90-minute group sessions over 4 months. If group CBT-ED is not available or the patient declines it, consider individual CBT-ED consisting of 16–20 sessions.
BULIMIA NERVOSA		Individual CBT-ED consisting of up to 20 sessions over 20 weeks. Consider twice-weekly sessions in the beginning.
MOOD DISORDERS		
BIPOLAR DISORDER		
	Depressive episodes	In primary care settings, offer either: • A psychological intervention specifically developed for BD. Duration not specified • A high-intensity psychological intervention in line with the NICE Guideline on depression Secondary care settings: • Family interventions in line with the NICE clinical guideline on psychosis and schizophrenia
	Manic/hypomanic episodes	Not specified
UNIPOLAR DEPRESSION		
	Mild to moderate; persistent subthreshold depressive symptoms	One or more low intensity psychosocial interventions, such as: • Individual guided self-help programmes based on CBT, 6-8 sessions (face-to-face and via telephone) over 9 to 12 weeks • Computerized-CBT, delivered over 9-12 weeks, including follow-up People who decline low-intensity approaches, should be offered: • Group-based CBT, 10-12 sessions over 12-16 weeks, including follow-up • Short-term psychodynamic psychotherapy, 16-20 sessions over 4-6 months
	Moderate to severe	A combination of antidepressant medication and a high-intensity psychological intervention, such as: • Individual CBT, 16 to 20 sessions over 3 to 4 months. Consider providing 2 sessions per week for the first 2 to 3 weeks of treatment, and follow-up sessions typically consisting of 3-4 sessions over the following 3 to 6 months • Interpersonal therapy (IPT), 16-20 sessions over 3 to 4 months. Consider providing 2 sessions per week for the first 2-3 weeks for people with severe depression For people who decline the above-mentioned treatment, consider: • Counselling, 6-10 sessions over 8 to 12 weeks • Short-term psychodynamic psychotherapy, 16-20 sessions over 4-6 months.

	Persistent subthreshold depressive symptoms; mild to moderate depression with inadequate response to initial interventions.	A high intensity psychological intervention, such as: • Individual CBT, 16 to 20 sessions over 3 to 4 months, and follow-up sessions typically consisting of 3-4 sessions over the following 3-6 months • Interpersonal therapy (IPT), 16-20 sessions over 3-4 months • Behavioural activation, 16-20 sessions over 3-4 months, and follow-up sessions typically consisting of 3-4 sessions over the following 3-6 months. Consider providing 2 sessions for the first 3-4 weeks of treatment with moderate or severe depression. Note, that the evidence is less robust than for CBT or IPT. • Behavioural couples therapy, 15-20 sessions over 5-6 months. The duration of treatment should normally be within the limits indicated in the guideline, and may be: a) reduced if remission has been achieved or b) increased if progress is being made, and there is agreement between the practitioner and the person with depression that further sessions would be beneficial.
	Severe and complex depression; risk to life; severe self-neglect	In inpatient settings, the full range of high-intensity interventions should be offered. Intensity and duration of the intervention may be increased. Duration not otherwise specified.
	Relapse prevention	One of the following psychological interventions: • Individual CBT, 16-20 sessions over 3-4 months. Duration may be extended to achieve remission, consider two sessions per week for the first 2-3 weeks, and include additional follow-up sessions, typically 4-6 sessions over the following 6 months. • Mindfulness-based CBT delivered in groups, weekly 2-hours meetings over 8 weeks, and 4 follow-up sessions in the 12 months after the end of treatment.
PERSONALITY DISORDERS		
BORDERLINE PERSONALITY DISORDER		Twice-weekly sessions, although the frequency of psychotherapy sessions should be adapted to the person's needs and context of living. Do not use brief psychological interventions of less than 3 months' duration.
ANTISOCIAL PERSONALITY DISORDER		Not specified
	People with APD who also meet the criteria for psychopathy or DSPD	Cognitive and behavioural interventions adapted for this group e.g. by extending the nature (e.g., concurrent individual and group sessions) and duration of the intervention, and by providing booster sessions, continued follow-up and close monitoring. To prevent relapse, offer individual and group psychological interventions. Duration not specified.
TRAUMA RELATED DISORDERS		

POST TRAUMATIC STRESS DISORDER		
	Symptoms presented more than 1 month after the traumatic event	Individual trauma-focused CBT interventions such as: Cognitive processing therapy, Cognitive therapy for PTSD, Narrative exposure therapy or Prolonged exposure therapy. The interventions should consist of 8-12 sessions, but more if clinically indicated. In addition, booster sessions should be added, if needed. Duration not otherwise specified.
	Symptoms presented between 1 and 3 months or more than 3 months after a non-combat related trauma	EMDR, 8-12 sessions, but more if clinically indicated.
	Symptoms presented more than 3 months after the traumatic event	Trauma-focused computerized CBT, 8-10 sessions.
PSYCHOTIC DISORDERS		
PSYCHOSIS AND SCHIZO-PHRENIA		Oral antipsychotic medication in conjunction with a psychological intervention, such as: • Individual CBT, 16 sessions. • Family intervention, 10 sessions carried out between 3 months and 1 year.

Note. BD = Bipolar Disorder. *CBT* = Cognitive Behavioural Therapy. *CBT-ED* = Cognitive Behavioural Therapy for Eating Disorders. *EMDR* = Eye Movement Desensitization and Reprocessing. *ERP* = Exposure Response Prevention Therapy. *FPT* = Eating-disorder-focused focal psychodynamic therapy. *IPT* = Interpersonal Therapy. *MANTRA* = Maudsley Anorexia Nervosa Treatment for Adults. *NICE Guideline* = National Institute for Health & Care Excellence Guideline. *SSCM* = Specialist supportive clinical management. *SSRI* = Selective Serotonin Reuptake Inhibitor.

***** The intensity of psychological treatment has been defined as the hours of therapist input per patient. By this definition, most group treatments are defined as low intensity treatment (less than 10 hours therapist input per patient), although each patient may receive a much greater number of hours of therapy.

In sum, different durations of psychological interventions have been recommended in the NICE clinical guidelines [16-30]. However, an appropriate empirical assessment of the optimal psychotherapy duration for adult psychiatric disorders would require a systematic review of randomised clinical trial randomizing participants to different durations of the same psychotherapy type. We have not identified such a systematic review and, therefore, these recommendations must be interpreted with caution. We have performed such a systematic review of the literature, which is presented in this thesis as **Study 1**.

The uncontrolled, dose-response literature in psychotherapy

The dose-response relationship in psychotherapy refers to the relationship between the number of therapy sessions (dose) and patient improvement (response) [32]. While the optimal methodological design, as mentioned above, is to assess the dose-response relationship in a randomised clinical trial where two "doses" are directly compared, there is a number of uncontrolled, naturalistic studies aimed at assessing the optimal dose of psychotherapy [32]. A systematic review of such uncontrolled, naturalistic studies was recently published [32]. The authors conclude that the dose-response literature in psychotherapy is characterized by large heterogeneity in methodological approaches, participant diagnoses, interventions, and outcomes. Consequently, inconsistent "optimal dose" recommendations have been proposed in different uncontrolled, naturalistic studies.

Based on a narrative review of 26 uncontrolled studies, the authors conclude that symptom remission is rarely observed in extremely brief treatments, and they recommend that psychotherapy should last at least 4 sessions as a minimally acceptable treatment dose [32]. The authors highlight low-intensity guided self-help (GSH) interventions for mild-to-moderate disorders and conclude that at least 6 sessions are optimal. Non-responders after 6 sessions should be referred to more intensive psychotherapy programs. Regarding more conventional psychotherapy programs, the authors conclude that at least 8 sessions are needed for moderate-to-severe disorders, and that a formal review of the progress should be made after 8 sessions. A decision about whether to extend the treatment thereafter must be based on an assessment of the patient's obstacles for improvement, e.g. motivation to change, non-compliance with the therapy program, therapeutic alliance deficits, and social support deficits [32]. Furthermore, the potential for occupational and social functioning and the continued potential risks to self or others must be carefully considered [32].

However, it must be noted that results from uncontrolled, naturalistic studies must always be interpreted with great caution, as they can only show that participants change during the course of treatment. Whether the improvement is caused by the treatment can only be assessed in

randomised clinical trials. Therefore, the results from uncontrolled, naturalistic studies must be considered hypothesis-generating only [33,34].

Selecting which patients' treatment to extend and which patients' treatment to terminate after a pre-specified treatment plan has been debated [32,35,36]. Some argue that patients who did not benefit from the initially planned time frame should be extended [32,35]. However, others argue that only patients who benefitted from the pre-defined treatment plan should be extended [36]. The assessment of which patients' treatment to extent is thus based on arbitrary judgements in clinical practice, considering the scarce empirical evidence and the conflicting theoretical opinions currently available.

Borderline personality disorder

Borderline personality disorder is one psychiatric disorder, for which the optimal treatment duration has been, and still is, continuously debated. Some argue that these patients can only benefit from long-term psychotherapy, because of the complexity and rigidity of personality disorders [37,38], while others argue that short-term psychotherapy may be sufficient [39-41]. In addition, some argue the need for a stepped-care approach, where patients are offered an initial psychotherapy program and are subsequently stepped up or down depending on the outcome of the initial phase [35]. However, to this date, the optimal psychotherapy duration for borderline personality disorder is unclear [40,42]. Because of this, combined with the fact that borderline personality disorder is a highly prevalent and treatment-demanding psychiatric disorder [43], we chose this disorder as the primary focus in **Study II** of this thesis.

The diagnosis of borderline personality disorder has a long clinical history. It was the American psychiatrist and psychoanalyst Adolph Stern who introduced the term 'borderline' in the essay from 1938 titled "*Psychoanalytic investigation of and therapy in the borderline group of neuroses"* [44]. Stern emphasized characteristic symptoms for this disorder, such as disturbed ego-function, narcissism, hypersensitivity, rigidity, and primitive defense mechanisms. Stern argued that, together, these symptoms constitute a diagnosis that fits neither into the psychotic nor the neurotic categories. Instead, he referred to this group of patients as 'border line'.

> *"It is well known that a large group of patients fit frankly neither into the psychotic nor into the psychoneurotic group, and that this border line group of patients is extremely difficult to handle effectively by any psychotherapeutic method"* (Adolph Stern, 1938) [44].

After Stern, the psychoanalytic literature on borderline personality disorder dramatically increased, and in the beginning of the 1970's, a number of American psychoanalysts discussed the best operationalization of the borderline diagnosis [45]. Of these psychoanalysts, Otto Kernberg can be highlighted as one of the most influential. Kernberg proposed the term 'borderline personality organization', which refers both to a descriptive categorization of borderline pathology, but also to a structural analysis of the etiology of the disorder [46]. According to Kernberg, borderline personality organization includes non-specific ego disturbances, a shift towards primary process thinking, primitive defense mechanisms, and pathological, internalized object relationships [46]. Furthermore, Kernberg argued that identity diffusion and primitive defenses are commonalities between borderline and psychotic patients, and that borderline patients maintain a reality testing equal to the neurotic patients. Therefore, Kernberg agreed with the understanding of borderline as a diagnosis between the neurotic and the psychotic [46].

Today, the categorization of borderline personality disorder does not include psychoanalytic theories of etiology and categorization. Rather, borderline personality disorder is now, largely thanks to the works of John Gunderson [47], considered a psychiatric disorder characterized by the following theory-free diagnostic criteria in the Diagnostic and Statistical Manual of Mental Health Disorders – 5th edition (DSM-5) [48]: 1) frantic efforts to avoid abandonment, 2) intense and instable relationships, 3) identity diffusion, 4) impulsivity, 5) suicidality and self-harm, 6) affective instability, 7) chronic feelings of emptiness, 8) anger, and 9) stress-induced dissociation [48].

Borderline personality disorder is a serious and debilitating psychiatric disorder affecting 1 to 6% of the population [49,50]. Borderline personality disorder is associated with exceedingly high rates of self-harming behavior [51], and suicide-related mortality [52-54]. Furthermore, patients with borderline personality disorder are highly represented in primary care settings [55]

and in mental health care settings [56]. In addition, borderline personality disorder is a serious health concern causing a significant socioeconomic burden, not only because of direct health care costs [57], but also because of indirect costs like social and occupational dysfunction [58].

While pharmacotherapy is often used to treat co-morbidities related to borderline personality disorder, including depression and anxiety [59,60], there is still no convincing evidence that pharmacotherapy is the most suitable treatment option for borderline personality disorder [59,60]. Today, psychotherapy is the most widely used treatment for borderline personality disorder [61].

Long-term psychotherapy for borderline personality disorder

Long-term psychotherapy has traditionally been the chosen treatment for borderline personality disorder. There is no generally accepted standard duration for long-term psychotherapy. For example, long-term psychodynamic psychotherapy has been defined by experts in the field to range from a minimum of 3 months to a maximum of 20 years [38]. Regardless of the exact definition of long-term psychotherapy, specialized long-term treatments (as defined by the trialists) have been developed or adapted to treat patients with borderline personality disorder. These include, but are not limited to, long-term psychodynamic therapy (assessed for complex psychiatric disorders including borderline personality disorder) lasting minimum a year [38], dialectical behavior therapy up to one year [62], transference-focused psychotherapy up to three years [63], schema therapy up to three years [63], and mentalization-based therapy, which was originally manualized and tested for 18 months [64,65] but is sometimes being delivered in longer durations in clinical practice, e.g. up to three years of outpatient treatment [66].

Short-term psychotherapy for borderline personality disorder

Short-term psychotherapy has also been developed or adapted to treat patients with borderline personality disorder. These include, but are not limited to, brief dialectical behavior therapy (DBT) for 20 weeks [67], emotion regulation group therapy (ERGT) for 14 weeks [68], and systems training for emotional predictability and problem solving (STEPPS) for 20 weeks [69]. However, all these randomised clinical trials have either compared a short-term experimental group to a short-term control group or tested the short-term treatment as an adjunctive to treatment as usual. While these trial designs may be used to assess the effects of a short-term

treatment program compared with a control intervention, these trial designs cannot be used to assess the optimal treatment duration for patients with borderline personality disorder.

The optimal psychotherapy duration for borderline personality disorder

The optimal psychotherapy duration for patients with borderline personality disorder is currently unknown. To answer this question, it would require a systematic review of randomised clinical trials in which participants were randomised to different durations of the same psychotherapy type. However, such a systematic review has not previously been performed. One trial protocol is published describing the preplanned methodology of six versus 12 months dialectical behavior therapy for borderline personality disorder [39]. For a detailed description of this trial and the preliminary unpublished trial results, please see **Study I** of this thesis. Furthermore, **Study II** of this thesis will likewise contribute to the evidence of the optimal psychotherapy duration for borderline personality disorder. However, given the lack of such randomised clinical trials and a systematic review summarizing the evidence, we currently rely on indirect evidence when determining the optimal psychotherapy duration for borderline personality disorder. The following two systematic reviews provide such indirect evidence.

The first is a systematic review with meta-analysis of psychotherapy for borderline personality disorder published in 2017 in JAMA Psychiatry [42]. Treatment duration in the included randomised clinical trials ranged from 2.5 to 24 months, and the number of sessions (for individual and group therapy taken together) ranged from 6 to 312. This systematic review concluded that dialectical behavior therapy (g = 0.34; 95% CI, 0.15-0.53) and psychodynamic approaches (g = 0.41; 95% CI, 0.12-0.69) were the only types of psychotherapies more effective than control interventions on borderline-relevant outcomes. Furthermore, the authors concluded that treatment intensity (both treatment duration and exposure) was not related to the treatment outcomes considered. However, this conclusion must be interpreted with caution, as it is based on indirect evidence, as the systematic review did not include trials randomizing participants to different durations of the same psychotherapy type. Moreover, while the effects were small, they were also potentially inflated by risk of bias and publication bias [42].

The second is a Cochrane systematic review assessing psychological therapies for borderline personality disorder published in 2020 [61]. Treatment duration in the included randomised

clinical trials ranged from one to 36 months. This systematic review found beneficial effects on all primary outcomes in favor of borderline personality disorder-tailored psychotherapy compared with treatment as usual. However, only the outcome of borderline personality disorder severity reached the pre-defined minimal clinically important difference (MCID) cut-off for a clinically meaningful improvement [61]. Consistent with the previous systematic review published in JAMA [42], this systematic review concluded that dialectical behavioural therapy and mentalization-based therapy had the highest number of primary trials, and that compared to treatment as usual, dialectical behavior therapy was more effective at reducing borderline personality disorder severity (SMD −0.60, 95% CI −1.05 to −0.14; 3 trials, 149 participants), self-harm (SMD −0.28, 95% CI −0.48 to −0.07; 7 trials, 376 participants) and improving psychosocial functioning (SMD −0.36, 95% CI −0.69 to −0.03; 6 trials, 225 participants). Mentalization-based therapy appeared to be more effective than treatment as usual at reducing self-harm (RR 0.62, 95% CI 0.49 to 0.80; 3 trials, 252 participants), suicidality (RR 0.10, 95% CI 0.04, 0.30, 3 trials, 218 participants) and depression (SMD −0.58, 95% CI −1.22 to 0.05, 4 trials, 333 participants) [61]. However, all outcomes were based on low certainty evidence, and must be interpreted with caution.

The authors performed a predefined subgroup analysis of the effects of less than six months versus six to 12 months versus above 12 months duration of psychotherapy for the following two outcomes: borderline personality disorder symptom severity and psychosocial functioning. The authors found no evidence of significant differences between these subgroups on either borderline personality disorder severity (test for subgroup differences: $Chi^2 = 3.86$, df = 2 (P = 0.15), $I^2 = 48.2\%$) or psychosocial functioning (test for subgroup differences: $Chi^2 = 2.24$, df = 2 (P = 0.33), $I^2 = 10.9\%$) [61]. Again, this subgroup analysis result should be considered hypothesis-generating only, as the authors did not include trials randomizing participants to different durations of the same psychotherapy type.

Clinical severity as a prognostic factor

The current lack of an evidence-based treatment duration for borderline personality disorder results in often arbitrary individual assessments of which patients' treatments to extend in clinical practice. Many treatment services for personality disorders currently attempt to allocate patients to treatment according to severity of their symptoms [65]. However, to this date, there

is no agreed measure of severity of personality pathology [65]. This may change once the 11th revision of the International Classification of Diseases (ICD-11) is successfully implemented in the public health care sector, in which personality disorders should be organized according to severity, ranging from mild to moderate to severe [43,70,71]. However, clinician-administered assessment instruments to reliably assess severity of personality pathology are currently lacking [72]. One study suggests that age is the only predictor of referral to more intensive psychotherapy for borderline personality disorder, indicating that clinicians have difficulties in identifying severity [73]. Furthermore, whether or not severe personality pathology indicates a need for more extensive treatment remains unclear. One could argue that severe personality pathology takes years to develop and, subsequently, takes years to improve [74]. For example, an observational study suggests that patients with unresolved attachment and low level of reflective functioning at baseline had the least chance for change in attachment patterns during the first year of psychotherapy compared with patients with high levels of reflective functioning at baseline [75]. However, one could also argue that patients with severe personality pathology, who are often characterized by severe attachment problems [76], may become overwhelmed by engaging in long-lasting therapeutic relationships, often including several therapists and co-patients, which may be sometimes considered harmful [77], for example if the therapeutic relationship(s) become characterized with dependency. Therefore, the notion that more severe personality pathology correlates with the need for more extensive psychotherapy can be discussed.

Mentalization-based therapy

Mentalization-based therapy (MBT) is a structured psychotherapy program developed by Anthony Bateman and Peter Fonagy from the Anna Freud Centre in United Kingdom, specifically aimed at treating patients with borderline personality disorder [64,65,78].

The theory of mentalizing

Mentalization-based therapy is based on the theory of mentalizing, which refers to the process by which we make sense of each other and ourselves, implicitly and explicitly, in terms of subjective states and mental processes [78]. Given the generality of this definition, most psychiatric disorders will inevitably involve some difficulties with mentalizing [78]. However,

the key issue is whether mentalizing dysfunction is considered the core of the disorder and if a mentalizing focus is considered to provide an appropriate domain for therapeutic intervention [78]. The theory of mentalizing proposes that all people, but particularly patients with borderline personality disorder, are vulnerable to so-called non-mentalizing modes. Patients with borderline personality disorder are considered to have a fragile mentalizing capacity causing vulnerable social and interpersonal interactions, which is a core diagnostic criterion of the disorder. According to Bateman and Fonagy, a successful treatment for borderline personality disorder must either have mentalizing as its focus or at the very least stimulate development of mentalizing as an epiphenomenon [78].

Non-mentalizing modes are characterized by 1) psychic equivalence mode, in which internal and external reality is considered to be identical, 2) teleological mode, in which behavior is erroneously interpreted only as an observable outcome, while disregarding desires, plans, and feelings associated with the behavior, and 3) pretend mode, in which internal and external reality is completely separated, causing dissociation or depersonalization in extreme cases [65]. The theoretical assumption is that patients with borderline personality disorder are particularly vulnerable to non-mentalizing modes when experiencing emotional distress, especially in the context of attachment relationships, and the aim of the therapist becomes to identify these shifts and to bring the patient back into a mentalizing mode [65]. When in a mentalizing mode, understandings of own and others internal mental states are assumed to enhance emotional and interpersonal functioning [78].

The therapeutic stance

The overall aim of MBT is to develop a therapeutic process in which the mind of the patient becomes the focus of joint attention. MBT is primarily focused on internal mental states and less on behavior. Through a curious and not-knowing stance, the therapist seeks to understand the patients mental states by use of open-ended questions, validation of affective states, and subsequently by presenting alternative perspectives with no assumption about whose viewpoint has greater validity [65,78]. The therapeutic task is to determine the mental processes that have led to a viewpoint and to consider each perspective in relation to the other, accepting that divergent viewpoints may be acceptable. If differences in viewpoints are apparent and cannot be resolved initially, they should be identified, formulated, and accepted until resolution

becomes possible, for example when the arousal level is appropriate for the patient to be able to entertain multiple viewpoints simultaneously [65]. Through this therapeutic process, the aim is to help the patient to form more stable interpersonal relationships by understanding and respecting own and others mental states.

Different scales have been developed to assess the therapist's adherence and competence in delivering MBT in accordance with the manual [79,80]. One of the scales has recently been developed and its psychometric properties are currently unknown [79], whereas another scale has shown good psychometric properties both in expert settings [81] and in clinical practice [82].

Long-term mentalization-based therapy

Mentalization-based therapy currently has empirical support as an 18-months program for borderline personality disorder [61]. The treatment comprises of four essential components: 1) development of a case formulation at the beginning of treatment, which is continuously reassessed throughout, 2) psychoeducation, 3) weekly group therapy, and 4) weekly individual therapy [65]. All of the constituent parts of the program are not divisible, and the frequent absence from one will lead to a discussion about continuation in treatment.

Short-term mentalization-based therapy

While the original 18-months MBT program is prescribed by the MBT manual, this duration is rarely available, and the long and costly treatment combined with a highly prevalent disorder result in insufficient access to evidence-based care. The Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark is one treatment facility with a long history of delivering mentalization-based therapy, which has been struggling with accumulating wait-lists for borderline personality disorder treatment packages. Because of this, combined with the scarce evidence for 18 months being the most optimal treatment duration for borderline personality disorder, the clinic decided to implement a shorter treatment program to meet the rising needs for specialized treatment. While maintaining the long-term program at the clinic, we found it appropriate to set up a randomised clinical trial comparing the beneficial and harmful effects of short-term compared

with long-term mentalization-based therapy for borderline personality disorder, which constitutes **Study II** of this thesis.

The short-term program presented in **Study II** is overall similar to the existing manualized long-term program, but differs structurally in the following ways: 1) the length of treatment and the amount of individual psychotherapy, 2) the same therapists provide both group and individual sessions in the short-term program (conjoined psychotherapy), whereas group- and individual therapy is provided by different therapists in the long-term program (combined psychotherapy), and 3) the short-term program is structured in closed groups, whereas the long-term program is structured as slow-open groups.

Termination in psychotherapy

When conducting time-limited psychotherapy, and perhaps especially when conducting psychotherapy in short durations, the termination phase of treatment inevitably becomes important. An interpersonal bond has potentially been developed between the therapist and the patient, and if the patient experiences symptom relief throughout this period, terminating such a constructive process may be experienced as sad or even counterintuitive.

Despite the critical importance assigned to the termination phase by many psychotherapists, only a small proportion of the psychotherapy literature has been devoted to the demands and challenges arising from termination psychotherapy [36]. However, the available literature varies by theoretical orientation. The majority of psychotherapy literature on termination stems from the psychodynamic and the psychoanalytical approaches [36]. On the contrary, the cognitive-behavioural literature on treatment termination is sparse [36]. This variation is probably due to the different foci in these psychotherapy approaches: termination is perhaps less frequently addressed in a psychotherapy that highlights skills development relative to a psychotherapy that highlights relational functioning.

Interestingly, therapists' actual termination behaviors seem to be the similar despite the varying amount of attention given to the termination phase in different psychotherapy approaches. A recent study aimed to identify core termination behaviors of therapists across theoretical

orientations in a successful course of treatment. 65 experts across theoretical orientations reported the frequency with which they used 80 termination-related tasks in a planned, mutually agreed termination of individual psychotherapy [83]. The experts obtained consensus on 51 items, 27 items did not obtain consensus, and 2 items were consensually employed infrequently. Termination behaviors or tasks reaching the strongest consensus concerned supporting patient progress, promoting patient growth post termination, following the ethics code, consolidating gains made, and highlighting patient's recognition of competence [83]. The authors conclude that these core termination behaviors may therefore be considered transtheoretical [83].

Termination in MBT has been briefly addressed in the MBT manual [65]. According to the MBT manual, the ending phase should focus on mentalizing affective states associated with separation, and there should be a focus on how to maintain gains that have been made during treatment [65]. However, there will be many variations to the clinical application of the ending phase between clinicians, with different types of patients, and in different time formats (e.g. short-term or long-term, predefined or open-ended). Furthermore, patients may challenge the termination phase in different ways, which may challenge the therapists in their adherence to the manual. MBT is not immune to these challenges, but it may offer ways to understand and deal with them. For a discussion of the mentalization-based approach to termination in psychotherapy with patients suffering from borderline personality disorder, please see **Study III** of this thesis.

Clinical research methodology

Advocates of "evidence-based medicine" [84] classify studies according to grades of evidence on the basis of the research design, using internal validity (i.e. the extent to which a study establishes a trustworthy degree of causality between the treatment and an outcome) as the criterion for hierarchical rankings [85]. In the hierarchy of evidence, the results of systematic reviews with meta-analysis of randomised controlled trials are considered the to be the evidence of the highest grade, followed by results from single randomised controlled trials. Observational studies (e.g. studies with repeated measurements of a population without a control group) are viewed as having less internal validity, because they are likely to overestimate treatment effects, and because it is difficult to distinguish an effect of the treatment from spontaneous change over time (i.e. regression towards the mean) [86,87]. Expert theories and opinions constitute

the bottom of the hierarchy of evidence [88]. However, all levels of the hierarchy may be threatened by systematic errors, design errors, and random errors [33,89,90].

Systematic reviews

Systematic reviews of randomised clinical trials are considered the most valid way of summarizing the available evidence and assessing beneficial and harmful effects of interventions [91]. In fact, it is unusual to have a single randomised clinical trial validly assessing the effects of any intervention [92,93]. A conclusive evaluation of an intervention should always be based on aggerated evidence gathered from several trials, e.g. systematic reviews of all available randomised clinical trials [92].

Systematic reviews following Cochrane recommendations [89] are considered the gold standard. The methodology of such reviews is pre-published in a protocol in which the following core methods are described: scope and objective, eligibility criteria, literature search methods, data extraction methods, bias risk assessments, meta-analysis methodology, and summary of findings.

Randomised clinical trials and non-randomised studies

In the randomised clinical trial, participants are randomly allocated to an experimental or a control intervention. The idea that bias in participant selection (termed 'selection bias' [89]). may influence the results of clinical studies has established the randomised clinical trial as the gold-standard for evaluating treatment effects in medical research [89]. For a trial to be considered adequately randomised, the allocation sequence must be randomly generated, for example by coin toss or via a computer-based allocation sequence program. Furthermore, the allocation sequence must be concealed for all investigators involved in the trial to ensure lack of predictability of the random sequence [89]. If the randomization procedure has been sufficiently implemented, and if the sample size is high enough to avoid baseline differences occurring by chance, the randomised clinical trial will be able to assess the intervention effects in two comparable groups of participants, thereby avoiding selection bias. Typically, the randomised clinical trial is designed to prevent other types of bias as well. For example, blinding of key persons involved in the randomised clinical trial is essential to minimize the

risk of having their personal preferences interfere with the outcomes (termed 'detection bias' [89]). For more information on bias in trials, please see the next section.

Studies can be controlled, yet not randomised. The role of non-randomised studies in evaluating treatment effects is an area of continued debate. Deliberate allocation, rather than random allocation, of participants to a treatment implies that observed outcomes may be caused by differences among participants being given the two treatments (if two treatments are compared in a non-randomised controlled study), rather than the treatments alone. There has been considerable debate about whether the results of non-randomised studies are consistent with the results of randomised clinical trials [85,94-96]. Non-randomised controlled studies have been reported to overestimate or underestimate treatment effects [97,98]. These findings have supported the notion of a hierarchy of evidence with systematic reviews and randomised clinical trials at the top, non-randomised controlled studies in the middle, and uncontrolled studies (observational pre-post assessments) and opinion at the bottom. However, there is also some evidence indicating nonsignificant differences in results between randomised clinical trials and observational studies [85,94]. Nevertheless, due to the discrepancy in the literature, results from non-randomised studies must be considered hypothesis-generating only.

Systematic errors in randomised clinical trials

The methodological quality of randomised clinical trials included in systematic reviews may impact the effect estimates of the studied interventions, which in turn may alter the effect estimates of the meta-analyses, and ultimately the conclusion of the review. Systematic errors (bias) do not skew the results in spurious ways. On the contrary, meta-epidemiological studies have shown that randomised clinical trials with systematic errors have a tendency to overestimate the beneficial effects and underestimate the harmful effects of the experimental intervention [99-106]. Therefore, randomised clinical trials with inadequate methods may therefore ultimately mislead health-care decision making if not properly accounted for.

Until recently, Cochrane encouraged the use of the Cochrane Risk of Bias tool (ROB) originally published in the Cochrane Handbook for Systematic Review of Interventions in 2008 and updated in 2011 [107]. Review authors can use this tool to assess bias in randomised clinical trials using the following domains: 1) generation of the allocation sequence, 2) allocation

concealment, 3) blinding of participants and treatment providers, 4) blinding of the outcome assessor, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other sources of bias, e.g. for profit bias [108]. Risk of bias on each domain is assessed by two independent review authors as low, unclear or high. Subsequently, these judgements lead to a bias risk assessment on an outcome level as well as on a trial level. Whether the Cochrane ROB tool is an appropriate tool for assessing systematic errors in psychotherapy trials can be discussed. Particularly domain 3 (blinding of participants and treatment providers) is very rarely adequately implemented in randomised clinical trials of psychological interventions [109]. However, whether lack of blinding of participants and treatment providers is a bias risk that needs to be controlled for can be discussed [109].

Cochrane has recently updated the assessment tool to Cochrane Risk of Bias tool – version 2 (ROB2) [89,110]. However, as this tool was not published before we planned our study (**Paper I** and **Paper II**), we followed the original Cochrane ROB tool.

Meta-analysis

Meta-analysis is the statistical procedure of combining the results from two or more randomised clinical trials. The advantage of a properly performed meta-analysis is improvement in precision, because the information size increases when results from more randomised clinical trials are combined. However, it may also seriously mislead the conclusions if bias, heterogeneity (variation across trials), and study design errors are not properly considered. The meta-analysis result itself is a precision weighted average of the effect estimates from the included trials. The weighting is based on the inverse variance within each trial in the fixed effect model and the variance in each trial added to the between trial variance in the random effects model [89]. During the process of preparing the meta-analysis, many decisions and judgements are made including choice of meta-analytic model(s), which may influence the results and thus have an impact on the conclusion. Scenarios for when to choose the most appropriate model has been thoroughly discussed [111]. It has been recommended always to perform both the fixed-effect and random-effects model and subsequently chose the most conservative results. The most conservative result is the result with the highest p-value or the widest confidence interval [111].

Heterogeneity

Heterogeneity in meta-analyses refers to any kind of variability across trials. In a meta-analysis, the included trials will not be completely identical. Heterogeneity may affect the interpretation of results, which may further affect the generalizability of the conclusion [89]. Authors conducting systematic reviews must therefore carefully look for signs of heterogeneity and may ultimately decide that a meta-analysis is not warranted due to heterogeneity. In these cases, the results should be reported in a qualitative way [89].

Different types of heterogeneity may occur across trials in a systematic review. Heterogeneity can be either clinical, methodological, or statistical [89,112]. Clinical heterogeneity is characterized by variability across trials in types of participants, treatment settings, interventions, comparators, the use of co-interventions, and the types and timing of outcome assessments. Judgments about clinical heterogeneity can be made by putting forward a convincing argument about similarities (or differences) between the included trials [113]. For example, if there is an indication that the included trials assessed participants at different levels of disease severity, a subgroup analysis or meta-regression study may be used to explore whether these subgroups of trials yield different effect estimates. However, results from subgroup analysis must always be interpreted with caution, especially if they were not pre-defined, and should be considered hypothesis-generating only [89]. Methodological heterogeneity is characterized by variability in trial design and risk of bias [112]. Judgements about methodological heterogeneity can be made by evaluating risk of bias in the included trials [110]. Statistical heterogeneity is characterized by variability in treatment effects between trials. Judgements about statistical heterogeneity can be made by visually inspecting the forest plots and by calculating the Chi2 and I^2 statistics [89,112]. The I^2 statistic is most commonly used and describes the percentage of total variation across studies that is due to heterogeneity rather than chance [112]. A naïve categorization of values for I^2 would not be appropriate for all circumstances, but it has been suggested to assign adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75% [112].

Assessment of random errors in meta-analyses

Systematic reviews with meta-analysis of randomised clinical trials are considered the best available evidence [89,91]. However, the best available evidence may not be equal to sufficient

evidence. In order to quantify if the evidence is sufficient, it is important to control for type I and type II errors (i.e. random errors). Trial Sequential Analysis (TSA) can be applied to assess the risk of random errors and a required information size in a meta-analysis can be calculated [1,111,114-122]. The required information size is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect. The cumulative Z-curve's breach of relevant trial sequential monitoring boundaries (e.g. the boundary for benefit, the boundary for harm, or futility) establishes, if the treatment is beneficial, harmful, or ineffective, and can be visually inspected by looking at TSA graphs.

Firm evidence for benefit, harms, or futility, disregarding risk of bias and overall certainty of evidence, may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, which suggest that further trials may be redundant. On the contrary, if the boundaries are not reached, it can be concluded that it is necessary to include additional trials and participants before a certain intervention effect can be detected or rejected [123].

Calculating the required information size in Trial Sequential Analysis resembles a sample size calculation on an individual trial level. This goes for all the variables used in the sample size calculation for dichotomous and continuous outcomes. For dichotomous outcomes, the required information size is based on the unweighted cumulated event proportion in the control group, the assumption or anticipation of a relative risk reduction or relative risk increase, the heterogeneity variance of the meta-analysis, and the chosen risks of type I and type II errors [1,111,114-122]. For continuous outcomes, the Trial Sequential Analysis use the observed standard deviation (SD) in the control group, a minimal clinically important difference, the chosen risks of type I and type II errors, and the observed diversity as suggested by the trials in the meta-analysis [1,111,114-122].

Grading the certainty of evidence

Grading Recommendations, Assessment, Development and Evaluation (GRADE) is an approach to grading certainty of evidence and strength of potential recommendations that can be drawn from the systematic review [124-127]. Once the evidence has been collected, methodologically assessed, and summarized, the certainty of evidence for each pre-defined

review outcome is appraised and presented in a Summary of Findings-table. According to the GRADE approach, randomised clinical trials begin as high-quality evidence. Five factors may lead to downgrading the certainty; 1) risk of bias in the included trials 2) indirectness of the evidence, 3) heterogeneity, 4) imprecision of effect estimates, and 5) risk of publication bias. Ultimately, the certainty of evidence for each outcome falls into one of four categories: high, moderate, low, or very low certainty of evidence [124-127].

Patient centered outcomes

When clinicians treat patients in short-term treatment formats, or when researchers conduct research on the efficacy of short-term versus long-term psychotherapy, it is important to establish a set of explicit treatment outcomes (as in any clinical intervention trial). What do we expect to change with these interventions? What is most important to this patient?

Within the field of evidence-based medicine, regardless of the health specialty, importance of outcomes is likely to vary within and across cultures or when considered from the perspective of patients, clinicians, or policy makers [128]. When conducting research or clinical guidelines for any diagnosis, researchers or clinical guideline panels must decide what perspective they are taking. Although different researchers or panels may elect to take different perspectives (e.g., the patient perspective, or a societal perspective), the relative importance given to outcomes should reflect the perspective of those who are affected. This will typically be the patients. Therefore, outcomes must almost always be selected based on how patient-important, they are. However, many, if not most, systematic reviews fail to address some key outcomes, particularly harms, associated with an intervention [128].

An overview of targets and outcomes in psychotherapy was recently published in World Psychiatry [129]. Here, a summary of the main targets and outcomes of psychotherapies for psychiatric disorders along with the research status for each outcome were presented:

Table 2: Summary of main targets and outcomes of psychotherapies for psychiatric disorders (adapted from Cuijpers, 2019 [129])

Type of target and outcome	Status of research
Symptom reduction	Most research on the effects of psychotherapy is focused on symptom reduction
Patient-defined targets and outcomes (idiographic measures or qualitative research)	Limited systematic research available
Quality of life and related targets and outcomes	Relatively well-studied, but more research is clearly needed
Intermediate outcomes: mediators and working mechanisms	Limited systematic research available
Negative outcomes (harmful effects and serious adverse events)	Limited systematic research available
Economic outcomes (cost-utility and cost-effectiveness analyses)	Limited systematic research available

Selection of outcomes may account for some of the controversy previously presented in the literature and clinical practice on short-term compared with long-term psychotherapy for any mental health problem. If the goal of the treatment is personality change or uncovering of unconscious psychological material, then it is perhaps unlikely that short-term treatments will be sufficient. However, if the goal of the treatment is symptom reduction or general quality of life, then short-term treatments are perhaps efficient for some patients. For an overview of the selected outcomes in the present PhD thesis, see the **Methods** section.

OBJECTIVES

This PhD thesis includes three separate studies. The overall objective of the thesis was to assess the beneficial and harmful effects of short-term versus long-term psychotherapy for adults with psychiatric disorders in a systematic review with meta-analysis and trial sequential analysis (**Study I**), to plan a randomised clinical trial contributing to this evidence assessing the effects of short-term versus long-term mentalization-based therapy for outpatients with borderline personality disorder (**Study II**), and to discuss the clinical challenges arising from delivering time-limited mentalization-based therapy for these patients (**Study III**).

We hypothesized that evidence was sparse or even absent regarding harmful effects of psychotherapy, of low to very low certainty, and with insufficient information sizes. The specific aims and hypotheses of the conducted studies of this thesis were:

Study I: Systematic review with meta-analysis and trial sequential analysis

Paper I: The protocol for the systematic review aimed at pre-defining the systematic review methodology.

Paper II: The systematic review aimed at forming the basis for evidence-based guideline recommendations for the appropriate duration of psychotherapy for adult psychiatric disorders taking both beneficial and harmful effects, bias risk (systematic errors), play of chance (random errors), and certainty of the findings into consideration.

Study II: Randomised clinical trial

Paper III: The protocol for the randomised clinical trial aimed at pre-defining the trial methodology of a randomised clinical trial assessing the beneficial and harmful effects of short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder (MBT-RCT).

Paper IIII: The detailed statistical analysis plan aimed at increasing the validity of the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or

diagnosed borderline personality disorder randomised clinical trial (MBT-RCT) by mitigation of analysis-bias.

Study III: Termination challenges in mentalization-based therapy

Paper V: The paper aimed at discussing a mentalization-based approach to termination challenges in therapy with patients suffering from borderline personality disorder. The secondary aim was to propose possible clinical solutions to these challenges.

METHODS

This section briefly describes the methods for each of the studies.

Study I – Systematic review with meta-analysis

In this thesis, there are two papers included describing the pre-planned methodology and the results of a systematic review with meta-analysis of randomised clinical trials comparing short-term versus long-term psychotherapy for adults with psychiatric disorders. The methodology of the two papers (**Paper I** and **Paper II**) is described below.

Papers I and II were performed according to the recommendations by the Cochrane Collaboration [107], an eight-step procedure for better validation of meta-analytic results in systematic reviews [111], and they were reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline (**Paper I**) [130] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [131] (**Paper II**).

Eligibility criteria

In this systematic review of randomised clinical trials, trials were included if they compared a short-term and a long-term version of the same psychotherapy type for one or more adult psychiatric disorders. Trials were included in the systematic review irrespective of trial design (e.g. number of intervention arms), setting, publication status, publication year, language, and the reporting of our pre-defined review outcomes. We relied on the trialists defining their compared interventions as short-term and long-term (or similar terminology, e.g. 'brief', 'massed', 'spaced').

Search methods for identification of randomised clinical trials

We searched for eligible trials in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-

EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH). Additionally, we checked the reference lists of relevant publications for any unidentified trials.

Outcomes

Table 3 summarizes the prespecified outcomes for the systematic review.

Table 3. Prespecified outcomes for Study I

Primary outcomes	Quality of life (continuous data)
	Serious adverse events (dichotomous data). We used the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonging of existing hospitalization and resulted in persistent or significant disability or jeopardized the patient [132]. If the trialists did not use the ICH-GCP definition, we included the data if the trialists used the term "serious adverse event." If the trialists did not use the ICH-GCP definition nor used the term serious adverse event, then we would also include the data, if the event clearly fulfilled the ICH-GCP definition for a serious adverse event.
	Symptom severity assessed by any valid disease-specific symptom scale (continuous data). Symptoms were analysed separately for each disorder.
Secondary outcomes	Suicide or suicide attempts as defined by trialists (dichotomous data)

	Self-harm as defined by trialists (dichotomous data)
	Level of functioning as defined by trialists (continuous data)

Data collection, data extraction and risk of bias assessment

Two review authors (the author of this thesis and a co-author) independently screened titles and abstracts, identified eligible trials, and assessed trial methodology using the Cochrane Risk of Bias tool (ROB) [107], assessing the following domains: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other bias. Any disagreements were resolved through discussion or, if required, through discussion with a third review author.

We assessed trials as at 'overall low risk of bias' if the trial was assessed to be at low risk of bias on all bias risk domains. Conversely, trials were assessed as at 'overall high risk of bias' when unclear or high risk of bias was assessed in one or more domains. We contacted the corresponding author of the included trial reports when a bias domain was assessed at unclear risk of bias; if no reply was received, the bias domain remined unclear. Furthermore, we asked about insufficiently reported information, and for additional data on our prespecified review outcomes, if these were not reported on.

Data synthesis

We used conventional meta-analytic statistics to calculate pooled effects estimates of each outcome using Review Manager (RevMan) [133]. We planned to use relative risks (RR) with 95% confidence intervals (CI) for dichotomous outcomes. For continuous outcomes, we planned to use mean difference for homogeneous outcomes assessed with homogeneous methods (e.g. if all depression outcomes were assessed with the Hamilton Rating Scale for Depression (HDRS)), or standardised mean difference for homogeneous outcomes assessed with heterogeneous methods (e.g. if depression outcomes were assessed with different scales,

e.g. the HDRS or the Beck Depression Inventory (BDI)), and we reported 95% CI. Intervention effects were assessed with both fixed-effect and random-effects meta-analysis models. We used the model presenting the more conservative p-value of the two [111]. If there were considerable discrepancies between the random-effects and the fixed-effect meta-analyses results, we planned to report and discuss both.

We planned to use Trial Sequential Analysis to calculate the meta-analytic required information size considering risk of random errors due to sparse data, multiple outcomes, and multiple testing of accumulating data [114-122].

The GRADE approach was used to assess the overall certainty of evidence for all pre-defined outcomes [124-127]. We assessed the certainty of evidence and, hence, our confidence in the effect estimates using the following domains: risk of bias, heterogeneity, indirectness, imprecision and publication bias. We rated the overall certainty of evidence for all our pre-specified review outcomes as high, moderate, low, or very low [124-127].

Study II – Randomised clinical trial

In this thesis, there are two papers included describing the trial methodology of the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder randomised clinical trial (MBT-RCT). The methodology of the two papers (**Paper III** and **Paper IIII**) is described below.

Paper III is a trial protocol for a randomised clinical comparing short-term (5 months) with long-term (14 months) mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocols of clinical trials [134].

Design

The trial was designed as an investigator-initiated single-centre randomised clinical superiority trial. Participants were recruited from the Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark.

Participants

Participants were eligible for inclusion in the trial, if they complied with the eligibility criteria outlined in Table 4. There are inclusion and exclusion criteria as part of the procedure for clinical intake at the trial site, at criteria specific to the trial.

Table 4. Eligibility criteria for the randomised clinical trial

	Criteria exclusive to the outpatient clinic	**Criteria exclusive to the trial**
Inclusion criteria	- Aged 18–60 - Personality disorder(s) considered to be the primary diagnosis/diagnoses	- A minimum of four confirmed DSM-V diagnostic criteria for borderline personality disorder - Written informed consent
Exclusion criteria	- Possibility of a learning disability (IQ < 75) - A full diagnosis of schizotypal personality disorder or antisocial personality disorder - Presence of a comorbid psychiatric disorder that requires specialist treatment - Current (past 2 months) substance dependence including alcohol - Concurrent psychotherapeutic treatment outside the clinic	- Unable to understand Danish - Lack of informed consent

Interventions

The short-term MBT program is a 5-months psychotherapy program, in which two therapists and seven to nine participants start and finish the program together (i.e. closed groups). The program is comprised of 20 weekly sessions and begins with five sessions of introductory MBT (MBT-I) [135] followed by 15 sessions of MBT in groups (MBT-G) manualized by Bateman and Fonagy [65]. The group program is conjoined with individual therapy sessions every second

week with one of the two group therapists. Each participant in the short-term MBT group has two therapists in total (i.e. two group therapists, one of them also being the individual therapist).

The long-term MBT program is a 14-months psychotherapy program, which has been implemented at the trial site for the past 10 years. The long-term program begins with 6 weeks of MBT-I [135] in closed groups. A maximum of 12 participants can enter an MBT-I group, and one or two therapists run the psychoeducative groups. The participants will subsequently be allocated to one of eight slow-open MBT-G groups also manualized by Bateman and Fonagy [65]. MBT-G comprises of 12 months of weekly MBT in groups combined with individual therapy every second week with a different therapist than the two group therapists. Each participant in the long-term group has three therapists in total plus one or two therapists delivering the initial MBT-I group, adding up to a maximum of five therapists throughout the course of treatment.

Randomization and blinding

Copenhagen Trial Unit, a Danish centre for clinical intervention research located at Rigshospitalet, Copenhagen University Hospital, will be responsible for the central randomization. Randomization will be performed with a 1:1 allocation according to a computer-generated allocation sequence with permuted blocks of various sizes generated by Copenhagen Trial Unit and kept unknown to the investigators, secretaries, and clinical staff at the trial site. The randomization is stratified by sex (male/female) and high/low scores on the primary outcome measure, the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) [136] at baseline.

Outcome-assessors, data managers, statisticians, the data safety and monitoring committee, and decision makers will be blinded to treatment allocation [109]. Participants and therapists will not be blind to treatment allocation due to the difficulties of implementing an efficient blinding procedure in trials assessing psychological interventions [109].

Outcomes

Table 5 summarizes the prespecified outcomes for the randomised clinical trial.

Table 5. Prespecified outcomes for Study II

Primary outcome	Borderline symptomatology assessed with the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) [136].
Secondary outcomes	Functional impairment assessed with the Work and Social Adjustment Scale (WSAS) [137].
	Quality of life assessed with the Short-Form Health Survey (SF-36) – mental component [138].
	Global functioning assessed with the Global Assessment of Functioning scale (GAF) [139]
	Severe self-harm (the proportion of participants with severe self-harm defined as deliberate acts of self-harm resulting in visible tissue damage)
Exploratory outcomes	Symptom distress (assessed with the Symptom Checklist 90 (SCL-90) [140])
	Quality of life (assessed with the Short-Form Health Survey (SF-36) physical component [138])

Paper IIII is a detailed statistical analysis plan designed to specify the pre-planned statistical analyses for the primary and secondary outcomes for the primary time-point of interest of the MBT-RCT trial.

We will use the 16-month time point as the primary time-point of interest, as it is the time-point closest to end of treatment in the long-term MBT group. Data from the 24-month time point as

well as results of the exploratory outcomes will be analysed using the same principles as described in **Paper IIII** and will be published in a separate publication.

General analysis principles

All statistical analyses will be conducted according to the intention-to-treat principle (ITT). The intention-to-treat population will include all randomised participants, regardless of missing data, lost to follow up, or adherence to the intervention. We will perform a per protocol analysis if the number of participants who prematurely drops out of treatment exceeds 5% of the total trial population in both groups.

It is generally recommended that regression analyses should be adjusted for the stratification variables used in the randomisation [141-143]. Thus, all analyses in the MBT-RCT trial will primarily be adjusted for the baseline value of the outcome of interest (for continuous outcomes) and the stratification variables used in the randomisation. We will secondly adjust all analyses for the following adjustment variables: age (18-30, 30-60), baseline global functioning as assessed with the GAF score (0-48, 49-100), and baseline proportion of participants with severe self-harm incidents the past 8 months (participants with one or more events compared to participants with no events).

Subgroup analyses

The following subgroup analyses will be performed:

- Baseline severity of borderline symptomatology (ZAN-BPD scores 0-11, 12-36)
- Sex (male/female)
- Age (18-30, 30-60),
- Baseline global functioning (GAF score 0-48, 49-100)
- Baseline proportion of participants with severe self-harm incidents the past 8 months (participants with one or more events compared to participants with no events).

We will present the results of the subgroup analyses in forest plots.

Analysis of continuous data

Continuous outcomes will be presented as means and standard deviations for each group along with 95% confidence interval for the means of the groups and the mean differences between the groups. Continuous outcomes will be analysed using linear regression. All variables will be included as fixed effects

Analysis of dichotomous data

Dichotomous outcomes will be presented as proportions of participants in each group with the event, as well as risk ratios with 95% confidence intervals. Dichotomous outcomes will be analysed using logistic regression. All variables will be included as fixed effects.

The threshold for significance will be assessed according to a five-step procedure, suggested by Jakobsen et al. [144].

Handling of missing data

We will consider using multiple imputation and present best-worst and worst best case scenarios if it is not valid to ignore missing data [145]. Best-worst and worst-best case scenarios assess the potential range of impact of the missing data for the trial results [145]. In the 'best-worst' case scenario, it is assumed that all participants lost to follow-up in the short-term group have had a beneficial outcome (had no self-harm incidents), and all those with missing outcomes in the control group have had a harmful outcome (had one or more self-harm incidents) [145]. Conversely, in the 'worst-best' case scenario, it is assumed that all participants who were lost to follow-up in the experimental group have had a harmful outcome, and that all those lost to follow-up in the control group have had a beneficial outcome [145]. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two SDs of the group mean, and a 'harmful outcome' will be defined as the group mean minus two SDs of the group mean [145].

Study III – Termination challenges in time-limited mentalization-based therapy

The last paper of this thesis (**Paper V**) is a theoretical discussion paper. Here, we discuss the clinical challenges arising from terminating time-limited MBT for patients with borderline

personality disorder, who are often characterized by severe psychopathology often (and sometimes particularly) once the ending phase approaches. The ending phase of MBT has not previously been sufficiently described in the MBT literature [65]. In the latest MBT treatment manual, Bateman and Fonagy suggest that the ending phase should involve mentalizing the often complicated and mixed feelings associated with loss of the therapeutic relationship [65]. However, the ways to address these and other challenges to the termination phase is unclear. Based on clinical discussions with one of the developers of MBT, Dr. Anthony Bateman, we developed an extension of the MBT manual aiming at guiding the clinician through challenging treatment terminations.

RESULTS

Study I – Systematic review with meta-analysis

We included 16 trials randomizing 2,651 participants. All trials were at high risk of bias. One single trial showed no evidence of a difference between short-term versus long-term dialectical behavioural therapy for borderline personality disorder and reached the required information size when assessing quality of life, symptom severity, and level of functioning. One single trial showed no evidence of a difference between short-term versus long-term psychodynamic psychotherapy for mood- or anxiety disorders and reached the required information size when assessing symptom severity and level of functioning. The remaining single trials did not meet the required information sizes needed to confirm or reject realistic intervention effects.

It was only possible to conduct two meta-analyses. Meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms at end of treatment (SMD: 0.08; 95% CI: -0.47 to 0.63; p = 0.77; I^2 = 73%; four trials; very low certainty). Meta-analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy for mood- and anxiety disorders on level of functioning (SMD 0.16; 95% CI -0.08 to 0.40; p = 0.20; I^2 = 21%; two trials; very low certainty). It was not possible to perform other pre-planned meta-analyses due to lack of relevant data.

Study II – Randomised clinical trial

No results from the MBT-RCT trial are available yet. The recruitment of the target sample size of 166 participants began September 29, 2018 and ended December 3, 2020. Data collection for the 8-, 16-, and 24 months assessments will be completed by December 2022.

With the pre-defined trial protocol and the detailed statistical analysis plan for the MBT-RCT trial we follow the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. The trial protocol and the statistical analysis plan were prepared before completion of enrolment and should increase the validity of the MBT-RCT trial by mitigation of analysis-bias and selective outcome reporting.

Study III – Termination challenges in time-limited mentalization-based therapy

Time-limited psychotherapy for borderline personality disorder is often characterized by challenges once the ending phase of treatment approaches. Both the clinician and the patient may experience difficulties in ending the therapeutic relationship. Time-limited psychotherapy in different durations is available to treat patients with borderline personality disorder worldwide, but the proportion of psychotherapy literature addressing the demands and challenges arising from the ending phase is small. Mentalization-based therapy is one treatment option for borderline personality disorder, which is being delivered in different time-limited formats worldwide. In this paper, we describe a mentalization-based approach to understand and intervene against termination challenges. We propose that termination challenges in mentalization-based therapy can be attributed to the following factors, which are potentially overlapping: 1) patient factors, 2) therapist factors, 3) therapeutic relationship factors.

When *patient factors* challenge the ending phase, the patient may experience one or more pre-mentalizing modes in relation to ending the treatment. If the patient is in a psychic equivalence mode, the patient may become hyperaroused and overwhelmed by feelings of abandonment, potentially resulting in aggressive or clinging behaviors. If the patient is in teleological mode, the patient may only experience improvement if the therapist is physically present, resulting in wishes to postpone termination to maintain improvement. If the patient is in pretend mode, he or she may prematurely detach arguing that the treatment was a success, meanwhile quality of life or the level of functioning indicate the opposite. Furthermore, a patient dominated by epistemic mistrust, i.e. an inability to benefit from social communication, may not trust the therapists' reinforcements of autonomy or validations of good mentalizing, but may instead see these therapeutic interventions as means of abandonment.

When *therapist factors* challenge the ending phase, the therapist may react to the patients pre-mentalizing modes in nonproductive ways. For example, faced with a patient dominated by psychic equivalence mode, the therapist may experience overwhelming emotional responses to the patient (in MBT and other psychodynamic therapies known as countertransference) such as helplessness/inadequacy, overinvolvement, overprotection, or feelings of being overwhelmed

or disorganized. When faced with a patient dominated by teleological mode, the therapist may in turn wish to postpone treatment to meet the patient's appeal for more therapy. When faced with a patient dominated by pretend mode, the therapist may avoid switching the therapeutic dialoque from cognitive to affective mentalizing, thus delivering therapy that merely "looks like therapy".

When *therapeutic relationship factors* challenge the ending phase, the patient and therapist may have developed a supportive relationship, in which neither of them has addressed important topics during the course of treatment. This could be provocation of affect or formulating alternative perspectives to the patient's problems. Furthermore, when preparing the case formulation, the goals may have been formulated either too strictly or too vaguely, both of which may cause termination challenges, when gains and processes are reviewed in the ending phase of treatment.

To overcome these termination challenges, we propose the following: 1) that the therapist probes a mentalizing dialogue of the feelings associated with loss of the therapeutic relationship, 2) that the therapist manages the treatment structure more carefully, e.g. so the transition to the ending phase becomes transparent, and 3) that the original case formulation in which the patient's main goals and mentalizing capacities are outlined in the beginning of treatment [146], is extended with a *termination formulation*. A termination formulation is a short document that the patient is asked fill out at home an bring back to the therapist, in which the patient re-examines treatment outcomes, addresses how to amend mentalizing failures in the future, and writes down future mentalizing goals.

DISCUSSION

In this section I will describe the principal findings of this thesis, discuss the methodological strengths and limitations of the findings, and relate the findings to the current evidence and its implications. Lastly, I will discuss the future directions for research in psychotherapy durations with specific focus on how to improve the methodological quality of research.

Principal findings

We conducted the first systematic review assessing the effects of short-term versus long-term psychotherapy for adult psychiatric disorders. We included 16 trials randomising a total of 2,651 participants to a short-term or a long-term version of the same psychotherapy type. All trials and outcome results were at high risk of bias, and the certainty of the evidence according to GRADE was `very low' for all outcomes.

One single trial showed no evidence of a difference between short-term versus long-term dialectical behavioural therapy for borderline personality disorder and reached the required information size needed to reject realistic intervention effects when assessing quality of life, symptom severity, and level of functioning. One single trial showed no evidence of a difference between short-term versus long-term psychodynamic psychotherapy for mood- or anxiety disorders and reached the required information size needed to reject realistic intervention effects when assessing symptom severity and level of functioning. The remaining single trials did not meet the required information sizes needed to confirm or reject realistic intervention effects.

It was only possible to conduct two meta-analyses. Meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms at end of treatment. Meta-analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy for mood- and anxiety disorders on level of functioning.

An exploratory meta-analysis of short-term compared with long-term psychotherapy for internalizing adult psychiatric disorders showed no evidence of a difference on symptom

severity at maximum follow-up. The certainty of the evidence was assessed as 'very low' for all outcomes. It was not possible to perform Trial Sequential Analysis or tests for publication bias. Further, due to poor reporting in the included trials, we only performed one planned sensitivity analysis to assess the potential impact of missing data. Only a few trials reported on harmful effects, i.e. only one trial reported on serious adverse events, two trials reported on suicide and suicide attempts, and one trial reported on self-harm.

We successfully designed and implemented a randomised clinical trial enrolling 166 outpatients with subthreshold or diagnosed borderline personality disorder to short-term versus a long-term mentalization-based therapy. We reached the target sample size and are still collecting data from outcome assessments. Once data is available from the trial, it will contribute to the evidence of short-term compared with long-term psychotherapy for borderline personality disorder and will be eligible for inclusion if the systematic review is to be updated in the future.

We discussed the clinical challenges arising from terminating mentalization-based therapy for borderline personality disorder. We concluded that challenging terminations are likely to be an inherent part of all forms of personality disorder treatments regardless of treatment modality. We proposed a termination approach based on mentalization-based therapy to detect and intervene against such challenges. We have proposed that termination challenges can be attributed to 1) patient factors, 2) therapist factors, and 3) therapeutic relationship factors. We have suggested that explicit mentalizing of the often complicated and mixed feelings associated with separation and loss of the therapeutic relationship is an important part of the termination phase. To facilitate this process, we have proposed the use of a *termination formulation* in extension to the case formulation, in which patient's outcomes, interpersonal issues in therapy, and future goals are recapitulated in the termination phase.

Methodological strengths and limitations of the findings

The systematic review has several strengths. We followed our protocol which was registered prior to the systematic literature search (PROSPERO ID: CRD42019128535). Data were double-extracted by independent authors minimizing the risk of inaccurate data extraction, and we assessed the risk of bias in all trials according to Cochrane methodology [147]. We used

GRADE to assess the certainty of the evidence [125-127], and the eight-step assessment suggested by Jakobsen and colleagues to assess if the thresholds for significance were crossed [111]. Hence, this systematic review considered both risks of random errors and risks of systematic errors which adds further robustness to our results and conclusions. Another strength of our review is that we pragmatically accepted any short-term psychotherapy type and any long-term psychotherapy type, thus results may therefore guide a clinician when choosing between different treatment durations.

The randomised clinical trial has several strengths. First, it uses inclusive eligibility criteria causing a high degree of external validity, i.e. borderline personality disorder is a clinical heterogeneous group, and most patients suffer from multiple psychiatric co-morbidities [49]. Second, the methodology is based on CONSORT [148], and was predefined and described in detail before randomization began, including e.g. blinding procedures of all possible parties and implementation of a central randomization system both for generating the allocation sequence and for concealing allocation. Furthermore, a detailed statistical analysis plan was developed prior to unblinding of the results minimizing the risk of data-driven results.

The discussion paper on termination of mentalization-based therapy has several strengths. The theoretical discussions were developed in close collaboration with Dr. Anthony Bateman, one of the developers of mentalization-based therapy, who is also a co-author of the paper. Hence, the proposed mentalization-based strategies are consistent with the MBT manual as it was originally formulated by Bateman and Fonagy [65]. Furthermore, all authors of the paper have years of experience in conducting MBT for patients with borderline personality disorder.

The systematic review also has some limitations. First, all trials were at high risk of bias. Therefore, there is a risk that our present results overestimated the beneficial effects and underestimated the harmful effects of the experimental interventions being studied [99-106]. Second, we only identified 16 trials, and we analysed the data using SMD as the effect estimate. A limitation of using SMD is that it is not possible to perform Trial Sequential Analysis. Therefore, it was not possible to assess if the required information size for the meta-analysis results was reached or not. This is a major limitation, as we are not able to assess if the shown lack of difference is an indication of a “true” lack of difference, or if more data is needed.

Therefore, the meta-analysis results should be interpreted with caution. However, the point estimates are small (SMD=0.08 for short-term versus long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms, and SMD=0.16 for short-term and long-term psychodynamic psychotherapy for mood- and anxiety disorders on level of functioning), which may be considered minimal and without importance to the average patient. Guiding rules for interpreting SMDs (or 'Cohen's effect sizes') exist [89]. One example is the following: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect [149]. However, such interpretations can be problematic because patient importance of a finding is context-dependent [89]. In light of this, the meta-analysis effect estimates (SMD= 0.08 and SMD=0.16) indicate that there might be no clinically important differences between short-term and long-term psychotherapy for mood- and anxiety disorders, but more trials using the same measurement scales are needed to confirm or reject these results. Since we could not perform Trial Sequential Analysis, we performed post-hoc sample size calculations for all single trials on all our pre-defined outcomes using, but most trials did not meet these tentative required information sizes. Third, only few trials reported on serious adverse events, suicide, suicide attempts, and self-harm, which is consistent with the general psychotherapy literature [129]. It is of utmost importance to always assess beneficial and harmful intervention effects on patient-important outcomes [89,147]. Finally, the included trials differed in time points of outcome assessments, therapy durations (length of treatment), and therapy dosages (number of sessions).

The randomised clinical trial also has some limitations. First, no systematic review of the effects of short-term compared with long-term psychotherapy for borderline personality disorders was available prior to commencing the trial. We have now conducted such a systematic review. We conclude that the evidence on the beneficial and harmful effects of short-term versus long-term psychotherapy for borderline personality disorder is still scarce. We identified unpublished data for one trial assessing six versus 12 months of DBT for borderline personality disorder [39]. This trial did not find evidence of a difference between short-term and long-term DBT on any of our pre-defined review outcomes, and the trial reached the required information size on borderline symptoms, quality of life, and level of functioning. However, this data was not available when we began our trial to guide or trial design in terms of e.g. sample size calculation, and strata used in the randomisation. Second, we expect substantial missing data on our trial outcomes. Third, the long-term MBT group, which is 14 months of treatment in the

trial differs from the original 18-months program, which is manualized by Bateman and Fonagy [65] and assessed in a randomised clinical trial compared to structured clinical management [64]. This is due to the fixed length of the treatment packages implemented in the Danish mental health care system. Fourth, we cannot account for any potential confounding variables caused by structural differences between the two groups.

The discussion paper also has some limitations. The primary limitation is the recommendations were not based on a systematic review of the literature. Hence, there may have been others who have attempted to address termination challenges from a mentalization-based perspective. However, we are not aware of such literature. Second, the conclusions may have changed if the theoretical speculations were supported by empirical research (either qualitatively or quantitatively) of the therapist's experiences with terminating MBT for patients with borderline personality disorder. We are currently conducting a qualitative study assessing seven trial therapist's experiences with changing from a long-term to a short-term MBT program for patients with borderline personality disorder.

Current evidence and implications

From systematically reviewing the literature on short-term versus long-term psychotherapy for adult psychiatric disorders we found that there seems to be no evidence of a difference between short-term and long-term psychotherapy for mood and anxiety disorders. However, these results must still be regarded as preliminary due to the methodological limitations of the included trials. Due to lack of relevant data, it remains unclear whether participants with more severe psychopathology would benefit more or less from short-term psychotherapy compared with long-term psychotherapy. One unpublished trial assessing 6 versus 12 months dialectical behavioural therapy for borderline personality disorder reached the required information size from our post-hoc sample size calculation when assessing quality of life, symptom severity, and level of functioning. However, these results should be pooled with future similar trials, e.g. the future results of **Study II** of this thesis, before any conclusions can be considered evidence-based. More randomised clinical trials at low risk of bias and at low risk of random errors as well as trials comparing patients at different levels of psychopathological distress are urgently needed. Clinicians are advised to offer evidence-based treatment programs but should exert

caution in advising patients about optimal treatment intensity and duration for most psychiatric disorders.

Future directions – improving the quality of research in psychotherapy durations

The cornerstone of evidence-based medicine is the belief that high-quality research should form the basis for practice and decision-making [150]. High-quality research should be able to benefit the decision about the care for individual patients [150]. In evidence-based medicine, the systematic review of randomised clinical trials is considered the gold standard when assessing intervention effects [91]. However, even though randomised clinical trials have been adequately attempted, bias may occur in the design, conduct, analysis, interpretation, and publication of trial results. These bias from individual trials may ultimately bias the results and conclusions drawn from systematic reviews of these trials.

In psychotherapy research in general, is has been well established that the quality of trial methodology currently is suboptimal [8]. For example, there is a need for more large-scale randomised clinical trials without industry sponsorship, trial pre-registration, adequate reporting, and data sharing [8] to avoid bias, which often lead to an overestimation of beneficial effects and underestimation of harmful effects of the experimental intervention [99-106]. Furthermore, we have recently shown that blinding of key persons involved in randomised clinical trials of psychological interventions is lacking [109]. Even the blinding status of key persons who are easily blinded (e.g. data managers, statisticians, the data safety and monitoring committee, and decision makers) are currently either rarely blinded, or the blinding status is unclear due to inadequate reporting [109].

From systematically reviewing the effect of short-term compared with long-term psychotherapy for all adult psychiatric disorders (**Study I**), we identified some specific methodological problems that should improve in the future of this particular research field. I have divided these problems into the following subsections: *1) balancing beneficial and harmful effects, 2) systematic errors, 3) conflict of interest and publication bias, 5) replication of single trial results, 6) choosing the right outcomes.*

Balancing beneficial and harmful effects

'First do no harm' is an important injunction in all medical interventions [151]. While beneficial effects (e.g. symptom reduction and quality of life) has been thoroughly assessed in the psychotherapy literature, research on harmful effects is still lagging behind [129,152,153]. Although the importance of assessing harmful effects of psychotherapy has been described for several decades [154,155], it is only recently that harmful effects has been suggested to be one of the core issues to be prioritized in psychotherapy research [129,153,156-158]. To this day, there is a consensus among researchers in the field of psychotherapy research that harmful effects should be assessed more frequently and that they have been almost neglected in much of the past research [152,153]. A review of the degree of reporting of harms in randomised clinical trials of psychological interventions for mental and behavioural disorders was published in 2014 [159]. The review identified 132 eligible randomised clinical trials. Only 28 trials (21%) included information that indicated any monitoring of harms. Four (3%) trials provided a description of adverse events and the data collection method. Five (4%) trials reported adverse events but did not report the data collection method. Four (3%) trials briefly stated that no adverse events occurred, whereas 15 (11%) trials only reported on deterioration or indicated monitoring of deterioration. Furthermore, the probability of including harm-related information was related to the journal impact factor. Other studies have shown that journals with high journal impact factor are known to have lower risks of bias compared to journals with lower journal impact factor [160,161], and it is therefore not unlikely, that the benefit-harm ratio with psychological research is equally more well-reported in journals with high journal impact factor.

The appropriate way of assessing harmful effects of psychotherapy has been discussed [152,162]. Typical harmful effects could be clinical deterioration [158], and the proportion of participants with one or more serious adverse events [1]. However, there are many other types of harmful effects that have been reported [163], for example drop-out rates or treatment non-response. However, the problem with outcomes such as response, non-response, or deterioration is that they are often based on a dichotomization of a continuous scale. For example, trialists often dichotomize the HDRS by transforming the overall HDRS score between 0 and 52 into a dichotomous score comparing responders (≥50% improvement) to non-responders (≤50% improvement) [164]. However, several studies have shown that such

transformation of continuous data into two groups is problematic, and dichotomization has been shown to bias results [165,166]. In addition, a patient who improves by ≥50% is defined as a responder, whereas a patient who improves by 49% is defined as a non-responder, thus the apparent difference between these patients becomes inflated [166]. On the contrary, a patient who improves by ≥50% is categorized as being equal to a patient whose symptoms disappear completely, and a patient with 49% improvement is categorized the same as a patient showing no improvement at all [164].

In the studies included in this thesis, we have used the proportion of participants with one or more serious adverse events as defined by the ICH-GCP guidelines [132] for the assessment of harms. According to ICH-GCP, a serious adverse event is defined as any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity [132]. In the randomised clinical trial (**Study II**), we will report the serious adverse events separately. An advantage of assessing harms with this method is that we avoid any problems associated with disease-specific harmful effects, for example suicide or suicide attempts, as it can potentially be difficult to differentiate a disease-related event, e.g. a suicide or a suicide attempt from a non-disease-related event, e.g. an accident [167]. When employing the ICH-GCP definition, a potential suicide or suicide-attempt will be included as an event, and can be categorized in a serious adverse events table. If the number of randomised participants is high enough, the non-disease-related serious adverse events (e.g. car accidents) will be equal in both groups. Besides assessing serious adverse events, we have also included proportion of participants with severe self-harm defined as deliberate acts of self-harm resulting in visible tissue-damage as a secondary outcome in both **Study I** and **Study II** of this thesis. Based on the results of our systematic review, we concluded that the evidence on harmful effects of short-term compared with long-term psychotherapy is lacking, since only few trials reported on serious adverse events, suicide or suicide-attempts, and self-harm. The inclusion of these outcomes should be improved in future trials assessing the optimal psychotherapy duration for adult psychiatric disorders.

Systematic errors

In our systematic review, all the included trials were assessed as at overall high risk of bias. The included trials were particularly biased regarding incomplete outcome data, risks of selective outcome reporting, and lack of blinding (**Study I**). Only few trials pre-registered their methodology in a trial registration platform (e.g. www.clinicaltrials.gov) or published a protocol, increasing the risk of data-driven results. As mentioned previously, trials at high risk of bias are prone to overestimate the beneficial effects and underestimate the harmful effects of interventions [99-106,168]. Thus, more large-scale trials at low risk of systematic error are needed, if we should approach an answer to the question "which length for whom?" in the treatment of adult psychiatric disorders.

The importance of reducing bias in psychological research has recently been discussed in a meta-analysis investigating 15 different psychotherapies for major depressive disorder [169]. The authors concluded that all psychotherapies seem to work similarly for depressive symptoms, and the effect size of specialized interventions is small if the high levels of heterogeneity, publication bias, and high risk of bias in the included studies are considered. Thus, designing large-scale trials at low risk of bias by implementing is urgently needed in psychological research in general.

Conflict of interest and assessment of publication bias

Psychotherapy research has long struggled with the potential bias of trialists who believe in the superiority of one psychological intervention over another, a phenomenon typically referred to as researcher allegiance [170]. However, researcher allegiance is a heterogeneous construct covering a broad spectrum from developing the treatment manual to advocating for it to contributing to a related disease model to, ultimately, performing a randomised clinical trial showing results favoring the new treatment model [171]. Industry-associated financial conflict of interest has been documented to bias the outcomes and interpretations of randomised clinical trials [108,172], meta-analyses [173], and clinical guidelines [174] of medical treatments. As a result, conflict of interest disclosures are now often required from all authors of work published in biomedical journals [170]. However, the discussion of financial conflicts of interest associated with psychotherapy has remained underdeveloped. Financial conflicts of interest in psychotherapy research could be that trialists performing a randomised clinical trial assessing

the effects of a psychological intervention also have financial gains from e.g. professional trainings of that particular intervention, books, therapy manuals, courses, speaker's fees, paid advisory positions, grants etc [170].

One way of assessing the potential impact of conflicts of interest is to carefully look for sign of publication bias when performing a meta-analysis. Publication bias refers to the publication or non-publication of research findings, depending on the nature and direction of the results [89]. Trialists with strong allegiances to one of the assessed interventions in a randomised clinical trial may decide not to publish the trial results, assuming the result are not in line with their expectations. Assessment of publication bias can be performed by visually inspecting funnel plots [89] and by statistically testing the funnel plot asymmetry using various tests depending on the outcome of interest [89]. In our systematic review (**Study I**) we did not perform tests for funnel plot asymmetry, because of lack of trials. Cochrane Handbook recommends to only perform tests for funnel plot asymmetry when there are at least 10 trials included in the meta-analysis. Fewer than 10 trials may results in the power of the tests to be too low to distinguish chance from real asymmetry [89]. Therefore, we were not able to assess the potential impact of publication bias on our systematic review results. This is a further argument for our conclusion that more trials assessing different durations of psychotherapy for adult psychiatric disorders are needed.

One way of controlling for researcher allegiance on a trial level is to secure blinding of all possible key persons involved in data collection, analysis, interpretation, and dissemination of the trial results. For a detailed description of blinding procedures for these key persons, please consult Juul and colleagues [109].

Replication of single trial results

It has been claimed that most published research findings are false [90] and that up to 85% of biomedical research is wasted [175] despite the existence of guidelines on how to conduct and report the results of randomised trials, e.g. the CONSORT statement [148]. Research on the effects on psychotherapy durations is no exception to this predicament. In our systematic review of different psychotherapy durations for psychiatric disorders, the 16 included trials differed substantially in their assessed PICOs (participants, interventions, comparators, and outcomes)

(**Study I).** Therefore, it was only possible to pool trials in two pre-planned meta-analyses, and the majority of included trials were not eligible for meta-analysis due to the fact that no similar trials existed. Furthermore, an adequate description of the assessed trial interventions is required for investigators to design replication trials and for clinicians and patients to reliably implement interventions [176,177]. Both the experimental and the control conditions need to be described in detail [178]. To improve reporting of interventions, the template for intervention description and replication checklist and guide (TIDieR) has been developed [177].

Despite the need for more trials with similar designs and interventions, the need to replicate existing findings (and thereby increasing the required information size needed to confirm or reject realistic intervention effects) is an aim that pragmatically conflicts with the wish for more personalized psychotherapy. The more subgroups of patients that are identified (e.g. patients with different levels of disease severity), the more participants are needed in the analyses. In a systematic review with meta-analysis of randomised clinical trials comparing two psychotherapies directly in depressed patients with a specific patient characteristic, the authors identified 27 specific patient characteristics that could be targeted with psychotherapy. However, when participants are assessed in subgroups, more participants are required to confirm or reject realistic intervention effects. In this systematic review, it was estimated, based on sample size calculations, that it will take another 326 years to have sufficient statistical power to confirm or reject an effect size of $g = 0.50$ of the 27 distinct patient characteristics, and 1,372 years to confirm or reject an effect size of 0.24. Although several dozens of trials have compared the effects of psychotherapies in specific target groups, we are still very far from identifying personalized treatments for depression, as an example [179].

Choosing the right outcomes

There is currently no consensus in the research field on what the core outcome set of randomised clinical trials of psychotherapies should be [129]. Because of this lack of consensus, many different outcomes and instruments are used across trials [129]. This was also evident in our systematic review of randomised clinical trials of short-term versus long-term psychotherapy for adult psychiatric disorders (**Study I**). Even if the instruments measured the same construct (e.g. depression), it was reported with heterogeneous instruments (e.g. with the HDRS [180] or the Beck Depression Inventory (BDI) [181]). The heterogeneity in outcome

selection may cause inconsistencies in reporting and difficulties in comparing and combining the findings in systematic reviews and meta-analyses, particularly due to the problems associated with using SMD [182-184] Furthermore, the quality of outcome measures varies widely, and in many cases the most reliable and valid outcome measures are not selected [182]. Standardization of the selection of outcomes and their measures is therefore very much needed both in psychotherapy research in general [129], and in research of the optimal psychotherapy duration for adult psychiatric disorders.

REFERENCES

1. Juul S, Poulsen S, Lunn S, Sorensen P, Jakobsen JC, Simonsen S. Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis. Syst Rev. 2019;8(1):169.

2. Juul S, Jakobsen JC, Jørgensen CK, Poulsen S, Sørensen P, Simonsen S. Short-term versus long-term psychotherapy for adult psychiatric disorders: a systematic review with meta-analysis Submitted to British Journal of Psychiatry. 2021 [In review]

3. Juul S, Lunn S, Poulsen S, Sørensen P, Salimi M, Jakobsen JC, et al. Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomized clinical trial. Trials. 2019;20(1):196.

4. Juul S, Simonsen S, Poulsen S, Lunn S, Sørensen P, Bateman A, et al. Detailed statistical analysis plan for the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder randomized clinical trial (MBT-RCT). Submitted to Trials. 2021 [Submitted].

5. Juul S, Simonsen S, Bateman A. The capacity to end: termination of mentalization-based therapy for borderline personality disorder. J Contemp Psychother. 2020;50:331-8.

6. Norcross JC, Wampold BE. What works for whom: Tailoring psychotherapy to the person. J Clin Psychol. 2011;67(2):127-32.

7. Wampold BE. The great psychotherapy debate: models, methods, and findings: London, Routledge; 2013.

8. Leichsenring F, Steinert C, Ioannidis JPA. Toward a paradigm shift in treatment and research of mental disorders. Psychol Med. 2019;49(13):2111-7.

9. Jackson SW. Care of the psyche: A history of psychological healing: New York, Yale University Press; 1999.

10. Barlow DH. The Oxford Handbook of Clinical Psychology: Updated Edition: London, Oxford University Press; 2014.

11. Breuer J, Freud S. Studies on hysteria, vol. 2. In: The standard edition of the complete psychological works of Sigmund Freud. London, Hogarth Press; 1895:1953-86.

12. Freud S. On beginning the treatment (further recommendations on the technique of psycho-analysis I). In: The standard edition of the complete psychological works of Sigmund Freud, Vol 12 (1911-1913), London, Hogarth Press; 1958:121-44.

13. Garfield SL. The practice of brief psychotherapy: London, John Wiley & Sons; 1998.

14. Ferenczi S, Rank O. The development of psychoanalysis. Nervous and Mental Disease Publishing Co, New York, USA 1925.

15. Joint Commission on Mental Illness and Health. Action for mental health: final report, 1961: London, Basic Books; 1961.

16. National Institute for Health and Care Excellence. Eating disorders: recognition and treatment. London: NICE; 2017. Updated December 16, 2020 [Available from: https://www.nice.org.uk/guidance/ng69] [Accessed January 28, 2021].

17. National Institute for Health and Care Excellence. Depression in adults: recognition and management. London: NICE; 2009. [Available from: https://www.nice.org.uk/guidance/cg90 [Accessed January 28, 2021].

18. National Institute for Health and Care Excellence. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence. London: NICE; 2011. [Available from: https://www.nice.org.uk/guidance/cg115 [Accessed January 28, 2021].

19. National Institute for Health and Care Excellence. Drug misuse in over 16s: psychosocial interventions. London: NICE; 2007. [Available from: https://www.nice.org.uk/guidance/cg51 [Accessed January 28, 2021].

20. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. London: NICE; 2011. Updated July 26, 2019 [Available from: https://www.nice.org.uk/guidance/ng69] [Accessed January 28, 2021].

21. National Institute for Health and Care Excellence. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. London: NICE; 2015. [Available from: https://www.nice.org.uk/guidance/cg31 [Accessed January 28, 2021].

22. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. London: NICE; 2013. [Available from: https://www.nice.org.uk/guidance/cg159 [Accessed January 28, 2021].

23. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management. London: NICE; 2018. Updated September 13, 2019 [Available from: https://www.nice.org.uk/guidance/ng87 [Accessed January 28, 2021].

24. National Institute for Health and Care Excellence. Autism spectrum disorder in adults: diagnosis and management. London: NICE; 2012. Updated August 18, 2016 [Available from: https://www.nice.org.uk/guidance/cg142 [Accessed January 28, 2021].

25. National Institute for Health and Care Excellence. Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings. London: NICE; 2011. [Available from: https://www.nice.org.uk/guidance/cg120 [Accessed January 28, 2021].

26. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. London: NICE; 2014. Updated February 11, 2020 [Available from: https://www.nice.org.uk/guidance/ng87 [Accessed January 28, 2021].

27. National Institute for Health and Care Excellence. Borderline personality disorder: recognition and management. London: NICE; 2009. [Available from: https://www.nice.org.uk/guidance/cg78 [Accessed January 28, 2021].

28. National Institute for Health and Care Excellence. Antisocial personality disorder: prevention and management. London: NICE; 2009. Updated March 27, 2013 [Available from: https://www.nice.org.uk/guidance/cg77 [Accessed January 28, 2021].

29. National Institute for Health and Care Excellence. Post-traumatic stress disorder. London: NICE; 2018. [Available from: https://www.nice.org.uk/guidance/ng116 [Accessed January 28, 2021].

30. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. London: NICE; 2014. Updated March 1, 2014 [Available from: https://www.nice.org.uk/guidance/cg178 [Accessed January 28, 2021].

31. Alonso-Coello P, Irfan A, Sola I, Gich I, Delgado-Noguera M, Rigau D, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care. 2010;19(6):e58.

32. Robinson L, Delgadillo J, Kellett S. The dose-response effect in routinely delivered psychological therapies: A systematic review. Psychother Res. 2020;30(1):79-96.

33. Jakobsen JC, Gluud C. The necessity of randomized clinical trials. Br J Med Med Res. 2013;3(4):1453-68.

34. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27).

35. Paris J. Stepped care: an alternative to routine extended treatment for patients with borderline personality disorder. Psychiatr Serv. 2013;64(10):1035-7.

36. Joyce AS, Piper WE, Ogrodniczuk JS, Klien RH. Termination in psychotherapy: A psychodynamic model of processes and outcomes. Washington, USA: American Psychological Association; 2007.

37. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. JAMA. 2008;300(13):1551-65.

38. Leichsenring F, Rabung S. Long-term psychodynamic psychotherapy in complex mental disorders: update of a meta-analysis. Br J Psychiatry. 2011;199(1):15-22.

39. McMain S. The effectiveness of 6 versus 12-months of dialectical behaviour therapy for borderline personality disorder: the feasibility of a shorter treatment and evaluating responses (FASTER) trial. 2021[Unpublished data - obtained through personal communication with the authors].

40. McMain SF. Advances in the treatment of borderline personality disorder: an introduction to the special issue. J Clin Psychol. 2015;71(8):741-6.

41. Winston A, Laikin M, Pollack J, Wallner Samstag L, McCullough L, Muran JC. Short-term psychotherapy of personality disorders. Am J Psychiatry. 1994;151(2):190-4.

42. Cristea IA, Gentili C, Cotet CD, Palomba D, Barbui C, Cuijpers P. Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. JAMA Psychiatry. 2017;74(4):319-28.

43. Tyrer P, Reed GM, Crawford MJ. Classification, assessment, prevalence, and effect of personality disorder. Lancet. 2015;385(9969):717-26.

44. Stern A. Psychoanalytic investigation of and therapy in the borderline group of neuroses. Psychoanal Q. 1938;7(467-489).

45. Stone MH. Essential papers on borderline disorders: One hundred years at the border. New York, USA: NYU Press; 1986.

46. Kernberg O. Borderline personality organization. J Am Psychoanalyt Ass. 1967;15(3):641-85.

47. Gunderson J. Borderline personality disorder. N Eng J Med. 2011;364:2037-42.

48. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, USA: American Psychiatric Pub; 2013.

49. Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2008;69(4):533.

50. Torgersen S, Kringlen E, Cramer V. The prevalence of personality disorders in a community sample. Arch Gen Psychiatry. 2001;58(6):590-6.

51. Skodol AE, Gunderson JG, Pfohl B, Widiger TA, Livesley WJ, Siever LJ. The borderline diagnosis I: psychopathology, comorbidity, and personaltity structure. Biol Psychiatry. 2002;51(12):936-50.

52. Cheng AT, Mann A, Chan K. Personality disorder and suicide: A case-control study. Br J Psychiatry. 1997;170(5):441-6.

53. Lesage AD, Boyer R, Grunberg F, Vanier C, Morissette R, Ménard-Buteau C, et al. Suicide and mental disorders: a case-control study of young men. Am J Psychiatry. 1994;151(17):1063-68

54. Black DW, Blum N, Pfohl B, Hale N. Suicidal behavior in borderline personality disorder: prevalence, risk factors, prediction, and prevention. J Personal Dis. 2004;18(3):226-39.

55. Gross R, Olfson M, Gameroff M, Shea S, Feder A, Fuentes M, et al. Borderline personality disorder in primary care. Arch Intern Med. 2002;162(1):53-60.

56. Zanarini MC, Frankenburg FR, Hennen J, Silk KR. Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. J Clin Psychiatry. 2004;65(1):28-36

57. Soeteman DI, Roijen LH-v, Verheul R, Busschbach JJ. The economic burden of personality disorders in mental health care. J Clin Psychiatry. 2008;69(2):259.

58. Sansone RA, Sansone LA. Employment in borderline personality disorder. Innov Clin Neurosci. 2012;9(9):25.

59. Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database of Syst Rev. 2010(6):1465-858.

60. Stoffers-Winterling J, Storebo OJ, Lieb K. Pharmacotherapy for borderline personality disorder: an update of published, unpublished and ongoing studies. Curr Psychiatry Rep. 2020;22(8):37.

61. Storebø OJ, Stoffers-Winterling JM, Völlm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, et al. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2020(5).

62. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry. 2006;63(7):757-66.

63. Giesen-Bloo J, van Dyck R, Spinhoven P, van Tilburg W, Dirksen C, van Asselt T, et al. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch Gen Psychiatry. 2006;63(6):649-58.

64. Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1355-64.

65. Bateman, Fonagy P. Mentalization-based treatment for personality disorders: a practical guide. Oxford, United Kingdom: Oxford University Press; 2016.

66. Kvarstein EH, Pedersen G, Folmo E, Urnes Ø, Johansen MS, Hummelen B, et al. Mentalization-based treatment or psychodynamic treatment programmes for patients with borderline personality disorder – the impact of clinical severity. Psychology Psychother. 2019;92(1):91-111.

67. McMain SF, Guimond T, Barnhart R, Habinski L, Streiner DL. A randomized trial of brief dialectical behaviour therapy skills training in suicidal patients suffering from borderline disorder. Acta Psychiatr Scand. 2017;135(2):138-48.

68. Gratz K, Tull M, Levy R. Randomized controlled trial and uncontrolled 9-month follow-up of an adjunctive emotion regulation group therapy for deliberate self-harm among women with borderline personality disorder. Psychol Med. 2014;44(10):2099.

69. Blum N, St. John D, Pfohl B, Stuart S, McCormick B, Allen J, et al. Systems Training for Emotional Predictability and Problem Solving (STEPPS) for outpatients with borderline personality disorder: a randomized controlled trial and 1-year follow-up. Am J Psychiatry. 2008;165(4):468-78.

70. Tyrer P, Crawford M, Mulder R, Blashfield R, Farnam A, Fossati A, et al. The rationale for the reclassification of personality disorder in the 11th revision of the International Classification of Diseases (ICD-11). Personal Ment Health. 2011;5(4):246-59.

71. Crawford MJ, Koldobsky N, Mulder R, Tyrer P. Classifying personality disorder according to severity. J Pers Disord. 2011;25(3):321-30.

72. Bach B, Simonsen S. How does level of personality functioning inform clinical management and treatment? Implications for ICD-11 classification of personality disorder severity. Curr Opin Psychiatry. 2021;34(1):54-63.

73. Simonsen S, Heinskou T, Sørensen P, Folke S, Lau M. Personality disorders: patient characteristics and level of outpatient treatment service. Nord J Psychiatry. 2017;71(5):325-31.

74. Bateman A, Campbell C, Luyten P, Fonagy P. A mentalization-based approach to common factors in the treatment of borderline personality disorder. Curr Opin Psychol. 2018;21:44-9.

75. Tmej A, Fischer-Kern M, Doering S, Alexopoulos J, Buchheim A. Changes in attachment representation in psychotherapy: is reflective functioning the crucial factor? Z Psychosom Med Psychother. 2018;64(3):222-36.

76. Fonagy P, Target M, Gergely G. Attachment and borderline personality disorder: A theory and some evidence. Psychiatric Clin. 2000;23(1):103-22.

77. Knox J. The harmful effects ofpsychotherapy: when the therapeutic alliance fails. Br J Psychother. 2019;35(2):245-62.

78. Bateman A, Fonagy P. Mentalization based treatment for borderline personality disorder. World Psychiatry. 2010;9(1):11.

79. Bateman A, Fonagy P. MBT Adherence Scale: Anna Freud Centre. Available at: https://www.annafreud.org/training/mentalization-based-treatment-training/mbt-adherence-scale/ [Accessed January 6, 2021]

80. Karterud S, Pedersen G, Engen M, Johansen MS, Johansson PN, Schlüter C, et al. The MBT Adherence and Competence Scale (MBT-ACS): Development, structure and reliability. Psychother Res. 2013;23(6):705-17.

81. Karterud S, Pedersen G, Engen M, Johansen MS, Johansson PN, Schlüter C, et al. The MBT Adherence and Competence Scale (MBT-ACS): development, structure and reliability. Psychother Res. 2013;23(6):705-17.

82. Simonsen S, Juul S, Kongerslev M, Bo S, Folmo E, Karterud S. The mentalization-based therapy adherence and quality scale (MBT-AQS): Reliability in a clinical setting. Nord Psychol. 2019;71(2):104-15.

83. Norcross JC, Zimmerman BE, Greenberg RP, Swift JK. Do all therapists do that when saying goodbye? A study of commonalities in termination behaviors. Psychother. 2017;54(1):66.

84. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992;268(17):2420.

85. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Eng J Med. 2000;342(25):1887-92.

86. Bland JM, Altman DG. Regression towards the mean. BMJ. 1994;308(6942):1499.

87. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol. 2004;34(1):215-20.

88. Garattini S, Jakobsen JC, Wetterslev J, Bertele V, Banzi R, Rath A, et al. Evidence-based clinical practice: Overview of threats to the validity of evidence and how to minimise them. Eur J Intern Med. 2016;32:13-21.

89. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019): The Cochrane Collaboration; 2019. Available at: https://training.cochrane.org/cochrane-handbook-systematic-reviews-interventions [Accessed January 29, 2021]

90. Ioannidis JPA. Why most published research findings are false. PLOS Med. 2005;2(8):e124.

91. Garattini S, Jakobsen JC, Wetterslev J, Bertelé V, Banzi R, Rath A, et al. Evidence-based clinical practice: overview of threats to the validity of evidence and how to minimise them. Eur J Intern Med. 2016;32:13-21.

92. IntHout J, Ioannidis JP, Borm GF. Obtaining evidence by a single well-powered trial or several modestly powered trials. Stat Method Clin Med. 2016;25(2):538-52.

93. Borm GF, Lemmers O, Fransen J, Donders R. The evidence provided by a single trial is less reliable than its statistical analysis suggests. J Clin Epidemiol. 2009;62(7):711-5.e1.

94. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Eng J Med. 2000;342(25):1878-86.

95. Chalmers TC, Celano P, Sacks HS, Smith Jr H. Bias in treatment assignment in controlled clinical trials. N Eng J Med. 1983;309(22):1358-61.

96. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. Stat Med. 1989;8(4):441-54.

97. Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. JAMA. 2001;286(7):821-30.

98. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ. 1998;317(7167):1185-90.

99. Gluud LL. Bias in clinical intervention research. Am J Epidemiol. 2006;163(6):493-501.

100. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med. 2001;135(11):982-9.

101. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.

102. Moher D, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13.

103. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273(5):408-12.

104. Hrobjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol. 2014;43(4):1272-83.

105. Hrobjartsson A, Skou Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ. 2013;185(4).

106. Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ. 2012;344:e1119.

107. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration. 2011. Available at: https://handbook-5-1.cochrane.org/ [Accessed January 28, 2021]

108. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome: systematic review with meta-analysis. Intensive Care Med. 2018;44(10):1603-12.

109. Juul S, Gluud C, Simonsen S, Frandsen FW, Kirsch I, Jakobsen JC. Blinding in randomised clinical trials of psychological interventions: a retrospective study of published trial reports. BMJ Evid Based Med. 2020:bmjebm-2020-111407.

110. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:I4898

111. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14(1):120.

112. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

113. Fletcher J. What is heterogeneity and is it important? BMJ. 2007;334(7584):94-6.

114. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol. 2008;61(1):64-75.

115. Copenhagen Trial Unit. TSA - Trial sequential analysis. Available at: http://www.ctu.dk/tsa/ [Accessed January 28, 2021]

116. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol. 2008;61(8):763-9.

117. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol. 2008;38(1):287-98.

118. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, C. G. User manual for trial sequential analysis (TSA). Available at: http://wwwctudk/tsa/files/tsa_manualpdf. [Accessed January 29, 2021]

119. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol. 2009;9(1):86.

120. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clin Epidemiol. 2010;2:57.

121. Thorlund K, Devereaux P, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol. 2008;38(1):276-86.

122. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ open. 2016;6(8):e011890.

123. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. BMC Med Res Methodol. 2017;17(1):1-18.

124. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14(1):120.

125. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

126. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

127. Schünemann HJ, Best D, Vist G, Oxman AD, Group GW. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. CMAJ. 2003;169(7):677-80.

128. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64(4):395-400.

129. Cuijpers P. Targets and outcomes of psychotherapies for mental disorders: an overview. World Psychiatry. 2019;18(3):276-85.

130. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349.

131. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Med. 2009;6(7):e1000097.

132. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). ICH Harmonised Guideline: Integrated Addemdum to ICH E6(R1): Guideline for Good Clinical Practice (ICH-GCP). 2015. Available at: www.ich-gcp.net [Accessed January 29, 2021]

133. Review Manager (RevMan). Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2020 [Software]

134. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.

135. Karterud S, Bateman A. Manual for mentaliseringsbasert psykoedukativ gruppeterapi (MBT-I): Oslo. Gyldendal Akademisk; 2011.

136. Zanarini MC. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Pers Disord. 2003;17(3):233-42.

137. Pedersen G, Kvarstein EH, Wilberg T. The Work and Social Adjustment Scale: Psychometric properties and validity among males and females, and outpatients with and without personality disorders. Personal Ment Health. 2017;11(4):215-28.

138. Brazier JE, Harper R, Jones N, O'cathain A, Thomas K, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160-4.

139. Hall RC. Global assessment of functioning: a modified scale. Psychosom. 1995;36(3):267-75.

140. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale–preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.

141. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2011;31:328-40.

142. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 2012;345:e5840.

143. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol. 2003;3:26.

144. Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance - a five-step procedure for evaluation of intervention effects in randomised clinical trials. BMC Med Res Methodol. 2014;14(34).

145. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol. 2017;17(1):162.

146. Karterud S, Kongerslev MT. Case formulations in mentalization-based treatment (MBT) for patients with borderline personality disorder. In: Kramer U, editor. Case formulation for personality disorders: Elsevier; 2019:41-60.

147. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration. 2011. Available at: https://handbook-5-1.cochrane.org/ [Accessed January 28, 2021]

148. Schulz KF, Altman DG, Moher D, The CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.

149. Cohen J. Statistical power analysis in the behavioral sciences. 2nd edition. Lawrence Erlbaum Associates, Inc.; 1988.

150. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;321:71-2.

151. Sokol DK. “First do no harm” revisited. BMJ. 2013;347:f6426.

152. Dimidjian S, Hollon SD. How would we know if psychotherapy were harmful? Am Psychologist. 2010;65(1):21.

153. Barlow DH. Negative effects from psychological treatments: a perspective. Am Psychologist. 2010;65(1):13.

154. Hadley SW, Strupp HH. Contemporary views of negative effects in psychotherapy: an integrated account. Arch Gen Psychiatry. 1976;33(11):1291-302.

155. Mohr DC. Negative outcome in psychotherapy: a critical review. Clin Psychol. 1995;2(1):1-27.

156. Berk M, Parker G. The elephant on the couch: side-effects of psychotherapy. Sage Publications Sage UK: London, England; 2009.

157. Lilienfeld SO. Psychological treatments that cause harm. Perspect Psychol Sci. 2007;2(1):53-70.

158. Cuijpers P, Reijnders M, Karyotaki E, de Wit L, Ebert DD. Negative effects of psychotherapies for adult depression: a meta-analysis of deterioration rates. J Affect Disord. 2018;239:138-45.

159. Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: A review of current practice. Contemp Clin Trials. 2014;38(1):1-8.

160. Bala MM, Akl EA, Sun X, Bassler D, Mertz D, Mejza F, et al. Randomized trials published in higher vs. lower impact journals differ in design, conduct, and analysis. J Clin Epidemiol. 2013;66(3):286-95.

161. Gluud LL, Sørensen TI, Gøtzsche PC, Gluud C. The journal impact factor as a predictor of trial quality and outcomes: cohort study of hepatobiliary randomized clinical trials. Am J Gastroenterol. 2005;100(11):2431-5.

162. Boisvert CM. Negative treatment effects: is it time for a black box warning? Am Psychol. 2010;65:680-1.

163. Linden M. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. Clin Psychol Psychother. 2013;20(4):286-96.

164. Jakobsen JC, Gluud C, Kirsch I. Should antidepressants be used for major depressive disorder? BMJ Evid Based Med. 2019:bmjebm-2019-111238.

165. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.

166. Kirsch I, Moncrieff J. Clinical trials and the response rate illusion. Contemp Clin Trials. 2007;28(4):348-51.

167. Jakobsen JC, Wetterslev J, Gluud C. Considerations on the strengths and limitations of using disease-related mortality as an outcome in clinical research. BMJ Evid Based Med. 2019: DOI: 10.1136/bmjebm-2018-111154.

168. Kahale LA, Khamis AM, Diab B, Chang Y, Lopes LC, Agarwal A, et al. Potential impact of missing outcome data on treatment effects in systematic reviews: imputation study. BMJ. 2020;370:m2898.

169. Cuijpers P, Karyotaki E, de Wit L, Ebert DD. The effects of fifteen evidence-supported therapies for adult depression: A meta-analytic review. Psychother Res. 2019:1-15.

170. Cristea I-A, Ioannidis JPA. Improving disclosure of financial conflicts of interest for research on psychosocial interventions. JAMA Psychiatry. 2018;75(6):541-2.

171. Munder T, Flückiger C, Gerger H, Wampold BE, Barth J. Is the allegiance effect an epiphenomenon of true efficacy differences between treatments? A meta-analysis. J Couns Psychol. 2012;59(4):631.

172. Ahn R, Woodbridge A, Abraham A, Saba S, Korenstein D, Madden E, et al. Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study. BMJ. 2017;356:i6770.

173. Ebrahim S, Bance S, Athale A, Malachowski C, Ioannidis JP. Meta-analyses with industry involvement are massively published and report no caveats for antidepressants. J Clin Epidemiol. 2016;70:155-63.

174. Lenzer J, Hoffman JR, Furberg CD, Ioannidis JP. Ensuring the integrity of clinical practice guidelines: a tool for protecting patients. BMJ. 2013;347:f5535.

175. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86-9.

176. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med. 2008;148(4):295-309.

177. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348.

178. Guidi J, Brakemeier E-L, Bockting CL, Cosci F, Cuijpers P, Jarrett RB, et al. Methodological recommendations for trials of psychological interventions. Psychother Psychosom. 2018;87(5):276-84.

179. Cuijpers P, Ebert DD, Acarturk C, Andersson G, Cristea IA. Personalized psychotherapy for adult depression: a meta-analytic review. Behav Ther. 2016;47(6):966-80.

180. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56.

181. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio: Psychol Corp. 1996;78(2):490-8.

182. Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" – a practical guideline. Trials. 2016;17(1):449.

183. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials. 2012;13(1):132.

184. Gorst SL, Gargon E, Clarke M, Blazeby JM, Altman DG, Williamson PR. Choosing important health outcomes for comparative effectiveness research: an updated review and user survey. PLOS One. 2016;11(1):e0146444.

APPENDICES

The following appendices are attached in the following order:

Paper I

Paper II

Paper III

Paper IIII

Paper V

Co-author statements

Paper I

Juul et al. Systematic Reviews (2019) 8:169
https://doi.org/10.1186/s13643-019-1099-0

Systematic Reviews

PROTOCOL Open Access

Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis

Sophie Juul[1,2*], Stig Poulsen[2], Susanne Lunn[2], Per Sørensen[1], Janus Christian Jakobsen[3,4] and Sebastian Simonsen[1]

Abstract

Background: Psychiatric disorders are highly prevalent and associated with great symptomatic, functional, and health economic burdens. Psychotherapy is among the recommended and used interventions for most psychiatric disorders and is becoming widely accessible in mental health systems. The effects of specific forms of psychotherapy (e.g., psychodynamic therapies, cognitive and behavioral therapies, humanistic therapies, and systemic therapies) have been assessed previously in systematic reviews, but the appropriate psychotherapy duration for psychiatric disorders has not been reviewed. The aim of this systematic review will be to synthesize the evidence of the effects of short-term compared with long-term psychotherapy for all adult psychiatric disorders.

Methods/design: A comprehensive search for relevant published literature will be undertaken in Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH) to identify relevant trials. We will search all databases from their inception to the present. We will include randomized clinical trials comparing a short-term and a long-term version of the same psychotherapy type for adult psychiatric disorders including attention deficit hyperactivity disorder, psychotic disorders, depressive disorders, bipolar disorders, anxiety disorders, obsessive-compulsive disorder, trauma- and stressor-related disorders, eating disorders, and personality disorders (as defined by standardized diagnostic criteria). We will rely on the trialists defining their compared interventions as short term and long term (or similar terminology). Primary outcomes will be quality of life, serious adverse events, and symptom severity. Secondary outcomes will be suicide or suicide attempts, self-harm, and level of functioning. Two review authors will independently extract data and perform risk of bias assessment using the Cochrane risk of bias tool. A meta-analysis will be performed as recommended by the Cochrane Handbook for Systematic Review of Interventions, bias will be assessed with domains, and Trial Sequential Analysis will be conducted to control random errors. Certainty of the evidence will be assessed by GRADE.

(Continued on next page)

* Correspondence: sophie.juul@regionh.dk
[1]Stolpegaard Psychotherapy Centre, Mental Health Services, Capital Region of Denmark, Stolpegaardsvej 20, 2820 Gentofte, Denmark
[2]Department of Psychology, University of Copenhagen, Østre Farimagsgade 2A København K, 1353 Copenhagen, Denmark
Full list of author information is available at the end of the article

(Continued from previous page)
Discussion: As psychotherapy is among the treatments of choice for most adult psychiatric disorders, a systematic review evaluating the benefits and harms of short-term compared with long-term psychotherapy is urgently needed. It is the hope that this review will be able to inform best practice in treatment and clinical research of these highly prevalent and burdensome disorders.

Systematic review registration: PROSPERO CRD42019128535

Keywords: Psychotherapy duration, Psychiatric disorders, Short-term psychotherapy, Long-term psychotherapy, Dose-effect

Background

It is estimated that each year, 38.2% of the European population suffer from a psychiatric disorder [1]. The economic burden from psychiatric disorders is excessive, not only because of high direct health care costs, but also because of indirect costs like sick days, disability, and early retirement [1]. Psychotherapy is among the recommended and widely used interventions for most disorders [2]. Specific types of psychotherapy have already been systematically reviewed, but the appropriate length of psychotherapy for all adult psychiatric disorders has not been reviewed previously. To present a complete overview of the evidence and to increase the statistical power, we will therefore in the present review include any adult psychiatric disorder. The major categories of adult psychiatric disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V) [3] are the following.

Attention Deficit Hyperactivity Disorder (*ADHD*) is characterized by a persistent pattern of inattention and/or hyperactivity and impulsivity that significantly interferes with functioning and development [3]. ADHD is one of the most common psychiatric disorders of childhood and adolescence, and it often persists into adulthood. The predominant characteristics of adult ADHD differ from typical ADHD characteristics in children. Symptoms of hyperactivity or impulsivity are typically less obvious in adults, whereas symptoms of inattention are more dominant [4]. Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the USA and 3.4% internationally [4, 5]. The total economic burden of ADHD in America has been estimated to be 31.6 billion US dollars in 2010 [6] including both direct costs, other health care costs, health care costs for family members, and work loss of patients and their relatives.

Psychotic disorders are characterized by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking, disorganized or abnormal motor behavior, and negative symptoms [3]. The estimated annual prevalence of all psychotic disorders is 2.6% [7]. The most common psychotic disorder is schizophrenia with an estimated median lifetime prevalence of 4.0 per 1000 and a lifetime morbid risk of 7.2 per 1000 [8]. Annual costs for the schizophrenia population have been systematically reviewed and estimated to range from 94 million to 102 billion US dollars. Indirect costs contributed to 50–85% of the total costs associated with schizophrenia [9].

Bipolar disorders are characterized by serious mood changes involving mood elevation (mania or hypomania) either alone or followed by major depressive episodes [3]. Bipolar disorder subtypes include bipolar I and bipolar II. Bipolar I disorder is associated with manic episodes nearly always followed by major depressive and hypomanic episodes. Bipolar II disorder is associated with at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. The international annual prevalence is estimated to be 0.4% for bipolar I disorder and 0.3% for bipolar II disorder [10]. In 2009, the estimated annual direct and indirect costs of bipolar I and II disorders were 30.7 and 120.3 billion US dollars, respectively [11].

Depressive disorders are characterized by the presence of a sad, empty, and irritable mood often accompanied by somatic and cognitive changes resulting in significant functional impairment [3]. The most common depressive disorder is major depressive disorder (unipolar depression) with an annual prevalence of approximately 7% both in Europe [1] and in the USA [12]. The estimated annual economic burden of adults with major depressive disorder, including direct medical costs, workplace costs, and costs associated with comorbidities exceeded 200 billion US dollars [13] in the USA in 2010.

Anxiety disorders are characterized by excessive and counterproductive feelings of fear and anxiety often accompanied by behavioral disturbances such as pervasive avoidance behaviors [3]. Different anxiety disorders exist, which differ from one another in the types of objects or situations that induce hyperarousal or avoidance behavior [3]. The prevalence of anxiety disorders is estimated to be 18% in the USA [14] and 14% in European countries [1], placing them among the most prevalent psychiatric disorders worldwide. Costs associated with

anxiety disorders have previously been reported to be 46.6 billion US dollars in the USA [15] including both direct and indirect costs.

Obsessive-compulsive disorder (*OCD*) is characterized by recurrent intrusive thoughts, images, or urges (obsessions) with or without repetitive mental or behavioral acts (compulsions) [3]. OCD among adults has an annual prevalence of 1.2% and a lifetime prevalence of 2.3% [16, 17]. The annual economic burden of OCD is estimated to be 2272 euros per patient when including both direct and indirect costs [18].

Trauma- and stressor-related disorders are characterized by psychological distress following exposure to a traumatic or stressful event. The most common trauma disorder is post-traumatic stress disorder (PTSD) [3]. PTSD is a prevalent and disabling disorder associated with delayed help seeking [19]. The estimated annual prevalence of PTSD is 2% in Europe [1] and 4.7% in the USA [20], and the estimated lifetime prevalence is 3.9% across 26 countries ranging from low to high income [21]. The total costs of PTSD per patient have been estimated to 1082 million euros including both direct and indirect costs [18].

Eating disorders are characterized by a persistent disturbance in eating behavior resulting in altered consumption or absorption of food that significantly impairs health and psychosocial functioning [3]. The most common eating disorders are anorexia nervosa, bulimia nervosa, and binge-eating disorder. Lifetime prevalence of anorexia nervosa, bulimia nervosa, and binge-eating disorder are estimated to be 0.9, 1.5, and 3.5%, respectively, among women and 0.3, 0.5, and 2.0%, respectively, among men [22]. The estimated annual prevalence of eating disorders is 0.9% in the European population [1]. Annual costs per patient are estimated to range from 1288 to 8042 US dollars [23].

Personality disorders are characterized by enduring and inflexible patterns of emotional, behavioral, and interpersonal problems that deviate markedly from cultural expectations. According to DSM-V, the following nine personality disorders exist. Personality disorders onset in adolescence or early adulthood and are associated with great psychosocial distress and impairment [3]. In a systematic review of the economic burden of personality disorders, the estimated direct and indirect costs were 11,126 euros for patients 12 months prior to seeking treatment. Direct medical costs accounted for two thirds of these costs, while the remaining costs were related to productivity losses [24].

Description of the interventions

Different schools of psychotherapy exist. They are often divided into the following categories: *psychodynamic therapies*, *cognitive and behavioral therapies*, *humanistic therapies*, and *systemic therapies* [2].

Psychodynamic (*or psychoanalytical*) *therapies* encompass the many approaches that are influenced by Freud's psychoanalysis but have developed into different independent schools [2]. Traditionally, psychodynamic therapies have been considered as long-term therapies, perhaps due to the notion that the uncovering of unconscious emotions and conflicts cannot be achieved with a fixed time limit [25]. Long-term psychoanalytical psychotherapy has previously been systematically reviewed yielding different results [26, 27]. Today, different lengths of psychodynamic therapies have been developed to treat different forms of psychopathology. In addition to traditional psychoanalysis, examples of long-term psychodynamic treatments are transference-focused psychotherapy (TFP), a psychodynamic treatment rooted in object relations theory lasting up to 3 years [28, 29], and mentalization-based therapy [30], an 18-month psychodynamic treatment rooted in attachment theory. Both are developed specifically to treat borderline personality disorder. Further, different variations of short-term psychodynamic therapy have been developed to treat a variation of common psychiatric disorders, most notably anxiety disorders, depressive disorders, certain behavior disorders, and personality disorders [31]. Short-term psychodynamic therapies vary in treatment duration but typically last between 12 and 24 sessions [31].

Cognitive and behavioral therapies (CBT) encompass many integrative approaches. Historically, behavior therapy (first wave CBT) developed from the learning theories of Pavlov [32] and Skinner [33]. An integration of a cognitive component to classical behavioral theories was first established by Beck [34, 35], who developed what is now often referred to as second-wave CBT. CBT is now often delivered as a short-term treatment, typically lasting between 12 and 20 sessions, for a variation of common psychiatric disorders like depressive disorders [34], anxiety disorders [36], obsessive-compulsive disorder [37], personality disorders [38], and eating disorders [39]. Different durations of CBT are also available for the treatment of schizophrenia [40, 41]. Today, so-called third-wave cognitive therapies have emerged, characterized by more integrative approaches to psychotherapy, incorporating techniques from Buddhist mindfulness, psychodynamic therapies, or Gestalt therapy [2]. These include dialectical behavior therapy [42] and schema-focused therapy (SFT) [29, 43], which are both long-term therapies for borderline personality disorder (up to 3 years), and acceptance and commitment therapy (ACT) [44] and compassion-focused therapy (CFT) [45], which are often delivered as short-term treatments for various psychiatric disorders [46, 47].

Humanistic therapies are characterized by psychotherapy approaches derived from humanistic and existentialist philosophy. Major approaches within this orientation are person-centered therapy [48], Gestalt therapy [49], existential psychotherapy [50], and process-experiential/emotion-focused therapy [51]. All humanistic therapies share the notion of empathic understanding, the promotion of in-therapy experiencing, and a belief in the uniquely human growth tendency by applying a consistent person-centered view involving concern for each patient's individual experience and differing needs [2]. Humanistic therapies have not been developed to treat specific types of disorders and are traditionally considered open-ended, which is also aligned with the person-centered way of thinking. However, different lengths of humanistic therapies have been studied, e.g., PE-EFT as a short-term treatment (down to 5 weeks) for depressive disorders [52] and as a 20-week treatment for trauma-related disorders [53].

Systemic therapies are characterized by a systemic approach to psychotherapy defining patients' problems as contextually rather than individually derived. Most often, the context of interest is the partner or the family, but it can also be a broader context, such as the extended family or a classroom [2]. Different systemic therapies exist for different types of psychopathology. Examples are family-based therapy for eating disorders [54], attachment-based family therapy for depressed adolescents (ABFT) [55], parent management training for childhood conduct disorders [56], psychoeducational family interventions for schizophrenia [57] and bipolar disorder [58], and systemic treatments for substance-use disorders [59, 60]. Different lengths of systemic therapies exist. However, the typical duration is between 10 and 25 sessions.

Other forms of psychotherapy exist, e.g., interpersonal therapy (IPT) [61] or cognitive-analytic therapy (CAT) [62]. However, it is beyond the scope of this review to mention all new approaches to psychotherapy since the field is constantly expanding. Further, despite the existence of well-established manualized and evidence-based approaches to psychotherapy, a large proportion of practicing psychotherapists define themselves as eclective or integrative [63].

How the interventions might work

It is a common opinion among clinicians and researchers that patients suffering from complex psychiatric distress require longer and more intensive psychotherapy [27]. Complex psychiatric distress can be defined as disorders, which by definition are enduring and inflexible [27], such as personality disorders or schizophrenia, chronic psychiatric disorders (defined as lasting at least a year), or multiple psychiatric disorders. A related assumption is that complex and severe problems typically take longer to improve than less complex or acute psychiatric distress [25, 64]. This is due to the inherent inflexibility of the psychopathology and the complexity of the required therapeutic techniques. Such potential therapeutic techniques could be provocation of affect or working with the therapeutic alliance [25]. These are techniques that are potentially hard to carry out when faced with time constraints. However, it is often argued that such techniques are essential to effective psychotherapy [65].

In contrast, one could argue that long-term therapies can become counterproductive, given that the same therapeutic techniques will be repeated for a long period of time without continuous assessment of their effects. It is possible that given the limited therapeutic time, planned short-term psychotherapy forces both patients and therapists to establish and maintain a focus throughout the treatment process [66]. Further, issues regarding termination of treatment are particularly important when conducting short-term psychotherapy, where concerns about termination are, almost by definition, always present [67, 68]. Thus, a possible advantage of short-term therapies is that both therapist and patient are forced to address difficult themes associated with separation and loss from the very beginning instead of postponing them for later.

Why is it important to do this review?

It is essential to investigate the optimal duration of psychotherapy for psychiatric disorders, because of the potential patient and health economic burden from long-term psychotherapy and because of the potential harmful effects of terminating treatment prematurely [69]. If short-term psychotherapy is the optimal treatment approach, then this could result in a reduction of waitlists and thus a greater access to evidence-based care. On the contrary, if long-term psychotherapy is the most optimal treatment, then it becomes sensible for mental health systems to invest in these treatments, as they would translate into greater health and occupational benefits [70].

The relationship between the number of sessions (dose) and patient improvement (effect) in psychotherapy has previously been studied with mixed results [70, 71]. There are studies indicating that increased number of sessions is associated with diminishing results [72]. There are also studies indicating that the speed of improvement is dependent on patients pretreatment functioning [73] and that some patients require different dosages to receive the same effect. However, most research on the association between dose and effect is based on uncontrolled studies [70–72, 74, 75] which can only show that patients improve during treatment. Whether this improvement can be attributed to the treatment, can only be established with randomized controlled trials, in which shorter and longer

therapies are directly compared. A systematic review of such randomized clinical trials might allow us to assess the safety profile of the different treatment options directly. We are already aware of two randomized clinical trials comparing a short-term and a long-term version of the same psychotherapy type for one or more adult psychiatric disorders [76, 77]. We have performed a preliminary literature search in the Cochrane Database of Systematic Reviews (search terms, short-term or brief and long-term or standard psychotherapy) for previous systematic reviews comparing a short-term and a long-term version of the same psychotherapy type for one or more adult psychiatric disorders. We identified 1114 hits. From this preliminary literature search, we have only identified one empty systematic review [78].

The present systematic review aims at forming the basis for evidence-based guideline recommendations for the optimal duration of psychotherapy for adult psychiatric disorders taking bias risk (systematic errors), play of chance (random errors), and certainty of the findings into consideration. The objective of this review will be to assess the beneficial and harmful effects of short-term psychotherapy compared with long-term psychotherapy for adult psychiatric disorders.

Methods

The present protocol has been registered in the PROSPERO database (registration number, CRD42019128535) and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [79, 80] (see checklist in Additional file 1).

Criteria for considering studies for this review

Types of studies

We will include randomized clinical trials irrespective of trial design, setting, publication status, publication year, and language. We will not include quasi-randomized trials and observational studies.

Types of participants

Adults (as defined by trialists) with a primary diagnosis of any of the following psychiatric disorders: attention deficit hyperactivity disorder, psychotic disorders, depressive disorders, bipolar disorders, anxiety disorders, obsessive-compulsive disorder, trauma- and stressor-related disorders, eating disorders, and personality disorders, as defined by standardized diagnostic criteria from either ICD-10 [81], DSM-5 [3], or earlier versions (ICD-10 codes: F20–29, F30–39, F40–49, F50–59, F60–69, and F90–90.9). Participants will be included irrespective of sex and comorbidities.

Types of interventions

Experimental group: we will accept any type of short-term psychotherapy (or similar terms used by the trialists).

Control group: we will accept any type of long-term psychotherapy (or similar terms used by the trialists).

We will rely on the trialists defining their compared interventions as short-term and long-term (or similar terminology). We will include trials comparing a short-term and a long-term version of the same psychotherapy type (e.g., short-term psychodynamic therapy compared to long-term psychodynamic therapy). We will not include trials comparing short-term psychotherapy (e.g., short-term cognitive behavioral therapy) with a different type of psychotherapy (e.g., long-term psychodynamic therapy) delivered as long-term therapy. Further, we will include trials with the same dose (sessions) but with different frequencies, e.g., 12 sessions delivered over 6 weeks compared to 12 sessions delivered over 12 weeks.

Outcome measures

Primary outcomes

1. Quality of life (continuous data)
2. Serious adverse events (dichotomous data). We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonging of existing hospitalization and resulted in persistent or significant disability or jeopardized the patient [82]. If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term "serious adverse event." If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data, if the event clearly fulfills the ICH-GCP definition for a serious adverse event.
3. Symptom severity assessed by any valid disease-specific symptom scale (continuous data). Symptoms will be analyzed separately for each disorder.

Secondary outcomes

1. Suicide or suicide attempts as defined by trialists (dichotomous data)
2. Self-harm as defined by trialists (dichotomous data)
3. Level of functioning as defined by trialists (continuous data)

Assessment time points

The primary assessment time point will be the time point closest to the end of treatment in the trials' long-term intervention group for all outcomes. For example, if a trial compares a 6-month and a 12-month version of the same psychotherapy type and outcomes are assessed every second month throughout the trial, we will select the assessment time point closest to the end of the 12-month intervention as the primary assessment time point for all outcomes. We will secondarily assess all outcomes at maximum follow-up if longer term follow-up is assessed.

Search methods for identification of studies

Electronic searches

We will search Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH) to identify relevant trials. We will search all databases from their inception to the present. For a detailed search strategy for all electronic databases, see Additional file 2. The search strategy for PsycINFO will be given at the review stage.

Searching other resources

The reference lists of relevant publications will be checked for any unidentified randomized trials. We will contact the authors of included studies by email asking for unpublished randomized trials. Further, we will search for ongoing trials on the following:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http://www.ema.europa.eu/ema/)
- US Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.sfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatoryagency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)
- Cochrane Database of Systematic Reviews
- http://www.evidencebasedpsychotherapies.org/index.php?id=25

Additionally, we will hand search conference abstracts from psychiatry conferences for relevant trials. We will also consider relevant-for-the-review unpublished and gray literature trials if we identify these.

Data collection and analysis

We will perform the review following recommendations of the Cochrane Collaboration [83]. The analyses will be performed using Trial Sequential Analysis [84] and Stata version 16 (StataCorp LLC, College Station, TX, USA) [85].

Selection of studies

Two authors (SJ and SS) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publications, and two review authors (SJ and SS) will independently screen the full text and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (JCJ). Trial selection will be displayed in an adapted flow diagram as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [86].

Data extraction and management

Two authors (SJ and SS) will independently extract data from included trials. Disagreements will be resolved by discussion with a third author (JCJ). We will assess duplicate publications and companion papers of a trial together to evaluate all available data simultaneously (maximize data extraction, correct bias assessment). We will contact the trial authors by email to specify any additional data, which may not have been reported sufficiently or at all in the publication.

Trial characteristics

We will extract the following data: bias risk components (as defined below), trial design (parallel, factorial, or crossover), number of intervention arms, length of follow-up, estimation of sample size, and inclusion and exclusion criteria.

Participant characteristics and diagnosis

We will extract the following data: number of randomized participants, number of analyzed participants, number of participants lost to follow-up/withdrawals/crossover, compliance with interventions, age range (mean or median), sex ratio, and type of psychiatric disorder.

We will additionally report the proportion of participants in the compared groups who receive psychotropic medication.

Short-term psychotherapy characteristics

We will extract the following data: short-term psychotherapy type, treatment duration, number of sessions (dose), session lengths (minutes), number of sessions per week, and treatment format.

Long-term psychotherapy characteristics

We will extract the following data: long-term psychotherapy type, treatment duration, number of sessions (dose), session lengths (minutes), number of sessions per week, and treatment format.

Co-intervention characteristics

We will extract the following data: type of co-intervention, treatment duration of co-intervention, number of sessions (or dose), and treatment format.

Outcomes

All outcomes listed above will be extracted from each randomized clinical trial, and we will identify if outcomes are incomplete or selectively reported according to the criteria described later in "incomplete outcome data" bias domain and "selective outcome reporting" bias domain.

Notes

Funding of the trial and notable conflicts of interest of trial authors will be extracted, if available. We will note in the "Characteristics of included studies" table if outcome data were not reported in a usable way. Two review authors (SJ and SS) will independently transfer data into the Stata file [85]. Disagreements will be resolved through discussion, or if required, we will consult with a third author (JCJ).

Assessment of risk of bias in included studies

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* [83] in our evaluation of the methodology and hence the risk of bias of the included trials. We will evaluate the methodology in respect of the following:

- Random sequence generation
- Allocation concealment
- Blinding of participants and treatment providers
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other risk of bias
- Overall risk of bias

Random sequence generation

- *Low risk*: If sequence generation was achieved using computer random number generator or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice will also be considered adequate if performed by an independent adjudicator.
- *Unclear risk*: If the method of randomization was not specified, but the trial was still presented as being randomized
- *High risk*: If the allocation sequence was not randomized or only quasi-randomized. These trials will be excluded.

Allocation concealment

- *Low risk*: If the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, or containers prepared by an independent investigator
- *Uncertain risk*: If the trial was classified as randomized but the allocation concealment process was not described
- *High risk*: If the allocation sequence was familiar to the investigators who assigned participants

Blinding of participants and treatment providers

- *Low risk*: If the participants and the treatment providers were blinded to intervention allocation and this was described
- *Uncertain risk*: If the procedure of blinding was insufficiently described
- *High risk*: If blinding of participants and the treatment providers was not performed

Blinding of outcome assessment

- *Low risk of bias*: If it was mentioned that outcome assessors were blinded and this was sufficiently described
- *Uncertain risk of bias*: If it was not mentioned if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described
- *High risk of bias*: If no blinding or incomplete blinding of outcome assessors was performed

Incomplete outcome data

- *Low risk of bias*: If missing data were unlikely to make treatment effects depart from plausible values. This could be either (1) there were no drop-outs or

withdrawals for all outcomes or (2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups. Generally, the trial is judged as at a low risk of bias due to incomplete outcome data if drop-outs are less than 5%. However, the 5% cut-off is not definitive.
- *Uncertain risk of bias*: If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- *High risk of bias*: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g., last observation carried forward).

Selective outcome reporting

- *Low risk of bias*: If a protocol was published before or at the time the trial begun and the outcomes specified in the protocol were reported on
- *Uncertain risk of bias*: If no protocol was published
- *High risk of bias*: If the outcomes in the protocol were not reported on

Other risk of bias

- *Low risk of bias*: If the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias
- *Unclear risk of bias*: If the trial may or may not be free of other components that could put it at risk of bias
- *High risk of bias*: If there are other factors in the trial that could put it at risk of bias (for example, authors conducted trials on the same topic, for-profit bias)

Overall risk of bias

- *Low risk of bias*: The trial will be classified as overall "low risk of bias" only if all of the bias domains described in the above paragraphs are classified as low risk of bias.
- *High risk of bias*: The trial will be classified as "high risk of bias" if any of the bias risk domains described above are classified as "unclear" or high risk of bias.

We will assess the domains "blinding of outcome assessment," "incomplete outcome data," and "selective outcome reporting" for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcome results with overall low risk of bias. Both our primary and secondary conclusions will be presented in the summary of findings tables.

Differences between protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the "Differences between the protocol and the review" section of the systematic review.

Measures of treatment effect

Dichotomous outcomes We will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes, as well as the Trial Sequential Analysis-adjusted CIs (see below).

Continuous outcomes We will calculate the mean differences (MDs) and consider calculating the standardized mean difference (SMD) with 95% CI for continuous outcomes. We will also calculate trial sequential analysis-adjusted CIs (see below).

Dealing with missing data

We will, as the first option, contact all trial authors to obtain any relevant missing data (i.e., for data extraction and for assessment of risk of bias, as specified above).

Dichotomous outcomes We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see paragraph below), we will impute data.

Continuous outcomes We will primarily analyze scores assessed at single time points. If only changes from baseline scores are reported, we will analyze the results together with follow-up scores [83]. If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible. We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see paragraph below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic [87, 88]. We will investigate possible heterogeneity through subgroup analyses. We

may ultimately decide that a meta-analysis should be avoided [83].

Assessment or reporting biases

We will use a funnel plot to assess reporting bias if ten or more trials are included. We will visually inspect funnel plots to assess the risk of bias. We are aware of the limitations of a funnel plot (i.e., a funnel plot assesses bias due to small sample size). From this information, we assess possible reporting bias. For dichotomous outcomes, we will test asymmetry with the Harbord test [89] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test [90] and the adjusted rank correlation [91].

Unit of analysis issues We will only include randomized clinical trials. For trials using crossover design, only data from the first period will be included [83, 92]. There will therefore not be any unit of analysis issues. We will not include cluster randomized trials.

Data synthesis

Meta-analysis We will undertake the meta-analysis according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* [83], Keus et al. [93], and the eight-step assessment suggested by Jakobsen et al. [94]. We will use the statistical software Stata version 16 [85] to analyze data. We will assess our intervention effects with both random-effects meta-analyses [95] and fixed-effects meta-analyses [96]. We will use the more conservative point estimate of the two [94]. The more conservative point estimate is the estimate closest to zero effect. If the two estimates are similar, we will use the estimate with the widest CI. We assess a total of six primary and secondary outcomes, and we will therefore consider a P value of 0.014 or less as the threshold for statistical significance [94]. We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that a meta-analysis should be avoided [83]. We will use the eight-step procedure to assess if the thresholds for significance are crossed [94]. Our primary conclusion will be based on results with low risk of bias [94]. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting [83]. Trials with a factorial design will be included. In case of, e.g., a 2×2 factorial designed trial, the two groups receiving short-term interventions will be considered short-term control groups, while the two groups receiving long-term control interventions will be considered long-term control groups. If quantitative synthesis is not appropriate due to considerable heterogeneity or a small number of included trials, we will report the results in a narrative way.

Trial sequential analysis Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control the risks of type I errors and type II errors. We will therefore perform Trial Sequential Analysis on the outcomes, in order to calculate the required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries [84, 97–104]. A more detailed description of trial sequential analysis can be found in the trial sequential analysis manual [103] and at http://www.ctu.dk/tsa/.

For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an alpha of 1.4% for all our outcomes, a beta of 20%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will in the trial sequential analysis use the observed SD, a mean difference of the observed SD/2, an alpha of 1.4% for all outcomes, a beta of 20%, and the observed diversity as suggested by the trials in the meta-analysis.

Subgroup analysis and integration of heterogeneity

Subgroup analysis We will perform the following subgroup analyses when analyzing the primary outcomes (quality of life, serious adverse events, and symptom severity).

1. High risk of bias trials compared to low risk of bias trials
2. Types of psychiatric disorders
3. Types of psychotherapy comparisons
4. Trials above and below the mean difference in intervention lengths

We will use the formal test for subgroup interactions in Stata [85].

Sensitivity analysis To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following sensitivity analyses on both the primary and secondary outcomes.

- "*Best-worst-case*" *scenario*: We will assume that all participants lost to follow-up in the short-term experimental group had no serious adverse event, had no suicides, had no suicide attempts, and had no self-harm and that all those participants lost to follow-up in the long-term control group did not survive, had a serious adverse event, had a suicide attempt, and had at least one episode of self-harm.

- "*Worst-best-case*" *scenario*: We will assume that all participants lost to follow-up in the short-term control group did not survive, had serious adverse event, had a suicide attempt, and had at least one episode of self-harm and that all those participants lost to follow-up in the long-term control group have survived, had no serious adverse event, had no suicide attempts, and had no self-harm.

We will present results of both scenarios in our review. When analyzing quality of life, symptom severity, and level of functioning, a "beneficial outcome" will be the group mean plus two standard deviations (SDs) (we will secondly use one SD in another sensitivity analysis) of the group mean and a "harmful outcome" will be the group mean minus two SDs (we will secondly use one SD in another sensitivity analysis) of the group mean [94]. To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

- Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review. Other post hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results [94].

"Summary of findings" table We will create a summary of findings table using each of the prespecified outcomes (quality of life, serious adverse events, symptom severity, suicide and suicide attempts, self-harm, and level of functioning) We will use the five GRADE considerations (bias risk of the trials, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes [94, 105–107]. We will assess imprecision using Trial Sequential Analysis. Otherwise, we will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* [83] using GRADEpro software. We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the Summary of Findings table based on the results from the trials with low risk of bias, and secondly, we will present the results based on all trials.

Discussion

This protocol aims at comparing the effects of short-term psychotherapy with the effects of long-term psychotherapy for common adult psychiatric disorders to determine the best length of treatment. The outcomes will be quality of life, serious adverse events, symptom severity, suicide or suicide attempts, self-harm, and level of functioning.

This protocol has a number of strengths. The predefined methodology is based on the *Cochrane Handbook for Systematic Reviews of Interventions* [83], the eight-step assessment suggested by Jakobsen et al. [94], Trial Sequential Analysis [84], and GRADE assessment [105–107]. Hence, this protocol considers both risks of random errors and risks of systematic errors. Another strength of this protocol is that we pragmatically compare two overall treatment strategies with each other, i.e., the results of this review will potentially reflect the effects of the two strategies in clinical everyday practice.

Our protocol also has some limitations. The primary limitation is the potential for large heterogeneity as a result of including all psychiatric disorders and all types of psychotherapy. Therefore, we may ultimately decide that a meta-analysis is not warranted. Further, psychotherapy always consists of multiple treatment elements and it is likely that different interventions have different effects. Hence, if we show a difference between the compared strategies, it will be difficult to conclude what exactly caused the difference in effect. To minimize this limitation, a number of subgroups are planned, but results of subgroup analyses should always be interpreted with great caution. Another limitation is the large number of comparisons which increase the risk of type 1 error. We have adjusted our thresholds for significance according to the number of primary outcomes, but as mentioned, we have also included multiple subgroup analyses. This large risk of type 1 error will be considered when interpreting the review results. Further, we expect that no trials will have blinded treatment providers and patients. Even though blinding of patients should be relatively easy, blinding of treatment providers is theoretically possible but much more difficult to carry out. Finally, we rely on the trialists defining their

compared interventions as short-term and long-term (or similar terminology). Hence, we will not include trials comparing a short-term and a long-term version of the same psychotherapy type, if the trialists did not explicitly define their interventions with such terminology. Using trialists' definitions of short-term and long-term psychotherapy potentially introduces problems with heterogeneity. However, we believe that our choice of methodology from a pragmatic point of view is the best solution there is. First, trialists often report poorly and often do not themselves use thresholds and important data might be excluded from our review if we demand exact definitions of lengths. Further, we do not expect to include many trials in this systematic review. Hence, relying on trialists definitions of short-term versus long-term psychotherapy may increase the number of trials being eligible for inclusion. Finally, we believe this pragmatic methodology will lead to the inclusion of the most relevant trials.

Additional files

Additional file 1: PRISMA-P 2015 Checklist. (DOCX 30 kb)
Additional file 2: Search strategies. (DOC 46 kb)

Abbreviations

ABFT: Attachment-based family therapy; ACT: Acceptance and commitment therapy; ADHD: Attention deficit hyperactivity disorder; CAT: Cognitive-analytic therapy; CBT: Cognitive behavioral therapy; CENTRAL: Cochrane Central Register of Controlled Trials; CFT: Compassion-focused therapy; CI: Confidence interval; CPCI-S: Conference Proceedings Citation Index—Science; CPCI-SSH: Conference Proceedings Citation Index—Social Science & Humanities; DSM-V: Diagnostic and statistical manual of mental disorders, 5th edition; EMA: European Medicines Agency; EMBASE: Excerpta Medica database; GRADE: The Grading of Recommendations Assessment, Development and Evaluation; ICD-10: International Classification of Diseases and Related Health Problems – 10th edition; ICH-GCP: International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice; ICTRP: International Clinical Trials Registry Platform; MD: Mean differences; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA: Preferred reporting items for systematic review and meta-analysis; PRISMA-P: Preferred reporting items for systematic review and meta-analysis – protocols; PROSPERO: International Prospective Register of Systematic Reviews; PTSD: Post-traumatic stress disorder; RR: Risk ratio; SCI-EXPANDED: Science index citation expanded; SD: Standard deviation; SFT: Schema-Focused Therapy; SMD: Standardized mean difference; SSCI: Social Science Citation Index; TFP: Transference-focused psychotherapy; TRIP: Turning research into practice; WHO: World Health Organization

Acknowledgements

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy is hugely appreciated.

Authors' contributions

SJ wrote up the protocol with regular supervision from SP, SL, JCJ, and SS. JCJ and SJ wrote the methods section. PS read and commented on the final manuscript before it was submitted for publication. All authors read and approved the final manuscript.

Funding

This study is funded by the Mental Health Services, Capital Region of Denmark Research Fund and TrygFoundation, grant no. 123488. The funding bodies will not be involved in design, collection, analysis, interpretation of data, and in writing up the manuscripts.

Availability of data and materials

Data sharing is not applicable to this protocol article. We will publish all data including code in the supplementary material of the systematic review.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Stolpegaard Psychotherapy Centre, Mental Health Services, Capital Region of Denmark, Stolpegaardsvej 20, 2820 Gentofte, Denmark. [2]Department of Psychology, University of Copenhagen, Østre Farimagsgade 2A København K, 1353 Copenhagen, Denmark. [3]Copenhagen Trial Unit, Tagensvej 22, København N, 2200 Copenhagen, Denmark. [4]Department of Cardiology, Holbæk Hospital, Smedelundsgade 60, 4300 Holbæk, Denmark.

Received: 15 March 2019 Accepted: 5 July 2019
Published online: 13 July 2019

References

1. Wittchen HU, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011; 21(9):655–79.
2. Barlow DH. The Oxford handbook of clinical psychology: updated edition. New York: Oxford University Press; 2014.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Pub; 2013.
4. Kessler RC, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716–23.
5. Fayyad J, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry. 2007;190:402–9.
6. Birnbaum HG, et al. Costs of attention deficit–hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. Curr Med Res Opin. 2005;21(2):195–205.
7. Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe-a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol. 2005; 15(4):357–76.
8. McGrath J, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30(1):67–76.
9. Chong HY, et al. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016;12:357.
10. Merikangas KR, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011;68(3): 241–51.
11. Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. J Affect Disord. 2011;129(1–3):79–83.
12. Compton WM, et al. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991-1992 and 2001-2002. Am J Psychiatry. 2006;163(12):2141–7.
13. Greenberg PE, et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry. 2015;76(2):155–62.
14. Kessler RC, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602.
15. DuPont RL, et al. Economic costs of anxiety disorders. Anxiety. 1996;2(4): 167–72.
16. Kessler RC, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27.
17. Ruscio AM, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15(1):53–63.

18. Olesen J, et al. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155–62.
19. Kessler RC, et al. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995;52(12):1048–60.
20. Goldstein RB, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016;51(8):1137–48.
21. Koenen K, et al. Posttraumatic stress disorder in the world mental health surveys. Psychol Med. 2017;47(13):2260–74.
22. Hudson JI, et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61(3):348–58.
23. Stuhldreher N, et al. Cost-of-illness studies and cost-effectiveness analyses in eating disorders: a systematic review. Int J Eat Disord. 2012;45(4):476–91.
24. Soeteman DI, et al. The economic burden of personality disorders in mental health care. J Clin Psychiatry. 2008;69:259–65.
25. Crits-Christoph P, Barber JP. Long-term psychotherapy. In: Snyder CR, Ingram RE, editors. Handbook of psychological change: Psychotherapy processes & practices for the 21st century. New York: Wiley, Inc.; 2000. p. 455–73.
26. Smit Y, et al. The effectiveness of long-term psychoanalytic psychotherapy - a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2012;32(2):81–92.
27. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. JAMA. 2008;300(13):1551–65.
28. Kernberg OF, et al. Transference focused psychotherapy: overview and update. Int J Psychoanal. 2008;89(3):601–20.
29. Giesen-Bloo J, et al. Outpatient psychotherapy for borderline personality disorder: randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch Gen Psychiatry. 2006;63(6):649–58.
30. Bateman A, Fonagy P. Mentalization-based treatment for personality disorders: a practical guide. New York: Oxford University Press; 2016.
31. Abbass AA, et al. Short-term psychodynamic psychotherapies for common mental disorders. Cochrane Database Syst Rev. 2014;(7):CD004687.
32. Pavlov I. Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex. New York: Oxford University Press; 1927.
33. Skinner BF. Science and human behavior. New York: Macmillan; 1953.
34. Beck AT. Cognitive therapy of depression. New York: Guilford press; 1979.
35. Beck AT. Depression: clinical, experimental, and theoretical aspects. Philadelphia: University of Pennsylvania Press; 1967.
36. Beck A, Rush A. A cognitive model of anxiety formation and anxiety resolution. Stress Anxiety. 1975;2:69–80.
37. Salkovskis PM. Obsessional-compulsive problems: a cognitive-behavioural analysis. Behav Res Ther. 1985;23(5):571–83.
38. Beck AT, Davis DD, Freeman A. Cognitive therapy of personality disorders. New York: Guilford Publications; 2015.
39. Fairburn CG. Cognitive behavior therapy and eating disorders. New York: Guilford Press; 2008.
40. Grant PM, et al. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. Arch Gen Psychiatry. 2012;69(2):121–7.
41. Sensky T, et al. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. Arch Gen Psychiatry. 2000;57(2):165–72.
42. Linehan MM, et al. Dialectical behavior therapy for high suicide risk in individuals with borderline personality disorder: a randomized clinical trial and component analysis. JAMA Psychiatry. 2015;72(5):475–82.
43. Farrell JM, Shaw IA, Webber MA. A schema-focused approach to group psychotherapy for outpatients with borderline personality disorder: a randomized controlled trial. J Behav Ther Exp Psychiatry. 2009;40(2):317–28.
44. Hayes SC. Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. Behav Ther. 2004; 35(4):639–65.
45. Gilbert P. An introduction to compassion focused therapy in cognitive behavior therapy. Int J Cogn Ther. 2010;3(2):97–112.
46. Ruiz FJ. A review of acceptance and commitment therapy (ACT) empirical evidence: correlational, experimental psychopathology, component and outcome studies. Int J Psychol Psychol Ther. 2010;10(1): 125.
47. Leaviss J, Uttley L. Psychotherapeutic benefits of compassion-focused therapy: an early systematic review. Psychol Med. 2015;45(5):927–45.
48. Rogers CR. A theory of therapy, personality and interpersonal relationships in the client-centred framework. In: Koch S, editor. Psychology: a study of science. Vol III, Formulations of the person in social context. New York: McGraw Hill; 1959. p. 184–256.
49. Perls F, Hefferline G, Goodman P. Gestalt therapy. Excitement and growth in the human personality. New York: Julian; 1951.
50. Yalom ID. Existential psychotherapy. Vol. 1. New York: Basic Books; 1980.
51. Greenberg LS, Van Balen R. The theory of experience-centered therapies. In: Greenberg LS, Watson JC, Lietaer G, editors. Handbook of experiential psychotherapy. New York: Guilford Press; 1998. p. 28–57.
52. Shinohara K, et al. Behavioural therapies versus other psychological therapies for depression. Cochrane Database Syst Rev. 2013;(10).
53. Paivio SC, Nieuwenhuis JA. Efficacy of emotion focused therapy for adult survivors of child abuse: a preliminary study. J Trauma Stress. 2001;14(1):115–33.
54. Lock J, le Grange D. Family-based treatment of eating disorders. Int J Eat Disord. 2005;37(S1):S64–7.
55. Diamond G, Siqueland L, Diamond GM. Attachment-based family therapy for depressed adolescents: programmatic treatment development. Clin Child Fam Psychol Rev. 2003;6(2):107–27.
56. Brestan EV, Eyberg SM. Effective psychosocial treatments of conduct-disordered children and adolescents: 29 years, 82 studies, and 5,272 kids. J Clin Child Psychol. 1998;27(2):180–9.
57. Lam DH. Psychosocial family intervention in schizophrenia: a review of empirical studies. Psychol Med. 1991;21(2):423–41.
58. Miklowitz DJ, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry. 2003;60(9):904–12.
59. O'Farrell TJ, Clements K. Review of outcome research on marital and family therapy in treatment for alcoholism. J Marital Fam Ther. 2012;38(1):122–44.
60. Stanton MD, Shadish WR. Outcome, attrition, and family–couples treatment for drug abuse: a meta-analysis and review of the controlled, comparative studies. Psychol Bull. 1997;122(2):170.
61. Cuijpers P, et al. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatr. 2011;168(6):581–92.
62. Ryle A, Poynton AM, Brockman BJ. Cognitive-analytic therapy: active participation in change: A new integration in brief psychotherapy. Oxford: Wiley; 1990.
63. Norcross JC. A primer on psychotherapy integration. In: Norcross JC, Goldfried MR, editors. Handbook of psychotherapy integration. New York: Basic Books; 2005. p. 3–23.
64. Critchfield KL, Benjamin LS. Principles for psychosocial treatment of personality disorder: summary of the APA Division 12 Task Force/NASPR review. J Clin Psychol. 2006;62(6):661–74.
65. Norcross J. Empirically supported therapy relationships. In: Norcross JC, editor. Psychotherapy relationships that work: Therapist contributions and responsiveness to patients. New York: Oxford University Press; 2002. p. 3–16.
66. Piper WE, et al. A comparative study of four forms of psychotherapy. J Consult Clin Psychol. 1984;52(2):268.
67. Hoyt MF. Therapist resistances to short-term dynamic psychotherapy. J Am Acad Psychoanal. 1985;13(1):93–112.
68. Bloom B. Planned short-term psychotherapies. In: Snyder CR, Ingram RE, editors. Handbook of psychological change: Psychotherapy processes & practices for the 21st century. New York: Wiley; 2000. p. 429–54.
69. Lilienfeld S. Psychological treatments that cause harm. Perspect Psychol Sci. 2007;2(1):53–70.
70. Cuijpers P, et al. How much psychotherapy is needed to treat depression? A metaregression analysis. J Affect Disord. 2013;149(1–3):1–13.
71. Castonguay LG, et al. Practice-oriented research: approaches and applications. Bergin Garfield's Handb Psychother Behav Chang. 2013;6:85–133.
72. Howard KI, et al. The dose-effect relationship in psychotherapy. Am Psychol. 1986;41(2):159–64.
73. Lambert MJ, Hansen NB, Finch AE. Patient-focused research: using patient outcome data to enhance treatment effects. J Consult Clin Psychol. 2001;69(2):159.
74. Stulz N, et al. Dose–effect relationship in routine outpatient psychotherapy: does treatment duration matter? J Couns Psychol. 2013;60(4):593–600.
75. Kopta SM, et al. Patterns of symptomatic recovery in psychotherapy. J Consult Clin Psychol. 1994;62(5):1009–16.
76. Knekt P, et al. Randomized trial on the effectiveness of long-and short-term psychodynamic psychotherapy and solution-focused therapy on psychiatric symptoms during a 3-year follow-up. Psychol Med. 2008;38(5):689–703.

77. Lorentzen S, et al. Comparison of short- and long-term dynamic group psychotherapy: randomised clinical trial. Br J Psychiatry. 2013;203(3):280–7.
78. Naeem F, Farooq S, Kingdon D. Cognitive behavioural therapy (brief versus standard duration) for schizophrenia. Cochrane Database Syst Rev. 2015;(10).
79. Moher D, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
80. Shamseer L, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:7647.
81. WorldHealthOrganization, International classification of diseases, 10th revision (ICD-10). 2009.
82. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH harmonised guideline: integrated addemdum to ICH E6(R1): guideline for good clinical practice (ICH-GCP). 2015.
83. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions 5.1. 0: The Cochrane Collaboration; 2011.
84. Copenhagen Trial Unit. TSA - trial sequential analysis. http://www.ctu.dk/tsa/. [Web page]. Accessed 10 July 2019.
85. StataCorp. Stata statistical software: release 16. College Station, TX: StataCorp LLC; 2019. http://www.stata.com
86. Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
87. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
88. Higgins JP, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557.
89. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25(20):3443–57.
90. Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315(7109):629–34.
91. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–101.
92. Elbourne DR, et al. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002;31(1):140–9.
93. Keus F, et al. Evidence at a glance: error matrix approach for overviewing available evidence. BMC Med Res Methodol. 2010;10(1):90.
94. Jakobsen JC, et al. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14(1):120.
95. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
96. DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. Stat Med. 1987;6(3):341–8.
97. Wetterslev J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol. 2008;61(1):64–75.
98. Brok J, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol. 2008;61(8):763–9.
99. Brok J, et al. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol. 2008;38(1):287–98.
100. Thorlund K, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol. 2008;38(1):276–86.
101. Wetterslev J, et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol. 2009;9(1):86.
102. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clin Epidemiol. 2010;2:57.
103. Thorlund K, et al., User manual for trial sequential analysis (TSA). http://www.ctu.dk/tsa/files/tsa_manual.pdf, 2011.
104. Imberger G, et al. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ Open. 2016;6(8):e011890.
105. Guyatt GH, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924–6.
106. Schünemann HJ, et al. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. Can Med Assoc J. 2003;169(7):677–80.
107. Guyatt GH, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380–2.

Publisher's Note

Additional file 1: PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	-
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	73
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-29
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	687-690
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	-
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	682-685
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	682-685
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	684-685
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	79-252

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	254-258
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	265-315
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	317-347
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	324-325
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	348-352
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	354-367
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	354-367
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	370-403
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	290-307
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	406-486
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	532-601
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	532-601

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	567-601
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	548-550
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	520-526
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	603-613

Additional file 2

Search strategies for
Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis (Juul et al.)

Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 6) in the Cochrane Library (1 hits)

#1 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees
#2 (attention deficit hyperactivity disorder or adhd).ti,ab
#3 #1 or #2
#4 MeSH descriptor: [Psychotic Disorders] explode all trees
#5 MeSH descriptor: [Schizophrenia] explode all trees
#6 (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) near (think* or motor*)) or schizophreni*).ti,ab
#7 #4 or #5 or #6
#8 MeSH descriptor: [Bipolar Disorder] explode all trees
#9 (bipolar or mood elevation or mania or hypomania or depress*).ti,ab
#10 #8 or #9
#11 MeSH descriptor: [Depressive Disorder] explode all trees
#12 (depressi* or mood or unipolar).ti,ab
#13 #11 or #12
#14 MeSH descriptor: [Anxiety Disorders] explode all trees
#15 (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab
#16 #14 or #15
#17 MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees
#18 (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*))).ti,ab
#19 #17 or #18
#20 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees
#21 (post-trauma* or trauma*).ti,ab
#22 #20 or #21
#23 MeSH descriptor: [Feeding and Eating Disorders] explode all trees
#24 (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab
#25 #23 or #24
#26 MeSH descriptor: [Personality Disorders] explode all trees
#27 (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab
#28 #26 or #27
#29 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
#30 MeSH descriptor: [Psychotherapy] explode all trees
#31 (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab
#32 #30 or #31
#33 (brief or extended or standard or intensiv* or ((short* or long*) and term)).ti,ab
#34 #32 and #33
#35 #29 and #34

MEDLINE Ovid (1946 to June 2019) (5249 hits)

1. exp Attention Deficit Disorder with Hyperactivity/
2. (attention deficit hyperactivity disorder or adhd).ti,ab.
3. 1 or 2
4. exp Psychotic Disorders/
5. exp Schizophrenia/
6. (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) adj (think* or motor*)) or schizophreni*).ti,ab.
7. 4 or 5 or 6
8. exp Bipolar Disorder/
9. (bipolar or mood elevation or mania or hypomania or depress*).ti,ab.

10. 8 or 9
11. exp Depressive Disorder/
12. (depressi* or mood or unipolar).ti,ab.
13. 11 or 12
14. exp Anxiety Disorders/
15. (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab.
16. 14 or 15
17. exp Obsessive-Compulsive Disorder/
18. (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive adj (mental or behavior*))).ti,ab.
19. 17 or 18
20. exp Stress Disorders, Post-Traumatic/
21. (post-trauma* or trauma*).ti,ab.
22. 20 or 21
23. exp "Feeding and Eating Disorders"/
24. (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab.
25. 23 or 24
26. exp Personality Disorders/
27. (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab.
28. 26 or 27
29. 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
30. exp psychotherapy/
31. (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab.
32. 30 or 31
33. (brief or extended or standard or intensiv* or ((short* or long*) and term)).ti,ab.
34. 32 and 33
35. 29 and 34
36. limit 35 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
37. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
38. 36 and 37

Embase Ovid (1974 to June 2019) (5891 hits)
1. exp attention deficit disorder/
2. (attention deficit hyperactivity disorder or adhd).ti,ab.
3. 1 or 2
4. exp psychosis/
5. exp schizophrenia/
6. (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) adj (think* or motor*)) or schizophreni*).ti,ab.
7. 4 or 5 or 6
8. exp bipolar disorder/
9. (bipolar or mood elevation or mania or hypomania or depress*).ti,ab.
10. 8 or 9
11. exp depression/
12. (depressi* or mood or unipolar).ti,ab.
13. 11 or 12
14. exp anxiety disorder/
15. (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab.
16. 14 or 15
17. exp obsessive compulsive disorder/
18. (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive adj (mental or behavior*))).ti,ab.
19. 17 or 18
20. exp posttraumatic stress disorder/
21. (post-trauma* or trauma*).ti,ab.
22. 20 or 21

23. exp eating disorder/
24. (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab.
25. 23 or 24
26. exp personality disorder/
27. (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab.
28. 26 or 27
29. 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
30. exp psychotherapy/
31. (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab.
32. 30 or 31
33. (brief or extended or standard or intensiv* or ((short* or long*) and term)).ti,ab.
34. 32 and 33
35. 29 and 34
36. limit 35 to (adult <18 to 64 years> or aged <65+ years>)
37. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
38. 36 and 37

LILACS (Bireme; 1982 to June 2019) (1163 hits)
(attention deficit hyperactivity disorder or adhd) or (psychotic or delusion$ or hallucination$ or ((disorgani$ed or abnormal) and (think$ or motor$)) or schizophreni$) or (bipolar or mood elevation or mania or hypomania or depress$) or (depressi$ or mood or unipolar) or (anxiet$ or fear or avoidance behavior$ or phobia$ or panic$ or agoraphobia) or (obsessive compulsive disorder or OCD or urge$ or obsessi$ or (repetetive and (mental or behavior$))) or (post-trauma$ or trauma$) or (eating behavior or anorexia$ or bulimia$ or binge-eating$) or (schizotypal$ or paranoid$ or schizoid$ or histrionic$ or narcissistic$ or antisocial$ or borderline$ or avoidant$ or dependent or obsessive-compulsi$) [Words] and (((psycho$ or cognitive or behavior$ or humanistic or systemic) and therap$) or psychotherap$ or self care or self-care) [Words] and (brief or extended or standard or intensiv$ or ((short$ or long$) and term)) [Words]

Science Citation Index Expanded (SCI-EXPANDED) (1900 to June 2019); Social Sciences Citation Index (SSCI) (1956 to June 2019); Conference Proceedings Citation Index- Science (CPCI-S) (1990 to June 2019); and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) (1990 to June 2019) (Web of Science) (5401 hits)
#7 #6 AND #5
#6 TS=(random* or blind* or placebo* or meta-analys*)
#5 #4 AND #1
#4 #3 AND #2
#3 TS=(brief or extended or standard or intensiv* or ((short* or long*) and term))
#2 TS=(((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care)
#1 TI=((attention deficit hyperactivity disorder or adhd) or (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) and (think* or motor*)) or schizophreni*) or (bipolar or mood elevation or mania or hypomania or depress*) or (depressi* or mood or unipolar) or (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia) or (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*))) or (post-trauma* or trauma*) or (eating behavior or anorexia* or bulimia* or binge-eating*) or (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*))

Paper II

Short-term versus long-term psychotherapy for adult psychiatric disorders: a systematic review with meta-analysis

Authors:
Sophie Juul[1 2 3 *], Janus Christian Jakobsen[3,4], Caroline Kamp Jørgensen[1 2 3], Stig Poulsen[2], Per Sørensen[1], Sebastian Simonsen[1]

Contact information:

* Corresponding author**:** Sophie Juul, sophie.juul@regionh.dk

Janus Christian Jakobsen: janus.jakobsen@ctu.dk
Caroline Kamp Jørgensen: caroline.kamp.joergensen@regionh.dk
Stig Poulsen: stig.poulsen@psy.ku.dk
Per Sørensen: per.soerensen@regionh.dk
Sebastian Simonsen: Sebastian.simonsen@regionh.dk

Affiliations:
[1] Stolpegaard Psychotherapy Centre, Mental Health Services, Capital Region of Denmark, Gentofte, Denmark, Stolpegaardsvej 20, 2820, Gentofte, Denmark.
[2] Department of Psychology, University of Copenhagen, Copenhagen, Denmark, Østre Farimagsgade 2A, 1353 Copenhagen K, Denmark.
[3] Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, Tagensvej 22, 2200 Copenhagen N, Denmark
[4] Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

Word count:
Abstract: 380
Main text: 5583

Abstract

Background: Psychotherapy is among the recommended interventions for most adult psychiatric disorders. The optimal psychotherapy duration for specific psychiatric disorders has not been systematically identified.

Aims: To assess the beneficial and harmful effects of short-term versus long-term psychotherapy for adult psychiatric disorders.

Method: We searched for randomised clinical trials comparing different durations of the same psychotherapy type for adult psychiatric disorders before June 18, 2020. Our methodology was based on PRISMA, Cochrane methodology, and an eight-step procedure. The certainty of the evidence was assessed with GRADE. Primary outcomes were quality of life, serious adverse events, and symptom severity. Secondary outcomes were suicide or suicide-attempts, self-harm, and level of functioning.

Results: We included 16 trials randomizing 2,651 participants. All trials were at high risk of bias.
One single trial showed no evidence of a difference between short-term versus long-term dialectical behavioral therapy for borderline personality disorder and reached the required information size when assessing quality of life, symptom severity, and level of functioning. One single trial showed no evidence of a difference between short-term versus long-term psychodynamic psychotherapy for mood- or anxiety disorders and reached the required information size when assessing symptom severity and level of functioning. The remaining single trials did not meet the required information sizes needed to confirm or reject realistic intervention effects.
It was only possible to conduct two meta-analyses. Meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms at end of treatment (SMD: 0.08; 95% CI: -0.47 to 0.63; $p = 0.77$; $I^2 = 73\%$; four trials; very low certainty). Meta-analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy for mood- and anxiety disorders on level of functioning (SMD 0.16; 95% CI -0.08 to 0.40; $p = 0.20$; $I^2 = 21\%$; two trials; very low certainty). It was not possible to perform other pre-planned meta-analyses due to lack of relevant data.

Conclusions

Our results indicate that there is no evidence of a difference between short-term and long-term psychotherapy for major depressive disorder, anxiety disorders, post-traumatic stress disorder, and borderline personality disorder. However, we only identified 16 randomised clinical trials. More trials

at low risk of bias and at low risk of random errors assessing participants at different levels of psychopathological severity are urgently needed.

Systematic review registration: PROSPERO CRD42019128535

Introduction

The annual prevalence of psychiatric disorders is estimated to be 38.2% of the European population [1]. The economic burden from psychiatric disorders is high, both because of direct health care costs, but also because of indirect costs like sick days, disability, and early retirement [1-3]. Psychotherapy is among the recommended and widely used interventions for most disorders [4]. Accordingly, it would be highly relevant to identify the optimal duration of psychotherapy for various psychiatric disorder and conditions. If short-term psychotherapy is the optimal treatment approach for a given disorder, this could result in a reduction of waitlists and thus a greater access to evidence-based care for psychiatric patients. On the contrary, if long-term psychotherapy is the most optimal treatment, it would be sensible for mental health systems to invest in these treatments, as they would translate into greater long-term health and occupational benefits [5,6].

The relationship between dose and effect in psychotherapy has been studied with mixed results in non-controlled studies [5,7]. While several non-controlled studies indicate that there is a curve linear or negatively accelerating relationship between number of psychotherapy sessions and outcome for most psychiatric disorders [8,9], these findings have been criticized on methodological grounds [10].

The inconclusiveness of the existing research and the general lack of internal validity of non-controlled studies [11,12] indicate the need for a systematic review of well-designed randomised clinical trials directly comparing psychotherapies of different durations for clearly specified populations, including patients treated for psychiatric disorders in secondary mental health care settings [11,12]. However, such systematic review has not previously been performed [6].

The present systematic review aims at forming the basis for evidence-based guideline recommendations for the optimal duration of psychotherapy for adult psychiatric disorders taking both benefits and harms, bias risk (systematic errors), play of chance (random errors), and certainty of the findings into consideration.

Methods

We report this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (**Supplementary 1**) [13,14]. The Cochrane methodology used in this systematic review is described in detail in our protocol [6], which was also registered in the PROSPERO database (CRD42019128535) prior to the systematic literature search.

Search strategy and selection criteria

Electronic searches

An experienced information specialist searched for eligible trials comparing a short-term with a long-term version of the same psychotherapy type for one or more adult psychiatric disorders published before June 18, 2020 in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), Latin American and Caribbean Health Sciences Literature (LILACS), PsycINFO, Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index—Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH). The electronic search strategies can be found in **Supplementary material 2**. Additionally, we checked the reference lists of relevant

publications for any unidentified trials. Trials were included irrespective of trial design, setting, publication status, publication year, language, and the reporting of our outcomes. We relied on the trialists defining their compared interventions as short-term and long-term (or similar terminology).

Searching other resources

We searched for ongoing trials on the following webpages:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- Google Scholar (https://scholar.google.dk/)
- The Turning Research into Practice (TRIP) Database (https://www.tripdatabase.com/)
- European Medicines Agency (EMA) (http://www.ema.europa.eu/ema/)
- US Food and Drug Administration (FDA) (www.fda.gov)
- China Food and Drug Administration (CFDA) (http://eng.sfda.gov.cn/WS03/CL0755/)
- Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatoryagency)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/)
- Cochrane Database of Systematic Reviews
- http://www.evidencebasedpsychotherapies.org/index. php?id=25

Additionally, we hand searched conference abstracts from psychiatry conferences for relevant trials. We also considered unpublished and gray literature trials if these were identified.

Data extraction and risk of bias assessment

Two review authors (SJ, CKJ) independently screened relevant trials, extracted data using a standardised data extraction sheet, and assessed the risk of bias according to the Cochrane Handbook of Systematic Reviews of Interventions [15]. Any discrepancies were resolved through discussion or, if required, through discussion with a third author (JCJ, SS). We contacted trial authors by e-mail if relevant data were unclear or missing.

Outcomes and subgroup analyses.

Our primary outcomes were quality of life, serious adverse events (as defined by the ICH-GCP guidelines) [16], and symptom severity. Our secondary outcomes were suicide or suicide attempts, self-harm, and level of functioning. For all outcomes, we used the trial results reported at the time point closest to the end of treatment in the long-term treatment group.

We planned the following subgroup analyses on our primary outcomes:

- High risk of bias trials compared to low risk of bias trials
- Types of psychiatric disorders
- Types of psychotherapy comparisons
- Trials above and below the mean difference in intervention lengths

Assessment of statistical and clinical significance

We performed our meta-analyses according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions [15], Keus et al. [17], and the eight-step procedure

suggested by Jakobsen et al. [18] for better validation of meta-analytic results in systematic reviews. Review Manager 5.4 and Stata 16 were used for all meta-analyses [19,20]. We planned to use risk ratios (RR) for dichotomous outcomes, mean differences (MD) for continuous outcomes assessed with homogeneous measures, and standardised mean difference (SMD) for continuous outcomes with heterogeneous measures. We performed both random-effects and fixed-effect meta-analysis (inverse variance) and chose the most conservative result as our primary result [18]. The more conservative result was the result with the highest *p*-value and the widest 95% confidence interval (CI). If there was substantial discrepancy between the results of the two methods, we reported and discussed the results [18]. We used the best-worst/worst-best case scenarios to assess the potential impact of missing outcome data [6,18]. We planned to use Trial Sequential Analysis to control for random errors and to report Trial Sequental Analysis-adjusted CIs if the cumulative Z-curves did not reach the futility area or passed the diversity-adjusted required information size (DARIS) [6,18,21-29]. Trial Sequential Analysis estimates the DARIS (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect). When analysing continuous outcomes, we pragmatically anticipated an intervention effect equal to the MD of the observed SD/2 [30]. Heterogeneity was assessed by calculating inconsistency (I^2) for traditional meta-analyses and diversity (D^2) for Trial Sequential Analysis. If it was not possible to perform Trial Sequential Analysis to estimate if there was enough information, we calculated the required information size for each single trial result and assessed if there was adequate power to confirm or reject realistic intervention effects of single trial results. For dichotomous outcomes, we used the proportion of participants with an event in the control group, a relative risk reduction of 20%, an alpha of 1.4%, and a beta of 20% as predefined in our protocol [6]. For continuous outcomes, we used the observed mean and standard deviation for the control group, the observed mean in the control group plus or minus the observed standard deviation in the control group/2 for the experimental group, an alpha of

1.4%, and a beta of 20% as predefined in our protocol [6]. We assessed a total of six primary and secondary outcome and, hence, considered a *p*-value of 0.014 as the threshold for statistical significance [18,31]. We performed independent samples t-tests to calculate *p*-values for single trial results for continuous outcomes, and Fisher's exact test for single trial results for dichotomous outcomes. We used The Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of evidence [18,32-34].

Results

Study characteristics

On June 18, 2020 our literature search identified a total of 19,472 records after duplicates were removed **(Fig 1**). We included 16 randomised clinical trials enrolling a total of 2,651 participants [35-50] (**Supplementary material 3**).

Fig 1. PRISMA flow diagram

--- INSERT FIGURE 1 HERE ---

Characteristics of included trials can be found in **Table 1.** All trials were assessed as at high risk of bias (**Supplementary material 4**). Five trials compared short-term versus long-term cognitive behavioural therapy for anxiety disorders [37-39,43,49]. Four trials compared short-term versus long-term cognitive behavioural therapy for major depressive disorder [40-42,44]. Three trials compared short-term versus long-term psychodynamic psychotherapy for major depressive disorder [41,42,45]. Two trials compared short-term versus long-term psychodynamic psychotherapy for mood- and anxiety disorders [35,36]. Two trials compared short-term versus long-term prolonged exposure for

post-traumatic stress disorder [47,48]. One trial compared short-term versus long-term interpersonal therapy for major depressive disorder [40]. One trial compared short-term versus long-term cognitive behavioural therapy for post-traumatic stress disorder [46]. One trial compared short-term versus long-term dialectical behavioural therapy for borderline personality disorder [50,51].

All trials compared different durations (weeks of treatment), dosages (number of sessions), and session lengths (minutes) (**Table 1**). Furthermore, trialists' definitions of short-term and long-term psychotherapy were not consistent across studies. Most trials compared different numbers of sessions delivered over different durations (e.g. 8 sessions delivered over 8 weeks compared with 16 sessions delivered over 16 weeks) [35,36,41-43,45,46,49,50]. Some trials compared different numbers of sessions delivered over the same duration (e.g. six sessions delivered over 12 weeks compared with 12 sessions delivered over 12 weeks) [38,39]. Some trials compared the same number of sessions over different durations (e.g. 10 sessions delivered over two weeks compared with 10 sessions delivered over 8 weeks) [37,40,47]. Two trials compared the same number of sessions, but with different sessions lengths in minutes (e.g. 10-15 sessions of 60 minutes compared with 10-15 sessions of 90 minutes) [44,48]. We planned to assess serious adverse events. However, only one of the trials reported on this outcome [50]. For several of our review outcomes it was not possible to conduct meta-analysis due to insufficient data. Four trials did not report the results in a usable way [41-44], i.e. they reported the results on a graph and/or did not include standard deviations for each point estimate on a group level. We contacted trial authors to receive relevant data, but we have not received any responses. It was not possible to perform Trial Sequential Analyses to assess the risk of random errors on any of our review outcomes because of lack of relevant data. Only a few trials reported on our dichotomous outcomes, and the continuous outcomes were assessed with heterogeneous

measures. We therefore performed sample size calculations for all single trial results. Results of these sample size calculations can be found in **Supplementary material 5**.

Table 1. Characteristics of included studies

--- INSERT TABLE 1 HERE ---

Single trial results

Trials including participants with borderline personality disorder

We identified one unpublished trial randomizing 240 participants with borderline personality disorder to six months versus 12 months dialectical behavioral therapy [50,51]. We retrieved the data through personal communication with the trialists. This trial reported data on all our pre-defined review outcomes. It was not possible to include the trial in a pre-defined meta-analysis, as it was the only trial including participants with borderline personality disorder. The trial reached their pre-calculated sample size of 240 participants [51]. The trial showed no evidence of a difference between short-term and long-term dialectical behavioral therapy when assessing quality of life (p = 0.831, required information size reached), serious adverse events (p = 1, required information size not reached), symptom severity (p = 0.833, required information size reached), suicide or suicide attempts (p = 1, required information size not reached), self-harm (p = 0.28, required information size not reached), and level of functioning (p = 0.731, required information size reached) (**Table 2, Supplementary material 5**). This trial was assessed as at overall high risk of bias due to lack of blinding of participants and personnel, and due to incomplete outcome data (**Supplementary material 4**), and the certainty of evidence was assessed as "very low" for all outcomes (**Supplementary material 6**).

We are currently performing a similar randomised clinical trial assessing the effects of five months versus 14 months of mentalization-based therapy for borderline personality disorder [52]. We are

planning a protocol for an individual patient data meta-analysis of short-term versus long-term psychotherapy for borderline personality disorder, which will be conducted once data from the two trials become available. Results of the individual patient data meta-analysis will increase the possibility of identifying subgroups of participants with specific effects of the assessed interventions.

Trials including participants with mood- and anxiety disorders

We identified two trials assessing the effects of short-term versus long-term psychodynamic psychotherapy for mood- and anxiety disorders [35,36].

One trial randomising 229 participants with mood- and anxiety disorders to 20 weeks versus 156 weeks of psychodynamic psychotherapy [35] showed no evidence of a difference when assessing symptom severity (p = 0.037, required information size reached), considering our adjusted threshold for significance was pre-defined at 0.014 in our protocol [6], or level of functioning (p = 0.066, required information size reached). The trial almost reached their sample size (230 participants) [35], but it was unclear whether this sample size was pre-defined. One trial randomising 167 participants with mood- and anxiety disorders to 20 weeks versus 80 weeks of psychodynamic psychotherapy [36] showed no evidence of a difference when assessing the proportion of participants with a suicide or a suicide attempts (zero events in both groups) or level of functioning (p = 0.889, required information size not reached) (**Table 2, Supplementary material 5**). Both trials were assessed at high risk of bias (**Supplementary material 4**) and the certainty of evidence was assessed as "very low" for all outcomes (**Supplementary material 7**).

Trials including participants with major depressive disorder

We identified five trials including eight comparisons assessing the effects of short-term versus long-term psychotherapy for participants with major depressive disorder [40-42,44,45]. Four trials

compared short-term versus long-term cognitive behavioural therapy for major depressive disorder [40-42,44]. Three trials compared short-term versus long-term psychodynamic psychotherapy for major depressive disorder [41,42,45]. One trial compared short-term versus long-term interpersonal therapy for major depressive disorder [40]. It was not possible to perform meta-analyses, as the trials differed in the assessed psychotherapy traditions, and only two trials reported on our pre-defined review outcomes [40,45].

One trial randomising 200 participants with major depressive disorder to once- versus twice weekly cognitive behavioral therapy or interpersonal therapy [40] showed no evidence of a difference when assessing quality of life and symptom severity for either cognitive behavioral therapy (p = 0.77 and p = 0.38, required information size not reached) or interpersonal therapy (p = 0.14 and p = 0.42, required information size not reached). One trial randomising 103 participants with major depressive disorder to eight versus 16 sessions of short-term psychodynamic supportive psychotherapy [45] showed no evidence of a difference when assessing quality of life (p = 0.911, required information size not reached) or symptom severity (p = 0.512, required information size not reached) (**Table 2, Supplementary material 5**). Both trials were assessed at high risk of bias (**Supplementary material 4**) and the certainty of evidence was assessed as "very low" for all outcomes (**Supplementary material 8, 9, and 10**).

Trials including participants with post-traumatic stress disorder

We identified three trials assessing the effects of short-term versus long-term psychotherapy for participants with post-traumatic stress disorder [46-48]. Two trials compared short-term versus long-term prolonged exposure for post-traumatic stress disorder [47,48]. One trial compared short-term versus long-term cognitive behavioral therapy for post-traumatic stress disorder [46]. It was not

possible to perform meta-analyses, as the trials differed in the assessed psychotherapy traditions, and one of them did not report standard deviations [47]. The two remaining trials reported on some of our pre-defined review outcomes.

One trial randomising 61 participants with post-traumatic stress disorder to intensive (5 weeks) versus standard (12 weeks) cognitive therapy [46] showed no evidence of a difference when assessing quality of life (p = 0.061, required information size not reached), symptom severity (p = 0.466, required information size not reached), or level of functioning (p = 0.757, required information size not reached). One trial randomising 40 participants with post-traumatic stress disorder to 60 minutes versus 90 minutes sessions of prolonged exposure therapy [48] showed no evidence of a difference when assessing symptom severity (p = 0.719, required information size not reached) (**Table 2, Supplementary material 5**). Both trials were assessed at high risk of bias (**Supplementary material 4**) and the certainty of evidence was assessed as "very low" for all outcomes (**Supplementary material 11 and 12**).

Trials including participants with anxiety disorders

We identified five trials assessing the effects of short-term versus long-term cognitive behavioral therapy for anxiety disorders [37-39,43,49]. One trial did not report the results in a usable way; i.e. the results were reported on a graph and standard deviations were not reported [43].

One trial randomising 29 participants with panic disorder to five versus 12 sessions cognitive behavioral therapy [38] showed no evidence of a difference when assessing symptom severity (p = 0.615, required information size not reached). One trial randomising 34 participants with social anxiety disorder to 12 versus 18 weeks of cognitive behavioral therapy [37] showed no evidence of a difference when assessing symptom severity (p = 0.018, required information size not reached),

considering our adjusted threshold for significance was pre-defined at 0.014 in our protocol [6]. One trial randomising 81 participants to six versus 12 weeks of cognitive behavioral therapy for participants with panic disorder [49] showed no evidence of a difference when assessing symptom severity (p = 0.0195, required information size not reached), considering our adjusted threshold for significance was pre-defined at 0.014 in our protocol [6]. One trial randomising 65 participants with panic disorder and agoraphobia to 7 sessions versus 14 sessions cognitive behavioral therapy [39] showed no evidence of a difference when assessing symptom severity (p = 0.77, required information size not reached). All trials were assessed at high risk of bias (**Supplementary material 4**) and the certainty of evidence was assessed as "very low" for all outcomes (**Supplementary material 13**).

It was only possible to perform two pre-planned meta-analyses: one assessing the effects of short-term versus long-term cognitive behavioral therapy for anxiety disorders at end of treatment and at maximum follow-up, and another one assessing the effects of short-term versus long-term psychodynamic psychotherapy for mood and anxiety disorders at end of treatment.

Table 2. Single trial results

---- INSERT TABLE 2 HERE ----

Short-term versus long-term cognitive behavioural therapy for anxiety disorders

We identified five trials assessing the effects of short-term versus long-term cognitive behavioural therapy for anxiety disorders [37-39,43,49]. All trials were assessed as at high risk of bias (**Supplementary material 4**). One trial was not eligible for meta-analysis, as the results were not reported in a usable way; i.e. the results were reported on a graph and standard deviations were not reported [43].

Four trials randomising a total of 209 participants reported on anxiety symptoms [37-39,49]. Four different symptom scales were used: Beck Anxiety Inventory (BAI) [38], Social Phobia Anxiety Inventory – Social Phobia [37], State Trait Anxiety Inventory-Trait (STAI-T) [49], and Panic and Agoraphobia Scale (PAS) [39]. One trial included participants with social anxiety disorder [37]. Two trials included participants with panic disorder [38,49]. One trial included participants with panic disorder and agoraphobia [39]. We chose to analyse anxiety symptoms using SMD.

Meta-analysis of anxiety symptoms at end of treatment

Random-effects meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety disorders on anxiety symptoms at end of treatment (SMD: 0.08; 95% CI: -0.47 to 0.63; p = 0.77; I^2 = 73%; four trials; very low certainty) (**Fig 2**). Visual inspection of the forest plot and measures to quantify heterogeneity indicated substantial heterogeneity (I^2 = 73%). The end of treatment assessment time point was 12 weeks [38,49], 15 weeks [39], and 18 weeks [37]. It was not possible to assess the possible impact of missing outcome data, due to unclear or lack of reporting of number of analysed participants in some of the included trials. It was not possible to perform Trial Sequential Analysis for this outcome, because the outcome was assessed using SMD [25]. This outcome result was assessed as at high risk of bias. Certainty of the evidence was assessed as 'very low'. See **Supplementary material 13**.

Fig 2. Forest plot of short-term versus long-term cognitive behavioural therapy for anxiety disorders on severity of anxiety symptoms at end of treatment

--- INSERT FIGURE 2 HERE ---

Short-term versus long-term psychodynamic therapy for mood and anxiety disorders

We identified two trials assessing the effects of short-term versus long-term psychodynamic therapy for mood- and anxiety disorder [35,36,53]. Both trials were assessed as at high risk of bias (**Supplementary material 4)**.

Two trials randomising a total of 393 participants reported on level of functioning [35,36]. Two different assessment scales were used, including Global Assessment of Functioning – Function (GAF-F) [36] and the work subscale (SAS-Work) of the Social Adjustment Scale [35]. We chose to analyze level of functioning using standardised mean difference. In order to assure the scales pointed in the right direction, we multiplied the mean in one of the trials with '-1'.

Meta-analysis of level of functioning at end of treatment

Random effects meta-analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy for mood and anxiety disorders on level of functioning at end of treatment (SMD 0.16; 95% CI -0.08 to 0.40; $p = 0.20$; $I^2 = 21\%$; two trials; very low certainty) (**Fig 3**). Visual inspection of forest plot and measures to quantify heterogeneity ($I^2 = 21\%$) showed some heterogeneity. The end of treatment time point of assessment was 36 months after randomisation for both trials. It was not possible to perform Trial Sequential Analysis for this outcome, because the outcome was assessed using SMD [25]. This outcome result was assessed as at high risk of bias. Certainty of the evidence was assessed as 'very low'. See **Supplementary material 7**.

Fig 3. Forest plot of short-term versus long-term psychodynamic therapy for mood- and anxiety disorders on level of functioning at end of treatment

--- INSERT FIGURE 3 HERE ---

Incomplete outcome data

Random effects meta-analysis of the best-worst case scenario adding 2 SD (SMD -0.16; 95% CI -8.13 to 7.81; p =<0.00001; I^2 = 95%) and adding 1 SD (SMD -0.15; 95% CI -4.26 to 3.95; p = <0.94; I^2 = 100%) for missing data showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy. Random effects meta-analysis of the worst-best case scenario adding 2 SD (SMD -0.14; 95% CI -7.62 to 7.35; p = <0.97; I^2 = 100%) and adding 1 SD (SMD -0.14; 95% CI -3.76 to 3.48; p = <0.94; I^2 = 100%) for missing values showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy.

Because of lack of relevant data, it was not possible to conduct other pre-defined meta-analyses. It was only possible to perform one sensitivity analysis (best-worst worst-best scenarios) to assess the potential impact of incomplete outcome data. We also planned several subgroup analyses to test for heterogeneity [6], but it was not possible to conduct them because of lack of relevant data. Further, it was not possible to assess the risk of publication bias by testing for funnel plot asymmetry due to lack of trials. Last, it was not possible to perform Trial Sequential Analyses because all included outcomes were assessed using SMD.

Exploratory analysis

As an exploratory analysis, we pooled all possible trials in one meta-analysis to assess the overall effects of short-term compared with long-term psychotherapy for adult psychiatric disorders

regardless of psychotherapy type. We pooled trials that included participants with internalizing disorders (i.e. anxiety disorders, major depressive disorder, post-traumatic stress disorder, obsessive compulsive disorder etc.) as these have previously been suggested to belong to the same cluster of psychiatric disorders [54-56]. We chose to analyze internalizing disorders (instead of externalizing disorders such as borderline personality disorder) as this was the cluster of disorders with the most data. We chose symptom severity at end of treatment as the outcome (regardless of the type of internalizing disorder), as this was the review outcome with the most data. This meta-analysis was not pre-defined and was planned after data was extracted, and hence, it should be interpreted as hypothesis-generating only.

Eight trials randomising a total of 802 participants reported on symptom severity [35,37-40,45,46,49]. All trials were at high risk of bias (**Supplementary material 4**). Six different assessment scales were used, including Beck Depression Inventory (BDI) [40], Beck Anxiety Inventory (BAI) [38], Hamilton Depression Rating Scale (HDRS) [35,45], Clinician Administered PTSD Scale (CAPS) [46], Social Phobia Anxiety Inventory – Social Phobia [37], State Trait Anxiety Inventory-Trait (STAI-T) [49], and Panic and Agoraphobia Scale (PAS) [39]. We chose to analyze symptom severity using SMD.

Meta-analysis of symptom severity at end of treatment

Random effects meta-analysis showed no evidence of a difference between short-term and long-term psychotherapy for internalizing adult psychiatric disorders (SMD 0.13; 95% CI -0.07 to 0.33; p = 0.21; I^2 = 40%; eight trials) (**Fig 4**). Visual inspection of the forest plot and measures to quantify heterogeneity (I^2 = 40%) showed heterogeneity. The end of treatment time-point of assessment varied from 12 weeks [38,49] to 36 months [35]. It was not possible to assess the possible impact of missing outcome data, due to unclear or lack of reporting of number of analysed participants in some of the

included trials. It was not possible to perform Trial Sequential Analysis for this outcome, because the outcome was assessed using SMD [25].

Fig 4. Forest plot of short-term versus long-term psychotherapy for internalizing adult psychiatric disorders on symptom severity at end of treatment

--- INSERT FIGURE 4 HERE ---

The possible contribution of ongoing trials

We identified two ongoing trials [52,57] that might contribute to the current evidence on short-term versus long-term psychotherapy for adult psychiatric disorders. These ongoing trials will contribute to the evidence on quality of life, serious adverse events, symptom severity, suicide and suicide attempts, self-harm, and level of functioning.

Discussion

We conducted the first systematic review assessing the effects of short-term versus long-term psychotherapy for adult psychiatric disorders. We included 16 trials randomising a total of 2,651 participants to a short-term or a long-term version of the same psychotherapy type. All trials and outcome results were at high risk of bias, and the certainty of the evidence according to GRADE was `very low' for all outcomes.

One single trial showed no evidence of a difference between short-term versus long-term dialectical behavioral therapy for borderline personality disorder and reached the required information size needed to confirm or reject realistic intervention effects when assessing quality of life, symptom

severity, and level of functioning [50,51]. One single trial showed no evidence of a difference between short-term versus long-term psychodynamic psychotherapy for mood- or anxiety disorders and reached the required information size needed to confirm or reject realistic intervention effects when assessing symptom severity and level of functioning [35]. The remaining single trials did not meet the required information size needed to confirm or reject realistic intervention effects. It was only possible to perform two pre-planned meta-analyses. Meta-analysis showed no evidence of a difference between short-term and long-term cognitive behavioural therapy for anxiety symptoms at end of treatment or at maximum follow-up. Meta-analysis showed no evidence of a difference between short-term and long-term psychodynamic psychotherapy on level of functioning at end of treatment. An exploratory meta-analysis of short-term compared with long-term psychotherapy for internalizing adult psychiatric disorders showed no evidence of a difference on symptom severity at maximum follow-up. The certainty of the evidence was assessed as 'very low' for all outcomes. It was not possible to perform Trial Sequential Analysis or tests for publication bias. Further, due to poor reporting in the included trials, we only performed one planned sensitivity analysis to assess the potential impact of missing data. Only one trial reported on serious adverse events [50]. Two trials reported on suicide and suicide attempts [36,50], and one trial reported on self-harm [50].

Our review has several strengths. We followed our protocol which was registered prior to the systematic literature search (PROSPERO ID: CRD42019128535). Data were double-extracted by independent authors minimizing the risk of inaccurate data extraction, and we assessed the risk of bias in all trials according to Cochrane methodology [15]. We used GRADE to assess the certainty of the evidence [32-34], and the eight-step assessment suggested by Jakobsen et al. to assess if the thresholds for significance were crossed [18]. Hence, this systematic review considered both risks of random errors and risks of systematic errors which adds further robustness to our results and

conclusions. Another strength of our review is that we pragmatically accepted any short-term psychotherapy type and any long-term psychotherapy type, thus results may therefore guide a clinician when choosing between different treatment durations.

Our review also has several limitations. First, all trials were at high risk of bias. Therefore, there is a risk that our present results overestimated the beneficial effects and underestimated the harmful effects of the experimental interventions being studied [58-65]. Second, we only identified 16 trials, and it was not possible to assess the risk of random errors in the meta-analyses with Trial Sequential Analysis due to the inclusion of continuous outcomes assessed with heterogeneous measures (i.e. we assessed the effects with standardised mean difference). This is a major limitation, as we cannot assess if the shown lack of difference is an indication of a "true" lack of difference, or if it is an indication that more trials are needed. We calculated the required information sizes for single trial results post-hoc, but these should primarily be considered exploratory, as they rely on the observed means and standard deviations instead of pre-defined minimal clinically important differences on the assessed scales. Third, only few trials reported on serious adverse events, suicide, suicide attempts, and self-harm. It is of utmost importance to always assess beneficial *and* harmful intervention effects on patient-important outcomes [15,66]. Finally, the included trials differed in time points of outcome assessments, therapy durations (length of treatment), and therapy dosages (number of sessions).

We have identified one previous systematic review comparing short-term and long-term psychotherapy for schizophrenia [67]. However, the review did not identify any trials. We have also identified a meta-regression study investigating the effects of psychotherapy for major depressive disorder[5]. This study found no significant association between the duration of psychotherapy and effect-size, which is similar to the conclusion of the present review. However, in the meta-regression

study, there was a strong association between number of sessions per week and effect size. An increase from one to two sessions per week increased the effect size with $g = 0.45$, while keeping the total number of treatment sessions constant [5]. The results of the present review could neither confirm nor reject that two sessions per week were more efficacious than one session per week.

The included trials in this review typically assessed the effects of different durations of psychotherapy for anxiety disorders, major depressive disorder, and post-traumatic stress disorder. Our findings indicate that there may be no evidence of a difference between short-term and long-term psychotherapy when assessing symptom severity and level of functioning. There are, however, indications from non-controlled studies that patients with complex and severe psychopathology, defined by the presence of, e.g., co-morbid psychiatric disorders, longer duration and early onset of the disorder, and unemployment, may have better outcomes in high-intensity than in low-intensity treatments [68,69]. We included one trial including participants with borderline personality disorder. This trial did not find evidence of a difference between six versus 12 months dialectical behavioral therapy, and the trial reached the required information size needed to confirm or reject realistic intervention effects for quality of life, symptom severity, and level of functioning. However, the trial was assessed as at high risk of bias and the certainty of evidence was "very low" for all outcomes. Accordingly, future randomized clinical trials comparing the outcomes of short- and long-term psychotherapy for patients with low and high problem complexity should be conducted. We identified no trials including participants with other severe personality pathology, schizophrenia, or other psychotic disorders. Hence, it is still unclear whether patients with severe psychopathology requires short-term or long-term psychotherapy.

Evidence-based practice and decision-making should be based on the best available evidence, patient preferences, and the clinician's expertise [70]. For severe and complex cases there is evidence of beneficial effects of psychotherapy of specific treatment lengths (e.g. long-term specialized treatment for borderline personality disorder [71]) but very poor evidence to guide clinicians in choosing the optimal treatment duration. Evidently, clinicians should by default offer psychotherapy in a duration supported by the best available evidence. But when there is a question of treatment duration, e.g. a patient asking for a shorter treatment because of life circumstances, the clinician is advised to balance this preference with clinical experience which may include knowledge of specific prognostic factors such as early onset of the disorder or complex comorbidity, while also considering the poor evidence regarding the optimal treatment duration currently available.

Conclusions

Our results indicate that there is no evidence of a difference between short-term and long-term psychotherapy for major depressive disorder, anxiety disorders, post-traumatic stress disorder, and borderline personality disorder. However, we only identified 16 randomised clinical trials. More trials at low risk of bias and at low risk of random errors assessing participants at different levels of psychopathological severity are urgently needed.

Differences between the protocol and the review

In addition to assessing all outcomes at end of treatment, we planned to assess all outcomes at maximum follow-up as a secondary analysis. However, only few trials reported data at maximum follow-up. Because of lack of relevant data, we chose to only report data at end of treatment.

Declaration of Interest

None

Funding

This work was funded by Trygfonden (SJ, grant number: 123488), and by the Mental Health Services in the Capital Region of Denmark Research Fund (SJ and SS, grant number: N/A)

Acknowledgements

The expert help from Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Copenhagen, Denmark) in making the search strategy and conducting electronic searches is hugely appreciated.

Author Contribution

SJ and CKJ independently assessed eligibility and extracted data with ongoing supervision from JCJ and SS. SJ conducted data analyses and wrote up the manuscript draft. All authors read, commented on, and approved the final manuscript.

Data Availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

References

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655-79.

2. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B, group Cs, et al. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155-62.

3. Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe-a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol. 2005;15(4):357-76.

4. Barlow DH. The Oxford Handbook of Clinical Psychology: Updated Edition: Oxford University Press; 2014.

5. Cuijpers P, Huibers M, Ebert DD, Koole SL, Andersson G. How much psychotherapy is needed to treat depression? A metaregression analysis. J Affect Disord. 2013;149(1-3):1-13.

6. Juul S, Poulsen S, Lunn S, Sorensen P, Jakobsen JC, Simonsen S. Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis. Syst Rev. 2019;8(1):169.

7. Castonguay LG, Barkham M, Lutz W, McAleavey A. Practice-oriented research: Approaches and applications. Bergin and Garfield's handbook of psychotherapy and behavior change. 2013;6:85-133.

8. Howard KI, Kopta SM, Krause MS, Orlinsky DE. The Dose-Effect Relationship in Psychotherapy. American Psychologist. 1986;41(2):159-64.

9. Robinson L, Delgadillo J, Kellett S. The dose-response effect in routinely delivered psychological therapies: A systematic review. Psychother Res. 2020;30(1):79-96.

10. Bone C, Delgadillo J, Barkham M. A systematic review and meta-analysis of the good-enough level (GEL) literature. J Couns Psychol. 2020: DOI: 10.1037/cou0000521 [Preprint].

11. Jakobsen JC, Gluud C. The necessity of randomized clinical trials. Br J Med Med Res. 2013;3(4):1453-68.

12. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27).

13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2010.

14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. BMJ. 2009;339(b2700).

15. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions 5.1. 0. The Cochrane Collaboration. 2011.

16. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). ICH Harmonised Guideline: Integrated Addemdum to ICH E6(R1): Guideline for Good Clinical Practice (ICH-GCP). 2015.

17. Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. BMC medical research methodology. 2010;10(1):90.

18. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14(1):120.

19. StataCorp. Stata Statistical Software: Release 16 2019 [College Station, TX: StataCorp LLC http://www.stata.com.].

20. Cochrane Collaboration. Review manager (Version 5.3) [Computer Software]. The Nordic Cochrane Centre; 2014 [

21. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of clinical epidemiology. 2008;61(1):64-75.

22. Copenhagen Trial Unit. TSA - Trial Sequential Analysis. http://www.ctu.dk/tsa/ [Web page]. [

23. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of clinical epidemiology. 2008;61(8):763-9.

24. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International journal of epidemiology. 2008;38(1):287-98.

25. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, C. G. User manual for trial sequential analysis (TSA). http://wwwctudk/tsa/files/tsa_manualpdf. 2011.

26. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC medical research methodology. 2009;9(1):86.

27. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clinical Epidemiology. 2010;2:57.

28. Thorlund K, Devereaux P, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? International journal of epidemiology. 2008;38(1):276-86.

29. Imberger G, Thorlund K, Gluud C, Wetterslev J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ open. 2016;6(8):e011890.

30. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care. 2003:582-92.

31. Jakobsen JC, Wetterslev J, Lange T, Gluud C. Viewpoint: taking into account risks of random errors when analysing multiple outcomes in systematic reviews. Cochrane Database of Systematic Reviews. 2016(3).

32. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.

33. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6.

34. Schünemann HJ, Best D, Vist G, Oxman AD, Group GW. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. Canadian Medical Association Journal. 2003;169(7):677-80.

35. Knekt P, Lindfors O, Harkanen T, Valikoski M, Virtala E, Laaksonen MA, et al. Randomized trial on the effectiveness of long-and short-term psychodynamic psychotherapy and solution-focused therapy on psychiatric symptoms during a 3-year follow-up. Psychol Med. 2008;38(5):689-703.

36. Lorentzen S, Ruud T, Fjeldstad A, Hoglend P. Comparison of short- and long-term dynamic group psychotherapy: randomised clinical trial. Br J Psychiatry. 2013;203(3):280-7.

37. Herbert JD, Rheingold AA, Gaudiano BA, Myers VH. Standard Versus Extended Cognitive Behavior Therapy for Social Anxiety Disorder: A Randomized-Controlled Trial. Behavioural and Cognitive Psychotherapy. 2004;32(2):131-47.

38. Clark DM, Salkovskis PM, Hackmann A, A. W, Ludgate J, Gelder M. Brief Cognitive Therapy for Panic Disorder: A Randomized Controlled Trial. Journal of Consulting and Clinical Psychology. 1999;67(4):583-9.

39. Roberge P, Marchand A, Reinharz D, Savard P. Cognitive-Behavioral Treatment for Panic Disorder With Agoraphobia A Randomized, Controlled Trial and Cost-Effectiveness Analysis. Journal of Behavior Modification. 2008;32(3):333-51.

40. Bruijniks SJE, Lemmens L, Hollon SD, Peeters F, Cuijpers P, Arntz A, et al. The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients. Br J Psychiatry. 2020;216(4):222-30.

41. Barkham M, Rees A, Shapiro DA, Stiles WB, Agnew RM, Halstead J, et al. Outcomes of time-limited psychotherapy in applied settings: replicating the Second Sheffield Psychotherapy Project. J Consult Clin Psychol. 1996;64(5):1079.

42. Shapiro DA, Barkham M, Rees A, Hardy GE, Reynolds S, Startup M. Effects of treatment duration and severity of depression on the effectiveness of cognitive-behavioral and psychodynamic-interpersonal psychotherapy. J Consult Clin Psychol. 1994;62(3):522.

43. Bohni M, Spindler H, Arendt M, Hougaard E, Rosenberg N. A randomized study of massed three-week cognitive behavioural therapy schedule for panic disorder. Acta Psychiatr Scand. 2009;120(3):187-95.

44. Christensen H, Griffiths K, Mackinnon A, Brittliffe K. Online randomized controlled trial of brief and full cognitive behaviour therapy for depression. Psychol Med. 2006;36(12):1737.

45. Dekker J, Molenaar PJ, Kool S, Van Aalst G, Peen J, de Jonghe F. Dose–effect relations in time-limited combined psycho-pharmacological treatment for depression. Psychol Med. 2005;35(1):47-58.

46. Ehlers A, Hackmann A, Grey N, Wild J, Liness S, Albert I, et al. A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused supportive therapy. Am J Psychiatry. 2014;171(3):294-304.

47. Foa EB, McLean CP, Zang Y, Rosenfield D, Yadin E, Yarvis JS, et al. Effect of prolonged exposure therapy delivered over 2 weeks vs 8 weeks vs present-centered therapy on PTSD symptom severity in military personnel: A randomized clinical trial. JAMA. 2018;319(4):354-64.

48. Nacasch N, Huppert JD, Su Y-J, Kivity Y, Dinshtein Y, Yeh R, et al. Are 60-Minute Prolonged Exposure Sessions With 20-Minute Imaginal Exposure to Traumatic Memories Sufficient to Successfully Treat PTSD? A Randomized Noninferiority Clinical Trial. Behav Ther. 2015;46(3):328-41.

49. Kenardy JA, Dow MG, Johnston DW, Newman MG, Thomson A, Taylor CB. A comparison of delivery methods of cognitive-behavioral therapy for panic disorder: an international multicenter trial. J Consult Clin Psychol. 2003;71(6):1068.

50. McMain S. The effectiveness of 6 versus 12-months of dialectical behaviour therapy for borderline personality disorder: the feasibility of a shorter treatment and evaluating responses (FASTER) trial. 2020(Unpublished data).

51. McMain SF, Chapman AL, Kuo JR, Guimond T, Streiner DL, Dixon-Gordon KL, et al. The effectiveness of 6 versus 12-months of dialectical behaviour therapy for borderline personality disorder: the feasibility of a shorter treatment and evaluating responses (FASTER) trial protocol. BMC Psychiatry. 2018;18(1):230.

52. Juul S, Lunn S, Poulsen S, Sorensen P, Salimi M, Jakobsen JC, et al. Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomized clinical trial. Trials. 2019;20(1):196.

53. Knekt P, Lindfors O, Laaksonen MA, Raitasalo R, Haaramo P, Jarvikoski A, et al. Effectiveness of short-term and long-term psychotherapy on work ability and functional capacity--a

randomized clinical trial on depressive and anxiety disorders. J Affect Disord. 2008;107(1-3):95-106.

54. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci. 2014;2(2):119-37.

55. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol. 2017;126(4):454-77.

56. Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol Bull. 2010;136(5):768-821.

57. Kool M, Van HL, Bartak A, de Maat SCM, Arntz A, van den Eshof JW, et al. Optimizing psychotherapy dosage for comorbid depression and personality disorders (PsyDos): a pragmatic randomized factorial trial using schema therapy and short-term psychodynamic psychotherapy. BMC Psychiatry. 2018;18(1):252.

58. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.

59. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of internal medicine. 2001;135(11):982-9.

60. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.

61. Moher D, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? The Lancet. 1998;352(9128):609-13.

62. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Jama. 1995;273(5):408-12.

63. Hrobjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol. 2014;43(4):1272-83.

64. Hrobjartsson A, Skou Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. CMAJ. 2013;185(4).

65. Hrobjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ. 2012;344:e1119.

66. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019.

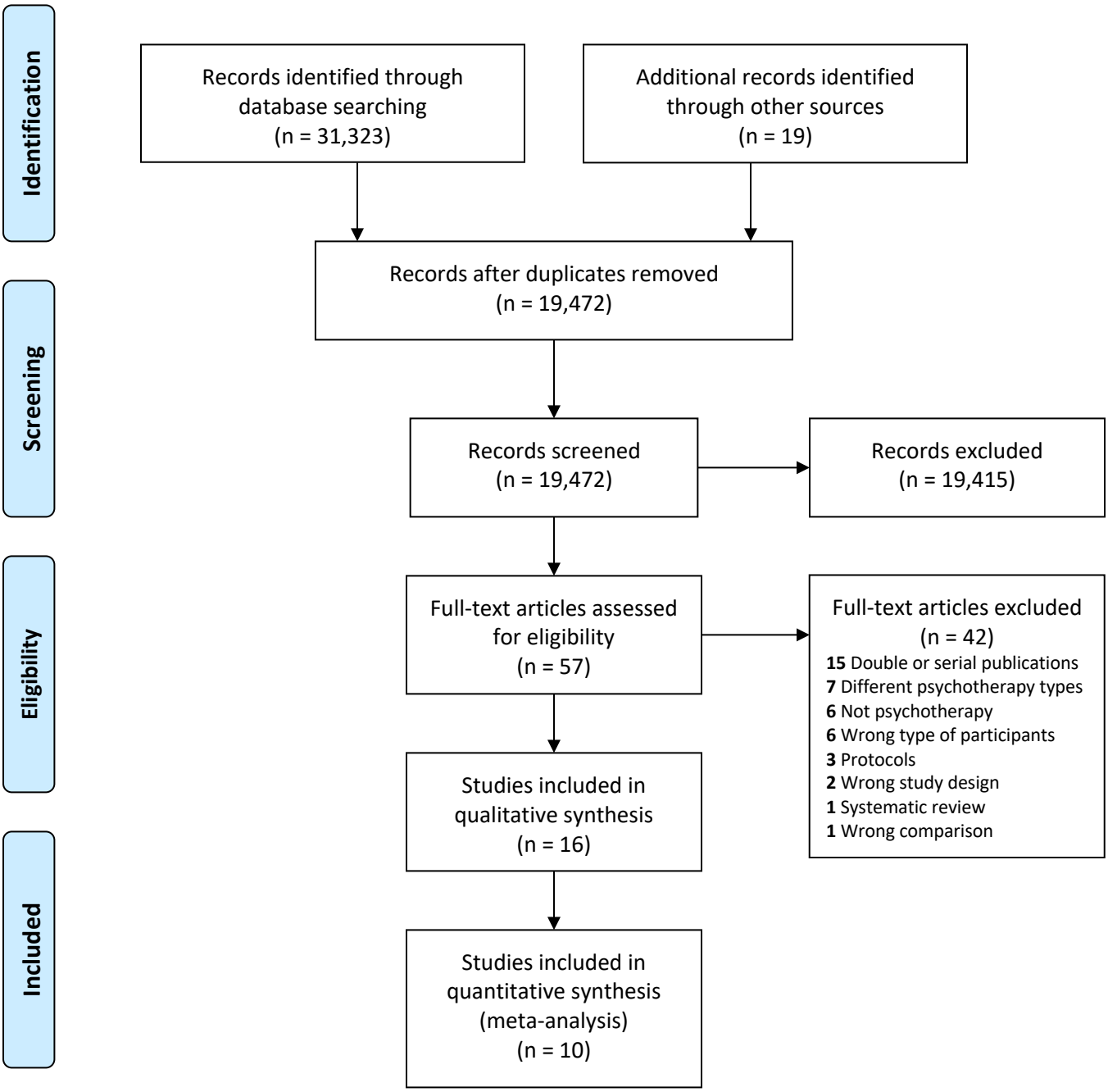
67. Naeem F, Farooq S, Kingdon D. Cognitive behavioural therapy (brief versus standard duration) for schizophrenia. Cochrane Database Syst Rev. 2015(10).

68. Delgadillo J, Moreea O, Lutz W. Different people respond differently to therapy: A demonstration using patient profiling and risk stratification. Behav Res Ther. 2016;79:15-22.

69. Delgadillo J, Huey D, Bennett H, McMillan D. Case complexity as a guide for psychological treatment selection. J Consult Clin Psychol. 2017;85(9):835.

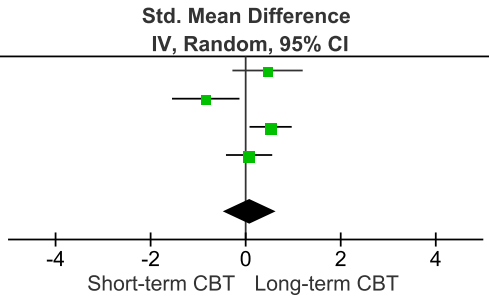
70. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;321:71-2.

71. Storebø OJ, Stoffers-Winterling JM, Völlm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, et al. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2020(5).


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 31,323)
Additional records identified through other sources (n = 19)
Records after duplicates removed (n = 19,472)
Records screened (n = 19,472)
Records excluded (n = 19,415)
Full-text articles assessed for eligibility (n = 57)
Full-text articles excluded (n = 42)
15 Double or serial publications
7 Different psychotherapy types
6 Not psychotherapy
6 Wrong type of participants
3 Protocols
2 Wrong study design
1 Systematic review
1 Wrong comparison
Studies included in qualitative synthesis (n = 16)
Studies included in quantitative synthesis (meta-analysis) (n = 10)

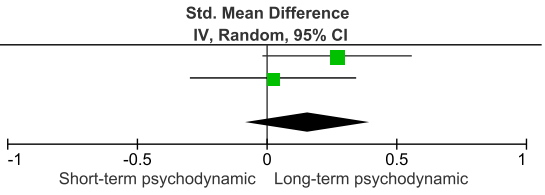
Study or Subgroup	Short-term CBT Mean	SD	Total	Long-term CBT Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Clark et al. 1999	5.7	5.3	14	3.4	4.4	15	21.5%	0.46 [-0.28, 1.20]
Herbert et al. 2004	76.71	47.18	15	113.77	39.56	19	22.2%	-0.84 [-1.55, -0.13]
Kenardy et al. 2003	47.86	12.31	39	41.1	13.14	42	28.6%	0.53 [0.08, 0.97]
Roberge et al. 2008	10.2	8.8	32	9.5	10.3	33	27.6%	0.07 [-0.41, 0.56]
Total (95% CI)			**100**			**109**	**100.0%**	**0.08 [-0.47, 0.63]**

Heterogeneity: Tau² = 0.23; Chi² = 11.00, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.29 (P = 0.77)



Study or Subgroup	Short-term psychodynamic Mean	SD	Total	Long-term psychodynamic Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Knekt et al. 2008	1.88	0.55	83	1.72	0.62	107	54.2%	0.27 [-0.02, 0.56]
Lorentzen et al. 2013	-67.8	11.7	71	-68.1	14.2	79	45.8%	0.02 [-0.30, 0.34]
Total (95% CI)			**154**			**186**	**100.0%**	**0.16 [-0.08, 0.40]**

Heterogeneity: Tau² = 0.01; Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 1.27 (P = 0.20)



Study or Subgroup	Short-term psychotherapy Mean	SD	Total	Long-term psychotherapy Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bruijniks et al. 2020a	24.16	15.09	37	21.25	12.9	35	11.5%	0.20 [-0.26, 0.67]
Bruijniks et al. 2020b	22.91	14.75	34	20.02	16.05	39	11.6%	0.18 [-0.28, 0.65]
Clark et al. 1999	9.8	6.7	14	8.4	8	15	6.1%	0.18 [-0.55, 0.91]
Dekker et al. 2004	11.1	6.8	45	12.1	7.6	45	13.1%	-0.14 [-0.55, 0.28]
Ehlers et al. 2014	32.22	27.2	30	26.97	28.68	31	10.4%	0.19 [-0.32, 0.69]
Herbert et al. 2004	76.71	47.18	15	113.77	39.56	19	6.4%	-0.84 [-1.55, -0.13]
Kenardy et al. 2003	47.86	12.31	39	41.1	13.14	42	12.1%	0.53 [0.08, 0.97]
Knekt et al. 2008	10.8	5.65	83	9	6	107	18.2%	0.31 [0.02, 0.59]
Roberge et al. 2008	10.2	8.8	32	9.5	10.3	33	10.8%	0.07 [-0.41, 0.56]
Total (95% CI)			**329**			**366**	**100.0%**	**0.13 [-0.07, 0.33]**

Heterogeneity: Tau² = 0.04; Chi² = 13.40, df = 8 (P = 0.10); I² = 40%
Test for overall effect: Z = 1.27 (P = 0.21)

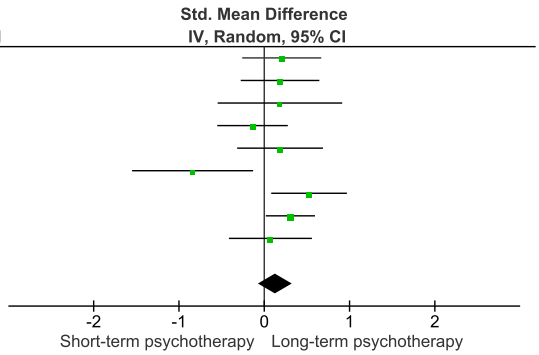


Table 1. Characteristics of included studies

Trial	Number of randomised	Participants	Short-term intervention	Long-term intervention	Overall risk of bias	Primary outcome
Barkham et al. 1996*	54	Major depressive disorder	8 sessions CBT (8 weeks)	16 sessions CBT (18 weeks)	High	No primary outcome was reported.
			8 sessions psychodynamic-interpersonal therapy (8 weeks)	16 sessions psychodynamic-interpersonal therapy (18 weeks)		
Bohni et al. 2009*	48	Panic disorder	8 sessions CBT (3 weeks)	13 sessions CBT (13 weeks)	High	No primary outcome was reported.
Bruijniks et al. 2020	200	Major depressive disorder	20 sessions CBT (24 weeks)	20 sessions CBT (16 weeks)	High	Primary outcome was depression severity as measured with the BDI-II.
			20 sessions interpersonal therapy (24 weeks)	20 sessions interpersonal therapy (16 weeks)		
Christensen et al. 2006*	931	Major depressive disorder	Brief online CBT and problem solving (unclear duration)	Extended online CBT and problem solving (unclear duration)	High	Primary outcome measure was score on the Goldberg Depression Scale
Clark et al. 1999	29	Panic disorder	5 sessions CBT (12 weeks)	12 sessions CBT (12 weeks)	High	No primary outcome was reported.
Dekker et al. 2004	103	Major depressive disorder	8 sessions short psychodynamic supportive psychotherapy (8 weeks)	16 sessions short psychodynamic supportive psychotherapy (24 weeks)	High	No primary outcome was reported.

Ehlers et al. 2014	61	PTSD	14 sessions cognitive therapy (5 weeks)	12 sessions cognitive therapy (12 weeks)	High	Primary outcome was severity of PTSD symptoms assessed with the Clinician- Administered PTSD Scale (CAPS).
Foa et al. 2018	219	PTSD	10 sessions prolonged exposure therapy (2 weeks)	10 sessions prolonged exposure therapy (8 weeks)	High	Primary outcome was severity of PTSD symptoms assessed with the PTSD Symptom Scale–Interview (PSS-I)
Herbert et al. 2004	34	Social anxiety disorder	12 sessions CBT (12 weeks)	12 sessions CBT (18 weeks)	High	No primary outcome was reported.
Kenardy et al. 2003	81**	Panic disorder	6 sessions CBT (6 weeks)	12 sessions CBT (12 weeks)	High	Primary measures included a comprehensive battery of panic and anxiety measures.
Knekt et al. 2008	229	Mood- and anxiety disorders	20 sessions psychodynamic therapy (20 weeks)	468 sessions psychodynamic therapy (156 weeks)	High	Primary outcomes were depressive and anxiety symptoms.
Lorentzen et al. 2013	167	Mood- anxiety- and personality disorders	20 sessions psychodynamic group therapy (20 weeks)	80 sessions psychodynamic group therapy (80 weeks)	High	No primary outcome was reported.
McMain et al. (unpublished data)	240	BPD	26 sessions DBT (26 weeks)	52 sessions DBT (52 weeks)	High	Primary outcome was frequency of suicidal or non-suicidal self-injurious episodes
Nacasch et al. 2015	40	PTSD	10-15 sessions prolonged exposure therapy (60 minutes)	10-15 sessions prolonged exposure therapy (90 minutes)	High	Primary outcome was severity of PTSD symptoms assessed with the Posttraumatic Symptom Scale-Interview (PSS-I).
Roberge et al. 2008	65	Panic disorder with agoraphobia	7 sessions CBT (16 weeks)	14 sessions CBT (15 weeks)	High	No primary outcome was reported.

Shapiro et al. 1990*	150	Major depressive disorder	8 sessions CBT (8 weeks)	16 sessions CBT (18 weeks)	High	No primary outcome was reported.
			8 sessions psychodynamic-relationship-oriented therapy (8 weeks)	16 sessions of psychodynamic-relationship-oriented therapy (18 weeks)		

*The results of these trials were not reported in a usable way; i.e. the results were reported in a graph, and standard deviations were not provided for the point estimates.
**This trial randomised a total of 186 participants to four groups. The number of randomised participants for the two relevant groups were not sufficiently reported, as only the number of participants who commenced treatment was reported.

BPD; borderline personality disorder, CBT; cognitive behavior therapy, DBT; dialectical behavior therapy, PTSD; post-traumatic stress disorder

Trials including participants with major depressive disorder*									
Trial characteristics			**Primary review outcomes**			**Secondary review outcomes**			**Trialists' own conclusions**
Trial ID	**Short-term intervention**	**Long-term intervention**	**Quality of Life**	**Serious Adverse Events**	**Symptom severity**	**Suicide/Suicide attempts**	**Self-harm**	**Level of functioning**	
Barkham et al. 1996	8 sessions CBT (8 weeks)	16 sessions CBT (18 weeks)	-	-	-	-	-	-	Clients given 16 sessions showed a statistically significant advantage over clients given 8 sessions on some measures at some assessments
	8 sessions psychodynamic-interpersonal therapy (8 weeks)	16 sessions psychodynamic-interpersonal therapy (18 weeks)							
Bruijniks et al. 2020	20 sessions CBT (24 weeks)	20 sessions CBT (16 weeks)	CBT: The mean RAND-36 scores at EoT were 50.13 (22.20) for the short-term group (n=49) and 51.53 (22.36) for the long-term group (n=39) (p=0.77) IPT: The mean RAND-36 scores at EoT were 46.8 (20.46) in the short-term group (n=36) and 53.46 (20.67) in the long-term group (n=47) (p=0.14)	-	CBT: The mean (SD) BDI scores at EoT were 24.16 (15.09) for the short-term group (n=37) and 21.25 (12.90) for the long-term group (n=35) (p=0.38) IPT: The mean (SD) BDI scores at EoT were 22.91 (14.75) for the short-term group (n=34) and 20.02 (16.05) for the long-term group (n=39) (p=0.42)	-	-	-	In clinical practice settings, delivery of twice weekly sessions of CBT and IPT for depression was superior to once weekly sessions when assessing depression outcomes.
	20 sessions interpersonal therapy (24 weeks)	20 sessions interpersonal therapy (16 weeks)							
Christensen 2006	Brief online CBT and problem solving (unclear duration)	Extended online CBT and problem solving (unclear duration)	-	-	-	-	-	-	Brief CBT-based interventions are not as effective as extended interventions.

Dekker et al. 2004	8 sessions short psychodynamic supportive psychotherapy (8 weeks)	16 sessions short psychodynamic supportive psychotherapy (24 weeks)	The mean (SD) QLDS scores at EoT were 22.6 (8.6) for the short-term group (n=45) and 22.8 (8.3) for the long-term group (n=45) (p=0.911)	-	The mean (SD) HDRS scores at EoT were 11.1 (6.8) for the short-term group (n=45) and 12.1 (7.6) for the long-term group (n=45) (p=0.512)	-	-	-	Eight or 16 psychotherapy sessions in addition to 8 sessions of pharmacotherapy over a period of 6 months would appear to be equally effective in terms of dealing with symptoms.
Shapiro et al. 1994	8 sessions CBT (8 weeks) 8 sessions psychodynamic-relationship-oriented therapy (8 weeks)	16 sessions CBT (18 weeks) 16 sessions of psychodynamic-relationship-oriented therapy (18 weeks)	-	-	-	-	-	-	There is no added benefit from 16 treatment sessions compared with 8.
Trials including participants with anxiety disorders*									
Trial characteristics			**Primary review outcomes**			**Secondary review outcomes**			**Trialists' own conclusions**
Trial ID	**Short-term intervention**	**Long-term intervention**	**Quality of Life**	**Serious Adverse Events**	**Symptom severity**	**Suicide/Suicide attempts**	**Self-harm**	**Level of functioning**	
Bohni et al. 2009	8 sessions CBT (3 weeks)	13 sessions CBT (13 weeks)	-	-	-	-	-	-	Patients in massed CBT achieved their results at a faster rate than patients in spaced CBT, with outcomes after 3 weeks in massed CBT comparable with those achieved after approximately 3 months in spaced CBT.
Clark et al. 1999	5 sessions CBT (12 weeks)	12 sessions CBT (12 weeks)	-	-	The mean (SD) BAI scores at EoT were 9.8 (6.7) for the short-term group (n=14) and 8.4 (8.0) for the long-term group (n=15)	-	-	-	Brief CT did not differ from full CT at posttreatment or at follow-up, and effect sizes were essentially the same.

					(p=0.615). This result is included in a meta-analysis.				
Herbert et al. 2004	12 sessions CBT (12 weeks)	12 sessions CBT (18 weeks)	-	-	The mean (SD) SPAI-SP scores at EoT were 76.71 (47.18) for the short-term group (n=15) and 113.77 (39.56) for the long-term group (n=19) (p=0.018). This result is included in a meta-analysis.	-	-	-	The results revealed that the standard treatment program in which therapy was provided over 12 successive weeks resulted in more rapid symptom reduction and lower dropout relative to the extended treatment delivered over 18 weeks.
Kenardy et al. 2003	6 sessions CBT (6 weeks)	12 sessions CBT (12 weeks)	-	-	The mean (SD) STAI-T scores at EoT were 47.86 (12.31) for the short-term group (n=39) and 41.10 (13.14) for the long-term group (n=42) (p=0.0195). This result is included in a meta-analysis.	-	-	-	A brief version performs significantly worse than the standard duration treatment at posttreatment.
Roberge et al. 2008	7 sessions CBT (16 weeks)	14 sessions CBT (15 weeks)	-	-	The mean (SD) PAS scores at EoT were 10.2 (8.8) for the short-term group (n=32) and 9.5 (10.3) for the long-term group (n=33) (p=0.77). This result is included in a meta-analysis.	-	-	-	Brief CBT effectiveness appears comparable to standard CBT in the short term.

Trials including participants with mood- and anxiety disorders*									
Trial characteristics			**Primary review outcomes**			**Secondary review outcomes**			**Trialists' own conclusions**
Trial ID	**Short-term intervention**	**Long-term intervention**	**Quality of Life**	**Serious Adverse Events**	**Symptom severity**	**Suicide/Suicide attempts**	**Self-harm**	**Level of functioning**	
Knekt et al. 2008	Short-term psychodynamic therapy	Long-term psychodynamic therapy	-	-	The mean (SD) HDRS scores at EoT were 10.8 (5.65) for the short-term group (n=83) and 9.0 (6.0) for the long-term group (n=107) (p=0.037).	-	-	The mean (SD) SAS-work scores at EoT were 1.88 (0.55) for the short-term group (n=83) and 1.72 (0.62) for the long-term group (n=107). (p=0.066). This result is included in a meta-analysis.	Patients receiving short-term psychodynamic psychotherapy recovered faster from both depressive and anxiety symptoms during the first year of follow-up. During the following 2 years, the symptoms persisted at the level reached in the brief therapy group, whereas in the long-term psychodynamic psychotherapy group the improvement continued during the entire 3-year period. In the long run, long-term psychodynamic psychotherapy thus gave greater benefits than those achieved by the brief therapies.
Lorentzen et al. 2013	Short-term psychodynamic group therapy	Long-term psychodynamic group therapy	-	-	-	There were 0/77 suicides or suicide attempts in the short-term group compared to 0/90 in the long-term group (p= not applicable)	-	The mean (SD) GAF scores at EoT were 67.8 (11.7) for the short-term group (n=71) and 68.1 (14.2) for the long-term group (n=79) (p=0.889). This result is included in a meta-analysis.	We observed that short- and long-term therapy were equally effective across 3 years, using IIP, GAF-S and GAF-F as the outcome variables. However, there was a trend in favour of long-term therapy (P=0.10) using GAF-S as the outcome variable.
Trials including participants with post-traumatic stress disorder*									

Trial characteristics			Primary review outcomes			Secondary review outcomes			Trialists' own conclusions
Trial ID	**Short-term intervention**	**Long-term intervention**	**Quality of Life**	**Serious Adverse Events**	**Symptom severity**	**Suicide/Suicide attempts**	**Self-harm**	**Level of functioning**	
Ehlers et al. 2014	Intensive cognitive therapy	Standard cognitive therapy	The mean (SD) Q-LES-Q scores at EoT were 52.67 (20.21) for the short-term group (n=30) and 62.93 (21.70) for the long-term group (n=31) (p=0.061).	-	The mean (SD) CAPS scores at EoT were 32.22 (27.20) for the short-term group (n=30) and 26.97 (28.68) for the long-term group (n=31) (p=0.466).	-	-	The mean (SD) SDS scores at EoT were 9.30 (8.20) for the short-term group (n=30) and 10.02 (9.76) for the long-term group (n=31) (p=0.757).	A novel 7-day intensive version of cognitive therapy for PTSD was well tolerated, achieved faster symptom reduction, and led to comparable overall outcomes as the standard once-weekly cognitive therapy delivered over 3 months.
Foa et al. 2018	Massed prolonged exposure	Extended prolonged exposure	-	-	The mean (SD) PSS-I scores at EoT were 18.88 (no SD reported) for the short-term group (n=110) and 18.34 (no SD reported) for the long-term group (n=110) (p=not applicable)	-	-	-	Among active duty military personnel with PTSD, massed prolonged exposure therapy (10 sessions delivered over 2 weeks) was noninferior to spaced pro-longed exposure therapy (10 sessions delivered over 8 weeks).
Nacasch et al. 2015	60 minutes sessions of prolonged exposure	90 minutes sessions of prolonged exposure	-	-	The mean (SD) PSS-I scores at EoT were 13.3 (9.52) for the short-term group (n=20) and 12.24 (8.02) for the long-term group (n=17) (p=0.719).	-	-	-	In sum, 20-minute imaginal exposure within 60-minute sessions yielded noninferior outcomes in PTSD symptoms and posttraumatic negative cognitions at posttreatment and follow-up to the 40-minute imaginal exposures and 90-minute sessions.

Trials including participants with borderline personality disorder*									
Trial characteristics			**Primary review outcomes**			**Secondary review outcomes**			**Trialists' own conclusions**
Trial	**Short-term intervention**	**Long-term intervention**	**Quality of Life**	**Serious Adverse Events**	**Symptom severity**	**Suicide/Suicide attempts**	**Self-harm**	**Level of functioning**	
McMain et al. (unpublished)	6 months of DBT	12 months of DBT	The mean (SD) overall EQ5DL scores at EoT were 60.7 (21.43) for the short-term group (n=91) compared with 61.41 (23.17) in the long-term group (n=90) (p=0.831)	2 / 90 participants had one or more serious adverse events in the short-term group at EoT compared with 2 / 93 in the long-term group (p=1) (based on suicide/ suicide attempt data only)	The mean (SD) BSL scores at EoT were 38.6 (22.4) for the short-term group (n=90) compared with 39.3 (22.2) in the long-term group (n=91) (p=0.833)	2 / 90 participants had one suicide or suicide-attempts in the short-term group at EoT compared with 2 / 93 in the long-term group (p=1)	28 / 90 participants had one or more deliberate self-harm incidents in the short-term group at EoT compared with 37/ 93 in the long-term group (p=0.28)	The mean (SD) SAS scores at EoT were 2.51 (0.58) for the short-term group (n=90) compared with 2.54 (0.59) in the long-term group (n=91) (p=0.731)	-

* Data is presented for the primary time-point of assessment (end of treatment)

BAI; Beck Anxiety Inventory; BSL: Borderline Symptom List-23; DBT; Dialectical Behavioural Therapy; CAPS: Clinician Administered PTSD Scale; CBT; Cognitive Behavioural Therapy; EoT: End of treatment; EQ5DL: Euroqol-5D-5; HDRS: Hamilton Depression Rating Scale; IPT; Interpersonal Therapy; PAS: Panic and Agoraphobia Scale; PSS-I: PTSD Symptom Scale Interview; SAS: Social Adjustment Scale; SD: Standard deviation; SDS: Sheehan Disability Scale; SPAI-SP: Social Phobia Anxiety Inventory – Social Phobia; STAI-T: State Trait Anxiety Inventory-Trait; QLDS: Quality of Life Depression Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported in section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	"Title page"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	"Abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	"Introduction"
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	"Introduction", "Methods", and subsection "Outcomes and subgroup analyses"
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	"Methods"
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	"Search strategies and selection criteria"
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	"Search strategies and selection criteria"
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	"Search strategies and selection criteria" and supplementary material 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	"Results", subsection "Study characteristics"
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	"Methods", subsection

PRISMA 2009 Checklist

			"Data extraction and risk of bias assessment"
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	"Methods", subsection "Data extraction and risk of bias assessment"
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	"Methods", subsection "Assessment of statistical and clinical significance"
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	"Methods", subsection "Assessment of statistical and clinical significance"

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	"Methods", subsection "Assessment of statistical and clinical significance", Protocol
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Protocol and "Methods" subsection "outcomes and subgroup analyses".
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	"Results", subsection

			"Study characteristics", Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	"Results"
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	"Results", supplementary material 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	"Results"
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	"Results"
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	"Results", supplementary material 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	"Results"
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	"Discussion"
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	"Discussion"
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	"Discussion"
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	"Funding"

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Search strategies for
Short-term versus long-term psychotherapy for adult psychiatric disorders: a systematic review with meta-analysis
Search performed 18 June 2020

Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 6) in the Cochrane Library (7270 hit)

#1 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees
#2 (attention deficit hyperactivity disorder or adhd).ti,ab
#3 #1 or #2
#4 MeSH descriptor: [Psychotic Disorders] explode all trees
#5 MeSH descriptor: [Schizophrenia] explode all trees
#6 (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) near (think* or motor*)) or schizophreni*).ti,ab
#7 #4 or #5 or #6
#8 MeSH descriptor: [Bipolar Disorder] explode all trees
#9 (bipolar or mood elevation or mania or hypomania or depress*).ti,ab
#10 #8 or #9
#11 MeSH descriptor: [Depressive Disorder] explode all trees
#12 (depressi* or mood or unipolar).ti,ab
#13 #11 or #12
#14 MeSH descriptor: [Anxiety Disorders] explode all trees
#15 (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab
#16 #14 or #15
#17 MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees
#18 (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*))).ti,ab
#19 #17 or #18
#20 MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees
#21 (post-trauma* or trauma*).ti,ab
#22 #20 or #21
#23 MeSH descriptor: [Feeding and Eating Disorders] explode all trees
#24 (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab
#25 #23 or #24
#26 MeSH descriptor: [Personality Disorders] explode all trees
#27 (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab
#28 #26 or #27
#29 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
#30 MeSH descriptor: [Psychotherapy] explode all trees
#31 (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab
#32 #30 or #31
#33 (brief or extended or standard or intensiv* or ((short* or long*) and term))
#34 #32 and #33
#35 #29 and #34

MEDLINE Ovid (1946 to June 2020) (5906 hits)

1. exp Attention Deficit Disorder with Hyperactivity/
2. (attention deficit hyperactivity disorder or adhd).ti,ab.
3. 1 or 2
4. exp Psychotic Disorders/
5. exp Schizophrenia/
6. (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) adj (think* or motor*)) or schizophreni*).ti,ab.
7. 4 or 5 or 6
8. exp Bipolar Disorder/
9. (bipolar or mood elevation or mania or hypomania or depress*).ti,ab.
10. 8 or 9
11. exp Depressive Disorder/

12. (depressi* or mood or unipolar).ti,ab.
13. 11 or 12
14. exp Anxiety Disorders/
15. (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab.
16. 14 or 15
17. exp Obsessive-Compulsive Disorder/
18. (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive adj (mental or behavior*))).ti,ab.
19. 17 or 18
20. exp Stress Disorders, Post-Traumatic/
21. (post-trauma* or trauma*).ti,ab.
22. 20 or 21
23. exp "Feeding and Eating Disorders"/
24. (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab.
25. 23 or 24
26. exp Personality Disorders/
27. (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab.
28. 26 or 27
29. 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
30. exp psychotherapy/
31. (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab.
32. 30 or 31
33. (brief or extended or standard or intensiv* or ((short* or long*) and term)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
34. 32 and 33
35. 29 and 34
36. limit 35 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
37. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
38. 36 and 37

Embase Ovid (1974 to June 2020) (7025 hits)
1. exp attention deficit disorder/
2. (attention deficit hyperactivity disorder or adhd).ti,ab.
3. 1 or 2
4. exp psychosis/
5. exp schizophrenia/
6. (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) adj (think* or motor*)) or schizophreni*).ti,ab.
7. 4 or 5 or 6
8. exp bipolar disorder/
9. (bipolar or mood elevation or mania or hypomania or depress*).ti,ab.
10. 8 or 9
11. exp depression/
12. (depressi* or mood or unipolar).ti,ab.
13. 11 or 12
14. exp anxiety disorder/
15. (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia).ti,ab.
16. 14 or 15
17. exp obsessive compulsive disorder/
18. (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive adj (mental or behavior*))).ti,ab.
19. 17 or 18
20. exp posttraumatic stress disorder/
21. (post-trauma* or trauma*).ti,ab.

22. 20 or 21
23. exp eating disorder/
24. (eating behavior or anorexia* or bulimia* or binge-eating*).ti,ab.
25. 23 or 24
26. exp personality disorder/
27. (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*).ti,ab.
28. 26 or 27
29. 3 or 7 or 10 or 13 or 16 or 19 or 22 or 25 or 28
30. exp psychotherapy/
31. (((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care).ti,ab.
32. 30 or 31
33. (brief or extended or standard or intensiv* or ((short* or long*) and term)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
34. 32 and 33
35. 29 and 34
36. limit 35 to (adult <18 to 64 years> or aged <65+ years>)
37. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
38. 36 and 37

LILACS (Bireme; 1982 to June 2020) (1273 hits)
(attention deficit hyperactivity disorder or adhd) or (psychotic or delusion$ or hallucination$ or ((disorgani$ed or abnormal) and (think$ or motor$)) or schizophreni$) or (bipolar or mood elevation or mania or hypomania or depress$) or (depressi$ or mood or unipolar) or (anxiet$ or fear or avoidance behavior$ or phobia$ or panic$ or agoraphobia) or (obsessive compulsive disorder or OCD or urge$ or obsessi$ or (repetetive and (mental or behavior$))) or (post-trauma$ or trauma$) or (eating behavior or anorexia$ or bulimia$ or binge-eating$) or (schizotypal$ or paranoid$ or schizoid$ or histrionic$ or narcissistic$ or antisocial$ or borderline$ or avoidant$ or dependent or obsessive-compulsi$) [Words] and (((psycho$ or cognitive or behavior$ or humanistic or systemic) and therap$) or psychotherap$ or self care or self-care) [Words] and (brief or extended or standard or intensiv$ or ((short$ or long$) and term)) [Words]

PsycINFO (EBSCO*host*; 1806 to June 2020) (5067 hits)
S37 S35 AND S36
S36 TX (random* or blind* or placebo* or meta-analys*)
S35 S29 AND S34
S34 S32 AND S33
S33 TI ((brief or extended or standard or intensiv* or ((short* or long*) and term))) OR AB ((brief or extended or standard or intensiv* or ((short* or long*) and term)))
S32 S30 OR S31
S31 TI ((((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care)) OR AB ((((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care))
S30 MA Psychotherapy
S29 S3 OR S7 OR S10 OR S13 OR S16 OR S19 OR S22 OR S25 OR S28
S28 S26 OR S27
S27 TI ((schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*)) OR AB ((schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*))
S26 MA Personality Disorders
S25 S23 OR S24
S24 TI ((eating behavior or anorexia* or bulimia* or binge-eating*)) OR AB ((eating behavior or anorexia* or bulimia* or binge-eating*))
S23 MA Feeding and Eating Disorders
S22 S20 OR S21
S21 TI ((post-trauma* or trauma*)) OR AB ((post-trauma* or trauma*))
S20 MA Stress Disorders, Post-Traumatic

S19 S17 OR S18
S18 TI ((obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*)))) OR AB ((obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*))))
S17 MA Obsessive-Compulsive Disorder
S16 S14 OR S15
S15 TI ((anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia)) OR AB ((anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia))
S14 MA Anxiety Disorders
S13 S11 OR S12
S12 TI ((depressi* or mood or unipolar)) OR AB ((depressi* or mood or unipolar))
S11 MA Depressive Disorder
S10 S8 OR S9
S9 TI ((bipolar or mood elevation or mania or hypomania or depress*)) OR AB ((bipolar or mood elevation or mania or hypomania or depress*))
S8 MA Bipolar Disorder
S7 S4 OR S5 OR S6
S6 TI ((psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) near (think* or motor*)) or schizophreni*)) OR AB ((psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) near (think* or motor*)) or schizophreni*))
S5 MA Schizophrenia
S4 MA Psychotic Disorders
S3 S1 OR S2
S2 TI ((attention deficit hyperactivity disorder or adhd)) OR AB ((attention deficit hyperactivity disorder or adhd))
S1 MA attention deficit disorder with hyperactivity

Science Citation Index Expanded (SCI-EXPANDED) (1900 to June 2020); Social Sciences Citation Index (SSCI) (1956 to June 2020); Conference Proceedings Citation Index- Science (CPCI-S) (1990 to June 2020); and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) (1990 to June 2020) (Web of Science) (5782 hits)
#7 #6 AND #5
#6 TS=(random* or blind* or placebo* or meta-analys*)
#5 #4 AND #1
#4 #3 AND #2
#3 TS=(brief or extended or standard or intensiv* or ((short* or long*) and term))
#2 TS=(((psycho* or cognitive or behavior* or humanistic or systemic) and therap*) or psychotherap* or self care or self-care)
#1 TI=((attention deficit hyperactivity disorder or adhd) or (psychotic or delusion* or hallucination* or ((disorgani*ed or abnormal) and (think* or motor*)) or schizophreni*) or (bipolar or mood elevation or mania or hypomania or depress*) or (depressi* or mood or unipolar) or (anxiet* or fear or avoidance behavior* or phobia* or panic* or agoraphobia) or (obsessive compulsive disorder or OCD or urge* or obsessi* or (repetetive near (mental or behavior*))) or (post-trauma* or trauma*) or (eating behavior or anorexia* or bulimia* or binge-eating*) or (schizotypal* or paranoid* or schizoid* or histrionic* or narcissistic* or antisocial* or borderline* or avoidant* or dependent or obsessive-compulsi*))

List of included papers

[1-16]

1. Knekt P, Lindfors O, Harkanen T, et al. Randomized trial on the effectiveness of long- and short-term psychodynamic psychotherapy and solution-focused therapy on psychiatric symptoms during a 3-year follow-up. *Psychol Med.* 2008;38(5):689-703.
2. Lorentzen S, Ruud T, Fjeldstad A, et al. Comparison of short- and long-term dynamic group psychotherapy: randomised clinical trial. *Br J Psychiatry.* 2013;203(3):280-7.
3. Herbert JD, Rheingold AA, Gaudiano BA, et al. Standard Versus Extended Cognitive Behavior Therapy for Social Anxiety Disorder: A Randomized-Controlled Trial. *Behavioural and Cognitive Psychotherapy.* 2004;32(2):131-47.
4. Clark DM, Salkovskis PM, Hackmann A, et al. Brief Cognitive Therapy for Panic Disorder: A Randomized Controlled Trial. *Journal of Consulting and Clinical Psychology.* 1999;67(4):583-9.
5. Roberge P, Marchand A, Reinharz D, et al. Cognitive-Behavioral Treatment for Panic Disorder With Agoraphobia A Randomized, Controlled Trial and Cost-Effectiveness Analysis. *Journal of Behavior Modification.* 2008;32(3):333-51.
6. Bruijniks SJE, Lemmens L, Hollon SD, et al. The effects of once- versus twice-weekly sessions on psychotherapy outcomes in depressed patients. *Br J Psychiatry.* 2020;216(4):222-30.
7. Barkham M, Rees A, Shapiro DA, et al. Outcomes of time-limited psychotherapy in applied settings: replicating the Second Sheffield Psychotherapy Project. *J Consult Clin Psychol.* 1996;64(5):1079.
8. Shapiro DA, Barkham M, Rees A, et al. Effects of treatment duration and severity of depression on the effectiveness of cognitive-behavioral and psychodynamic-interpersonal psychotherapy. *J Consult Clin Psychol.* 1994;62(3):522.
9. Bohni M, Spindler H, Arendt M, et al. A randomized study of massed three-week cognitive behavioural therapy schedule for panic disorder. *Acta Psychiatr Scand.* 2009;120(3):187-95.
10. Christensen H, Griffiths K, Mackinnon A, et al. Online randomized controlled trial of brief and full cognitive behaviour therapy for depression. *Psychol Med.* 2006;36(12):1737.
11. Dekker J, Molenaar PJ, Kool S, et al. Dose–effect relations in time-limited combined psycho-pharmacological treatment for depression. *Psychol Med.* 2005;35(1):47-58.
12. Ehlers A, Hackmann A, Grey N, et al. A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused supportive therapy. *Am J Psychiatry.* 2014;171(3):294-304.
13. Foa EB, McLean CP, Zang Y, et al. Effect of prolonged exposure therapy delivered over 2 weeks vs 8 weeks vs present-centered therapy on PTSD symptom severity in military personnel: A randomized clinical trial. *JAMA.* 2018;319(4):354-64.
14. Nacasch N, Huppert JD, Su Y-J, et al. Are 60-Minute Prolonged Exposure Sessions With 20-Minute Imaginal Exposure to Traumatic Memories Sufficient to Successfully Treat PTSD? A Randomized Noninferiority Clinical Trial. *Behav Ther.* 2015;46(3):328-41.
15. Kenardy JA, Dow MG, Johnston DW, et al. A comparison of delivery methods of cognitive-behavioral therapy for panic disorder: an international multicenter trial. *J Consult Clin Psychol.* 2003;71(6):1068.

16. McMain S. The effectiveness of 6 versus 12-months of dialectical behaviour therapy for borderline personality disorder: the feasibility of a shorter treatment and evaluating responses (FASTER) trial. 2020(Unpublished data).

Risk of bias

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Barkham et al. 1996	-	-	-	-	-	-	+	X
Bohni et al. 2009	-	-	-	X	X	-	+	X
Bruijniks et al. 2020	+	+	-	-	X	X	+	X
Christensen et al. 2006	-	-	-	-	-	-	+	X
Clark et al. 1999	-	-	-	-	-	-	X	X
Dekker et al. 2004	-	-	X	+	X	-	+	X
Ehlers et al. 2014	-	-	X	+	+	-	+	X
Foa et al. 2018	-	-	-	+	X	X	+	X
Herbert et al. 2004	-	-	X	X	X	-	+	X
Kenardy et al. 2003	-	-	-	-	-	X	X	X
Knekt et al. 2008	+	+	-	X	X	-	+	X
Lorentzen et al. 2013	X	-	-	-	X	X	+	X
McMain (unpublished)	+	+	X	+	X		+	X
Nacasch et al. 2015	+	+	-	+	X	-	+	X
Roberge et al. 2008	-	-	-	-	-	-	+	X
Shapiro et al. 1990	-	-	-	-	X	-	+	X

D1: Random sequence generation
D2: Allocation concealment
D3: Blinding of participants and personnel
D4: Blinding of outcome assessment
D5: Incomplete outcome data
D6: Selective reporting
D7: Other sources of bias

Judgement
X High
- Unclear
+ Low
No information

Supplementary material: Required information sizes for the predefined review outcomes

		Predefined review outcomes					
Trial	**Number randomized**	**Quality of life**	**Serious adverse events**	**Symptom severity**	**Suicide/ suicide-attempts**	**Self-harm**	**Level of functioning**
Barkham et al. 1996	54	-	-	-	-	-	-
Bohni et al. 2009*	48	-	-	-	-	-	-
Bruijniks et al. 2020	CBT: 100	CBT: RIS: 188	-	CBT: RIS: 190	-	-	-
	IPT: 100	IPT RIS: 186		IPT: RIS: 178			
Christensen et al. 2006	931	-	-	-	-	-	-
Clark et al. 1999	29	-	-	RIS: 148	-	-	-
Dekker et al. 2004	103	RIS: 174	-	RIS: 154	-	-	-
Ehlers et al. 2014	61	RIS: 174	-	RIS: 188	-	-	RIS: 170
Foa et al. 2018	219	-	-	N/A	-	-	-
Herbert et al. 2004	34	-	-	RIS: 178	-	-	-
Kenardy et al. 2003	81	-	-	RIS: 188	-	-	-
Knekt et al. 2008	229	-	-	RIS: 178	-	-	RIS: 218
Lorentzen et al. 2013	167	-	-	-	N/A	-	RIS: 188
McMain et al. (unpublished data)	240	RIS: 170	RIS: 49,084	RIS: 172	RIS: 49,084	RIS: 1,596	RIS: 172
Nacasch et al. 2015	40	-	-	RIS: 162	-	-	-
Roberge et al. 2008	65	-	-	RIS: 232	-	-	-
Shapiro et al. 1990	150	-	-	-	-	-	-

CBT; Cognitive Behavioural Therapy: IPT; Interpersonal Therapy: RIS; Required Information Size

Summary of Findings table

Short-term versus long-term dialectical behavioral therapy for borderline personality disorder at end of treatment

Patients or population: Borderline personality disorder
Setting: Any setting
Intervention: Short-term dialectical behavioral therapy
Comparison: Long-term dialectical behavioral therapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term DBT	Risk with Short-term DBT				
Quality of life Follow-up: 12 months	-	-	MD: -0.71 (-7.25 to 5.83)	181 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	
Serious adverse events Follow-up: 12 months	22 per 1,000	22 per 1,000	-	183 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Symptom severity Follow-up: 12 months	-	-	MD: -0.7 (-7.24 to 5.84)	181 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	
Suicide or suicide attempts Follow-up: 12 months	22 per 1,000	22 per 1,000	-	183 (1 RCT)	⨁◯◯◯ VERY LOW [a,b, c]	
Self-harm Follow-up: 12 months	397 per 1,000	311 per 1,000	-	183 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Level of functioning Follow-up: 12 months	-	-	MD: 0.73 (-0.2 to 0.14)	181 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence; **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded 2 for risk of bias
b. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings
c. Downgraded 2 for imprecision due to low number of participants

Summary of Findings table

Short-term versus long-term psychodynamic psychotherapy for mood- and anxiety disorders at end of treatment

Patients or population: Mood- and anxiety disorders
Setting: Any setting
Intervention: Short-term psychodynamic psychotherapy
Comparison: Long-term psychodynamic psychotherapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term psychodynamic	Risk with Short-term psychodynamic				
Quality of life	-	-	-	-	-	Outcome not yet measured or reported
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: 36 months	-	-	MD: 1.8 (0.112 to 3.48)	190 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	
Suicide or suicide attempts Follow-up: 36 months	0 per 1,000	0 per 1,000	-	167 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning Follow-up: mean 36 months	-	-	SMD -0.13; (-0.42 to 0.15)	340 (2 RCTs)	⊕◯◯◯ VERY LOW [a,c]	

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence; **SMD:** Standardized Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for indirectness as the results are from a single trial from a single country, therefore results may not be generalizable to other settings.
c. Downgraded 1 for imprecision due to low number of participants

Summary of Findings table

Short-term versus long-term cognitive behavioral therapy for major depressive disorder at end of treatment

Patients or population: Major depressive disorder
Setting: Any setting
Intervention: Short-term cognitive behavioral therapy
Comparison: Long-term cognitive behavioral therapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term CBT	Risk with Short-term CBT				
Quality of life Follow-up: 6 months	-	-	MD -1.4 (-10.33 to 7.53)	98 (1 RCT)	⊕◯◯◯ VERY LOW [a,b, c]	
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: 6 months	-	-	MD: 2.91 (-2.71 to 8.5)	98 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning	-	-	-	-	-	Outcome not yet measured or reported

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence; **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings

Summary of Findings table

Short-term versus long-term interpersonal therapy for major depressive disorder at end of treatment

Patients or population: Major depressive disorder
Setting: Any setting
Intervention: Short-term interpersonal therapy
Comparison: Long-term interpersonal therapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term interpersonal therapy	Risk with Short-term interpersonal therapy				
Quality of life Follow-up: 6 months	-	-	MD: -6.66 (-14.76 to 1.44)	102 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: 6 months	-	-	MD: 2.89 (-3.16 to 8.94)	102 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning	-	-	-	-	-	Outcome not yet measured or reported

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence, **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings

Summary of Findings table

Short-term versus long-term psychodynamic psychotherapy for major depressive disorder at end of treatment

Patients or population: Major depressive disorder
Setting: Any setting
Intervention: Short-term psychodynamic psychotherapy
Comparison: Long-term psychodynamic psychotherapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term psychodynamic psychotherapy	Risk with Short-term psychodynamic psychotherapy				
Quality of life Follow-up: 24 weeks	-	-	MD: -0.2 (-3.74 to 3.34)	90 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: 24 weeks	-	-	MD: -1 (-4.02 to 2.02)	90 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning	-	-	-	-	-	Outcome not yet measured or reported

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence, **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings

Summary of Findings table

Short-term versus long-term cognitive behavioral therapy for post-traumatic stress disorder at end of treatment

Patients or population: Post-traumatic stress disorder
Setting: Any setting
Intervention: Short-term cognitive behavioral therapy
Comparison: Long-term cognitive behavioral therapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term CBT	Risk with Short-term CBT				
Quality of life Follow-up: 14 weeks	-	-	MD: -10 (-21.01 to 0.49)	61 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: 14 weeks	-	-	MD: 5.25 (-9.07 to 19.57)	61 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning Follow-up: 14 weeks	-	-	MD: -0.72 (-5.34 to 3.90)	61 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	

CBT: cognitive behavioral therapy; **CI:** Confidence interval; **GRADE:** GRADE Working Group grades of evidence, **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings

Summary of Findings table

Short-term versus long-term prolonged exposure therapy for post-traumatic stress disorder at end of treatment

Patients or population: Post-traumatic stress disorder
Setting: Any setting
Intervention: Short-term prolonged exposure therapy
Comparison: Long-term prolonged exposure therapy

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term CBT	Risk with Short-term CBT				
Quality of life	-	-	-	-	-	Outcome not yet measured or reported
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: posttreatment (unclear)	-	-	MD: 1.06 (-4.87 to 6.99)	37 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning	-	-	-	-	-	Outcome not yet measured or reported

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence; **MD:** Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 1 for indirectness because the results are from a single trial from a single country, therefore results may not be generalizable to other settings

Summary of Findings table

Short-term versus long-term cognitive behavioral therapy for anxiety disorders at end of treatment

Patients or population: Anxiety disorders
Setting: Any setting
Intervention: Short-term cognitive behavioral therapy
Comparison: Long-term cognitive behavioral therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Long-term CBT	Risk with Short-term CBT				
Quality of life	-	-	-	-	-	Outcome not yet measured or reported
Serious adverse events	-	-	-	-	-	Outcome not yet measured or reported
Symptom severity Follow-up: mean 28.5 weeks	-	-	SMD: 0.08 (-0.47 to 0.63)	209 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	
Suicide or suicide attempts	-	-	-	-	-	Outcome not yet measured or reported
Self-harm	-	-	-	-	-	Outcome not yet measured or reported
Level of functioning	-	-	-	-	-	Outcome not yet measured or reported

CI: Confidence interval; **GRADE:** GRADE Working Group grades of evidence; **SMD:** Standardized Mean Difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Downgraded 2 for risk of bias
b. Downgraded 1 for imprecision due to low number of participants
c. Downgraded 2 for heterogeneity ($I^2 = 73\%$)

Paper III

Juul et al. Trials (2019) 20:196
https://doi.org/10.1186/s13063-019-3306-7

Trials

STUDY PROTOCOL Open Access

Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomized clinical trial

Sophie Juul[1,2*], Susanne Lunn[2], Stig Poulsen[2], Per Sørensen[1], Mehrak Salimi[1], Janus Christian Jakobsen[3], Anthony Bateman[4] and Sebastian Simonsen[1]

Abstract

Background: Psychotherapy for borderline personality disorder is often lengthy and resource-intensive. However, the current length of outpatient treatments is arbitrary and based on trials that never tested if the treatment intensity could be reduced. As a result, there is insufficient evidence to inform the decision between short-term and long-term psychotherapy for borderline personality disorder. Mentalization-based therapy is one treatment option for borderline personality disorder and consists traditionally of an 18-month treatment program.

Methods/design: This trial is an investigator-initiated single-center randomized clinical superiority trial of short-term (20 weeks) compared to long-term (14 months) mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder. Participants will be recruited from the Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre, Mental Health Services, Capital Region of Denmark. Participants will be included if they meet a minimum of four DSM-V criteria for borderline personality disorder. Participants will be assessed before randomization, and at 8, 16, and 24 months after randomization. The primary outcome is severity of borderline symptomatology assessed with the Zanarini Rating Scale for borderline personality disorder. Secondary outcomes include self-harm incidents, functional impairment (Work and Social Adjustment Scale, Global Assessment of Functioning) and quality of life (Short-Form Health Survey 36). Severity of psychiatric symptoms (Symptom Checklist 90-R) will be included as an exploratory outcome. Measures of personality functioning, attachment, borderline symptoms, group alliance, and mentalization skills will be included to explore potential predictors and mechanisms of change.

Discussion: This trial will provide evidence of the beneficial and harmful effects of short-term compared to long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder.

Trial registration: ClinicalTrials.gov, NCT03677037. Registered on September 19, 2018.

Keywords: Mentalization-based therapy, Borderline personality disorder, Randomized clinical trial, Treatment intensity

* Correspondence: sophie.juul@regionh.dk
[1]Stolpegaard Psychotherapy Centre, Mental Health Services, Gentofte, Capital Region of Denmark, Denmark
[2]Department of Psychology, University of Copenhagen, Copenhagen, Denmark
Full list of author information is available at the end of the article

Background

Borderline personality disorder is a psychiatric condition characterized by a pervasive pattern of symptoms such as interpersonal conflicts, identity diffusion, impulsivity, and emotional dysregulation [1]. According to epidemiological studies, 1.6% of the general population suffer from borderline personality disorder [2]. In clinical populations, it is the most common personality disorder [2], with a prevalence of between 9% and 22% of all psychiatric outpatients [3–5]. Borderline personality disorder is associated with high levels of psychiatric comorbidity, particularly depression, anxiety disorders, eating disorders, substance abuse [6–8], and other personality disorders [9]. Together, these findings emphasize the need for the development of efficacious and cost-effective treatments for this severe and highly prevalent disorder.

While pharmacological treatment may reduce some borderline-related symptoms, there is still no convincing evidence that it is suitable for treating all diagnostic criteria [10]. Although further evidence is still warranted, psychotherapy continues to be the primary treatment of choice for borderline personality disorder [11]. During the last 10–15 years, studies have established the efficacy of different forms of intensive, specialized long-term psychotherapy modalities. These have recently been evaluated in a systematic review and meta-analysis exploring the efficacy of psychotherapies for borderline personality disorder, in which it was concluded that dialectical behavior therapy and psychodynamic therapies (transference focused therapy and mentalization-based therapy) significantly improved borderline-relevant outcomes [12]. However, no single treatment modality has been established as the primary treatment of choice.

Mentalization-based therapy (MBT) is a psychodynamic therapy rooted in attachment and cognitive theory [13], which was developed specifically for treating borderline personality disorder [14]. Mentalization refers to the capacity to understand one's own and others' mental states. The theoretical assumption is that patients with borderline personality disorder are more vulnerable to lose this capacity when experiencing emotional distress. The MBT manual offers therapeutic techniques to identify these shifts and to bring the patient back into a mentalizing mode [14, 15]. The therapy program consists of four basic components: (1) psycho-education, (2) case formulation, (3) group therapy, and (4) individual therapy. All of these aim to enhance the patient's capacity to mentalize. Increasing mentalization skills is assumed to minimize borderline-related symptoms such as emotional dysregulation, impulsivity, and suicidal ideation. However, information about the mechanisms that produce a change in MBT, or in psychotherapy in general, is still limited [16, 17].

MBT for adult borderline personality disorder has been tested in cohort studies [18, 19] and one randomized but uncontrolled trial [20]. Two forms of MBT have been tested in randomized controlled trials: day hospital MBT [21, 22] and intensive outpatient MBT [13], each lasting a maximum of 18 months. For a systematic review of the current evidence base of MBT for borderline personality disorder, see Vogt and Norman [16].

Bateman and Fonagy [13] assessed the effects of intensive outpatient MBT in a randomized clinical trial, in which 134 participants with a confirmed borderline personality disorder diagnosis were randomized either to 18 months of outpatient MBT, combining weekly group and individual sessions with different therapists, or to structured clinical management. In this trial, MBT was superior to structured clinical management in terms of its effects on suicide attempts, severe incidents of self-harm, and on self-reported measures. Treatment effects were sustained at the 5-year follow-up [23]. Nevertheless, only 134 participants were randomized, which questions whether the trial was powered to assess the chosen outcomes, and only 41 were assessed after 5 years. Further, the trial investigators were also the developers of MBT. Thus, the small sample size and the substantial problems with incomplete outcome data, especially at the long-term follow-up, are threats to the validity of the study.

However, while intensive outpatient MBT currently has empirical support as an 18-month program for borderline personality disorder, evidence that this is the optimal length of the intervention is not available. Consequently, MBT is now offered for different lengths of time (both shorter and longer) in outpatient settings around the world [14]. Various other short-term psychotherapies for borderline personality disorder have already been developed and tested in randomized clinical trials, e.g., emotion regulation group therapy [24], systems training for emotional predictability and problem-solving [25, 26], and brief dialectical behavior therapy skills training [27]. However, all the trials have either compared a short-term experimental group to a short-term control group or tested the short-term treatment as an adjunctive to treatment as usual. Thus, these trials do not provide guidance on evidence-based decisions regarding the optimal length of treatment for borderline patients. In addition, no empirical evidence is available to identify which subtypes of patients would benefit from short-term treatment and which would require more intensive treatment [28].

We performed a preliminary literature search (PubMed and Cochrane Library) for trials comparing different lengths of psychotherapy for borderline personality disorder. No such trials were found. When we expanded our search terms to all types of psychiatric disorders, only few trials were identified [29, 30]. We are

currently working on a protocol for a more comprehensive systematic review, including a full assessment of risk of bias and a trial sequential analysis of short-term compared with long-term psychotherapy for all psychiatric disorders. The systematic review will be submitted for publication before data collection is completed in this trial.

Methods/design

Objective

The primary objective of this trial will be to evaluate the beneficial and harmful effects of short-term (20 weeks) MBT compared with long-term (14 months) MBT for adult outpatients with subthreshold or diagnosed borderline personality disorder. We will evaluate the treatments on the primary outcome (borderline symptomatology), secondary outcomes (self-harm incidents, quality of life, and functional impairment, and exploratory outcomes (psychiatric symptoms). Measures of personality functioning, attachment, borderline psychopathology, group cohesion, and mentalization skills will be included as predictor and mediator variables.

Design

We have designed an investigator-initiated parallel-group single-centre randomized clinical superiority trial of short-term versus long-term MBT for outpatients with subthreshold or diagnosed borderline personality disorder. The Consolidated Standards of Reporting Trials (CONSORT) flow chart for the trial is shown in Fig. 1. [31, 32]. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) participant timeline is given in Fig. 2, and the SPIRIT checklist is given in Additional file 1 [33].

We will consider for participation all patients referred to the trial site. Patients will be included in the trial, if they comply with the eligibility criteria listed in Table 1. There are inclusion and exclusion criteria as part of the procedure for clinical intake at the trial site, and criteria specific to this trial. For a detailed overview of typical

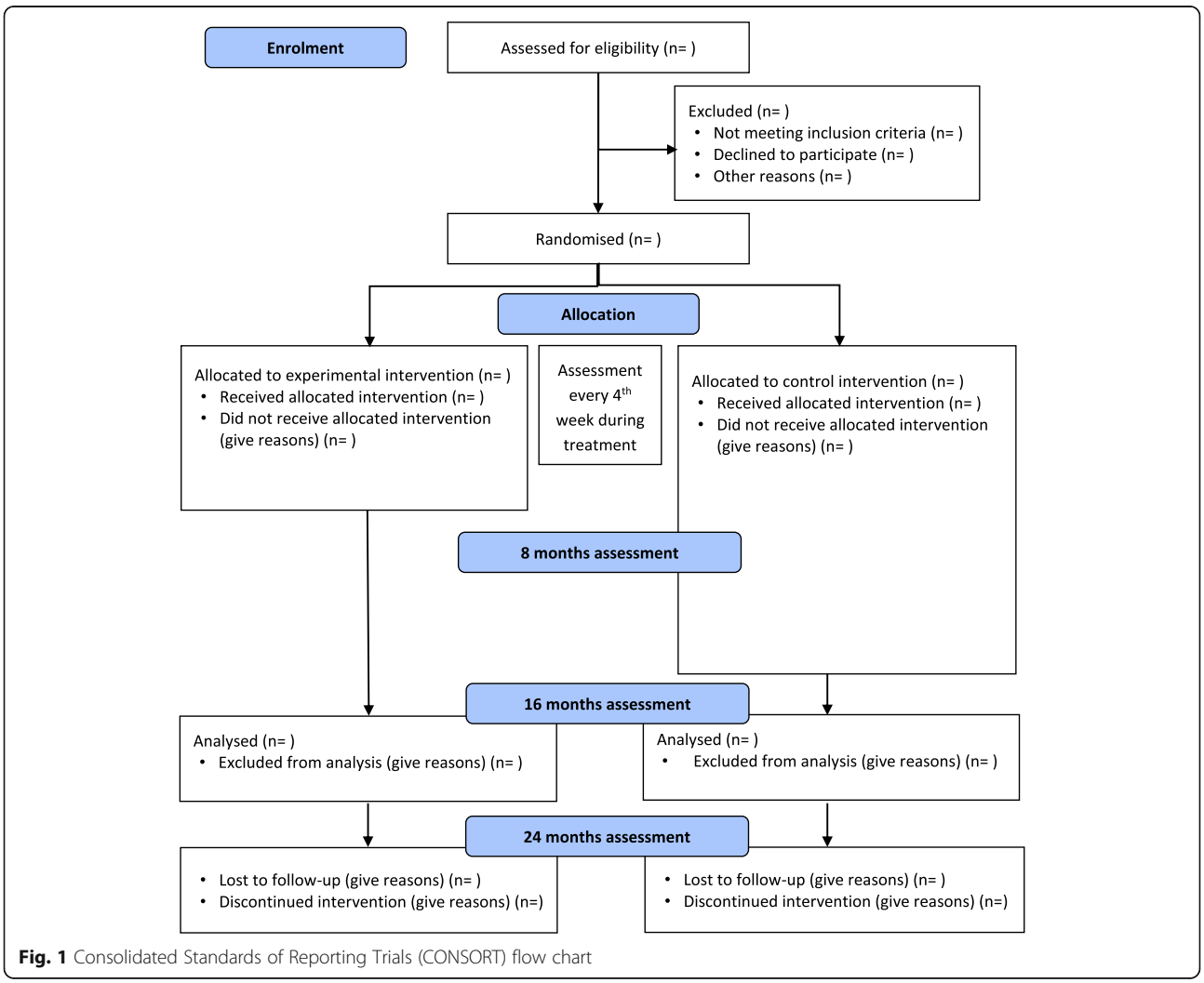


Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart

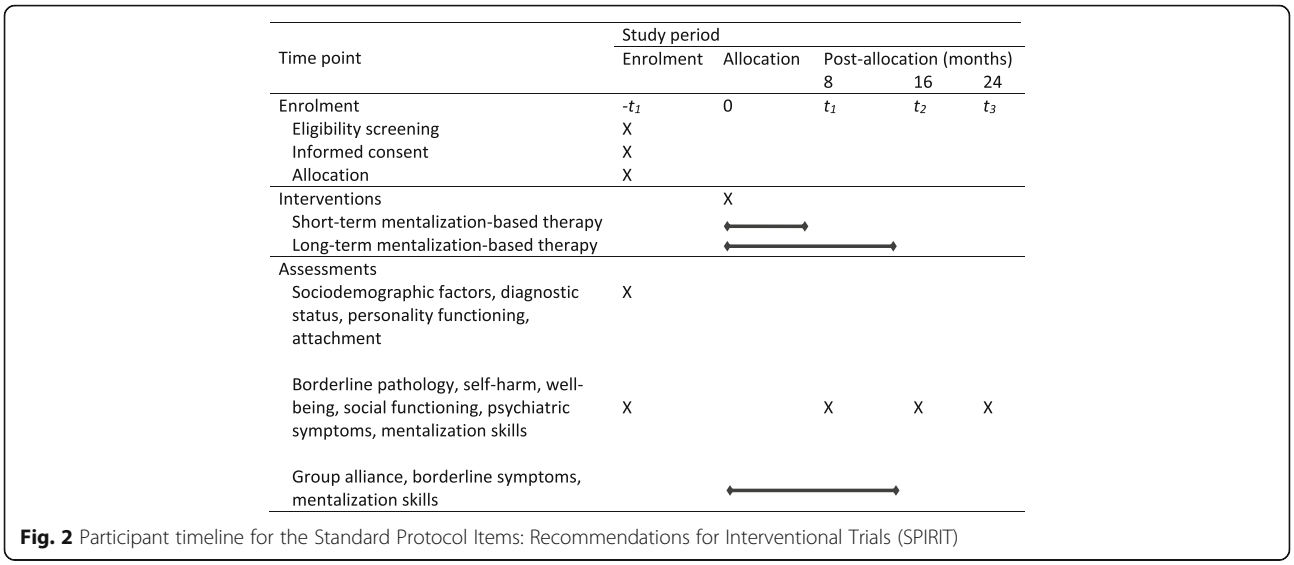


Fig. 2 Participant timeline for the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

patient characteristics at the trial site, see Simonsen et al. [34].

We will include participants with at least subthreshold borderline personality disorder. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) [1], the threshold for a full diagnosis is five out of nine diagnostic criteria. However, there is increasing evidence that even four confirmed diagnostic criteria are not qualitatively different from diagnosed borderline personality disorder in terms of impairment, and that the diagnostic threshold should be more inclusive than established by the DSM system to reflect the dimensionality of the construct [35, 36]. For this reason, previous trials have included participants with at least a subthreshold diagnosis [24, 37], and we will do the same in this trial.

Trial site and personnel

The trial site is the Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre, Mental Health Services, Capital Region of Denmark (from now on referred to as "the clinic"). The clinic specializes in MBT for borderline personality disorder. Patients are referred from the Capital Region of Denmark via a central visitation unit, where they are initially screened for eligibility before referral to the clinic. Once referred to the clinic, psychiatrists and attending physicians will perform the initial selection and screening of a participant to the trial and collect informed consent. The principal investigator, sponsor-investigator, or a trained research assistant will then conduct the baseline assessments of the participant. All post-baseline assessments will be carried out by trial investigators who are blind to treatment allocation.

Trial therapists provide therapy to both the short-term and long-term treatment groups. Before commencing the trial, all trial therapists at the clinic will have received training in the short-term MBT program by trial investigators and national and international MBT specialists. The training covers relevant topics like case formulations, termination of psychotherapy, and case-specific supervision. The training will continue throughout the trial period. Therapist treatment fidelity will be rated by an independent certified rater. This will allow us to investigate whether the delivered interventions adhere to the MBT manual.

Table 1 Eligibility criteria

	Criteria exclusive to the outpatient clinic	Criteria exclusive to the trial
Inclusion criteria	Aged 18–60 Personality disorder(s) considered to be the primary diagnosis/diagnoses	A minimum of four confirmed DSM-V diagnostic criteria for borderline personality disorder Written informed consent
Exclusion criteria	Possibility of a learning disability (IQ < 75) A full diagnosis of schizotypal personality disorder or antisocial personality disorder Presence of a comorbid psychiatric disorder that requires specialist treatment Current (past 2 months) substance dependence including alcohol Concurrent psychotherapeutic treatment outside the clinic	Unable to understand Danish Lack of informed consent

DSM-V Diagnostic and Statistical Manual of Mental Disorders, 5th edition

Randomization

Copenhagen Trial Unit, a Danish center for clinical intervention research, will be responsible for the central randomization. Trial investigators will call designated staff at Copenhagen Trial Unit using a central telephone to randomize eligible participants to either the experimental group or the control group with a 1:1 allocation according to a computer-generated allocation sequence with permuted blocks of various sizes generated by Copenhagen Trial Unit and unknown to the investigators, secretaries, and clinical staff at the trial site. This is done to eliminate any predictability in the random sequence. The randomization is stratified by (1) sex and (2) high/low scores on the primary outcome measure, the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) [38] at baseline.

Interventions

The short-term MBT program delivered in this trial is overall similar to the existing long-term program, but differs structurally in the following ways: (1) the short-term program is lower in treatment intensity (both duration and exposure), (2) the same therapists provide both group and individual sessions in the short-term program (conjoined psychotherapy), whereas the group therapy and individual therapy are provided by different therapists in the long-term program (combined psychotherapy), and (3) the short-term program is structured in closed groups, in which all participants start and finish the program together, whereas the long-term program is structured as slow-open groups, in which a new participant can enter a group when another finishes. Both interventions in this trial adhere to the treatment guidelines provided by the National Institute for Health and Care Excellence [39].

Experimental intervention

The short-term MBT program is designed as a 20-week psychotherapy program consisting of five sessions of introductory MBT (MBT-I) followed by 15 sessions of group MBT (MBT-G) accompanied by conjoined individual sessions every second week and two psycho-educative meetings with participants and their relatives. Seven to nine participants and two therapists will be included in each short-term MBT group. The groups are closed to enhance cohesion between group participants. A total of 11 short-term MBT groups will be included in this trial.

Originally, MBT-I was a 12-session introductory psycho-educative program covering relevant topics like personality disorders, attachment, and mentalization [40]. The original manual has been modified for our 5-week intervention. A copy of our modified manual is available upon request. After the completion of MBT-I, the same group of participants will move on to MBT-G, which consists of 15 sessions of mentalization-based psychotherapy in groups, as manualized by Bateman and Fonagy [14]. In our short-term MBT program, group sessions will be accompanied by individual psychotherapy every second week with one of the two group therapists. As part of the individual therapy, a case formulation will be prepared and subsequently shared by the participants in the group. The overall purpose of the individual sessions is for the therapist and participant to develop a consensus of the participant's main difficulties and to establish psychotherapeutic focus points in the group therapy. Furthermore, participants and relatives will be invited to two psycho-educative meetings hosted by the therapists at the beginning of the treatment program to enhance the mentalization work at home. The participants in the short-term MBT program will furthermore be offered three individual follow-up sessions after the end of treatment.

Control intervention

Long-term MBT is organized as a 14-month program and has been implemented at the clinic for the past 7 years. All participants randomized to long-term MBT will initially enter a 6-week MBT-I program manualized by Karterud and Bateman [40] and modified for our 6-week intervention in collaboration with the authors. New MBT-I groups commence every time new participants are recruited and randomized to long-term MBT. A maximum of 12 participants can enter an MBT-I group. When MBT-I finishes, participants will be allocated to one of eight slow-open MBT treatment groups. MBT-G is then organized as 12 months of weekly group therapy sessions, also manualized by Bateman and Fonagy [14]. In the long-term MBT program, group sessions will be accompanied by combined individual MBT sessions every 2 weeks throughout the program. As part of the individual therapy, a case formulation will be developed and subsequently shared with the group by the participant. Furthermore, participants and relatives will also be invited to two psycho-educative meetings hosted by the therapists to enhance the mentalization work at home. When a participant drops out or completes MBT-G, a new participant can start in the group. This procedure continues until the target sample size has been randomized to the long-term MBT program. The participants in the long-term MBT program will also be offered three individual follow-up sessions after the end of treatment.

Concomitant interventions

Participants who are receiving psychotropic treatment will be allowed to continue their medical treatment while participating in the trial. The medical protocol will

follow national as well as international medical recommendations for the treatment of borderline personality disorder and comorbid disorders [39, 41]. Psychiatrists or attending physicians at the clinic will assess the need for additional psychotropic treatment and are asked to adhere to the guidelines. All participants, regardless of treatment condition, will be asked about their current medication by trial personnel during trial interviews to allow us to measure any potential differences in the use of psychotropic medication between the groups.

Baseline assessment at trial intake

Baseline assessments will be carried out prior to randomization by the principal investigator, the sponsor-investigator, and a trained research assistant, all of whom are also clinical psychologists. *General psychopathology* will be assessed with the Mini International Neuropsychiatric Interview (MINI) [42]. *Personality disorders* will be assessed with the Structured Clinical Interview for DSM-V Personality Disorders (SCID-5-PD), formerly known as SCID-II [43]. The SCID-5-PD is considered the gold standard for clinician-administered semi-structured interviews designed to assess personality disorders according to DSM-V criteria [44].

Outcomes

Primary outcome

The primary outcome is the severity of borderline symptomatology assessed with the ZAN-BPD [38], which is a clinician-administered scale for the assessment of change in borderline psychopathology over time. Each of the nine borderline personality disorder criteria are rated on a 0 to 4 anchored scale reflecting the severity of symptoms. The rating is intended to reflect both the frequency and the severity of borderline psychopathology. The interview provides a total score of borderline psychopathology ranging from 0 to 36. ZAN-BPD will be assessed by investigators blind to treatment allocation at baseline, and at the 8-, 16-, and 24-month follow-ups. We will video-record interviews to allow an assessment of inter-rater reliability based on the intraclass correlation coefficient. The results will be evaluated using the guidelines provided by Cicchetti [45].

Secondary outcomes

Functional impairment will be assessed with the Work and Social Adjustment Scale (WSAS) [46, 47]. This self-report scale will be assessed at baseline, and at the 8-, 16-, and 24-month follow-ups. *Quality of life* will be assessed with the Short-Form Health Survey (SF-36) [48], which consists of a mental and a physical component. We will use the mental component as a secondary outcome and the physical component as an exploratory outcome. This self-report scale will be given at baseline, and at the 8-, 16-, and 24-month follow-ups. *Global functioning* will be measured with the Global Assessment of Functioning (GAF) split version [49]. GAF will be assessed by investigators blind to treatment allocation at baseline, and at the 8-, 16-, and 24-month follow-ups. Inter-rater reliability will be calculated using the previously mentioned guidelines. *Severe self-harm* (dichotomous data) will be measured as the proportion of participants with severe self-harm defined as deliberate acts of self-harm resulting in visible tissue damage. Self-harm will be assessed by investigators blind to treatment allocation using the Suicide and Self-harm Inventory (SSHI) (citation) at baseline, and at the 8-, 16-, and 24-month follow-ups.

Exploratory outcomes

Symptom distress will be measured with the Global Severity Index (GSI) of the Symptom Checklist 90-R (SCL-90-R) [50]. SCL-90-R will be given at baseline, and at the 8-, 16-, and 24-month follow-ups.

Potential predictors and mediators

Questionnaires are given at baseline and every fourth week throughout the intervention period for both intervention groups to allow us to explore predictors and mechanisms of change. In a separate statistical analysis plan, which will be submitted for publication before data collection is completed in this trial, we will describe how these exploratory analyses will be performed. The following predictors and mediators will be investigated.

Personality functioning will be assessed with the Levels of Personality Functioning Scale, Brief Form (LPFS-BF) [51], which is a newly developed brief 12-item self-report questionnaire assessing levels of personality functioning according to the DSM-V alternative model for personality disorders. *Attachment* will be assessed with the brief self-report Relationship Questionnaire (RQ), which gives continuous and categorical ratings of the four attachment styles [52]. *Borderline symptomatology* will be assessed using the Zanarini Rating Scale for Borderline Personality Disorder, Self-Report Version (ZAN-BPD-SRV) [53]. *Group alliance* will be assessed using the 12-item version of the Group Questionnaire (GQ) [54], which is a brief self-report measure of the three core components of group alliance: alliance to the other participants, alliance to the therapists, and group cohesion as a whole. *Mentalization skills* will be assessed with the 15-item Mentalization Questionnaire (MZQ) [55].

For an overview of all measures and the corresponding time of assessment, see Table 2.

Table 2 Assessments administered at baseline and each follow-up point throughout the trial

Assessment points	Self-report measures	Expert ratings
Baseline	LPFS-BF, RQ, SF-36, WSAS, SCL-90-R, MZQ	MINI, SCID-5-PD, ZAN-BPD, GAF, SSHI
Every 4 weeks	GQ, MZQ, ZAN-BPD-SRV	–
Follow-ups at 8, 16, and 24 months	SF-36, WSAS, SCL-90-R, MZQ	ZAN-BPD, SSHI, GAF

GAF Global Assessment of Functioning, *GQ* Group Questionnaire, *LPFS-BF* Level of Personality Functioning Scale, Brief Form, *MINI* Mini International Neuropsychiatric Interview, *MZQ* Mentalization Questionnaire, *RQ* Relationship Questionnaire, *SCID-5-PD* Structured Clinical Interview for DSM-V Personality Disorders, *SCL-90-R* Symptom Checklist 90-R, *SF-36* Short-Form Health Survey 36, *SSHI* Suicide and Self-Harm Inventory, *WSAS* Work and Social Adjustment Scale, *ZAN-BPD* Zanarini Rating Scale for Borderline Personality Disorder, *ZAN-BPD-SRV* Zanarini Rating Scale for Borderline Personality Disorder, Self-Report Version

Blinding

Trial participants and therapists will not be blind to treatment allocation. This is due to the difficulties of implementing an efficient blinding procedure in psychotherapy trials. Baseline assessments will be done before allocation of participants, and the outcome assessments will be performed by blinded assessors. Participants will be instructed to withhold information of their allocation group when assessed. The statistical analyses will be conducted by blinded external statisticians from Copenhagen Trial Unit with the intervention groups coded as A and B. The steering committee will write and agree on two abstracts while the blinding is intact; one assuming the experimental intervention group is A and the control intervention group is B, and the other assuming the opposite. After this, the randomization code will be broken [56, 57].

Participant discontinuation and withdrawal

Participants can withdraw from the trial at any time without giving a reason and without consequences for future treatment at the clinic. To secure data for the trial, a trial investigator will contact the participant and ask what aspects of the trial the participant wishes to withdraw from: (1) the trial intervention or control group, (2) the assessment interviews, or (3) use of already collected data in analyses. If the participant specifies that they wish to withdraw fully and thereby withdraw from all the points above, their data will be deleted and not used in any analysis. The trial investigator will encourage the participant to continue attending the follow-up assessments.

Data management

The data in this trial will be collected using electronic case report forms developed in the data collection system REDCap. The system has been approved by the Danish Data Protection Agency and fulfills the requirements for data security. Data from the interviews will be entered directly into REDCap on a tablet, and all self-report measures will be collected from REDCap. For a detailed overview of outcome measures and data collection time points, see Table 2. The only source data are participants' signed consent forms.

Student assistants employed in the research department but not otherwise involved in the trial will make sure that all self-report measures are sent to participants at the right times, and that the data are complete for all participants enrolled in the trial. The REDCap database has an integrated audit trail to document any access to and changes of the data. The validated data will be exported to SAS for further statistical analyses by statisticians from Copenhagen Trial Unit.

Statistical plan and data analysis

Sample size

The sample size was determined by the predicted change in the primary outcome measure, ZAN-BPD. A 3.5-point superiority margin is considered to be the minimal important difference. Consistent with previous trials that have used ZAN-BPD as an outcome measure for a patient group like ours [24, 58], we expect a standard deviation of 8. With power set at 80% and alpha set at 5% two-tailed, a sample size of 83 participants is needed in each treatment group, corresponding to a total of 166 participants.

Statistical methods

All continuous outcomes will be assessed using linear regression and dichotomous outcomes will be analyzed using logistic regression. The analyses will be based on an intention-to-treat population and will primarily be adjusted for the baseline value of the outcome of interest and the stratification variables used in the randomization. We will secondly adjust all analyses for the following design variables: age (18–30 and 30–60) and functional impairment as assessed with the overall baseline GAF score (0–48 and 49–100) [34].

We will use a five-step procedure [59] to assess if the thresholds for statistical and clinical significance are crossed and we will handle missing data according to the procedure suggested by Jakobsen et al. [60]. A detailed statistical analysis plan will be published before the analyses commence, in which we will provide a detailed description of all primary, secondary, and exploratory analyses. All analyses will be performed blinded with the two intervention groups concealed as A and B.

Interim analyses

An external data safety monitoring committee will perform interim analyses when 50% of the data have been collected according to the good clinical practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [61]. It will decide whether the trial should stop or carry on. Early stopping criteria will follow the recommendations of Jakobsen et al. [59].

Discussion

This trial will provide evidence of the beneficial and harmful effects of short-term compared to long-term MBT for outpatients with subthreshold or diagnosed borderline personality disorder. To the best of our knowledge, short-term MBT has never been tested before. Gaining more information on how different lengths of treatment work for specific subtypes of patients may help to minimize the potential burden from long-term psychotherapy for some, while at the same time it may identify subtypes of patients for whom short-term psychotherapy is contraindicated. This knowledge may enhance the cost-effectiveness of treatment options for borderline personality disorder. Further, this trial may provide information on the potential predictors and mediators of treatment response.

The present trial has several strengths. First, it has a high degree of external validity because of the relatively inclusive eligibility criteria. Second, the methodology is based on CONSORT, and was predefined and described in detail before randomization began, including, e.g., blinding of all possible parties and implementation of a central randomization system both for generating an allocation sequence and for concealing allocation. Third, the implementation of systematic treatment fidelity ratings allows us to investigate treatment fidelity in both groups.

Our trial also has limitations. First, no systematic review of the effects of short-term compared to long-term psychotherapy for psychiatric disorders is currently available. As mentioned earlier, we are currently performing such a review. Second, the long-term MBT intervention, which is 14 months of treatment in this trial, diverges in intensity (both duration and exposure) from the original 18-month program [13]. This is due to the fixed length of the treatment packages, which have been implemented in the Danish mental health care system. Third, we cannot account for any potential confounding variables because of the structural differences between the groups: the short-term MBT program is closed and conjoined, whereas the long-term program is slow-open and combined.

Dissemination policy

The Danish population will be informed of the trial as well as its final results through national media. The results of the trial will be presented at all outpatient clinics treating borderline personality disorder in the Mental Health Services, Capital Region of Denmark, by the principal investigator or sponsor-investigator. The final and interim results will be presented at national and international conferences. Further, associations for patients and relatives will be informed about the results of the trial and its future implications. The trial results will be written up by the steering committee and will be published in international peer-reviewed journals. The government of Denmark will be informed of the results before a press release is issued but will have no influence on the reporting of results.

Trial status

The current protocol is version 1, dated 9 October 2018. The first participant was enrolled on 24 September 2018. Recruitment is expected to be completed by September 1, 2020

Additional file

Additional file 1: SPIRIT checklist. (DOCX 61 kb)

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GAF: Global Assessment of Functioning; GQ: Group Questionnaire; GSI: Global Severity Index; LPFS-BF: Levels of Personality Functioning Scale, Brief Form; MBT: Mentalization-based therapy; MBT-G: Mentalization-based group therapy; MBT-I: Introduction to Mentalization-Based Therapy; MINI: Mini International Neuropsychiatric Interview; MZQ: Mentalization Questionnaire; RQ: Relationship Questionnaire; SCID-5-PD: Structured Clinical Interview for DSM-V Personality Disorders; SCL-90-R: Symptom Checklist 90-R; SF-36: Short-Form Health Survey 36; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SSHI: Suicide and Self-Harm Inventory; WSAS: Work and Social Adjustment Scale; ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder; ZAN-BPD-SRV: Zanarini Rating Scale for Borderline Personality Disorder, Self-Report Version

Acknowledgements

We are grateful to the participants and to our colleagues at the Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre for their hard work and good cooperation.

Funding

The trial is funded by research grants from TrygFonden and from the Mental Health Services Research Foundation, Capital Region of Denmark. Funding applications have undergone anonymous peer review. Neither the funding bodies nor the sponsor will be involved in the collection, analysis, or interpretation of the data, or in writing the manuscripts. The grants will be administered by the head of administration at Stolpegaard Psychotherapy Center. At the end of the trial, the budget will undergo external auditing independently of the trial sponsor and investigators.

Availability of data and materials

The trial investigators, the steering committee, and statisticians at the Copenhagen Trial Unit will have access to the data. After the end of the trial, approval for making the final dataset publicly available in a depersonalized format in the Danish Data Archive will be applied for through the Danish Data Protection Agency.

Trial sponsor
The sponsor of the trial is the Mental Health Services in the Capital Region of Denmark, Kristineberg 3, 2100 Copenhagen Ø.

Protocol amendments
No substantial deviations from the protocol will be implemented without the prior review and approval of the regulatory authorities, except where such may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the regulatory authorities as soon as possible. Any deviation, however minor, will be documented and made available in the trial master file in a designated table developed for this purpose.

Authors' contributions
SS and SJ conceived the initial idea of a randomized controlled trial comparing short-term and long-term MBT for borderline personality disorder, along with MS, the acting chief psychologist at the clinic. PS approved of the idea and provided organizational support. SS and SJ developed the trial design with contributions and supervision from JCJ, SL, SP, PS, and AB. SJ wrote the protocol, which was carefully discussed with SS, JCJ, SL, SP, PS, and AB. JCJ designed the plan for the statistical analyses and wrote the sections on sample size and statistical approach. All authors read and approved the final manuscript.

Ethics approval and consent to participate
There are no ethical concerns regarding this trial. Both the experimental intervention and control intervention follow the treatment guidelines published by the National Institute for Health and Care Excellence and the Danish Health and Medicines Authority. Any participants can, at any time, withdraw their consent without any implications for future treatment at the clinic. Prior to commencing the trial, ethical approval was obtained from the regional research ethics committee (ID number H-18023136) and approval was obtained from the Danish Data Protection Agency (I-suite number 6553). During the trial period, data on adverse events will be collected at four time points and will be reported to the regional research ethics committee.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Stolpegaard Psychotherapy Centre, Mental Health Services, Gentofte, Capital Region of Denmark, Denmark. [2]Department of Psychology, University of Copenhagen, Copenhagen, Denmark. [3]Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [4]St. Anns Hospital, London, England.

Received: 11 October 2018 Accepted: 19 March 2019
Published online: 05 April 2019

References
1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Arlington: American Psychiatric Pub; 2013.
2. Togersen J. In: Oldham J, Skodol AE, Bender DS, editors. Prevalence, Sociodemographics, and Functional Impairment, in Textbook of personality disorders. Washington DC: American Psychiatric Publishing; 2014. p. 109–31.
3. Fossati A, et al. Patterns of covariation of DSM-IV personality disorders in a mixed psychiatric sample. Compr Psychiatry. 2000;41(3):206–15.
4. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am J Psychiatr. 2005;162(10): 1911–8.
5. Korzekwa MI, et al. Estimating the prevalence of borderline personality disorder in psychiatric outpatients using a two-phase procedure. Compr Psychiatry. 2008;49(4):380–6.
6. Conklin CZ, Westen D. Borderline Personality Disorder in Clinical Practice. Am J Psychiatr. 2005;162:867–75.
7. Zanarini MC, et al. Axis I comorbidity of borderline personality disorder. Am J Psychiatr. 1998;155:1733–9.
8. Trull TJ, et al. Borderline personality disorder and substance use disorders A review and integration. Clin Psychol Rev. 2000;20(2):235–53.
9. Barrachina J, et al. Axis II comorbidity in borderline personality disorder is influenced by sex, age, and clinical severity. Compr Psychiatry. 2011;52(6):725–30.
10. Lieb K, et al. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry. 2010;196(1):4–12.
11. Bateman AW, Gunderson J, Mulder R. Treatment of personality disorder. Lancet. 2015;385(9969):735–43.
12. Cristea IA, et al. Efficacy of Psychotherapies for Borderline Personality Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74(4):319–28.
13. Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatr. 2009;166(12):1355–64.
14. Bateman A, Fonagy P. Mentalization-based treatment for personality disorders: a practical guide. Oxford: Oxford University Press; 2016.
15. Karterud S. Mentalization-Based Group Therapy (MBT-G): A theoretical, clinical, and research manual. Oxford: OUP Oxford; 2015.
16. Vogt KS, Norman P. Is mentalization-based therapy effective in treating the symptoms of borderline personality disorder? A systematic review. Psychol Psychother. 2018. https://doi.org/10.1111/papt.12194
17. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007;3:1–27.
18. Kvarstein EH, et al. Changing from a traditional psychodynamic treatment programme to mentalization-based treatment for patients with borderline personality disorder--does it make a difference? Psychol Psychother. 2015; 88(1):71–86.
19. Bales D, et al. Treatment outcome of 18-month, day hospital mentalization-based treatment (MBT) in patients with severe borderline personality disorder in the netherlands. J Personal Disord. 2012;26(4):568–82.
20. Jorgensen CR, et al. Outcome of mentalization-based and supportive psychotherapy in patients with borderline personality disorder: a randomized trial. Acta Psychiatr Scand. 2013;127(4):305–17.
21. Bateman A, Fonagy P. Effectiveness of partial hospitalization in the treatment of borderline personality disorder: a randomized controlled trial. Am J Psychiatr. 1999;156(10):1563–9.
22. Laurenssen EM, Luyten P, Kikkert MJ, Westra D, Peen J, Soons MB, Dekker JJ. Day hospital mentalization-based treatment v. specialist treatment as usual in patients with borderline personality disorder: randomized controlled trial. Psychol Med. 2018;48(15):2522–29
23. Bateman A, Fonagy P. 8-year follow-up of patients treated for borderline personality disorder: mentalization-based treatment versus treatment as usual. Am J Psychiatr. 2008;165(5):631–8.
24. Gratz KL, Tull MT, Levy R. Randomized controlled trial and uncontrolled 9-month follow-up of an adjunctive emotion regulation group therapy for deliberate self-harm among women with borderline personality disorder. Psychol Med. 2014;44(10):2099–112.
25. Blum N, St. John D, Pfohl B, Stuart S, McCormick B, Allen J, Arndt S, Black DW. Systems Training for Emotional Predictability and Problem Solving (STEPPS) for Outpatients With Borderline Personality Disorder: A Randomized Controlled Trial and 1-Year Follow-Up. Am J Psychiatr. 2008;165:468–78.
26. Bos EH, van Wel EB, Appelo MT, Verbraak MJ. A randomized controlled trial of a Dutch version of systems training for emotional predictability and problem solving for borderline personality disorder. J Nerv Ment Dis. 2010; 198(4):299–304.
27. McMain SF, et al. A randomized trial of brief dialectical behaviour therapy skills training in suicidal patients suffering from borderline disorder. Acta Psychiatr Scand. 2017;135(2):138–48.
28. McMain SF. Advances in the Treatment of Borderline Personality Disorder: An Introduction to the Special Issue. J Clin Psychol. 2015;71(8):741–6.
29. Knekt P, et al. Randomized trial on the effectiveness of long-and short-term psychodynamic psychotherapy and solution-focused therapy on psychiatric symptoms during a 3-year follow-up. Psychol Med. 2008; 38(5):689–703.
30. Lorentzen S, et al. Comparison of short- and long-term dynamic group psychotherapy: randomised clinical trial. Br J Psychiatry. 2013;203(3):280–7.
31. Boutron I, et al. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med. 2008;148(4):295–309.

32. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1:2.
33. Chan A, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med. 2013;158:200–7.
34. Simonsen S, Heinskou T, Sørensen P, Folke S, Lau ME. Personality disorders: patient characteristics and level of outpatient treatment service. Nord J Psychiatry. 2017;71(5):325–31.
35. Clifton A, Pilkonis PA. Evidence for a single latent class of Diagnostic and Statistical Manual of Mental Disorders borderline personality pathology. Compr Psychiatry. 2007;48(1):70–8.
36. Tyrer P, Reed GM, Crawford MJ. Classification, assessment, prevalence, and effect of personality disorder. Lancet. 2015;385(9969):717–26.
37. Beck E, et al. Mentalization-based treatment in groups for adolescents with borderline personality disorder (BPD) or subthreshold BPD versus treatment as usual (M-GAB): study protocol for a randomized controlled trial. Trials. 2016;17(1):314.
38. Zanarini. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Personal Disord. 2003;17(3):233–42.
39. National Insitute for Health and Care Excellence (NICE). Borderline Personality Disorder: the NICE Guideline on Treatment and Management. Br Psychol Soc R Coll Psychiatrists. 2009.
40. Karterud S, Bateman A. Manual for mentaliseringsbasert psykoedukativ gruppeterapi (MBT-I). Oslo: Gyldendal akademisk; 2011.
41. Sundhedsstyrelsen, National klinisk retningslinje for behandling af emotionel ustabil personlighedsstruktur, borderline type. 2015.
42. Lecrubier Y, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry. 1997;12:224–31.
43. First MB, et al. The Structured Clinical Interview for DSM-II-R Personality Disorders (SCID-II). Part II: Multi-site test-retest reliability study. J Personal Disord. 1995;9(2):92–104.
44. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clin Psychol Psychother. 2011;18(1):75–9.
45. Cicchetti DV. Guidelines, Criteria, an Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. Psychol Assess. 1994;6(4):284–90.
46. Pedersen G, Kvarstein EH, Wilberg T. The Work and Social Adjustment Scale: Psychometric properties and validity among males and females, and outpatients with and without personality disorders. Personal Ment Health. 2017;11(4):215–28.
47. Miles HH, Barrabee EL, Finesinger JE. Evaluation of psychotherapy: with a follow up study of 62 cases of anxiety neurosis. Psychosom Med. 1951 Mar-Apr;13(2):83-105.
48. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. Med Care. 1992;30(6):473–83.
49. Jones SH, et al. Reliability and Validity of the Global Assessment of Functioning (GAF). Br J Psychiatry. 1995;166:654–9.
50. Derogatis LR, Cleary PA. Confirmation of the dimensional structure of the SCL-90: a study in construct validation. J Clin Psychol. 1977;33(4):981–9.
51. Hutsebaut J, Feensta D, Kamphuis J. Development and Preliminary Psychometric Evaluation of a Brief Self-Report Questionnaire for the Assessment of the DSM–5 Level of Personality Functioning Scale: The LPFS Brief Form (LPFS-BF). Personal Disord Theory Res Treat. 2016;7(2):192–4.
52. Bartholomew K, Horowitz LM. Attachment Styles Among Young Adults: A Test of a Four-Category Model. J Pers Soc Psychol. 1991;61(2):226–44.
53. Zanarini, et al. Development of the self-report version of the Zanarini Rating Scale for Borderline Personality Disorder. Personal Ment Health. 2015;9(4):243–9.
54. Krogel J, et al. The Group Questionnaire: a clinical and empirically derived measure of group relationship. Psychother Res. 2013;23(3):344–54.
55. Hausberg M, Schulz H, Piegler T, Happach C, Klöpper M, Brütt A, et al. Is a self-rated instrument appropriate to assess mentalization in patients with mental disorders? Development and first validation of the Mentalization Questionnaire (MZQ). Psychother Res. 2012;22(6):699–709.
56. Gotzsche PC. Blinding during data analysis and writing of manuscripts. Control Clin Trials. 1996;17(4):285–90 discussion 290-3.
57. Jarvinen TL, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol. 2014;67(7):769–72.
58. Priebe S, et al. Effectiveness and cost-effectiveness of dialectical behaviour therapy for self-harming patients with personality disorder: a pragmatic randomised controlled trial. Psychother Psychosom. 2012;81(6):356–65.
59. Jakobsen JC, et al. The thresholds for statistical and clinical significance - a five-step procedure for evaluation of intervention effects in randomised clinical trials. BMC Med Res Methodol. 2014;14:34.
60. Jakobsen JC, et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol. 2017;17(1):162.
61. Englev E, Petersen KP. ICH-GCP Guideline: quality assurance of clinical trials. Status and perspectives. Dan Med J. 2003;165(16):1659–62.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-17
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14, 16

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	not relevant
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Paper IV

Detailed statistical analysis plan for the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder randomised clinical trial (MBT-RCT)

Authors

Sophie Juul[1 2 3 *], Sebastian Simonsen[1], Stig Poulsen [2], Susanne Lunn[2], Per Sørensen[1], Anthony Bateman[4], Janus Christian Jakobsen[3 5]

* Corresponding author: Sophie Juul. Stolpegaard Psychotherapy Centre, Stolpegårdsvej 20, 2820 Gentofte, Denmark. Mail: sophie.juul@regionh.dk

Affiliations

[1] Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark, Gentofte, Denmark

[2] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

[3] Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[4] Anna Freud Centre, Kantor Centre of Excellence, London, United Kingdom

[5] Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Denmark

Abstract

Background

Psychotherapy for borderline personality disorder is often extensive and resource-intensive. Mentalization-based therapy is one treatment option for borderline personality disorder, but the evidence on short-term compared with long-term mentalization-based therapy is currently unknown.

Methods/design

The Short-Term MBT Project (MBT-RCT) is a single-centre, parallel group, investigator-initiated, randomised clinical superiority trial in which short-term (20 weeks) will be compared with long-term (14 months) mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder. Outcome-assessors, data managers, the data safety and monitoring committee, statisticians, and decision makers will be blinded to treatment allocation. Participants will be assessed before randomisation, and at 8, 16, and 24 months after randomization. The primary outcome will be severity of borderline symptomatology assessed with the Zanarini Rating Scale for Borderline Personality Disorder. Secondary outcomes will be functional impairment (Work and Social Adjustment Scale), quality of life (Short-Form Health Survey 36 – mental component), global functioning (Global Assessment of Functioning), and proportion of participants with severe self-harm. In this paper, we present a detailed statistical analysis plan including a comprehensive explanation of the planned statistical analyses, methods to handle missing data, and assessments of underlying statistical assumptions. Final statistical analyses will be conducted independently by two statisticians following the present plan.

Discussion

We have developed this statistical analysis plan before unblinding of the trial results in line with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines, which should increase the validity of the MBT-RCT trial by mitigation of analysis-bias.

Trial registration: ClinicalTrials.gov, NCT03677037. Registered September 19, 2018, https://clinicaltrials.gov/ct2/show/NCT03677037

Background

The Short-Term MBT Project (MBT-RCT) is a single-centre, parallel group, investigator-initiated, randomised clinical superiority trial that assesses the effects of short-term (20 weeks) compared with long-term (14 months) mentalization-based therapy (MBT) for outpatients with subthreshold or diagnosed borderline personality disorder [1]. The Helsinki Declaration [2], the International Conference on Harmonization of Good Clinical Practice (ICH-GCP) [3] guidelines recommend that clinical trials should be analysed according to a pre-specified plan to prevent selective outcome reporting bias and data-driven analysis results [4-6].

In this publication, we describe the pre-planned statistical analyses of the primary and secondary outcomes in the MBT-RCT trial. The main publication of the trial results will adhere to this statistical analysis plan as approved by the steering group.

Methods

The design of the MBT-RCT trial has been described in detail previously [1]. The trial population will be adults (18 years of age or older) with subthreshold or diagnosed borderline personality disorder assessed with the Structural Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD). Participants will be eligible for enrolment if they meet all of the following inclusion criteria and none of the exclusion criteria as presented in **Table 1.**

Table 1: *Inclusion- and exclusion criteria*

	General criteria of the outpatient clinic	Criteria exclusive to the trial
Inclusion criteria	• Aged 18-60 • Personality disorder(s) considered to be primary diagnosis	• A minimum of four confirmed DSM-5 diagnostic criteria for borderline personality disorder • Written informed consent
Exclusion criteria	• Learning disability (IQ < 75) • A full diagnosis of schizotypal personality disorder or antisocial personality disorder • Presence of a comorbid psychiatric disorder that requires specialist treatment • Current (past 2 months) substance dependence including alcohol • Concurrent psychotherapeutic treatment outside the clinic	• Unable to understand Danish • Lack of informed consent

The MBT-RCT trial is registered at ClinicalTrials.gov (identifier: NCT03677037), is carried out in compliance with the Declaration of Helsinki [2], and is approved by the Danish Data Protection Agency (approval number: 6553), and by the Regional Research Ethics Committee of the Capital Region of Denmark (approval number: H-18023136).

Randomisation and blinding

Copenhagen Trial Unit, a Danish centre for clinical intervention research, will be responsible for the central randomisation. Randomisation will be performed with a 1:1 allocation according to a computer-generated allocation sequence with permuted blocks of various sizes. The allocation sequence will be concealed from all trial investigators. The randomisation is stratified by 1) sex and 2) high/low baseline scores on the primary outcome measure, the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) [7].

Outcome-assessors, data managers, statisticians, the data safety and monitoring committee, and decision makers will be blinded to treatment allocation [8]. Trial participants and therapists will not be blind to treatment allocation. This is due to the difficulties of implementing an efficient blinding procedure in trials assessing psychological interventions [8].

Trial interventions

Experimental intervention

The short-term MBT program is organized as a 20-weeks program consisting of 20 weeks of group therapy in closed groups commencing with five sessions of psychoeducative introduction to MBT [9] followed by 15 sessions of group MBT group therapy accompanied by conjoined individual sessions every second week. All participants are furthermore invited to two psychoeducative meetings with other participants and their relatives. The participants will be treated by two group therapists, one of them also being the individual therapist. Both group and individual therapy is manualized by Bateman and Fonagy [10].

Control intervention

Long-term MBT is organized as a 14-months program and has been implemented at the clinic for the past ten years. All participants randomized to long-term MBT will initially enter a 6-week

psychoeducative introduction to MBT [9]. New psychoeducative MBT groups commence every time new participants are recruited and randomized to long-term MBT. When the psychoeducative group finishes, participants will be allocated to one of eight slow-open MBT treatment groups. Treatment is then organized as 12 months of weekly group therapy sessions combined with individual therapy every second week. All participants are furthermore invited to two psychoeducative meetings with other participants and their relatives. The participants will be treated by two group therapists and a third individual therapist. Both group and individual therapy is manualized by Bateman and Fonagy [10].

Baseline characteristics

The baseline characteristics will be assessed from inclusion in the trial. A mock table of the complete pre-defined baseline table can be found in **Supplementary Material 1.** The baseline characteristics will be:

1. Demographic characteristics:
    a. Age
    b. Sex
    c. Civil status
    d. Living situation (alone/with others)
    e. Education level
    f. Employment status

2. Clinical characteristics
    a. Psychiatric comorbidity, e.g. a diagnosis of an anxiety disorder, major depressive disorder, post-traumatic stress disorder (reported if the frequency is above or equal to 10% in any of the intervention groups).
    b. Proportion of participants with subthreshold borderline personality disorder
    c. Mean number of borderline personality disorder diagnostic criteria
    d. Personality disorder comorbidity (reported if the frequency is above or equal to 10% in any of the intervention groups).
    e. Proportion of participants with one or more suicide attempts eight months prior to randomisation

f. Proportion of participants with severe self-harm incidents defined as deliberate acts of self-harm resulting in visible tissue damage eight months prior to randomisation
g. Proportion of participants on psychopharmacological medication (e.g antidepressants, antipsychotics) at baseline

Outcomes

The outcomes were predefined as primary, secondary, and exploratory [1]. This publication describes the statistical analysis plan of the primary and secondary outcomes only.

Primary outcome

- Severity of borderline symptomatology assessed with the Zanarini Rating Scale for Borderline Personality Disorder [7].

Secondary outcomes

- Functional impairment (assessed with the Word and Social Adjustment Scale (WSAS) [11].
- Quality of life (assessed with the Short-Form Health Survey (SF-36) mental component) [12].
- Global functioning (assessed with the Global Assessment of Functioning scale (GAF)) [13].
- Severe self-harm (defined as the proportion of participants with one or more deliberate act of self-harm resulting in visible tissue-damage)

Assessment time points

All outcomes will be assessed at baseline and at 8, 16, and 24 months after randomisation. Investigator-administered outcomes (severity of borderline symptomatology, severe self-harm, and global functioning) will be assessed by blinded assessors at all time-points. We will use the 16-month time point as the primary time-point of interest, as it is the time-point closest to end of treatment in the long-term MBT group. In an exploratory analysis, we will consider reporting the results of the comparison between end of treatment in both groups (i.e. data from the 8 months time point in the short-term group compared with data from the 16 months time point in the long-term group). Data from the 24-month time point, as well as results of the exploratory outcomes, will be analysed using

the same principles as described in this statistical analysis plan and published in a separate publication.

Safety

We will report the proportion of participants with one or more serious adverse events in both groups. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolonging of existing hospitalisation and resulted in persistent or significant disability or jeopardised the participant [3]. Two investigators will independently go through participants' medical journals and assess possible serious adverse events at the 16 and 24 months timepoint of assessment according to the ICH-GCP definition.

Sample size and power estimations

The sample size estimation was based on the primary outcome, and our primary conclusions will be based on the results of the primary outcome. The outcomes in our outcome hierarchy were ranked according to clinical relevance and we estimated the power of each non-primary outcome to ensure that we had sufficient power to confirm or reject minimally important intervention effects [14].

Sample size estimation

The sample size was determined by the predicted change in the primary outcome measure, ZAN-BPD. We considered a 3.5-point superiority margin to be the minimal important difference. Consistent with previous trials that have used ZAN-BPD as an outcome measure for a group of participants similar to ours [15,16] we expect a standard deviation of 8. With power set at 80% and alpha set at 5% two-tailed, a sample size of 83 participants will be needed in each treatment group, corresponding to a total of 166 participants.

Power estimation for secondary outcomes

For the secondary outcomes, we have performed power calculations as presented in **Table 2** and **Table 3** [17].

Table 2: *Power estimations for the secondary continuous outcomes*

Outcome	Minimal clinically important difference	Expected standard deviation	Alpha	Sample size	Power	Reference
	δ	σ	α	*n*	1-β	
Functional impairment (WSAS)	4.5	10	5	166	82	Phillips et. al. (2014) [18]
Quality of life (SF-36 – mental component)	5	11	5	166	83	Rollman et al. (2009) [19]
Global functioning (GAF)	4	8.5	5	166	85	Jørgensen et al. (2012) [20]

GAF; Global Assessment of Functioning; SF-36: Short-Form Health Survey 36; WSAS: Work and Social Adjustment Scale

Table 3: *Power estimations of secondary dichotomous outcomes:*

Outcome	Expected proportion in control group	Alpha significance level	Power	Reference
Severe Self Harm Incidents [a]	15%	5	14%	Simonsen et al. [21] Bateman & Fonagy [22]

[a] Even though the expected power is only 14%, we define severe self-harm incidents as a secondary outcome, because it is considered very important for this population.

General analysis principles

Statistical analyses will be performed in Stata [23]. All analyses will be conducted according to the intention-to-treat principle (ITT). The intention-to-treat population will include all randomised participants, regardless of missing data, lost to follow up, or adherence to the intervention. Thus, by performing an intention-to-treat analysis, we will assess the effects of being randomized to the interventions. We will consider performing a per protocol analysis, if the number of participants who prematurely drops out of treatment exceeds 5% of the total trial population. By performing a per-

protocol analysis, we will assess the effects of adhering to the intervention, which must be considered hypothesis-generating only.

It is generally recommended that regression analyses should be adjusted for the stratification variables used in the randomisation [24-26]. Thus, all analyses will primarily be adjusted for the stratification variables used in the randomisation (and the baseline value of the outcome of interest when assessing continuous outcomes). We will secondly adjust all analyses for the following adjustment variables: age (18-30/ 31-60), baseline global functioning as assessed with the GAF score (0-48/ 49-100), baseline proportion of participants with severe self-harm eight months prior to randomisation (participants with one or more events/ participants with no events), and proportion of participants who had their group therapy temporarily paused due to Covid-19 in March 2020 and January 2021 compared to the proportion of participants who did not have their group therapy temporarily paused.

We will perform the following subgroup analyses (test of interaction):

- Baseline severity of borderline symptomatology (ZAN-BPD scores 0-11/ 12-36)
- Sex (male/female)
- Age (18-30/ 31-60),
- Baseline global functioning (GAF score 0-48/ 49-100)
- Baseline proportion of participants with severe self-harm incidents eight months prior to randomisation (participants with one or more events/ participants with no events).
- Proportion of participants who had their group therapy temporarily paused due to Covid-19 in March 2020 and January 2021 compared to participants who did not have their group therapy temporarily paused.

We will present the results of the subgroup analyses in forest plots.

Trial profile

The flow of trial participants will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram [27]. The number of screened patients who were assessed for eligibility, and

the number included in the primary and secondary analyses, as well as all reasons for exclusions in the primary and secondary analyses will be reported.

Statistical analyses

Analysis of continuous data

Continuous outcomes will be presented as means and standard deviations for each group together with 95% confidence intervals for the means of the groups and the mean differences between the groups. We will analyse continuous outcomes using linear regression. All variables will be included as fixed effects.

Analysis of dichotomous data

Dichotomous outcomes will be presented as proportions of participants in each group with the event, together with risk ratios with 95% confidence intervals. We will analyse dichotomous outcomes using logistic regression. All variables will be included as fixed effects.

Level of significance

The threshold for significance will be assessed according to a five-step procedure, suggested by Jakobsen and colleages [28].

The first step will be to calculate and report confidence intervals and *p*-values for the primary and secondary outcomes. All confidence intervals will be 95% and two-sided. We will use a *p*-value of less than 0.05 as the threshold for statistical significance for our primary outcome (see 'Sample size estimation') since we plan to report on only one primary outcome. Since our primary conclusions will be based on one outcome result at one time point (16 months post randomisation), we will limit problems associated with multiple testing due to multiple outcome comparisons [29]. [30]. All remaining outcome results and assessment time-points will be considered hypothesis-generating only.

The second step will be to calculate and report Bayes factor [31] for primary and secondary outcomes. The Bayes factor is the ratio between the probability of the results given that the null hypothesis (H_0) is true divided by the probability of the results given that the alternative hypothesis (H_A) is true [31].

Calculating and reporting the Bayes factor will allow us to interpret the results of the primary outcome in relation to former trial results [15,16].

The third step will be to use Lan–DeMets monitoring boundaries if the trial is stopped before the sample size is reached [32]. This is done to avoid a potential false rejection of the null hypothesis caused by an insufficient sample size [33].

The fourth step regarding adjustment of *p*-values based on multiple testing of the primary outcome, is not applicable to our trial. We only have one single primary outcome, primarily assessed at one time-point (16 months post-randomisation) [28].

The fifth steep is assessment of the clinical significance. The assessment of the clinical significance of our trial results will be based on the intervention effects we predefined in the sample size and power estimations.

Interim analyses

We have pre-planned one interim analysis, which will be conducted after half of trial participants have been assessed at the 8 months post-randomisation time-point. The timing and prevalence of any additional interim analyses will be decided exclusively by the members of the data monitoring and safety committee. The role of the data monitoring and safety committee will beto make recommendations to the steering group to either continue, change, hold, or terminate the trial. This recommendation will primarily be based on safety considerations. The data monitoring and safety committee will be provided with the following trial data: number of participants randomised, number of participants per intervention group, baseline ZAN-BPD scores for all participants, ZAN-BPD scores at the 8-months post-randomisation time-point for participants in both intervention groups with available data at that time-point, proportion of participants with one or more deliberate acts of self-harm at the 8-months post-randomisation time-point, and serious adverse events. Based on evaluations of these data, the data monitoring and safety committee will decide whether they want further data from the principal investigator, and when next to perform analyses on data.

Handling of missing data

In short, if we experience missing data, we will consider to use multiple imputation and use best-worst/worst-best case scenarios to assess the potential impact of the missing data [34]. Missing data will be handled according to the recommendation of Jakobsen and colleagues [34]

Assessments of underlying statistical assumptions

We will assess underlying statistical assumptions for all statistical analyses [35,36]. We will test for major interactions between each covariate and the intervention variable for all regression analyses. We will, in turn, include each possible first order interaction between included covariates and the intervention variable. For each combination, we will test if the interaction term is significant and we will assess the effect size. We will only consider concluding that there is evidence of an interaction if 1) the interaction is statistically significant following the Bonferroni adjusted thresholds (0.05 divided by the number of possible interactions) and 2) if the interaction shows a clinically significant effect. If we conclude that the interaction is statistically significant, we will consider both presenting a separate analysis for each interaction as well as an overall analysis including the interaction term in the model [35].

Assessments of underlying statistical assumptions for linear regression

We will visually inspect quantile-quantile plots of the residuals [37,38] to assess if the residuals are normally distributed, and we will use residuals plotted against covariates and fitted values [37,38] to assess for homogeneity of variances. If the plots show deviations from the model assumptions, we will consider transforming the outcome i.e. by using log transformation or square root and/or use robust standard errors [37,38].

Assessments of underlying statistical assumptions for logistic regression

We will assess if the deviance divided by the degrees of freedom is significantly larger than 1 to assess for relevant overdispersion. If that is the case, we will consider using a maximum likelihood estimate of the dispersion parameter.

Statistical reports

Two independent statisticians will analyse blinded data on all outcomes with intervention groups concealed as e.g. 'A' and 'B'. Two independent statistical reports will be delivered to the principal investigator (SJ) and will be shared with the steering group. If there are discrepancies between the two primary statistical reports, these will be identified and we will then consider which is the most correct result. A final statistical report will be prepared, and all two (or three, if anything is to be corrected) statistical reports will be published as supplementary material. Mock tables are presented in **Supplementary material 1**.

Discussion

The primary aim of this paper is to minimize the risks of bias associated with selective outcome reporting and erroneous data-driven results. We therefore present a pre-defined statistical analysis plan for the MBT-RCT trial.

Strengths

Our methodology has several strengths. First, our methodology is pre-defined, and our analyses will adhere to this statistical analysis plan. Second, we have limited problems with multiplicity because we only assess one primary outcome and our conclusions will primarily be based on the results of the primary outcome [28]. Third, all analyses will be conducted according to the intention-to-treat principle and, if necessary, we will use multiple imputation and best-worst/worst-best case scenarios to assess the potential impact of missing data [34]. Furthermore, we plan to systematically assess if underlying statistical assumptions are fulfilled for all statistical analyses.

Limitations

A potential limitation of the MBT-RCT trial is that no systematic review of the effects of short-term compared to long-term psychotherapy for borderline personality disorder, or for psychiatric disorders in general, was available prior to planning of this trial. Hence, estimations of anticipated intervention effects, estimations of variances used in our sample size and power estimations, etc. may be erroneous. We are currently performing such a review, which will be submitted for publication prior to completion of this trial [39]. Second, we expect a significant amount of missing data, due to the instability of the trial population. Even though we plan to handle missing data appropriately, no

statistical method can guarantee validity of trial results if the missingness is substantial. Third, even though the trial will be sufficiently powered to confirm or reject intervention effects on the primary and secondary outcomes, the relatively small number of randomised participants may result in a risk of baseline differences which also may bias the trial results especially on non-primary outcomes. However, we will carefully consider the low sample size when interpreting the trial results. Fourth, as participants are not blinded to the allocated treatment, results from all participant-reported outcomes are at risk of bias [8]. Fifth, therapists are likewise not blinded to the allocated treatment and may have an allegiance to one of the interventions. We will carefully consider these limitations when interpreting the results.

Conclusion

We have developed this statistical analysis plan in line with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines, which should increase the validity of the MBT-RCT trial by mitigation of analysis-bias.

Declarations:

Ethics approval and consent to participate: There are no ethical concerns regarding this trial. Both the experimental intervention and control intervention follow the treatment guidelines published by the National Institute for Health and Care Excellence and the Danish Health and Medicines Authority. Any participants can, at any time, withdraw their consent without any implications for future treatment at the clinic. Prior to commencing the trial, ethical approval was obtained from the regional research ethics committee (ID number H-18023136) and approval was obtained from the Danish Data Protection Agency (I-suite number 6553). During the trial period, data on serious adverse events will be collected and will be reported to the regional research ethics committee.

Consent for publication: Not applicable.

Availability of data and materials Trial investigators, the steering committee, and statisticians at the Copenhagen Trial Unit will have access to the data. After the end of the trial, approval for making the final dataset publicly available in a depersonalized format in the Danish Data Archive will be applied for through the Danish Data Protection Agency.

Competing interests: The authors declare that they have no competing interests.

Funding The MBT-RCT trial is funded by research grants from TrygFonden and from the Mental Health Services Research Foundation, Capital Region of Denmark. Funding applications have undergone anonymous peer review. Neither the funding bodies nor the sponsor will be involved in the collection, analysis, or interpretation of the data, or in writing the manuscripts. The grants will be administered by the head of administration at Stolpegaard Psychotherapy Center. At the end of the trial, the budget will undergo external auditing independently of the trial sponsor and investigators.

Authors' contributions: SJ drafted this protocol update, receiving ongoing supervision from JCJ. All authors amended and approved the final manuscript.

Acknowledgements We are grateful to the participants and to our colleagues at the Outpatient Clinic for Personality Disorders at Stolpegaard Psychotherapy Centre for their hard work and good cooperation.

References

1. Juul S, Lunn S, Poulsen S, Sørensen P, Salimi M, Jakobsen JC, et al. Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomized clinical trial. Trials. 2019;20(1):196.

2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). ICH Harmonised Guideline: Integrated Addemdum to ICH E6(R1): Guideline for Good Clinical Practice (ICH-GCP). 2015. Available at: ich-gcp.net [Accessed January 10, 2021]

4. Dwan K, Gamble C, Williamson PR, Altman DG. Reporting of clinical trials: a review of research funders' guidelines. Trials. 2008;9(1):66.

5. Thomas L, Peterson ED. The value of statistical analysis plans in observational research: defining high-quality research from the start. JAMA. 2012;308(8):773-4.

6. Gabriel SE. Getting the methods right--the foundation of patient-centered outcomes research. N Eng J Med. 2012;367(9):787.

7. Zanarini MC. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Pers Disord. 2003;17(3):233-42.

8. Juul S, Gluud C, Simonsen S, Frandsen FW, Kirsch I, Jakobsen JC. Blinding in randomised clinical trials of psychological interventions: a retrospective study of published trial reports. BMJ Evid Based Med. 2020:bmjebm-2020-111407.

9. Karterud S, Bateman A. Manual for mentalization based psychoeducational group therapy (MBT-I). Oslo: Gyldendal Akademisk; 2011.

10. Bateman A, Fonagy P. Mentalization-based treatment for personality disorders: A practical guide. Oxford, England: Oxford University Press; 2016.

11. Pedersen G, Kvarstein EH, Wilberg T. The Work and Social Adjustment Scale: Psychometric properties and validity among males and females, and outpatients with and without personality disorders. Personal Ment Health. 2017;11(4):215-28.

12. Brazier JE, Harper R, Jones N, O'cathain A, Thomas K, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160-4.

13. Hall RC. Global assessment of functioning: a modified scale. Psychosom. 1995;36(3):267-75.

14. Jakobsen JC, Ovesen C, Winkel P, Hilden J, Gluud C, Wetterslev J. Power estimations for non-primary outcomes in randomised clinical trials. BMJ Open. 2019;9:e027092. doi: 10.1136/bmjopen-2018-027092.

15. Gratz K, Tull M, Levy R. Randomized controlled trial and uncontrolled 9-month follow-up of an adjunctive emotion regulation group therapy for deliberate self-harm among women with borderline personality disorder. Psychol Med. 2014;44(10):2099-112.

16. Priebe S, Bhatti N, Barnicot K, Bremner S, Gaglia A, Katsakou C, et al. Effectiveness and cost-effectiveness of dialectical behaviour therapy for self-harming patients with personality disorder: a pragmatic randomised controlled trial. Psychother Psychosom. 2012;81(6):356-65.

17. Jakobsen JC, Ovesen C, Winkel P, Hilden J, Gluud C, Wetterslev J. Power estimations for non-primary outcomes in randomised clinical trials. BMJ Open. 2019;9(6):e027092.

18. Phillips R, Schneider J, Molosankwe I, Leese M, Foroushani PS, Grime P, et al. Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. Psychol Med. 2014;44(4):741-52.

19. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-Delivered Collaborative Care for Treating Post-CABG Depression: A Randomized Controlled Trial. JAMA. 2009;302(19).

20. Jorgensen CR, Freund C, Boye R, Jordet H, Andersen D, Kjolbye M. Outcome of mentalization-based and supportive psychotherapy in patients with borderline personality disorder: a randomized trial. Acta Psychiatr Scand. 2013;127(4):305-17.

21. Simonsen S, Heinskou T, Sørensen P, Folke S, Lau M. Personality disorders: patient characteristics and level of outpatient treatment service. Nord J Psychiatry. 2017:1-7.

22. Bateman A, Fonagy P. Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. Am J Psychiatry. 2009;166(12):1355-64.

23. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.2019.

24. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2011;31:328-40.

25. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 2012;345:e5840.

26. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC Med Res Methodol. 2003;3:26.

27. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8(1):18.

28. Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance - a five-step procedure for evaluation of intervention effects in randomised clinical trials. BMC Med Res Methodol. 2014;14(34).

29. Zhang J, Quan H, Ng J, Stepanavage ME. Some statistical methods for multiple endpoints in clinical trials. Control Clin Trials. 1997;18(3):204-21.

30. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567:305-7.

31. Goodman SN. Introduction to Bayesian methods I: measuring the strength of evidence. Clin Trials J Soc Clin Trials. 2005;2:282-90.

32. Demets DL, Lan KG. Interim analysis: the alpha spending function approach. Stat Med. 1994;13(13-14):1341-52.

33. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. BMJ. 2012;344:e3863.

34. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–a practical guide with flowcharts. BMC Med Res Methodol. 2017;17(1):162.

35. Nielsen EE, Norskov AK, Lange T, Thabane L, Wetterslev J, Beyersmann J, et al. Assessing assumptions for statistical analyses in randomised clinical trials. BMJ Evid Based Med. 2019.

36. Nørskov AK, Lange T, Nielsen EE, Gluud C, Winkel P, Beyersmann J, et al. Assessment of assumptions of statistical analysis methods in randomised clinical trials: the what and how. BMJ Evid Based Med. 2020.

37. Frydenberg SJaM. An Introduction to Stata for Health Researchers, Fourth Edition. Stata Press. 2014.

38. Oliveira AG. Biostatistics Decoded. Wiley. 2013.

39. Juul S, Poulsen S, Lunn S, Sørensen P, Jakobsen JC, Simonsen S. Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis. Syst Rev. 2019;8(1):169.

Table 1

Baseline characteristics of the trial population

Characteristic	Short-term MBT (n=83)	Long-term MBT (n=83)
Demographic		
Age, mean (SD), years	XX (X)	XX (X)
Female sex – no. (%)	XX (X)	XX (X)
Civil status – no. (%)		
Married	X (X)	X (X)
Living together	X (X)	X (X)
Single	X (X)	X (X)
Living situation – no. (%)		
Alone	X (X)	X (X)
With others	X (X)	X (X)
Education level after high school – no. (%)		
Currently studying	X (X)	X (X)
Short education	X (X)	X (X)
Medium education	X (X)	X (X)
Long education	X (X)	X (X)
No higher education	X (X)	X (X)
Employment status – no. (%)		
On social welfare	X (X)	X (X)
Part time employed	X (X)	X (X)
Employed	X (X)	X (X)
Unemployed/homemaker	X (X)	X (X)
Clinical characteristics		
Psychiatric comorbidity (MINI) – no. (%)		
Anxiety disorders	X (X)	X (X)
Major depressive disorder	X (X)	X (X)
Post-traumatic stress disorder	X (X)	X (X)
Proportion of participants with subthreshold BPD – no. (%)	X (X)	X (X)
No. of BPD criteria (SCID-5-PD), mean (SD)	X (X)	X (X)
Personality disorder comorbidity (SCID-5-PD) – no. (%)		
Avoidant personality disorder	X (X)	X (X)
Obsessive-compulsive personality disorder	X (X)	X (X)
Dependent personality disorder	X (X)	X (X)
Paranoid personality disorder	X (X)	X (X)
Proportion of participants with one or more suicide-attempts the past 8 months – no. (%)	X (X)	X (X)
Proportion of participants with one or more acts of severe self-harm the past 8 months – no. (%)	X (X)	X (X)
Proportion of participants on antidepressants	X (X)	X (X)
Proportion of participants on antipsychotics		X (X)
Proportion of participants on other psychoactive drugs	X (X)	X (X)

BPD; Borderline Personality Disorder; MINI: Mini International Neuropsychiatric Interview; No.: Number; SCID-5-PD: Structured Clinical Interview for DSM-5 Personality Disorders; SD: Standard Deviation

Table 2
Primary and secondary outcome results (ITT Population)

Outcome	Short-term MBT group (n= 83)		Long-term MBT group (n= 83)		Estimate (95% CI)	*p*-value
	No. analyzed	Result	No. analyzed	Result		
Primary						
Borderline symptoms, ZAN-BPD, mean (SD)						
- Baseline	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 8 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 16 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
Secondary						
Functional impairment, WSAS, mean (SD)						
- Baseline	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 8 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 16 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
Quality of life, SF-36 – mental component, mean (SD)						
- Baseline	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 8 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 16 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*

Global functioning, GAF, mean (SD)						
- Baseline	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 8 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
- 16 months	X	XX (X)	X	XX (X)	Mean difference (XX to YY)	*p = ZZ*
Proportion of participants with severe self-harm the past 8 months						
- Baseline	X	XX/YY (ZZ%)	x	XX/YY (ZZ%)	Relative risk XX (YY to ZZ)	*p = ZZ*
- 8 months	X	XX/YY (ZZ%)	x	XX/YY (ZZ%)	Relative risk XX (YY to ZZ)	*p = ZZ*
- 16 months	X	XX/YY (ZZ%)	x	XX/YY (ZZ%)	Relative risk XX (YY to ZZ)	*p = ZZ*

GAF: Global Assessment of Functioning; ITT: Intention To Treat; SF-36: Short Form Health Survey – 36; SD: Standard Deviation; WSAS: Work and Social Adjustment Scale; ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder

Paper V

Journal of Contemporary Psychotherapy
https://doi.org/10.1007/s10879-020-09456-6

ORIGINAL PAPER

The Capacity to End: Termination of Mentalization-Based Therapy for Borderline Personality Disorder

Sophie Juul[1,2] · **Sebastian Simonsen**[1] · **Anthony Bateman**[3]

Abstract
Terminating a therapeutic relationship can be a challenging phase with patients suffering from borderline personality disorder. Despite the critical importance of the termination phase, the proportion of psychotherapy literature devoted to the demands and challenges of this phase is small. This paper describes a mentalization-based approach to detect and intervene against such challenges. It is proposed that termination challenges, while operating through overlapping and interactive mechanisms, can be attributed to (1) patient factors, (2) therapist factors, and (3) therapeutic relationship factors. The paper has clinical implications and suggests that the aim of enhancing mentalizing capacities should include mentalizing the often complicated and mixed feelings associated with separation and loss of the therapeutic relationship. To facilitate this process, we propose the use of a "termination formulation", in which patients' outcomes and future goals are recapitulated in the termination phase of mentalization-based therapy.

Keywords Borderline personality disorder · Mentalization-based therapy · Treatment termination

Introduction

Borderline personality disorder (BPD) is a prevalent psychiatric condition characterized by a pervasive pattern of symptoms such as intense and unstable relationships, chronic feelings of emptiness, intense anger, fear of abandonment, intolerance for aloneness, and a lack of a stable sense of self (American Psychiatric Association 2013). These fundamental aspects of BPD, particularly the relational aspects, can be understood as stemming from impairments in their underlying attachment organization (Levy et al. 2005).

Attachment theory, developed by Bowlby (1972, 1973, 1998), proposed that internal representations of self and others provide prototypes for all later relationships. Such representations exist outside of awareness and are quite resistant to change (Waters et al. 2000). Bowlby's suggestion that early experience with the caregiver organizes later attachment relationships, has been used to explain the development of BPD psychopathology (Fonagy et al. 2000). Patients with BPD typically experience considerable distortions of attachment representations, resulting in a disrupted capacity to depict mental states in themselves and others (Levy et al. 2005). Further, feelings of abandonment anxiety can be easily triggered in attachment situations, which are likely to be transferred to the therapeutic relationship.

Consequently, despite the obvious need for effective treatments, patients with BPD can be hard to engage effectively in treatment as they bring insecure pre-occupied, avoidant, or disorganized attachment strategies into their interaction with services and treatment (Choi-Kain et al. 2009). A common concern for clinicians when treating patients with BPD is premature treatment termination (De Panfilis et al. 2012; Wnuk et al. 2013) In a systematic review of therapy non-completion in patients with personality disorders, a median non-completion rate was estimated at 37% (McMurran et al. 2010). In contrast, some BPD patients are also likely to be frequent and continuous users of mental health services (Soeteman et al. 2008), often expressing a need for more help, presenting the treating clinicians with a difficult judgement of whether to terminate or to extend

✉ Sophie Juul
sophie.juul@regionh.dk

[1] Stolpegaard Psychotherapy Centre, Mental Health Services in the Capital Region of Denmark, Stolpegårdsvej 20, 2820 Gentofte, Denmark

[2] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

[3] Anna Freud Centre, Kantor Centre of Excellence, London, Great Britain

Published online: 16 March 2020

the treatment. There is reason to believe that such termination challenges characterized by high rates of premature treatment termination, prolonged treatments, and continuous referrals to specialist treatment, can to some extent be theoretically understood within an attachment framework, e.g. as a way of coping with anticipated and foreseen separation or loss. Thus, implicitly or explicitly, enhanced mentalizing of themes associated with separation and loss in the treatment of BPD could help prevent reenactment of attachment anxiety and it can help the patient form a new and more stable representation of interpersonal relationships.

Mentalization-based therapy is not immune to termination challenges activated by attachment anxiety. However, it may offer ways to understand and deal with them. Mentalization-based therapy is a psychodynamic therapy based on attachment theory that has originally been developed for treating BPD (Bateman and Fonagy 2016). Mentalization refers to the capacity to understand one's own and others internal mental states such as feelings, wishes, desires, and beliefs. Frequent and extensive failures to this capacity, especially in the context of attachment relationships, is believed to play an important role in the psychopathology of BPD (Fonagy and Luyten 2009). Mentalization-based therapy currently has empirical support as an 18-months program for BPD. This treatment program has been implemented in clinical settings worldwide, both in day-hospital (Bateman and Fonagy 1999; Smits et al. 2019) and outpatient (Bateman and Fonagy 2009; Kvarstein et al. 2015) settings, and is also being tested in a 20-weeks short-term version (Juul et al. 2019).

There are three main phases to the trajectory of mentalization-based therapy: a beginning-, a middle-, and an ending-phase. Each phase has a distinct aim and harnesses specific therapeutic processes. According to the treatment manual, the ending phase should focus on mentalizing affective states associated with separation, and there should be a focus on how to maintain gains that have been made during treatment (Bateman and Fonagy 2016). However, there will be many variations to the clinical application of the ending phase between clinicians, with different types of patients, and in different time format (e.g. short-term or long-term, predefined or open-ended).

In this paper, we will elaborate on the mentalization-based framework for understanding termination challenges, and we will propose possible clinical solutions to these challenges. While termination challenges are not restricted to mentalization-based therapy, we believe that enhanced mentalizing of feelings associated with termination can be helpful in any form of psychotherapy for BPD.

Termination Challenges

For the ending of mentalization-based therapy, and other psychotherapies for BPD, to be effective in stimulating long term improvement, it is important to outline challenges that can threaten this effectiveness. Knowing that these challenges operate in overlapping and interactive patterns, we have divided them into the following three distinct domains: *patient factors*, *therapist factors,* and *therapeutic relationship factors*.

Patient Factors

According to the mentalization theory, all people, but particularly patients with BPD, present with disrupted mentalizing, or nonmentalizing modes. There are three typical nonmentalizing modes termed *psychic equivalence mode, teleological mode,* and *pretend mode* (Bateman and Fonagy 2016; Fonagy and Luyten 2009). These are all likely to influence the termination phase of treatment.

Psychic equivalence mode involves thoughts and feelings becoming "too real" to a point where it is extremely difficult for the patient to entertain possible alternative perspectives. There is often a suspension of doubt forcing the individual to believe that his or her own perspective is the only one possible (Bateman and Fonagy 2019). In the termination phase of treatment, a patient presenting with psychic equivalence mode will become hyperaroused and overwhelmed by feelings of abandonment. Transference reactions can be dominated by feelings of rejection, dependence or splitting, and the patient can perceive the therapist as negligent or inattentive to his or her needs. We can refer to this as "the emotions form reality"-problem. This can result in both aggressive or clinging behaviors, separately or simultaneously. The patient might manifest increased dependency on the therapist, reflected in attempts to postpone termination (e.g. by presenting new symptoms or crises). For the patient, postponing therapy may serve to protect against anxious or angry feelings related to the experience of rejection, abandonment, and separation (Joyce et al. 2007).

Teleological mode involves states of mind being recognized only if their outcomes are physically observable (Bateman and Fonagy 2019). For example, affection is only perceived to be true, if it is accompanied by physical contact. In the termination phase of treatment, a patient presenting with a teleological mode of functioning will believe, that he or she can only experience real improvement in therapy, if the therapist is present and continuously available for support. We can refer to it as "the no therapist, no help"-problem. The presence of the therapist

is associated with comfort, while absence of the therapist is associated with distress. From an attachment point of view, the patient will present with an inability to form a stable psychic representation of the therapist, once the therapist is not physically present—a phenomenon similar to lack of *object constancy*, as formulated in psychoanalytic theory (Fraiberg 1969; Hartmann 1952).

Pretend mode involves thoughts and feelings becoming too disconnected from reality. In more extreme cases, this may lead to feelings of derealization and dissociation (Bateman and Fonagy 2019). A patient dominated by pretend mode may be prone to hypermentalizing—a state in which he or she may speak about mental states but with very little or no connection to real affective experiences. In the termination phase of treatment, a patient dominated by pretend mode may prematurely detach or perhaps become overly compliant arguing that the therapy has been a success, even though mentalizing or functional capacities indicate otherwise. We may refer to this as "the as-if"-problem. The patient may show considerable cognitive understanding of why the therapy must come to an end, but there may be little understanding of the underlying affective experiences induced by the loss of the therapist. Their restricted engagement may protect them from their feared intense or overwhelming response to termination. This phenomenon may be similar to a dissociative experience and may be further explained by notion of *the false self* as proposed by Winnicott (1960).

Further, it is likely that the concept of *epistemic trust* may influence the termination phase as well. Epistemic trust refers to an individual's willingness to consider new knowledge from another person as trustworthy, generalizable, and relevant to the self (Fonagy and Allison 2014). It is suggested that many forms of psychopathology may be underpinned by an inability to benefit from social communication due to *epistemic mistrust.* This results in these patients' reluctance to modify their beliefs and expectations, even when facing social experiences that clearly indicate the value of doing so (Fonagy et al. 2019). In the termination phase of treatment, a patient characterized by epistemic mistrust or increased epistemic vigilance may not trust the therapist's reinforcements of autonomy or validations of good mentalizing. Instead, the patient may experience these interventions as untrue or even as a sign of masked abandonment. In other words, patients may not trust their own ability to generate a representation of the therapist representing them, if the therapist is not physically present.

Therapist Factors

Therapists' own conflicts associated with the ending of therapy and the therapeutic relationship may also play an important role in the termination phase of treatment. Different therapist emotional responses (or countertransference) are likely to become activated when facing treatment termination. The relationship between BPD pathology and therapist countertransference has been studied both theoretically and empirically in the literature on personality pathology (Betan et al. 2005; Colli et al. 2014). Typical countertransference reactions include feelings of helplessness/inadequacy, overinvolvement, overprotection, or feelings of being overwhelmed and disorganized.

In the termination phase, a patient may react in a *psychic equivalent mode* of functioning e.g. by becoming overwhelmed by feelings of abandonment, and this may in turn evoke feelings of guilt, helplessness, overprotection or disorganization in the therapist. Thus, termination challenges arise, if the therapist acts on their own feelings and thus fails to intervene against the psychic equivalent mode. For example, rather than regulating arousal and facilitating independence or self-efficacy, the therapist reinforces the psychic equivalence by explicitly agreeing that more therapy is needed or validates the notion of abandonment. In this case, there is a risk that the intolerable feelings are worsened. Instead, a contrary move to a cognitive focus and diversion would be more appropriate to facilitate reflection on personal agency and life after treatment (Bateman and Fonagy 2016). The therapist could say: "I hear you saying that you feel anxious and sad about ending therapy. But you have also told me that you wish to be more independent. Can we entertain the last part for a little while? How would independence look like for you? In which situations would you know that you have become more independent?".

If the patient also presents with a *teleological mode*, arguing that he or she can only recover in the presence of a therapist, the therapist may feel overprotective and (teleologically) act on this feeling by deciding to prolong the therapy or to refer the patient to another therapist or treatment modality. In these cases, there is a risk that the challenging ending merely becomes postponed instead of mentalized. We are not arguing, that transferring to another therapist or treatment modality is never appropriate. Patients who resist termination through self-destructive acting out around the time of the termination phase may be offered additional care, but the therapist must reflect on his or her own ability to stimulate a mentalizing understanding of this behavior with the patient. In such cases therapists should have a supervision forum, which can be used to process feelings of e.g. guilt or remorse, if they must terminate the therapy with a patient who is still suffering emotionally and behaviorally. The same applies to forced terminations that can occur in clinical practice, for example when a training therapist must move to a new treatment setting or an experienced therapist must relocate for personal or professional reasons.

If the patient was dominated by a *pretend mode* of functioning throughout the therapy, and this was not properly

addressed, it can cause challenges to the termination phase of treatment. Pretend mode that is unaddressed results in endless therapy that merely "looks like" therapy. Therapists may then feel responsible if symptom severity is unchanged at the end of treatment and may thus decide to prolong the treatment because of continued treatment-demanding psychopathology (Sharp et al. 2013). With a patient dominated by pretend mode, another possibility is that the therapist avoids shifting from cognitive to affective mentalizing of feelings associated with ending. This lack of contrary move could cause both the patient and therapist to prematurely detach and agree that the therapy was a success and must come to an end. In this case, the therapist should stop and focus on the affective experience here-and-now, for example by saying: "You tell me that ending therapy is fine with you. How do you feel right now telling me that?". If still stuck in pretend mode, the patient may reply: "I don't really know what I am feeling", and this may be a cue that the affective experience of termination should be further explored.

Therapists often experience patients with severe personality disorders as "hard to reach" as evidenced by premature termination and poor outcomes (Fonagy et al. 2017a, b). However, somewhat paradoxically, such patients may also be the hardest to let go. In such cases therapists may themselves lack *epistemic trust* in their patients' capacity to end. Therapists may experience countertransference reactions that interfere with their ability to recognize the patient's strengths and resources (Joyce et al. 2007). In other words, termination challenges may arise when therapists are not sufficiently able to generate a mental representation of the patient which properly mirrors the patients' own sense of agency. In such cases the therapist often holds a fixed and rigid representation of the patient as someone who cannot manage without their support. The therapists may then ask themselves: "Am I able to generate a clear sense of my patient's clinical change?", and "Is my patient allowed to change in my mind?". With a lack of epistemic trust in the patients' ability to reach a certain level of autonomy and believe the patient's own reports, the therapist may run the risk of delivering therapy that maintains the patient in the belief that more therapy will always be needed and available.

Therapeutic Relationship Factors

Over the course of treatment, an emotional bond is usually developed between the patient and the therapist. Both parties may experience sadness and reservations about termination and may even be interested in continuing the relationship. In fact, the goal of the therapeutic relationship in mentalization-based therapy is to facilitate such a safe environment, in which both personal and interpersonal thoughts and feelings can be mentalized (Bateman and Fonagy 2016). However, willingness to manage sensitive topics and ask demanding questions within the therapeutic relationship also plays an important role in the competently delivered mentalization-based therapy session. Conversely, low rated sessions are characterized by therapists who are not adequately confrontative, who avoid difficult content, and who may exaggerate efforts to accommodate or please the patient (Folmo et al. 2019; Möller et al. 2016). We speculate that when both the patient and the therapist fail to engage in a trustful yet confronting therapeutic environment, it may lead to termination challenges. We believe that a therapeutic focus on the relational aspect in session may increase mentalizing of the patient's interpersonal patterns. On the contrary, therapy that is too supportive, in which both the patient and therapist avoid mentalizing difficult interpersonal themes, might suffer the problem that challenging interpersonal patterns will reveal themselves during the termination process. By then, it may be too late to properly address them.

Further, in the beginning phase of mentalization-based therapy, and in other treatments for BPD, a case formulation is developed in a collaboration between the therapist and the patient. The mentalization-based case formulation in is a collaborative clinical agreement, designed to foster agency and a sense of control, which in turn helps foster alliance and relaxes epistemic mistrust (Bateman et al. 2019; Karterud and Kongerslev 2019). We speculate that an mentalization-based case formulation with treatment goals that are not appropriate to the available length of treatment may increase the likelihood of a challenging termination. Treatment goals can be formulated either too vaguely (i.e. to improve mentalization) or too narrowly (i.e. stop self-harming after group therapy), both of which may result in termination challenges when gains and processes are reviewed and recapitulated in the ending phase of therapy.

Overcoming Termination Challenges Based on Mentalization-Based Therapy

In the following, we will offer some possible remedies for the challenges that arise when ending mentalization-based therapy and discuss their relevance to psychotherapy with BPD-patients in general. We focus on three main areas: mentalizing loss of the therapeutic relationship, management of treatment structure, and finally we propose to extend the case formulation with a termination formulation.

Mentalizing Loss of the Therapeutic Relationship

Some patients become overemotional, over-attached, or attribute incorrect attitudes to the therapist as a way of handling separation. Some patients may become confused, some become angry or devaluing, and others may continue to "deflate" the relationship. If not mentalized within the

context of the therapeutic relationship, these problematic strategies may influence what the patients carry forward into new relationships, e.g. "the good never lasts", "all people eventually let you down", "nobody will ever be able to understand me". Thus, ending badly increases epistemic mistrust and increases the possibility that patients become inflexible or rigid in the face of social change (Fonagy et al. 2019).

According to a review of the literature by Joyce et al. (2007), two perspectives have dominated the literature on termination of the therapeutic relationship; the "termination-as-loss" metaphor and the notion of "termination as transformation". The two perspectives are not mutually exclusive but will often occur simultaneously. In mentalization-based therapy, and other psychodynamic therapies for personality disorders, for example transference-focused therapy (Kernberg et al. 2008), the therapist will carefully assess the patient's implicit or explicit metaphor and its consequences for the ending phase. The therapist will validate and normalize the patient's emotional experiences of separation and loss as understandable based on their life narrative, but should also clearly communicate the possibility of other, more secure ways of saying goodbye i.e. acknowledging mixed feelings and recapitulating the relationship story.

Management of Treatment Structure

In order to enhance mentalizing of challenging terminations, we suggest that the finite nature of therapy should not only be specified from the beginning and addressed in the case formulation, but it should also be considered in the session structure throughout the course of therapy. In short-term mentalization-based groups this is done by therapists labeling the session number at the beginning of each session, e.g. by stating that this is the fourth out of 20 sessions. This effectively reminds patients about the boundaries of therapy and nudges them to bring up relevant material. Further, each session should leave sufficient time for the therapist and patient(s) to reflect on the treatment process in terms of mentalizing/understanding each other (Bateman et al. 2019). The group therapists should ask the group: "How did we do today? Did we understand each other? What have we managed to help with and what have we not; what do we need to think about over the week to discuss next time?". We believe that this process both has general benefits in terms of building epistemic trust but may also have more specific benefits in preparing and building a capacity to terminate therapy. Often the therapist will start this process by asking the patient to sum up topics and aspects of the session emphasizing his or her perspective on the process and issues of importance. The therapist will then reflect on this as a way of helping the patient compare his or her perspectives with that of the therapists. In this way patients get a clearer representation of what they themselves feel is important and helpful and this stronger sense of subjectivity (and otherness) we believe could be helpful both in terms of preparing separation and in supporting stronger agency and more secure attachment strategies. In addition, asking the patient to think about what has been left over during the week on their own builds a sense of personal agency.

Extending the Case Formulation with a Termination Formulation

The ending of therapy should be foreseen and prepared for in the case formulation at the beginning of therapy. The case formulation should include a relational passport (Karterud and Kongerslev 2019) specifying attachment patterns and foreseen reactions to the ending of treatment. The therapist should probe the patient for prior experiences with ending and loss and ask the patient for expectations about their reactions when the ending of treatment will be near. From a mentalization-based perspective we do not expect patients with BPD to be very conscious about separation reactions. Attachment and separation trauma tend to be implicitly represented in patients' minds. However, the explicit addressing of the issue in the case formulation serves the purpose of shedding light on previously non-mentalized aspects of relationship patterns, for example when patients have been unable to read and take advantage of socially inclusive cues. In mentalization-based therapy, a key purpose is for the patient to shift from implicit to explicit mentalizing of mental states (Bateman and Fonagy 2016). The therapy should seek to modify the patients' pathological activation of attachment processes by helping to avoid automatic processing of events. This automatic processing typically occurs when patients recruit negative memories of relationships and events to interpret new experiences (Winter et al. 2014). In the context of terminating therapy, patients may automatically expect the termination to confirm their negative memory bias. By entertaining a more explicit awareness of this bias in the case formulation, the therapist may potentially help the patient to a more deliberate and controlled way of being in a relationship and it may serve as a model for future separation.

When reviewing the case formulation, it is recommended that the patient and the therapist should reflect on strategies to maintain mentalizing capacities outside of the treatment system. This is important, given that patients with BPD often come from deprived social environments, and an increase in mentalizing following therapy may bring about psychological pain and vulnerability (Bo et al. 2017). This pain is exacerbated when patients continue to live in a family or social environment which promotes non-mentalizing responses to problems, for example using coercive or even violent control of others. Many patients might (rightfully)

see it as a best option to return to old strategies. In most cases, however, it is our experience that even within very deprived environments, it will be possible to identify one or two people with whom the patient can build a more stable and trusting relationship. It is important to recognize this early in therapy and perhaps include it in the case formulation to help support such relationships, while at the same time be transparent about the fact that the therapist will not always be available for support. Thus, the case formulation can be a particularly useful tool for enabling a smooth transition from therapy to real life.

In order to facilitate this transition, we propose to extend the case formulation with a simple form called the *termination formulation*. This form addresses three areas of termination and asks the patient to reflect on (a) what has been achieved and what needs further work; as mentioned, this process has been rehearsed at the end of sessions over time, (b) if there is anything the patient needs to address in the relationship with either the individual or group therapist or fellow group members before ending therapy, and (c) how the therapeutic progress can be retained or further developed after the therapy has ended. To foster agency and a sense of self-direction, the patient is given this form to take home and is asked to write down his or her own thoughts and feelings leaving three to four sessions to process the content and manage issues that come up. The termination formulation can be a useful tool in any form of psychotherapy tradition for BPD, as it entails pantheoretical themes of termination (Norcross et al. 2017).

Sometimes a case formulation is either not made, or it is made in ways that do not foster good outcomes (Bateman 2011; Simonsen et al. 2011). In such cases, implementing this simple termination formulation can be a particularly useful strategy to help identify main outcomes and support the maintenance of these outcomes once therapy has ended, even when these have not been clearly formulated at the beginning. If new issues or themes come up when preparing the termination formulation, or if countertransference issues may interfere with the development of the termination formulation in a problematic way, supervision becomes of the upmost importance. In mentalization-based supervision, supervisors are encouraged to help therapists clarify and extend their "roadmap" of realistic treatment trajectories and individualized outcomes for their patients. Furthermore, problems with overwhelming or confusing countertransference reactions are common when treating patients with BPD (Betan et al. 2005; Colli et al. 2014). Therefore, therapists performing mentalization-based therapy are encouraged to bring up patients, who are facing their ending phase of treatment, in supervision. We believe that mentalizing one's own feelings towards termination is an important step towards being able to facilitate a beneficial ending phase for the patient.

Conclusion

Challenging terminations are likely to be an inherent part of all forms of personality disorder treatments regardless of treatment modality. In this paper, we have proposed an approach based on mentalization-based therapy to detect and intervene against such challenges. We have proposed that termination challenges can be attributed to (1) patient factors, (2) therapist factors, and (3) therapeutic relationship factors. We have suggested that explicit mentalizing of the often complicated and mixed feelings associated with separation and loss of the therapeutic relationship is an important part of the termination phase. To facilitate this process, we have proposed the use of a *termination formulation* in extension to the case formulation, in which patient's outcomes, interpersonal issues in therapy, and future goals are recapitulated in the termination phase. At this point there is no empirical evidence that better mentalizing of termination issues causes better overall outcomes in the treatment of BPD. However, we are confident that providing therapists and patients with a more explicit framework for termination addresses a previously neglected issue and can enhance both therapists' and patients' capacity to end.

Funding Not applicable.

Data Availability Data sharing is not applicable to this article as no new data were created or analysed in this study.

Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington, DC: American Psychiatric Publishing.

Bateman, A. (2011). Commentary on 'Minding the difficult patient': Mentalizing and the use of formulation in patients with borderline personality disorder comorbid with antisocial personality disorder. *Personality and Mental Health, 5*(1), 85–90. https://doi.org/10.1002/pmh.156.

Bateman, A., & Fonagy, P. (1999). Effectiveness of partial hospitalization in the treatment of borderline personality disorder: A randomized controlled trial. *American Journal of Psychiatry, 156*(10), 1563–1569. https://doi.org/10.1176/ajp.156.10.1563.

Bateman, A., & Fonagy, P. (2009). Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. *American Journal of Psychiatry, 166*(12), 1355–1364. https://doi.org/10.1176/appi.ajp.2009.09040539.

Bateman, A., & Fonagy, P. (2016). *Mentalization-based treatment for personality disorders: A practical guide*. Oxford, United Kingdom: Oxford University Press.

Bateman, A., & Fonagy, P. (2019). *Handbook of mentalizing in mental health practice* (2nd ed.). Washington, DC: American Psychiatric Association Publising.

Bateman, A., Kongerslev, M., & Bo Hansen, S. (2019). Mentalization-based treatment group therapy (MBT-G) for adults and adolescents. In A. Bateman & P. Fonagy (Eds.), *Handbook of mentalizing in mental health practices*. Washington, DC: American Psychiatric Association Publishing.

Betan, E., Heim, A. K., Conklin, C. Z., & Westen, D. (2005). Countertransference phenomena personality pathology in clinical practice: An empirical investigation. *American Journal of Psychiatry, 162*, 890–898.

Bo, S., Sharp, C., Fonagy, P., & Kongerslev, M. (2017). Hypermentalizing, attachment, and epistemic trust in adolescent BPD: Clinical illustrations. *Personality Disorders, 8*(2), 172–182. https://doi.org/10.1037/per0000161.

Bowlby, J. (1972). *Attachment and loss: Volume I: Attachment*. London: Penguin Books.

Bowlby, J. (1973). *Attachment and loss: Volume II: Separation, anxiety and anger* (pp. 1–429). London: The Hogarth Press and the Institute of Psycho-Analysis.

Bowlby, J. (1998). *Attachment and loss: Volume III: Loss—sadness and depression*. London: Pimlico.

Choi-Kain, L. W., Fitzmaurice, G. M., Zanarini, M. C., Laverdière, O., & Gunderson, J. G. (2009). The relationship between self-reported attachment styles, interpersonal dysfunction, and borderline personality disorder. *The Journal of Nervous and Mental Disease, 197*(11), 816–821.

Colli, A., Annalisa Tanzilli, A., Dimaggio, G., & Lingiardi, V. (2014). Patient personality and therapist response: An empirical investigation. *American Journal of Psychiatry, 171*, 102–108.

De Panfilis, C., Marchesi, C., Cabrino, C., Monici, A., Politi, V., Rossi, M., et al. (2012). Patient factors predicting early dropout from psychiatric outpatient care for borderline personality disorder. *Psychiatry Research, 200*(2–3), 422–429.

Folmo, E. J., Karterud, S. W., Kongerslev, M. T., Kvarstein, E. H., & Stänicke, E. (2019). Battles of the comfort zone: Modelling therapeutic strategy, alliance, and epistemic trust—A qualitative study of mentalization-based therapy for borderline personality disorder. *Journal of Contemporary Psychotherapy*. https://doi.org/10.1007/s10879-018-09414-3.

Fonagy, P., & Allison, E. (2014). The role of mentalizing and epistemic trust in the therapeutic relationship. *Psychotherapy, 51*(3), 372.

Fonagy, P., Allison, E., & Campbell, C. (2019). Mentalizing, resilience, and epistemic trust. In A. Bateman & P. Fonagy (Eds.), *Handbook of mentalizing in mental health practice* (2nd ed.). Washington, DC: American Psychiatric Association Publishing.

Fonagy, P., & Luyten, P. (2009). A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. *Development and Psychopathology, 21*(4), 1355–1381. https://doi.org/10.1017/S0954579409990198.

Fonagy, P., Luyten, P., Allison, E., & Campbell, C. (2017a). What we have changed our minds about: Part 1. Borderline personality disorder as a limitation of resilience. *Borderline Personality Disorder and Emotion Dysregularity, 4*, 11. https://doi.org/10.1186/s40479-017-0061-9.

Fonagy, P., Luyten, P., Allison, E., & Campbell, C. (2017b). What we have changed our minds about: Part 2. Borderline personality disorder, epistemic trust and the developmental significance of social communication. *Borderline Personality Disorder and Emotion Dysregularity, 4*, 9. https://doi.org/10.1186/s40479-017-0062-8.

Fonagy, P., Target, M., & Gergely, G. (2000). Attachment and borderline personality disorder: A theory and some evidence. *Psychiatric Clinics, 23*(1), 103–122.

Fraiberg, S. (1969). Libidinal object constancy and mental representation. *The Psychoanalytic Study of the Child, 24*(1), 9–47.

Hartmann, H. (1952). The mutual influences in the development of ego and id. *The Psychoanalytic Study of the Child, 7*(1), 9–30.

Joyce, A. S., Piper, W. E., Ogrodniczuk, J. S., & Klien, R. H. (2007). *Termination in psychotherapy: A psychodynamic model of processes and outcomes*. Washington, DC: American Psychological Association.

Juul, S., Lunn, S., Poulsen, S., Sorensen, P., Salimi, M., Jakobsen, J. C., et al. (2019). Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: A protocol for a randomized clinical trial. *Trials, 20*(1), 196. https://doi.org/10.1186/s13063-019-3306-7.

Karterud, S., & Kongerslev, M. T. (2019). Case formulations in mentalization-based treatment (MBT) for patients with borderline personality disorder. In U. Kramer (Ed.), *Case formulation for personality disorders* (pp. 41–60). London: Elsevier.

Kernberg, O. F., Yeomans, F. E., Clarkin, J. F., & Levy, K. N. (2008). Transference focused psychotherapy: Overview and update. *The International Journal of Psychoanalysis, 89*(3), 601–620.

Kvarstein, E. H., Pedersen, G., Urnes, O., Hummelen, B., Wilberg, T., & Karterud, S. (2015). Changing from a traditional psychodynamic treatment programme to mentalization-based treatment for patients with borderline personality disorder–does it make a difference? *Psychology and Psychotherapy, 88*(1), 71–86. https://doi.org/10.1111/papt.12036.

Levy, K. N., Meehan, K. B., Weber, M., Reynoso, J., & Clarkin, J. F. (2005). Attachment and borderline personality disorder: Implications for psychotherapy. *Psychopathology, 38*(2), 64–74.

McMurran, M., Huband, N., & Overton, E. (2010). Non-completion of personality disorder treatments: A systematic review of correlates, consequences, and interventions. *Clinical Psychology Review, 30*(3), 277–287. https://doi.org/10.1016/j.cpr.2009.12.002.

Möller, C., Karlgren, L., Sandell, A., Falkenstrom, F., & Philips, B. (2016). Mentalization-based therapy adherence and competence stimulates in-session mentalization in psychotherapy for borderline personality disorder with co-morbid substance dependence. *Psychotherapy Research*. https://doi.org/10.1080/10503307.2016.1158433.

Norcross, J. C., Zimmerman, B. E., Greenberg, R. P., & Swift, J. K. (2017). Do all therapists do that when saying goodbye? A study of commonalities in termination behaviors. *Psychotherapy, 54*(1), 66.

Sharp, C., Ha, C., Carbone, C., Kim, S., Perry, K., Williams, L., et al. (2013). Hypermentalizing in adolescent inpatients: Treatment effects and association with borderline traits. *Journal of Personality disorders, 27*(1), 3–18.

Simonsen, S., Nørgaard, N. L., Larsen, K. A., & Bjørnholm, K. I. (2011). Mentalization-inspired case formulation: Minding the difficult patient. *Personality and Mental Health, 5*(1), 73–79. https://doi.org/10.1002/pmh.154.

Smits, M. L., Feenstra, D. J., Eeren, H. V., Bales, D. L., Laurenssen, E. M., Blankers, M., ... Verheul, R. (2019). Day hospital versus intensive out-patient mentalisation-based treatment for borderline personality disorder: Multicentre randomised clinical trial. *The British Journal of Psychiatry*, 1–6.

Soeteman, D. I., Hakkaart-van Roijen, L., Verheul, R., & Busschbach, J. J. V. (2008). The economic burden of personality disorders in mental health care. *Journal of Clinical Psychiatry, 69*, 259–265.

Waters, E., Merrick, S., Treboux, D., Crowell, J., & Albersheim, L. (2000). Attachment security in infancy and early adulthood: A twenty-year longitudinal study. *Child Development, 71*(3), 684–689.

Winnicott, D. W. (1960). Ego distortion in terms of true and false self. *The maturational process and the facilitating environment: Studies in the theory of emotional development* (pp. 140–157). New York: International Universities Press.

Winter, D., Elzinga, B., & Schmahl, C. (2014). Emotions and memory in borderline personality disorder. *Psychopathology, 47*(2), 71–85.

Wnuk, S., McMain, S., Links, P. S., Habinski, L., Murray, J., & Guimond, T. (2013). Factors related to dropout from treatment in two outpatient treatments for borderline personality disorder. *Journal of Personality Disorders, 27*(6), 716–726.

Co-author statements

Co-author statement

PhD student	Sophie Merrild Juul
Date of birth	08-10-91
Faculty (Department)	University of Copenhagen, Department of Psychology

"Attribution of authorship should in general be based on criteria a-d adopted from the Vancouver guidelines , and all individuals who meet these criteria should be recognized as authors:

A. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and
B. drafting the work or revising it critically for important intellectual content, and
C. final approval of the version to be published, and
D. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Article/paper/chapter/manuscript
This co-authorship declaration applies to the following:

*Title	Short-term versus long-term psychotherapy for adult psychiatric disorders: a protocol for a systematic review with meta-analysis and trial sequential analysis
*Author(s)	Sophie Juul, Stig Poulsen, Susanne Lunn, Per Sørensen, Janus Christian Jakobsen & Sebastian Simonsen.
Journal	Systematic Reviews
Volume (no)	8 (169)
Start page	https://doi.org/10.1186/s13643-019-1099-0
End page	

Contributions to the paper/manuscript made by the PhD student

What was the role of the PhD student in designing the study?

The PhD student had the main role in designing the study.

How did the PhD student participate in data collection and/or development of theory?

Data collection was not applicable to this protocol paper.

Which part of the manuscript did the PhD student write or contribute to?

The PhD student wrote up the whole manuscript with ongoing supervision from the co-authors.

Did the PhD student read and comment on the final manuscript?

Yes

Signatures

If an article/ paper/chapter/manuscript is written in collaboration with three or less researchers (including the PhD student), all researchers must sign the statement. However, if an article has more than three authors the statement may be signed by a representative sample, cf. article 12, section 4 and 5 of the Ministerial Order No. 1039, 27 August 2013. A representative sample consists of minimum three authors, which is comprised of the first author, the corresponding author, the senior author, and 1-2 authors (preferably international/non-supervisor authors).

By their signature, the authors agree that the article/paper/chapter/manuscript will be included as a part of the PhD thesis made by the PhD student mentioned above.

Date	12. jan. 2021	Name	Sophie Merrild Juul	Signature	Sophie Juul Sophie Juul (12. Jan 2021 12:06 GMT+1)
Date	13. jan. 2021	Name	Per Sørensen	Signature	
Date	13. jan. 2021	Name	Janus Christian Jakobsen	Signature	Janus Christian Jakobsen Janus Christian Jakobsen (13. Jan 2021 15:12 GMT+1)
Date	14. jan. 2021	Name	Sebastian Simonsen	Signature	Sebastian Simonsen Sebastian Simonsen (14. Jan 2021 08:27 GMT+1)

Paper 1 - Co-author statement

Endelig revisionsrapport 2021-01-14

Oprettet:	2021-01-11
Af:	Mette Hansen (mette.hansen@ctu.dk)
Status:	Underskrevet
Transaktions-id:	CBJCHBCAABAAf0_aR3Sbl2fzf-7QTsYyyMMaX_lbmMzz

Oversigt over "Paper 1 - Co-author statement"

Dokument oprettet af Mette Hansen (mette.hansen@ctu.dk)
2021-01-11 - 19:31:14 GMT- IP-adresse: 83.93.10.217

Dokumentet blev sendt til Sophie Juul (sophie.juul@regionh.dk) til underskrivelse
2021-01-11 - 19:38:53 GMT

E-mail blev vist af Sophie Juul (sophie.juul@regionh.dk)
2021-01-11 - 19:39:00 GMT- IP-adresse: 13.80.183.173

Dokumentet blev e-underskrevet af Sophie Juul (sophie.juul@regionh.dk)
Dato for signatur: 2021-01-12 - 11:06:11 GMT - tidskilde: server- IP-adresse: 176.23.225.115

Dokumentet blev sendt til Per Sørensen (per.soerensen@regionh.dk) til underskrivelse
2021-01-12 - 11:06:12 GMT

E-mail blev vist af Per Sørensen (per.soerensen@regionh.dk)
2021-01-13 - 13:02:24 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Per Sørensen (per.soerensen@regionh.dk)
Dato for signatur: 2021-01-13 - 13:12:36 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Dokumentet blev sendt til Janus Christian Jakobsen (janus.jakobsen@ctu.dk) til underskrivelse
2021-01-13 - 13:12:38 GMT

E-mail blev vist af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
2021-01-13 - 13:13:02 GMT- IP-adresse: 176.23.22.251

Dokumentet blev e-underskrevet af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
Dato for signatur: 2021-01-13 - 14:12:33 GMT - tidskilde: server- IP-adresse: 176.23.22.251

Dokumentet blev sendt til Sebastian Simonsen (sebastian.simonsen@regionh.dk) til underskrivelse
2021-01-13 - 14:12:34 GMT

E-mail blev vist af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

2021-01-14 - 07:26:40 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

Dato for signatur: 2021-01-14 - 07:27:08 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Aftale fuldført.

2021-01-14 - 07:27:08 GMT

Co-author statement

PhD student	Sophie Merrild Juul
Date of birth	08-10-91
Faculty (Department)	University of Copenhagen, Department of Psychology

"Attribution of authorship should in general be based on criteria a-d adopted from the Vancouver guidelines , and all individuals who meet these criteria should be recognized as authors:

A. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and
B. drafting the work or revising it critically for important intellectual content, and
C. final approval of the version to be published, and
D. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Article/paper/chapter/manuscript
This co-authorship declaration applies to the following:

*Title	Short-term versus long-term psychotherapy for adult psychiatric disorders: a systematic review with meta-analysis
*Author(s)	Sophie Juul, Janus Christian Jakobsen, Caroline Kamp Jørgensen, Stig Poulsen, Per Sørensen & Sebastian Simonsen.
Journal	Submitted to British Journal of Psychiatry
Volume (no)	
Start page	
End page	

Contributions to the paper/manuscript made by the PhD student

What was the role of the PhD student in designing the study?

The PhD student had a main role in designing the study

How did the PhD student participate in data collection and/or development of theory?

The PhD student collected all data

Which part of the manuscript did the PhD student write or contribute to?

The PhD student wrote up the whole manuscript with ongoing supervision from the co-authors.

Did the PhD student read and comment on the final manuscript?

Yes

Signatures

If an article/ paper/chapter/manuscript is written in collaboration with three or less researchers (including the PhD student), all researchers must sign the statement. However, if an article has more than three authors the statement may be signed by a representative sample, cf. article 12, section 4 and 5 of the Ministerial Order No. 1039, 27 August 2013. A representative sample consists of minimum three authors, which is comprised of the first author, the corresponding author, the senior author, and 1-2 authors (preferably international/non-supervisor authors).

By their signature, the authors agree that the article/paper/chapter/manuscript will be included as a part of the PhD thesis made by the PhD student mentioned above.

Date	12. jan. 2021	Name	Sophie Merrild Juul	Signature	Sophie Juul (12. Jan 2021 12:06 GMT+1)
Date	13. jan. 2021	Name	Janus Christian Jakobsen	Signature	Janus Christian Jakobsen (13. Jan 2021 15:13 GMT+1)
Date	13. jan. 2021	Name	Caroline Kamp Jørgensen	Signature	Caroline Kamp Jørgensen (13. Jan 2021 15:16 GMT+1)
Date	14. jan. 2021	Name	Sebastian Simonsen	Signature	Sebastian Simonsen (14. Jan 2021 08:28 GMT+1)

Paper 2 - Co-author statement

Endelig revisionsrapport 2021-01-14

Oprettet:	2021-01-11
Af:	Mette Hansen (mette.hansen@ctu.dk)
Status:	Underskrevet
Transaktions-id:	CBJCHBCAABAAErFgXdOJJ2wLyscCYC2DduggvNwYW2Ev

Oversigt over "Paper 2 - Co-author statement"

Dokument oprettet af Mette Hansen (mette.hansen@ctu.dk)
2021-01-11 - 19:42:06 GMT- IP-adresse: 83.93.10.217

Dokumentet blev sendt til Sophie Juul (sophie.juul@regionh.dk) til underskrivelse
2021-01-11 - 19:49:34 GMT

E-mail blev vist af Sophie Juul (sophie.juul@regionh.dk)
2021-01-11 - 19:52:39 GMT- IP-adresse: 87.49.44.43

Dokumentet blev e-underskrevet af Sophie Juul (sophie.juul@regionh.dk)
Dato for signatur: 2021-01-12 - 11:06:46 GMT - tidskilde: server- IP-adresse: 176.23.225.115

Dokumentet blev sendt til Janus Christian Jakobsen (janus.jakobsen@ctu.dk) til underskrivelse
2021-01-12 - 11:06:47 GMT

E-mail blev vist af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
2021-01-13 - 07:24:59 GMT- IP-adresse: 176.23.22.251

Dokumentet blev e-underskrevet af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
Dato for signatur: 2021-01-13 - 14:13:32 GMT - tidskilde: server- IP-adresse: 176.23.22.251

Dokumentet blev sendt til Caroline Kamp Jørgensen (caroline.kamp.joergensen@regionh.dk) til underskrivelse
2021-01-13 - 14:13:33 GMT

E-mail blev vist af Caroline Kamp Jørgensen (caroline.kamp.joergensen@regionh.dk)
2021-01-13 - 14:14:46 GMT- IP-adresse: 5.186.125.85

Dokumentet blev e-underskrevet af Caroline Kamp Jørgensen (caroline.kamp.joergensen@regionh.dk)
Dato for signatur: 2021-01-13 - 14:16:29 GMT - tidskilde: server- IP-adresse: 5.186.125.85

Dokumentet blev sendt til Sebastian Simonsen (sebastian.simonsen@regionh.dk) til underskrivelse
2021-01-13 - 14:16:31 GMT

E-mail blev vist af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

2021-01-14 - 07:28:07 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

Dato for signatur: 2021-01-14 - 07:28:47 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Aftale fuldført.

2021-01-14 - 07:28:47 GMT

Co-author statement

PhD student	Sophie Merrild Juul
Date of birth	08-10-91
Faculty (Department)	University of Copenhagen, Department of Psychology

"Attribution of authorship should in general be based on criteria a-d adopted from the Vancouver guidelines , and all individuals who meet these criteria should be recognized as authors:

A. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and
B. drafting the work or revising it critically for important intellectual content, and
C. final approval of the version to be published, and
D. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Article/paper/chapter/manuscript
This co-authorship declaration applies to the following:

*Title	Short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder: a protocol for a randomized clinical trial
*Author(s)	Sophie Juul, Susanne Lunn, Stig Poulsen, Per Sørensen, Mehrak Salimi, Janus Christian Jakobsen, Anthony Bateman & Sebastian Simonsen.
Journal	Trials
Volume (no)	20(196)
Start page	https://doi.org/10.1186/s13063-019-3306-7
End page	

Contributions to the paper/manuscript made by the PhD student

What was the role of the PhD student in designing the study?

The PhD student had a main role in designing the study

How did the PhD student participate in data collection and/or development of theory?

Data collection was not applicable to this protocol paper.

Which part of the manuscript did the PhD student write or contribute to?

The PhD student wrote up the whole manuscript with ongoing supervision from the co-authors.

Did the PhD student read and comment on the final manuscript?

Yes

Signatures

If an article/ paper/chapter/manuscript is written in collaboration with three or less researchers (including the PhD student), all researchers must sign the statement. However, if an article has more than three authors the statement may be signed by a representative sample, cf. article 12, section 4 and 5 of the Ministerial Order No. 1039, 27 August 2013. A representative sample consists of minimum three authors, which is comprised of the first author, the corresponding author, the senior author, and 1-2 authors (preferably international/non-supervisor authors).

By their signature, the authors agree that the article/paper/chapter/manuscript will be included as a part of the PhD thesis made by the PhD student mentioned above.

Date	12. jan. 2021	Name	Sophie Merrild Juul	Signature	Sophie Juul Sophie Juul (12. Jan 2021 12:07 GMT+1)
Date	12. jan. 2021	Name	Mehrak Salimi	Signature	Mehrak Salimi Mehrak Salimi (12. Jan 2021 12:45 GMT+1)
Date	13. jan. 2021	Name	Janus Christian Jakobsen	Signature	Janus Christian Jakobsen Janus Christian Jakobsen (13. Jan 2021 15:13 GMT+1)
Date	14. jan. 2021	Name	Sebastian Simonsen	Signature	Sebastian Simonsen Sebastian Simonsen (14. Jan 2021 08:27 GMT+1)

Paper 3 - Co-author statement

Endelig revisionsrapport 2021-01-14

Oprettet:	2021-01-11
Af:	Mette Hansen (mette.hansen@ctu.dk)
Status:	Underskrevet
Transaktions-id:	CBJCHBCAABAA5xwqXO3UrqOdKQ5Tb8c6dTkgywsBh9sV

Oversigt over "Paper 3 - Co-author statement"

Dokument oprettet af Mette Hansen (mette.hansen@ctu.dk)
2021-01-11 - 19:55:41 GMT- IP-adresse: 83.93.10.217

Dokumentet blev sendt til Sophie Juul (sophie.juul@regionh.dk) til underskrivelse
2021-01-11 - 20:00:24 GMT

E-mail blev vist af Sophie Juul (sophie.juul@regionh.dk)
2021-01-11 - 20:30:51 GMT- IP-adresse: 87.49.44.43

Dokumentet blev e-underskrevet af Sophie Juul (sophie.juul@regionh.dk)
Dato for signatur: 2021-01-12 - 11:07:08 GMT - tidskilde: server- IP-adresse: 176.23.225.115

Dokumentet blev sendt til Mehrak Salimi (mls@hejmdal.dk) til underskrivelse
2021-01-12 - 11:07:09 GMT

E-mail blev vist af Mehrak Salimi (mls@hejmdal.dk)
2021-01-12 - 11:40:25 GMT- IP-adresse: 62.116.216.222

Dokumentet blev e-underskrevet af Mehrak Salimi (mls@hejmdal.dk)
Dato for signatur: 2021-01-12 - 11:45:04 GMT - tidskilde: server- IP-adresse: 62.116.216.222

Dokumentet blev sendt til Janus Christian Jakobsen (janus.jakobsen@ctu.dk) til underskrivelse
2021-01-12 - 11:45:05 GMT

E-mail blev vist af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
2021-01-13 - 09:53:52 GMT- IP-adresse: 176.23.22.251

Dokumentet blev e-underskrevet af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)
Dato for signatur: 2021-01-13 - 14:13:11 GMT - tidskilde: server- IP-adresse: 176.23.22.251

Dokumentet blev sendt til Sebastian Simonsen (sebastian.simonsen@regionh.dk) til underskrivelse
2021-01-13 - 14:13:13 GMT

E-mail blev vist af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

2021-01-14 - 07:27:22 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Sebastian Simonsen (sebastian.simonsen@regionh.dk)

Dato for signatur: 2021-01-14 - 07:27:51 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Aftale fuldført.

2021-01-14 - 07:27:51 GMT

Co-author statement

PhD student	Sophie Merrild Juul
Date of birth	08-10-91
Faculty (Department)	University of Copenhagen, Department of Psychology

"Attribution of authorship should in general be based on criteria a-d adopted from the Vancouver guidelines , and all individuals who meet these criteria should be recognized as authors:

A. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and
B. drafting the work or revising it critically for important intellectual content, and
C. final approval of the version to be published, and
D. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Article/paper/chapter/manuscript
This co-authorship declaration applies to the following:

*Title	Detailed statistical analysis plan for the short-term versus long-term mentalization-based therapy for outpatients with subthreshold or diagnosed borderline personality disorder randomized clinical trial (MBT-RCT)
*Author(s)	Sophie Juul, Sebastian Simonsen, Susanne Lunn, Per Sørensen, Anthony Bateman & Janus Christian Jakobsen
Journal	Submitted to Trials
Volume (no)	
Start page	
End page	

Contributions to the paper/manuscript made by the PhD student

What was the role of the PhD student in designing the study?

The PhD student had a main role in designing the study.

How did the PhD student participate in data collection and/or development of theory?

Da collection was not applicable to this statistical analysis plan.

Which part of the manuscript did the PhD student write or contribute to?

The PhD student wrote up the whole manuscript with ongoing supervision from the co-authors.

Did the PhD student read and comment on the final manuscript?

Yes.

Signatures

If an article/ paper/chapter/manuscript is written in collaboration with three or less researchers (including the PhD student), all researchers must sign the statement. However, if an article has more than three authors the statement may be signed by a representative sample, cf. article 12, section 4 and 5 of the Ministerial Order No. 1039, 27 August 2013. A representative sample consists of minimum three authors, which is comprised of the first author, the corresponding author, the senior author, and 1-2 authors (preferably international/non-supervisor authors).

By their signature, the authors agree that the article/paper/chapter/manuscript will be included as a part of the PhD thesis made by the PhD student mentioned above.

Date	12. jan. 2021	Name	Sophie Merrild Juul	Signature	Sophie Juul Sophie Juul (12. Jan 2021 12:08 GMT+1)
Date	12. jan. 2021	Name	Sebastian Simonsen	Signature	Sebastian Simonsen Sebastian Simonsen (12. Jan 2021 12:10 GMT+1)
Date	13. jan. 2021	Name	Per Sørensen	Signature	
Date	13. jan. 2021	Name	Janus Christian Jakobsen	Signature	Janus Christian Jakobsen Janus Christian Jakobsen (13. Jan 2021 15:12 GMT+1)

Paper 4 - Co-author statement

Endelig revisionsrapport 2021-01-13

Oprettet:	2021-01-11
Af:	Mette Hansen (mette.hansen@ctu.dk)
Status:	Underskrevet
Transaktions-id:	CBJCHBCAABAAsTOKPtan2QZghIkwz3k3kSIhjlOeLVko

Oversigt over "Paper 4 - Co-author statement"

Dokument oprettet af Mette Hansen (mette.hansen@ctu.dk)
2021-01-11 - 20:03:28 GMT- IP-adresse: 83.93.10.217

Dokumentet blev sendt til Sophie Juul (sophie.juul@regionh.dk) til underskrivelse
2021-01-11 - 20:07:14 GMT

E-mail blev vist af Sophie Juul (sophie.juul@regionh.dk)
2021-01-11 - 20:30:53 GMT- IP-adresse: 87.49.44.43

Dokumentet blev e-underskrevet af Sophie Juul (sophie.juul@regionh.dk)
Dato for signatur: 2021-01-12 - 11:08:07 GMT - tidskilde: server- IP-adresse: 176.23.225.115

Dokumentet blev sendt til Sebastian Simonsen (sebastian.simonsen@regionh.dk) til underskrivelse
2021-01-12 - 11:08:09 GMT

E-mail blev vist af Sebastian Simonsen (sebastian.simonsen@regionh.dk)
2021-01-12 - 11:09:00 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Sebastian Simonsen (sebastian.simonsen@regionh.dk)
Dato for signatur: 2021-01-12 - 11:10:17 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Dokumentet blev sendt til Per Sørensen (per.soerensen@regionh.dk) til underskrivelse
2021-01-12 - 11:10:19 GMT

E-mail blev vist af Per Sørensen (per.soerensen@regionh.dk)
2021-01-13 - 08:22:39 GMT- IP-adresse: 128.0.73.9

Dokumentet blev e-underskrevet af Per Sørensen (per.soerensen@regionh.dk)
Dato for signatur: 2021-01-13 - 13:13:46 GMT - tidskilde: server- IP-adresse: 128.0.73.9

Dokumentet blev sendt til Janus Christian Jakobsen (janus.jakobsen@ctu.dk) til underskrivelse
2021-01-13 - 13:13:48 GMT

E-mail blev vist af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)

2021-01-13 - 14:11:43 GMT- IP-adresse: 176.23.22.251

Dokumentet blev e-underskrevet af Janus Christian Jakobsen (janus.jakobsen@ctu.dk)

Dato for signatur: 2021-01-13 - 14:12:09 GMT - tidskilde: server- IP-adresse: 176.23.22.251

Aftale fuldført.

2021-01-13 - 14:12:09 GMT

Co-author statement

PhD student	Sophie Merrild Juul
Date of birth	08-10-91
Faculty (Department)	University of Copenhagen, Department of Psychology

"Attribution of authorship should in general be based on criteria a-d adopted from the Vancouver guidelines , and all individuals who meet these criteria should be recognized as authors:

A. Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and
B. drafting the work or revising it critically for important intellectual content, and
C. final approval of the version to be published, and
D. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."

Article/paper/chapter/manuscript
This co-authorship declaration applies to the following:

*Title	The Capacity to End: Termination of Mentalization-Based Therapy for Borderline Personality Disorder
*Author(s)	Sophie Juul, Sebastian Simonsen & Anthony Bateman
Journal	Journal of Contemporary Psychotherapy
Volume (no)	50
Start page	331
End page	338

Contributions to the paper/manuscript made by the PhD student

What was the role of the PhD student in designing the study?

The PhD student had a main role in designing the study.

How did the PhD student participate in data collection and/or development of theory?

The PhD student had a main role in development of the theory in this paper.

Which part of the manuscript did the PhD student write or contribute to?

The PhD student wrote up the paper with ongoing supervision from the co-authors.

Did the PhD student read and comment on the final manuscript?

Yes.

Signatures

If an article/ paper/chapter/manuscript is written in collaboration with three or less researchers (including the PhD student), all researchers must sign the statement. However, if an article has more than three authors the statement may be signed by a representative sample, cf. article 12, section 4 and 5 of the Ministerial Order No. 1039, 27 August 2013. A representative sample consists of minimum three authors, which is comprised of the first author, the corresponding author, the senior author, and 1-2 authors (preferably international/non-supervisor authors).

By their signature, the authors agree that the article/paper/chapter/manuscript will be included as a part of the PhD thesis made by the PhD student mentioned above.

Date	12. jan. 2021	Name	Sophie Merrild Juul	Signature	Sophie Juul (12. Jan 2021 12:08 GMT+1)
Date	12. jan. 2021	Name	Sebastian Simonsen	Signature	Sebastian Simonsen (12. Jan 2021 12:13 GMT+1)
Date	12. jan. 2021	Name	Anthony Bateman	Signature	Anthony Bateman (12. Jan 2021 11:30 GMT)