Blending online and offline anxiety treatment in routine mental health care

Romijn, Gerritje Adriana

2022

Blending online and offline anxiety treatment in routine mental health care

Geke Romijn

Blending online and offline anxiety treatment in routine mental health care

Research on acceptability, effectiveness and cost-effectiveness of Internet-supported and blended cognitive behavioral therapy for patients with severe anxiety disorders

Geke Romijn

This thesis was prepared at the Faculty of Behavioural and Movement Sciences of the Vrije Universiteit Amsterdam.

Graphic design and printing: ProefschriftMaken || www.proefschriftmaken.nl

Please cite as: Romijn, G. (2022). Blending online and offline anxiety treatment in routine mental health care: Research on acceptability, effectiveness and cost-effectiveness of Internet-supported and blended cognitive behavioral therapy for patients with severe anxiety disorders. Amsterdam: Faculty of Behavioral and Movement Sciences, Vrije Universiteit Amsterdam.

ISBN: 978-94-6423-977-5

VRIJE UNIVERSITEIT

Blending online and offline anxiety treatment in routine mental health care

Research on acceptability, effectiveness and cost-effectiveness of Internet-supported and blended cognitive behavioral therapy for patients with severe anxiety disorders

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. J.J.G. Geurts,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Gedrags- en Bewegingswetenschappen
op donderdag 13 oktober 2022 om 11.45 uur
in een bijeenkomst van de universiteit,
De Boelelaan 1105

door
Gerritje Adriana Romijn
geboren te ‘s-Hertogenbosch

promotoren:	prof.dr. M.M. Riper
	prof.dr. A.J.L.M van Balkom
copromotoren:	dr. N.M. Batelaan
	dr. J.P.F. Koning
promotiecommisie**:**	prof.dr. E.M. Sijbrandij
	prof.dr. T. Berger
	prof.dr. A. de Bont
	prof.dr. J.E. Bosmans
	dr. E. Dozeman
	dr. T.R. Wind

Het leven is heerlijk, het leven is mooi
Maar - vlieg uit in de lucht en kruip niet in een kooi
Mens, durf te leven
Je kop in de hoogte, je neus in de wind
En lap aan je laars hoe een ander het vindt
Hou een hart vol van warmte en van liefde in je borst
Maar wees op je vierkante meter een vorst!
Wat je zoekt, kan geen ander je geven
Mens, durf te leven!

Dirk Witte, 1917

Table of contents

Chapter I

General introduction

The focus of this thesis is on Internet-supported treatment for anxiety disorders in routine mental health care. The general aim is to assess to what extent research findings on Internet-supported cognitive behavioral treatment (CBT) for patients with anxiety disorders apply to routine mental health care settings and to investigate the acceptability, effectiveness and cost-effectiveness of blended CBT in specialized routine health care.

Anxiety disorders

From an evolutionary perspective, anxiety is a useful emotion that helps us defend against a wide variety of threats. It increased fitness of our ancient ancestors in situations which threatened a loss of reproductive resources [1]. Although our environment and the dangerous situations we encounter have changed since ancient times, the function of fear and avoiding harm is still clear for all to see. Feelings of anxiety enable us to recognize dangerous situations and put the body in a state of alert in order to fight or avoid the danger. However, excessive fear can be disabling when it becomes irrational and interferes with the ability to function in daily life.

Anxiety disorders arise from dysregulation of normal defensive responses [2]. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is a categorical classification system of mental disorders with associated criteria. According to the latest edition, the DSM-5 [3], anxiety disorders include a wide range of different disorders (e.g. panic disorder with or without agoraphobia, social anxiety disorder, generalized anxiety disorders, and specific phobias), which are characterized by symptom clusters around excessive anxiety and worrying, disturbing somatic anxiety equivalents, irrational fear and avoidance behavior. The diagnosis anxiety disorder is based on an anamnesis, in which presence and severity of the DSM-5 symptom clusters are assessed. Such an anamnesis may be done for clinical or research purposes with a structured clinical interview such as The Structured Clinical Interview for DSM disorders axis I (SCID-I) [4] or the MINI international Neuropsychiatric Interview plus (MINI plus) [5,6].

Treatment of anxiety disorders

Most anxiety patients seeking help in clinical settings suffer from panic disorder with or without agoraphobia, social anxiety disorder or generalized anxiety disorder [7]. These disorders can be treated effectively with psychological treatment, pharmacotherapy, or a combination of both.

Cognitive behavioral therapy (CBT) is regarded as one of the preferred psychological treatments for anxiety disorders in the Netherlands, set out in the multidisciplinary guidelines for anxiety [8] and international treatment guidelines [9,10]. The key elements of CBT are cognitive restructuring and exposure to what is feared in order to identify and challenge destructive thought patterns and to develop new types of behavior.

There is a robust evidence base for the effectiveness of the treatment of adult anxiety disorders with CBT, with large effect sizes for generalized anxiety disorder (g=0.80), panic disorder (g=0.81) and social anxiety disorder (g=0.88) [11]. Despite this, anxiety disorders

often remain untreated [12]. Many individuals with diagnosable anxiety disorders don't seek treatment [13] and when they do seek treatment the treatments are not easily accessible [14] due to e.g., long waiting lists and costs of therapy [15]. One important strategy for improving accessibility and lowering costs to patients and providers in terms of travel costs, travel time, and missed work may be found in online delivery formats of CBT.

Internet-supported therapy

Internet-supported therapy is delivered via the Internet. This definition can be confusing as the Internet can be used for various types of activities and modes of communication with a patient [16]. In this thesis, the umbrella term Internet-supported CBT is used to refer to cognitive behavioral therapy that is delivered fully or partly via the Internet. It is often provided via a secured online treatment platform, which can contain functionalities such as a messaging service, a video conferencing function and treatment modules. Treatment modules generally contain text-based information, supported by graphics and video material and involve elements similar to that of regular face-to-face CBT sessions, such as psycho-education, cognitive restructuring, exposure exercises and relapse prevention. Different types of Internet-supported CBT can be distinguished according to several criteria:

1. *Type of guidance.* (i) unguided Internet interventions do not contain human support but can offer fully automated feedback. Participants are thus expected to work through the program by themselves [17]. In (ii) guided Internet-supported interventions, participants receive some form of online support from a coach or therapist. The term 'coach' usually refers to the type of support that is provided. This form is focused on supporting the participants to successfully guiding them through the intervention. Coaching can be provided by a number of health professionals who are specifically trained to provide online feedback on exercises, motivational messages and technical assistance [18]. On the other hand, therapeutic guidance is provided by a mental health professional and involves support of a psychotherapeutic nature. These health professionals are trained as well in online skills but they engage in therapeutic alliances and are trained psychotherapists. This type of guidance is often dedicated to participants with more severe psychological complaints [19].
2. *Synchronicity in communication.* Communication between participants and coaches/therapists can be synchronous or a-synchronous. (i) Synchronous communication happens in real time, where individuals are exchanging information, at the same time with each other. Synchronous forms of communication are i.e., chats, telephone calls, video-conferences or in-person meetings. (ii) Asynchronous communication is communication that is not occurring simultaneously in real time, i.e., through e-mail or written feedback messages.
3. *Text-based or face-to-face communication.* Communication during therapy can either be (i) text-based (e.g. through chat, e-mail or written feedback messages) or (ii) face-to-face (e.g. video-conferencing or in-person meetings at the treatment location).

4. *Fully Internet-based or blended treatment.* Lastly, Internet-supported therapy can either be (i) delivered completely via the Internet (Internet-based therapy) or (ii) it can be combined with face-to-face sessions at the clinic, telephone calls or video-conferencing. This combined format is referred to as blended therapy [20]. Blended therapy can consist of one integrated, standardized treatment protocol [21] or the online component can be offered as an add-on to the face-to-face treatment [22].

The different forms of Internet-supported therapy all have their own advantages and disadvantages. For example, unguided self-help formats seem to be eminently scalable, but are associated with low adherence (the extent to which individuals are exposed to the content of the intervention) and high drop-out (discontinuation of the intervention) [23]. A systematic review of Internet-supported CBT for anxiety and depression, for instance, showed that only half (56%) of the patients completed the full unguided program [24] and a meta-analysis by Richards and colleagues [25] reported an average drop-out rate of 74% in unguided Internet-based interventions for depression. Several predictors of attrition in unguided interventions have been identified, such as a low education, younger age [26], higher pre-treatment symptoms and comorbidity [27]. It has also been found that attrition tends to be lower when the intervention is guided [25,27]. For example, in the meta-analysis by Richards and colleagues (2012) drop-out rates for coach-supported or therapist-supported interventions ranged from 28% to 38% [25]. These rates appear to be comparable to face-to-face CBT, where estimated average drop-out rates are 26% [28].

As for communication modalities, an advantage of synchronous communication is that it involves more spontaneous interactions, possibly resulting in more uncensored disclosure of information [29]. However, synchronous communication leaves less room for reflection. Asynchronous communication is flexible since it does not have to be scheduled, but the spontaneity of synchronous communication is missing. Text-based communication may result in more openness to discuss sensitive problems, and can be especially helpful for patients who feel uncomfortable in face-to-face situations. However, this type of communications lacks nonverbal cues such as facial expressions, which can provide important information. Finally, in video conferencing the therapist can see the patient and evaluate nonverbal cues, but network connection issues may complicate communication and it can be difficult to respond quickly and effectively when a crisis happens [30].

Regarding fully Internet-based therapy, controlled studies show promising results, but implementation efforts so far have been rather disappointing in terms of upscaling. Several implementation barriers were identified in a systematic review by Vis and colleagues [31]. For example, factors that prevent therapists in routine care from providing Internet-based therapy to their patients are preferences for in-person face-to-face treatments, and concerns regarding the establishment of a positive therapeutic relationship. Furthermore, the review revealed that therapists worry about extra workload if they start using Internet-based therapy. Compared to fully Internet-based treatment, a possible benefit of blended therapy is that is more suitable to apply in routine care settings, because it may be integrated into the

regular workflow more easily which facilitates application in therapists' daily routine and makes it less disruptive to the organization of care than fully Internet-based treatment. A blended treatment format can also be attractive because the face-to-face contact address the needs of patients with more severe symptoms [32], while the Internet-based sessions can increase self-management.

Effects of Internet-supported treatment in routine care

Research on Internet-supported therapy has been on his way for over 20 years, with strong evidence from efficacy trials for Internet-supported treatment of anxiety [33–36], also in the long run [37], indicating that this form of treatment delivery can have enduring effects. However, most evidence stems from trials with strict inclusion criteria and self-referred participants recruited from the community. These *efficacy* trials investigate whether a treatment works under ideal circumstances, as opposed to *effectiveness* trials, that investigate whether a treatment works in the real world [38], or, in this case: routine mental health care. In the Netherlands, people who seek treatment for psychological problems in routine mental health care can go to their general practitioner, where a general practice mental health worker can provide support. If a patients' problems are too complex, the general practitioner may refer him to a primary mental healthcare provider (targeting mild to moderate mental health problems), or directly to specialized mental care (targeting more serious and complex psychiatric disorders).

Samples from efficacy trials often do not correspond to patient populations in these routine care settings in terms of sociodemographic characteristics, such as educational level and employment, and clinical characteristics, such as symptom severity and comorbidity. Patients in routine care might have more severe symptoms and be less motivated for Internet-based treatment compared to self-referred samples that are meeting the strict selection criteria of efficacy studies [39–41]. Therefore, clinical effects of Internet-supported CBT may be overestimated in highly controlled studies [42].

Regarding economic evaluations, evidence exists that guided online treatment for anxiety disorders is cost-effective when compared to waiting-list comparators [43]. However, direct comparisons between Internet-supported CBT and face-to-face CBT and economic evaluations conducted in routine care settings are lacking.

Moreover, although Internet-supported treatment is increasingly being applied in mental health care, insights into the extent to which therapists carry out these treatments as intended (therapist fidelity) are lacking. Without evidence of treatment fidelity, it can be difficult to understand differences between treatment formats for example in terms of clinical outcome, and consequently this hampers replication and dissemination of a treatment. Assessment of fidelity is particularly important when comparing Internet-supported to face-to-face treatment formats, since therapists in routine mental health care are extensively trained in providing face-to-face treatment, but providing Internet-supported treatment requires them to alter their usual therapeutic methods. As for blended CBT, this format requires therapists to apply therapeutic skills in both face-to-face and online sessions, as well

as combining the two modalities into a single treatment. Previous research has shown that particularly this integration of online and face-to-face modalities can be a challenge for therapists providing blended therapy [44,45]. One important recommendation to improve therapist application of blended CBT as intended is to provide therapists with appropriate treatment protocols, guidelines and training on how to use blended CBT [45,46]. Whereas recent studies on blended CBT for depression [47] and panic disorder [48] were the first to follow this recommendation by developing a highly structured blended CBT protocol, no data on therapist fidelity were collected in these studies.

Objectives and outline of this thesis

Earlier studies have shown the potential of Internet-supported cognitive behavioral in research settings. Whether these results generalize to clinical populations, however, is unclear. This dissertation examines the acceptability, effectiveness, and cost-effectiveness of Internet-supported and blended CBT for anxiety patients in routine outpatient clinics. **Chapter 2** is a meta-analysis that summarizes the current state of evidence on Internet-supported CBT and compares clinical effects obtained in trials with recruitment from the community versus results obtained in trials with clinical service recruitment. Furthermore, factors that may mediate differences in treatment outcome between these two types of trials are explored.

Chapters 3, 4 and 5 more specifically focus on one type of Internet-supported CBT, namely blended CBT. The blended format integrates online and face-to-face sessions into one treatment protocol and may be more appropriate for routine care settings. **Chapter 3** describes the protocol of a randomized controlled trial (RCT) investigating acceptability, effectiveness and cost-effectiveness of blended CBT versus face-to-face CBT in outpatient specialized mental health care to patients with panic disorder, social anxiety disorder and generalized anxiety disorder. In **chapter 4** the results of this RCT are presented. Acceptability is evaluated by assessing treatment preference, adherence, satisfaction, and therapeutic alliance. The primary clinical outcome is change in anxiety symptom severity as assessed with the Beck Anxiety Inventory [10]. Secondary outcomes are depressive symptoms, general psychopathology, work and social adjustment, quality of life and mastery. Health-economic outcomes are explored from a health care perspective (including direct medical costs) and from a societal perspective (including direct medical costs, direct non-medical costs and productivity costs). Costs and effects are assessed at post-treatment and one-year follow-up. The aim of the study in **chapter 5** is to explore therapist fidelity to the blended CBT protocol that was provided to therapists during the RCT. Assessing fidelity increases the reliability of outcomes regarding effects and costs, because it ensures that all participants receive blended treatment components in the prescribed manner. Further, it provides insights in the actual application of blended treatment by therapists. **Chapter 6** provides the general discussion of the main findings.

References

1. Öhman. Face the Beast and Fear the Face: Animal and Social Fears as Prototypes for Evolutionary Analyses of Emotion.
2. Marks I f. M, Nesse RM. Fear and fitness: An evolutionary analysis of anxiety disorders. Ethol Sociobiol. 1994;15: 247–261. doi:10.1016/0162-3095(94)90002-7
3. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). 2000. doi:10.1176/appi.books.9780890423349
4. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders [Internet]. New York State Psychiatric Institute. 2002. Available: http://www.scid4.org/revisions/november_2001_02.htm
5. Sheehan D V., Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998. pp. 22–33. doi:10.1016/S0924-9338(99)80239-9
6. Van Vliet IM, De Beurs E. Het Mini Internationaal Neuropsychiatrisch Interview (MINI): Een kort gestructureerd diagnostisch psychiatrisch interview voor DSM-IV-en ICD-10-stoornissen. Tijdschr Psychiatr. 2007;49: 393–397.
7. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci. 2015;17: 327–335. doi:10.1016/j.siny.2015.10.004
8. Van Balkom ALJM, Van Vliet IM, Emmelkamp PMG, Bockting CLH, Spijker J, Hermens MLM, et al. Multidisciplinaire Richtlijn Angststoornissen (3e revisie, 2013). Multidiciplinaire Richtlijn Angststoornissen (3e revisie, 2013). 2013. pp. 155–184. doi:10.1007/BF03059802
9. NICE. Generalised anxiety disorder and panic disorder in adults. Natl Inst Heal Clin Excell. 2011;
10. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. Clinical guideline 159. Available: http://guidance.nice.org.uk/cg159 [Internet]. 2013. doi:10.1016/S0140-6736(08)60488-2 [doi]
11. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJH. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016;15: 245–258. doi:10.1002/wps.20346
12. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. Dialogues Clin Neurosci. 2017;19: 93–106.
13. Johnson EM, Coles ME. Failure and delay in treatment-seeking across anxiety disorders. Community Ment Health J. 2013;49: 668–674. doi:10.1007/s10597-012-9543-9

14. Kazdin AE, Blase SL. Rebooting Psychotherapy Research and Practice to Reduce the Burden of Mental Illness. Perspect Psychol Sci. 2011;6: 21–37. doi:10.1177/1745691610393527
15. Andrade LH, Alonso J, Mneimneh Z, Wells JE, Al-Hamzawi A, Borges G, et al. Barriers to mental health treatment: Results from the WHO World Mental Health surveys. Psychol Med. 2014;44: 1303–1317. doi:10.1017/S0033291713001943
16. Barak A, Klein B, Proudfoot JG. Defining internet-supported therapeutic interventions. Ann Behav Med. 2009;38: 4–17. doi:10.1007/s12160-009-9130-7
17. Riper H, Cuijpers P. Telepsychology and ehealth. APA Handbook of Clinical Psychology: Applications and Methods. 3rd ed. American Psychological Association.; 2016.
18. Schueller SM, Tomasino KN, Mohr DC. Integrating Human Support Into Behavioral Intervention Technologies: The Efficiency Model of Support. Clin Psychol Sci Pract. 2017;24: 27–45. doi:10.1111/cpsp.12173
19. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: A model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res. 2011;13. doi:10.2196/jmir.1602
20. Erbe D, Psych D, Eichert HC, Riper H, Ebert DD. Blending face-to-face and internet-based interventions for the treatment of mental disorders in adults: Systematic review. J Med Internet Res. 2017;19. doi:10.2196/jmir.6588
21. Romijn G, Batelaan N, Koning J, Balkom A Van, Leeuw A de, Benning F, et al. Acceptability, effectiveness and cost-effectiveness of blended cognitive-behavioural therapy (bCBT) versus face-to-face CBT (ftfCBT) for anxiety disorders in specialised mental health care: A 15- week randomised controlled trial with 1-year follow-up. PLoS ONE 16 (11): e0259493. doi.org/10.1371/journal.pone.0259493
22. Klein JP, Hauer-Von Mauschwitz A, Berger T, Fassbinder E, Mayer J, Borgwardt S, et al. Effectiveness and safety of the adjunctive use of an internet-based self-management intervention for borderline personality disorder in addition to care as usual: Results from a randomised controlled trial. BMJ Open. 2021;11: 1–9. doi:10.1136/bmjopen-2020-047771
23. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res. H. Christensen, Centre for Mental Health Research, Australian National University, Canberra, ACT 0200, Australia; 2009;11. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354703306
24. Waller R, Gilbody S. Barriers to the uptake of computerized cognitive behavioural therapy: A systematic review of the quantitative and qualitative evidence. Psychol Med. 2009;39: 705–712. doi:10.1017/S0033291708004224
25. Richards D, Richardson T. Computer-based psychological treatments for depression: A systematic review and meta-analysis. Clin Psychol Rev. 2012;32: 329–342. doi:10.1016/j.cpr.2012.02.004

26. Karyotaki E, Kleiboer A, Smit F, Turner DT, Pastor AM, Andersson G, et al. Predictors of treatment dropout in self-guided web-based interventions for depression: An "individual patient data" meta-analysis. Psychol Med. 2015;45: 2717–2726. doi:10.1017/S0033291715000665
27. Christensen H, Griffiths KM, Farrer L. Adherence in Internet intervention for anxiety and depression: Systematic review. J Med Internet Res. Christensen, Helen, Centre for Mental Health Research, Australian National University, Canberra, ACT, Australia, 0200: Gunther Eysenbach; 2009;11: 1–16. doi:10.2196/jmir.1194
28. Fernandez E, Salem D, Swift JK, Ramtahal N, Fernandez E, Salem D, et al. Meta-analysis of dropout from cognitive behavioral therapy. J Consult Clin Psychol. 2015;83: 1108–1122.
29. Suler JR. Psychotherapy in Cyberspace: A 5-Dimensional Model of Online and Computer-Mediated Psychotherapy. CyberPsychology Behav. 2000;3: 151–159.
30. Oudshoorn CEM, Frielink N, Riper H, Embregts PJCM. Experiences of therapists conducting psychological assessments and video conferencing therapy sessions with people with mild intellectual disabilities during the COVID-19 pandemic. Int J Dev Disabil. Taylor & Francis; 2021;0: 1–9. doi:10.1080/20473869.2021.1967078
31. Vis C, Mol M, Kleiboer A, Bührmann L, Finch T, Smit J, et al. Improving implementation of emental health for mood disorders in routine practice: Systematic review of barriers and facilitating factors. J Med Internet Res. 2018;20. doi:10.2196/mental.9769
32. Topooco N, Riper H, Araya R, Berking M, Brunn M, Chevreul K, et al. Attitudes towards digital treatment for depression: A European stakeholder survey. Internet Interv. The Authors; 2017;8: 1–9. doi:10.1016/j.invent.2017.01.001
33. Olthuis J V, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. In: Olthuis J V, editor. Cochrane Database of Systematic Reviews. Chichester, UK, England: John Wiley & Sons, Ltd; 2016. p. CD011565. doi:10.1002/14651858.CD011565.pub2
34. Adelman CB, Panza KE, Bartley CA, Bontempo A, Bloch MH. A meta-analysis of computerized cognitive-behavioral therapy for the treatment of DSM-5 anxiety disorders. J Clin Psychiatry. 2014;75: e695-704. doi:10.4088/JCP.13r08894
35. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G. Computer-aided psychotherapy for anxiety disorders: A meta-analytic review. Cogn Behav Ther. 2009;38: 66–82. doi:10.1080/16506070802694776
36. Reger MA, Gahm GA. A meta-analysis of the effects of Internet- and computer-based cognitive-behavioral treatments for anxiety. J Clin Psychol. 2009;65: 53–75. doi:10.1002/jclp.20536
37. Andersson G, Rozental A, Shafran R, Carlbring P. Long-term effects of internet-supported cognitive behaviour therapy. Expert Rev Neurother. 2017;18: 1–8. doi:10.1080/14737175.2018.1400381
38. Streiner DL. The 2 "Es" of research: Efficacy and effectiveness trials. Can J Psychiatry. 2002;47: 552–556. doi:10.1177/070674370204700607

39. Persons JB, Silberschatz G. Are results of randomized controlled trials useful to psychotherapists? J Consult Clin Psychol. 1998;66: 126–135. doi:10.1037//0022-006X.66.1.126
40. Stirman SW, DeRubeis RJ, Crits-Christoph P, Brody PE. Are Samples in Randomized Controlled Trials of Psychotherapy Representative of Community Outpatients? A New Methodology and Initial Findings. J Consult Clin Psychol. 2003;71: 963–972. doi:10.1037/0022-006X.71.6.963
41. Titov N, Andrews G, Kemp A, Robinson E. Characteristics of adults with anxiety or depression treated at an internet clinic: Comparison with a national survey and an outpatient clinic. PLoS One. 2010;5. doi:10.1371/journal.pone.0010885
42. Wilks CR, Zieve GG, Lessing HK. Are Trials of Computerized Therapy Generalizable? A Multidimensional Meta-analysis. Telemed J E Health. United States; 2016;22: 450–457. doi:10.1089/tmj.2015.0129
43. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med. 2015; 1–20. doi:10.1017/S0033291715001427
44. Urech A, Krieger T, Möseneder L, Biaggi A, Vincent A, Poppe C, et al. A patient post hoc perspective on advantages and disadvantages of blended cognitive behaviour therapy for depression: A qualitative content analysis. Psychother Res. 2018; 1–13. doi:10.1080/10503307.2018.1430910
45. Mol M, van Genugten C, Dozeman E, van Schaik DJF, Draisma S, Riper H, et al. Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A Qualitative Study on Therapists' Perspectives. J Clin Med. 2019;9: 91. doi:10.3390/jcm9010091
46. Kenter RMF, van de Ven PM, Cuijpers P, Koole G, Niamat S, Gerrits RS, et al. Costs and effects of Internet cognitive behavioral treatment blended with face-to-face treatment: Results from a naturalistic study. Internet Interv. 2015;2: 77–83. doi:10.1016/j.invent.2015.01.001
47. Kooistra LC, Wiersma JE, Ruwaard J, Neijenhuijs K, Lokkerbol J, Van Oppen P, et al. Cost and effectiveness of blended versus standard cognitive behavioral therapy for outpatients with depression in routine specialized mental health care: Pilot randomized controlled trial. J Med Internet Res. 2019;21. doi:10.2196/14261
48. Bruinsma A, Kampman M, Exterkate CC, Hendriks GJ. An exploratory study of "blended" cognitive behavioural therapy (CBT) for patients with a panic disorder: results and patients' experiences. Tijdschr Psychiatr. 2016;58: 361–370.

Chapter 2

Internet-delivered cognitive behavioral therapy for anxiety disorders in open community versus clinical service recruitment: meta-analysis

Published as:
Romijn G, Batelaan N, Kok R, Koning J, van Balkom A, Titov N, Riper, H (2019)
Internet-Delivered Cognitive Behavioral Therapy for Anxiety Disorders in Open Community Versus Clinical Service Recruitment: Meta-Analysis.
Journal of Medical Internet Research 21 (4), e11706.

Abstract

Background: Ample studies have shown the effectiveness of internet-delivered cognitive behavioral therapy (CBT) for anxiety disorders. These studies recruited their participants mainly from the community and, to a lesser extent, from within routine care services. Little is known about whether different recruitment strategies lead to different treatment effects.

Objective: This meta-analysis compared clinical results obtained in trials with recruitment from the community versus results obtained in trials with clinical service recruitment and explored factors that may mediate differences in treatment outcome.

Methods: We included randomized controlled trials in which the clinical effects of Internet-delivered CBT for anxiety disorders were compared with a control condition (waitlist controls or face-to-face CBT). We classified trials as open recruitment trials (recruitment from the community) or clinical service recruitment trials (recruitment through outpatient clinics). Pooled effect sizes based on measures examining anxiety symptoms, depressive symptoms, and quality of life were computed for each type of trial. Subgroup analyses examined whether clinical results from open recruitment trials differed from those obtained in clinical service recruitment trials. Additional analyses explored which demographic, clinical, and treatment-related factors contributed to differences in effect sizes of open recruitment versus clinical service recruitment trials.

Results: We included 42 studies with 53 comparisons (43 open recruitment comparisons and 10 clinical recruitment comparisons). Analyses of anxiety measures revealed, first, that Internet-delivered CBT open recruitment studies with waitlist control comparators showed a significantly higher effect size for decrease in anxiety symptoms than did those with clinical recruitment (Q=10.09; P=.001). This association between recruitment method and effect size was no longer significant in a multivariate metaregression with treatment adherence and exclusion of patients with depressive symptoms entered as additional predictors of effect size. Second, effect size for decrease in anxiety symptoms did not differ significantly between clinical recruitment and open recruitment studies with face-to-face cognitive behavioral therapy comparators. The effects of open recruitment trials and clinical recruitment trials did not differ significantly for the secondary outcomes, compared with face-to-face cognitive behavioral therapy and waitlist controls.

Conclusions: Internet-delivered CBT was effective in samples recruited in clinical practice, but effect sizes were smaller than those found in trials with an open recruitment method for studies with waitlist control comparators. Hence, for patients with anxiety disorders in routine care, the impact of Internet-delivered CBT may not be as positive as for study participants recruited from the community. The difference between open recruitment trials and clinical service recruitment trials might be partly explained by patients' greater therapy adherence in open recruitment trials and the stricter exclusion of patients with severe depressive symptoms in these studies. Since most trials in this meta-analysis applied an open recruitment method, more studies with routine care populations are needed to further validate these findings.

Introduction

Background

Internet-delivered cognitive behavioral therapy for anxiety disorders has been tested in ample randomized controlled trials and several meta-analyses. These studies show the potential of Internet-delivered CBT to reduce anxiety symptoms among patients and general populations, indicating that Internet-delivered CBT is effective when compared with a waitlist control (WLC), with effect sizes in the moderate to large range. Studies also suggest that it is as effective as face-to-face cognitive behavioral therapy (CBT) in improving symptoms of anxiety [1-5], although these studies are limited in number. Furthermore, Internet-delivered CBT may minimize treatment barriers such as high costs due to reduced time needed by therapists to provide therapy [6,7] and scalability.

The majority of trials on Internet-delivered CBT apply an open recruitment (OR) strategy, inviting individuals with anxiety symptoms from within the community to directly partake in the research study. These participants refer themselves to such a study. Often these studies apply strict inclusion and exclusion criteria; for example, they may exclude patients taking psychoactive medication, patients with comorbid disorders, or severely depressed patients [8,9]. Clinical service recruitment (CSR) trials, on the other hand, invite patients already seeking treatment in clinical practices to participate. Trials with an OR method provide evidence more related to efficacy (investigating whether a treatment works under ideal circumstances, with high internal validity), as opposed to CSR trials that are more related to effectiveness and provide information on whether a treatment works in clinically representative conditions [10].

Only a minority of the patient samples in trials with an OR method correspond to patient populations in a regular clinical setting in terms of sociodemographic characteristics, motivation for treatment, level of suffering, and clinical characteristics such as severity of anxiety, comorbidity, or medical history [11-13]. Furthermore, the use of extensive exclusion criteria in OR trials can reduce the degree to which these study samples resemble clinical populations in routine care settings. A meta-analysis [14] found a strong and positive relationship (r=.70) between the number of exclusion criteria and the rate of clinically improved participants for studies on Internet-delivered CBT for anxiety disorders. These results suggest a lower clinical effectiveness in clinically representative studies than in highly controlled studies. This raises the question whether results from OR trials can be extrapolated to routine clinical practice.

On the other hand, uncontrolled effectiveness studies show large clinical effects [15-20], thereby suggesting that Internet-delivered CBT for anxiety disorders may be as effective in routine care settings as demonstrated in efficacy trials. One review investigated controlled research of Internet-delivered CBT in routine clinical practice [21]. Results showed that effect sizes obtained from effectiveness studies (ranging from 0.75 to 1.73) were in the same range as those obtained in efficacy trials, though only 3 randomized controlled trials were included.

Objective

Although several meta-analyses for (Internet-based treatment of) anxiety disorders have been conducted in recent years, to our knowledge, none of these studies have compared the potential differences in clinical effectiveness between OR and CSR trials. In this study, we aimed to (1) assess whether OR trials produced clinical effectiveness for anxiety symptoms similar to that of CSR trials and (2) explore predictors of potential effect differences, such as demographic, clinical, and treatment-related characteristics. We based these predictors on differences between OR and CSR trials in patient samples and methods found in previous studies [11,13,14].

Methods

Study retrieval

We report this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. We retrieved studies through systematic literature searches in PubMed, PsycINFO, and EMBASE databases. Searches were conducted with keywords and text words, in which words indicative of internet treatment were combined with words indicative of anxiety disorder, CBT, and randomized controlled trial (see Appendix 1 for the full search string). Furthermore, we checked reference lists of retrieved articles and of earlier reviews on Internet-delivered CBT for anxiety disorders [1-4].

Inclusion and exclusion criteria

We included randomized controlled trials published up to and including December 2017 on guided and unguided Internet-delivered CBT and blended CBT for adults. Blended CBT combines face-to-face treatment with internet components into a single integrated treatment protocol [23]. We included only randomized controlled trials that assessed a primary diagnosis of an anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised [DSM-III-R], DSM (Fourth Edition [DSM-IV]), or DSM (Fifth Edition [DSM-5]) established by a structured diagnostic interview. We excluded studies on obsessive compulsive disorder [24] and posttraumatic stress disorder [25], since they are not classified as anxiety disorders in DSM-5. We included only randomized controlled trials published in English or Dutch.

Interventions and comparators

We considered interventions to be CBT if they were based on cognitive behavioral principles [26] and consisted at least of cognitive restructuring or exposure (interoceptive exposure or exposure in vivo), or a combination of both. To be considered Internet-delivered CBT, the intervention must have been delivered (partly) via a computer or the internet through the use of webpages or email, or both. We included studies on Internet-delivered CBT targeting anxiety disorders and studies on transdiagnostic Internet-delivered CBT [27-31], addressing

multiple anxiety disorders or addressing both anxiety and mood disorders, but only if participants had a diagnosis of an anxiety disorder and measures of anxiety were reported. We did not include interventions when the Web-based part of the treatment was limited to exposure scenes on a screen (e.g., Heading et al [32]) because we considered this to be in virtuo exposure treatment, which is beyond the scope of this review.

Internet-delivered CBT was compared with WLC or regular face-to-face CBT treatment (including individual or group CBT delivered in a face-to-face format). We excluded studies with other comparisons such as transdiagnostic Internet-delivered CBT compared with disorder-specific Internet-delivered CBT, or guided Internet-delivered CBT versus self-help [24,25,33,34].

Outcome measures

Our primary outcome was anxiety symptom severity based on the score on a rating scale used to measure general symptoms of anxiety. We applied a hierarchy of preferred outcomes for all measures based on frequency of use in the included trials. For general measures of anxiety, the preferred order was as follows: Beck Anxiety Inventory (BAI [35]), anxiety scale of the Depression Anxiety Stress Scales [36], State-Trait Anxiety Inventory [37], and Anxiety Sensitivity Index [38]. When a general measure of anxiety was not available, we used a measure for specific anxiety symptoms (see Appendix 2 for the order of rating scales and Appendix 3 for the outcome measures we used for all studies).

Since anxiety disorders are frequently accompanied by symptoms of depression and a reduced quality of life [86], secondary outcome measures were effects on depression severity and on quality of life (see Appendix 2 for the order of rating scales).

Criteria for open recruitment and clinical service recruitment

We classified trials as OR trials if participants were recruited from the community and referred themselves to be interested in the study in response to the invitation from a research team, by means of advertisements in newspapers or magazines, banners on websites, or large-scale mailings. In CSR trials, recruitment was carried out among patients already seeking treatment in outpatient clinical mental health practices. In the case of mixed recruitment strategies, we classified trials according to the most prominent recruitment strategy.

Study selection and data extraction

Two of the authors (GR and NB) independently screened the list of titles and abstracts that resulted from the literature search. Reference lists were screened for additional studies of relevance. We obtained full articles for potentially relevant abstracts according to the inclusion criteria. If included trials did not provide complete information, we contacted the primary investigator by email to attempt to obtain unreported data. We sent a second email when we received no response. Two researchers (GR and NB) extracted the data using Microsoft Excel (2013) spreadsheets and differences in such data were resolved by discussion. Extracted data (see Appendix 3) included the study characteristics outlined in Textbox 1.

Textbox 1. Study characteristics extracted from the articles.

- Year of publication
- Number of participants
- Recruitment setting (open or clinical service recruitment)
- Demographic characteristics of participants included in the study (sex, age, employment status [total rate of employed participants and rate of full-time employed participants], education level [rate of participants with college degree or higher])
- Anxiety severity at baseline
- Axis I comorbidity rate
- Exclusion criteria with regard to medication use (benzodiazepines and other psychoactive medication) and depressive symptoms (indicated by a score above a cutoff level on an outcome measure for depressive symptoms)
- Details of treatment conditions (duration and type of support provided by professionals)
- Outcome data
- Number of therapy sessions according to protocol, treatment dose (number of completed therapy sessions), and treatment adherence (number of completed sessions divided by the total number of sessions according to protocol)

Risk-of-bias assessment

Two authors (GR and RK) independently assessed the risk of bias in the included studies based on 6 areas according to the Cochrane tool for assessing risk of bias [95]: (1) adequate generation of allocation sequence, (2) concealment of allocation to conditions (concealing allocation sequence from participants and investigators), (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) dealing with incomplete outcome data, and (6) selective outcome reporting (reported results give reason to suspect differences between reported and unreported findings). Because RK was an author of one of the included studies [50], this study was independently assessed by a third reviewer (NB). Discrepancies in scoring were resolved through discussion.

We assessed all areas as low, high, or unclear (i.e., not enough information) risk of bias (see Appendix 4). We assessed selective outcome reporting by comparing trial registrations with published articles, if available. When primary or secondary outcomes were missing, inserted, or changed in the article compared with the trial registration, or if secondary and primary outcomes had been switched, we deemed a study to be at high risk of selective outcome reporting. If no trial registration was available for a study, we coded the study as being at unknown risk for selective outcome reporting.

Statistical analyses

We used descriptive statistics to summarize demographic characteristics, and clinical and treatment-related characteristics of OR and CSR trials. We compared categorical variables

using chi-square tests and continuous variables using t tests. We also compared the percentage of at-risk OR and CSR trials for all risk-of-bias indicators with chi-square tests.
We then calculated the pooled overall effect sizes (Hedges g) indicating the difference between the conditions at posttest and their 95% confidence intervals using the random-effects model with Comprehensive Meta-Analysis software version 3.0 (Biostat). Hedges g is an effect size that corrects for biases due to small sample sizes [96]. Effect sizes of 0.2, 0.5, and 0.8 indicate a small, moderate, and large effect size, respectively [97]. We used the effect sizes based on intent-to-treat analysis when available (in 51 comparisons); otherwise, we used complete-sample analysis results (in 2 comparisons [51,52]).

We examined heterogeneity among studies using Higgins I2 statistic. I2=0% reflects no heterogeneity; 25%, 50%, and 75% indicate a low, medium, and high level of heterogeneity, respectively [98]. A higher observed statistical heterogeneity indicates a higher proportion of observed variance, which can point to underlying differences between the pooled studies. This makes interpreting the pooled effect size difficult, as it is hard to distinguish the observed effect size from the true population effect size [99]. We also calculated 95% confidence intervals around I2 with the noncentral chi-square approach in the heterogi module for Stata 13.0SE (StataCorp LLC) [100].

We first calculated overall effect sizes on anxiety, depression, and quality-of-life treatment outcomes of Internet-delivered CBT compared with WLC and compared with face-to-face CBT. We then carried out subgroup analyses to assess whether clinical results from OR trials differed from those obtained in CSR trials. We performed these subgroup analyses according to the mixed-effects model, in which studies within subgroups are pooled with the random-effects model, and the fixed-effects model is used to test for significant differences among them by the between-subgroups Q-statistic [101].

We tested publication bias by inspecting the funnel plot and Egger test [102] on our primary outcome measure and by the Duval and Tweedie trim-and-fill procedure [103].

To more fully understand differences in effect size between OR and CSR trials, we conducted additional exploratory analyses. By means of subgroup and metaregression analyses, we examined which demographic, clinical, and treatment-related factors differed between OR and CSR trials and were associated with effect size on the primary outcome. Next, to examine whether these predictors contributed to the difference of effect size between OR and CSR trials, we tested recruitment method and the significant predictors in a multivariate model, except in case of collinearity. We assessed possible collinearity problems between predictors with the variance inflation factors. We considered variance inflation factor scores higher than 2.5 to indicate multicollinearity [104].

We also calculated the number needed to treat (NNT), according to Kraemer and Kupfer [105], and rounded upward to the next higher whole number [106]. The NNT gives some clinical context to statistical information, as it translates the magnitude of a statistical effect size into clinical implications—that is, the number of patients who must be treated to generate one more positive outcome than the same number of patients in the control group.

Results

Study inclusion

The literature searches retrieved a total of 3954 abstracts. Checking references of earlier reviews resulted in 7 more citations for consideration. After we removed duplicates, we screened 2808 abstracts. After screening abstracts, we retrieved 134 full-text articles for a more detailed evaluation of eligibility. Subsequently, we excluded 92 articles because they did not meet the inclusion criteria (Figure 1). We did not include 1 study because means and standard deviations for anxiety measures were not reported [55] and we received no response from the addressed researchers to our email questions regarding these issues.

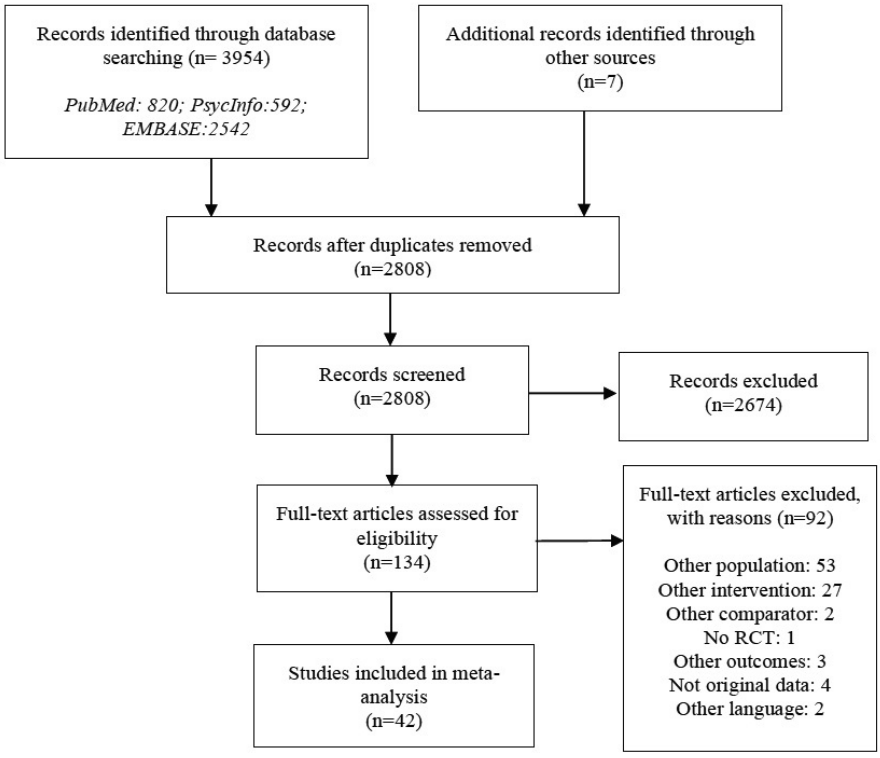


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the selection and inclusion process. RCT: randomized controlled trial.

Description of included studies

We included a total of 42 trials (Appendix 3). These trials entailed 53 comparisons of anxiety outcomes between Internet-delivered CBT and a control condition (WLC n=41, face-to-face CBT n=12) and included 3714 participants. A total of 45 comparisons entailed outcomes on depression and 21, on quality of life. Most studies were OR trials (31 trials with 41 comparisons), versus 8 CSR trials with 9 comparisons. In 3 studies both recruitment strategies were used [31,51, 53]. In 2 of these studies, most participants were self-referred (n=129, 92.8% [31] and n=70, 77% [53]) and therefore we classified these studies as OR trials. In the third study, most participants were recruited through a clinical procedure (n=76, 67%) and therefore we classified this study as a CSR trial [51]. Thus, we classified a total of 33 trials with 43 comparisons as OR trials and 9 trials with 10 comparisons as CSR trials.

Internet-delivered CBT typically consisted of weekly sessions (ranging from 4 to 12 sessions for studies comparing Internet-delivered CBT with WLC and from 4 to 23 sessions for studies comparing Internet-delivered CBT with face-to-face CBT), with durations ranging from 4 weeks to longer than 3 months [58]. In 4 trials a self-help Internet-delivered CBT intervention

(unguided) was offered; in the other trials Internet-delivered CBT was guided, meaning that online professional support was provided.

Table 1 displays demographic, clinical, and treatment-related characteristics of OR and CSR trials. We found significant differences between OR trials and CSR trials with regard to age of participants, sex, baseline severity, exclusion of severely depressed patients, treatment dose, and treatment adherence. We could compare baseline severity only for scores based on the BAI and the Social Phobia Scale, since these were the only outcome measures that were reported in both OR trials and CSR trials. We did not classify 3 OR trials [55-57] and 1 CSR trial [51] that mentioned exclusion of patients with depressive symptoms as such, because no definition in terms of a score on a measurement for depressive symptoms was provided.

No other variables differed (see Table 1). None of the included studies excluded patients who used psychoactive medication other than benzodiazepines, although a stable dose for the past 1 to 3 months was a criterion for inclusion in general.

Table 1. Comparison of demographic, clinical, and treatment-related characteristics of included studies[a]

Characteristics			Open recruitment	Clinical recruitment	Test statistic	*P* value
Demographic characteristics						
	Age (years), mean (SD)		37.5 (5.4)	34.1 (1.7)	t_{3657}=29.1	<.001
	Female sex, n (%)		1871 (67)	541 (58.7)	χ^2_1=21.2	<.001
	Education: college degree, n (%)		670 (53.4)	171 (49.4)	χ^2_1=1.7	.19
	Employed: full-time or part-time, n (%)		390 (58.7)	279 (59.7)	χ^2_1=0.1	.71
Clinical characteristics						
	Primary diagnosis: trials that applied this diagnosis as inclusion criterion, n (%)				χ^2_4=4.3	.37
		Panic Disorder	13 (30.2)	3 (30)		
		Social Anxiety Disorder	14 (32.6)	3 (30)		
		Generalized Anxiety Disorder	7 (16.3)	0 (0)		
		Specific phobia	2 (4.7)	0 (0)		
		Multiple anxiety disorders	7 (16.3)	4 (40)		
	Baseline Beck Anxiety Inventory score, mean (SD)		25.4 (11.8)	29.0 (11.1)	t_{1208}=−6.2	<.001
	Baseline Social Phobia Scale score, mean (SD)		36.0 (1.7)	43.0 (0.4)	t_{606}=−82.7	<.001
	Comorbidity: comorbid Axis I diagnosis, (%)		57.6	58.1	χ^2_1=0.0	.87
	Exclusion benzodiazepines: trials that applied this criterion, n (%)		10 (23.3)	0 (0)	χ^2_1=2.2	.14
	Exclusion psychoactive medication other than benzodiazepines: trials that applied this criterion, n (%)		0 (0)	0 (0)	N/A[b]	N/A
	Exclusion severe depression: trials that applied this criterion, n (%)		25 (58.1)	2 (20)	χ^2_1=4.7	.03
Treatment-related characteristics						
	Treatment dose: number of completed sessions, mean (SD)		6.1 (1.4)	5.1 (2.4)	t_{835}=9.45	<.001
	Treatment adherence: treatment completed (%)		77.9	53.1	t_{1599}=44.73	<.001

[a]Means and percentages are based on studies these data was available for. All available data are reported in Appendix 3.
[b]N/A: not applicable.

Risk-of-bias assessment

For both OR trials and CSR trials, most of the studies scored a low risk on sequence allocation (OR: 27/33, 82%; CSR: 8/9, 89%), blinding of outcome assessors (OR: 33/33, 100%; CSR: 8/9, 89%), and completeness of outcome data (OR: 27/33, 82%; CSR: 6/9, 67%) (see Appendix 4). On allocation concealment most CSR trials scored a low risk (7/9, 78%) compared with 12 of 33 (36%) OR trials. Only 4 of 33 (12%) OR and 2 of 9 (22%) CSR trials scored a low risk on selective outcome reporting, A total of 10 (30%) OR trials and 5 (56%) CSR trials scored a high risk because preregistered outcome measurements were not reported, or other outcome measurements that were not preregistered were inserted in the article. Additionally, 19 (58%) OR trials and 2 (22%) CSR trials were not registered in a trial database and we therefore scored them as having an unclear risk. We rated all included studies as having a high risk of bias on blinding of participants and personnel, because it is not possible to blind participants or therapists to the characteristics of the treatment that is offered.

We found no significant difference between the percentage of OR trials and the percentage of CSR trials with a high risk for any of the risk-of-bias indicators (P-values ranging from P=.08 for sequence generation to P=.49 for allocation concealment).

Overall effect

Primary outcome

The overall mean between-groups effect size of Internet-delivered CBT on anxiety symptom reduction when compared with WLC at posttest was g=0.72 (95% CI 0.60-0.83; P<.001) with moderate heterogeneity of I^2=53% (95% CI 31-66) and NNT=3. The difference in overall effect size for the decrease in anxiety symptoms between Internet-delivered CBT and face-to-face CBT at posttest was nonsignificant (g=0.12, 95% CI –0.02 to 0.26; P=.11; I^2=0%, 95% CI 0-75; NNT=15).

Secondary outcomes

Effect sizes of Internet-delivered CBT compared with WLC on depressive symptoms (g=0.61, 95% CI 0.46-0.75; P<.001; I^2=70%, 95% CI 57-78; NNT=3) and quality-of-life measurements (g=0.44, 95% CI 0.33-0.55; P<.001; I^2=5%, 95% CI 0-54; NNT=5) were moderate. For Internet-delivered CBT compared with face-to-face CBT, effect sizes on depression measurements (g=0.04, 95% CI –0.13 to 0.21; P=.65; I^2=19%. 95% CI 0-61; NNT=45) and quality-of-life outcomes (g=0.18, 95% CI –0.05 to 0.41; P=.12; I^2=0%, 95% CI 0-85; NNT=10) were both nonsignificant.

Open recruitment versus clinical service recruitment

Primary outcome

For studies with WLC comparators, we found a significant difference between OR and CSR trials) in favor of OR trials (Q=10.09; P=.001) (Table 2 and Figure 2). The effect size on anxiety symptom reduction for OR trials was significant and large (g=0.79; P<.001) in favor of Internet-delivered CBT, whereas CSR trials obtained a small effect size (g=0.28; P=.003) in favor of Internet-delivered CBT.

We found no difference in anxiety symptom reduction between OR (n=6) and CSR trials (n=6) comparing Internet-delivered CBT with face-to-face CBT (Q=0.82; P=.37) (Table 2 and Figure 3). Both OR trials (g=0.19; P=.09) and CSR trials (g=0.06; P=.51) reported a nonsignificant difference between Internet-delivered CBT and face-to-face CBT on decrease in anxiety symptoms.

Table 2. Main effects of open recruitment trials and clinical service recruitment trials comparing internet-delivered cognitive behavioral therapy versus waitlist control and versus face-to-face cognitive behavioral therapy at posttest, primary outcome.

		No. of comparisons	No. of respondents	Hedges *g* (95% CI)	*P* value	I^2 (95% CI)	NNT[a]	Between-groups Q (*P* value)
Waitlist control								
	Open recruitment	37	2474	0.79 (0.71 to 0.87)	<.001	44 (6 to 58)	3	10.09 (.001)
	Clinical recruitment	4	446	0.28 (0.10 to 0.47)	.003	20 (0 to 85)	7	
Face-to-face CBT								
	Open recruitment	6	336	0.19 (–0.03 to 0.40)	.09	0 (0 to 75)	10	0.82 (.37)
	Clinical recruitment	6	452	0.06 (–0.12 to 0.24)	.53	0 (0 to 75)	30	

[a]NNT: number needed to treat.

Secondary outcomes

With regard to depressive symptoms, we found no significant difference between OR trials and CSR trials with WLC comparators (Q=1.43; P=.23) or face-to-face comparators (Q=0.85; P=.36).

For quality-of-life measurements, we found no significant difference between OR trials and CSR trials for studies comparing Internet-delivered CBT with WLC (Q=0.05; P=.83) or for studies comparing Internet-delivered CBT with face-to-face CBT (Q=0.48; P=.49). Appendix 5 presents a complete overview of results of OR and CSR subgroup analyses of secondary outcomes.

Publication bias

Neither visual inspection of the funnel plots (see Appendix 6) and Egger test (WLC studies: intercept=0.83; 95% CI –0.90 to 2.56; P=.34; face-to-face CBT studies: intercept=1.12, 95% CI –0.93 to 3.17; P=.25) nor the Duval and Tweedie trim-and-fill procedure showed evidence of publication bias.

Additional exploratory analyses

As Table 1 shows, several demographic (age, sex), clinical (baseline severity, exclusion of severely depressive patients), and treatment-related (treatment dose, treatment adherence) variables differed significantly between OR trials and CSR trials. Of these variables, only exclusion of severely depressed patients (Q=8.06; P=.005), treatment dose (slope=0.10; P=.003), and treatment adherence (slope=0.01; P <.001) appeared to be significantly associated with effect size for WLC comparators in separate subgroup (exclusion of severely depressed patients) and metaregression (treatment dose, treatment adherence) analyses (see Appendix 7), meaning that the effect size was higher when severely depressed patients were excluded, when the treatment dose was higher, and when the adherence rate was higher.

In a multivariate analysis we explored whether the association between recruitment method and effect size for studies with WLC comparators was mediated by these variables. As the variance inflation factors between treatment dose and treatment adherence was 2.7, and treatment adherence was more significantly associated with effect size than treatment dose, we did not include treatment dose in the multivariate model.

Results showed that recruitment type (slope=0.30; P=.14) was no longer significantly associated with the effect size in the multivariate metaregression analysis, nor was treatment adherence (slope=0.01; P=.23) or exclusion of severely depressed patients (slope=0.13; P=.27).

Group by Trial	Study name	Hedges g	Lower limit	Upper limit	P Value
	Bell, 2012 [82]	0.008	-0.465	0.482	0.972
	Kok, 2014 [50]	0.206	-0.064	0.476	0.134
	Mathiasen, 2016 [85]	0.369	-0.110	0.847	0.131
	Norgren, 2014 [7]	0.573	0.176	0.970	0.005
Clinical recruitment		0.281	0.095	0.466	0.003
	Andersson, 2006 [58]	0.579	0.085	1.073	0.022
	Andersson, 2012a [56]	0.495	-0.039	1.029	0.069
	Andersson, 2012b [59]	0.607	0.328	0.887	0.000
	Berger, 2009 [60]	0.880	0.309	1.451	0.003
	Berger, 2014 standardized [61]	0.906	0.471	1.341	0.000
	Berger, 2014 tailored [61]	0.857	0.424	1.290	0.000
	Berger, 2017 [31]	0.396	0.062	0.730	0.020
	Botella, 2010 [62]	0.531	0.088	0.975	0.019
	Carlbring, 2001 [63]	1.186	0.533	1.839	0.000
	Carlbring, 2006 [65]	1.368	0.812	1.924	0.000
	Carlbring, 2007 [66]	0.734	0.200	1.268	0.007
	Carlbring, 2011 [67]	0.376	-0.154	0.907	0.165
	Christensen, 2014 [68]	1.014	-0.073	2.101	0.067
	Furmark, 2009 [69]	0.767	0.317	1.217	0.001
	Gallego, 2011 [52]	0.384	-0.413	1.180	0.345
	Johnston, 2011 clinician [28]	0.814	0.392	1.236	0.000
	Johnston, 2011 coach [28]	1.215	0.776	1.654	0.000
	Klein, 2006 [71]	0.383	-0.254	1.020	0.239
	Oromendia, 2016 non-scheduled [27]	0.791	0.234	1.348	0.005
	Oromendia, 2016 scheduled [27]	1.552	0.927	2.177	0.000
	Paxling, 2011 [72]	0.844	0.414	1.274	0.000
	Richards, 2006 iCBT [73]	-0.317	-1.152	0.518	0.457
	Richards, 2006 iCBT&stressmgmt [73]	0.634	-0.232	1.500	0.151
	Robinson, 2010 clinician [74]	1.199	0.774	1.625	0.000
	Robinson, 2010 technician [74]	1.265	0.834	1.696	0.000
	Schulz, 2016 iCBGT [75]	0.774	0.320	1.228	0.001
	Schulz, 2016 iCBT [75]	1.011	0.547	1.475	0.000
	Titov, 2008a [76]	1.035	0.618	1.451	0.000
	Titov, 2008b [77]	1.085	0.641	1.529	0.000
	Titov, 2008c guided [78]	1.053	0.547	1.559	0.000
	Titov, 2008c self-help [78]	0.406	-0.077	0.889	0.099
	Titov, 2009 [79]	1.217	0.589	1.845	0.000
	Titov, 2010 GAD [30]	0.095	-0.563	0.753	0.777
	Titov, 2010 PD [30]	1.254	0.349	2.159	0.007
	Titov, 2010 SAD [30]	0.436	-0.362	1.235	0.284
	Titov, 2011 [29]	0.267	-0.376	0.910	0.416
	Wims, 2010 [80]	0.587	0.070	1.103	0.026
Open recruitment		0.790	0.708	0.872	0.000
Overall		0.707	0.632	0.782	0.000

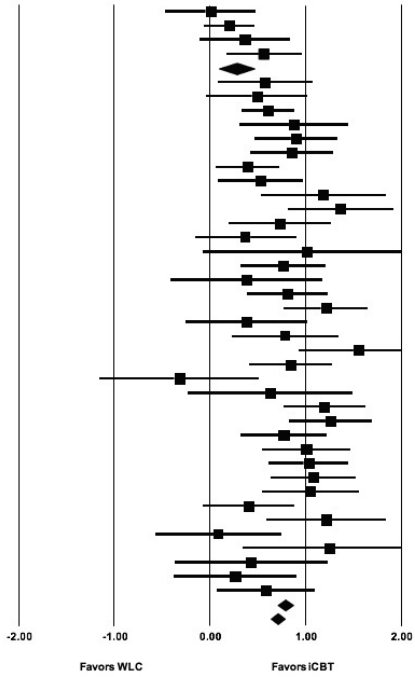


Figure 2. Forest plot of effects on anxiety symptoms of open recruitment trials and clinical service recruitment trials comparing internet-delivered cognitive behavioral therapy (iCBT) with waitlist control (WLC). GAD: generalized anxiety disorder; iCBGT: clinician-guided group iCBT; PD: panic disorder; SAD: social anxiety disorder.

Group by Trial	Study name	Hedges g	Lower limit	Upper limit	P Value
	Andrews, 2011 [81]	0.188	-0.463	0.840	0.571
	Bergstrom, 2010 [51]	-0.242	-0.648	0.163	0.241
	Bruinsma, 2016 [83]	0.125	-0.584	0.833	0.730
	Hedman, 2011 [84]	0.208	-0.140	0.556	0.241
	Nordgreen, 2016 PD [54]	0.122	-0.345	0.590	0.608
	Nordgreen, 2016 SAD [54]	0.037	-0.345	0.420	0.848
Clinical recruitment		0.058	-0.124	0.240	0.532
	Andersson, 2009 [55]	0.337	-0.400	1.075	0.370
	Andersson, 2013 [57]	0.617	-0.146	1.380	0.113
	Botella, 2010 [62]	0.027	-0.380	0.435	0.896
	Carlbring, 2005 [64]	0.186	-0.366	0.739	0.509
	Kiropoulos, 2008 [70]	0.339	-0.084	0.762	0.116
	Marks, 2004 [53]	-0.083	-0.636	0.471	0.770
Open recruitment		0.188	-0.027	0.403	0.086
Overall		0.113	-0.026	0.251	0.112

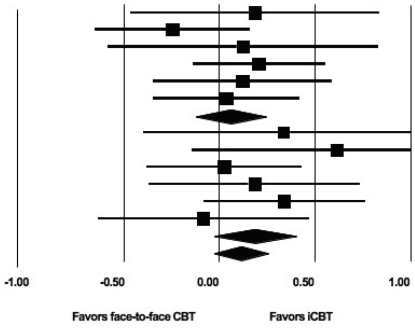


Figure 3. Forest plot of effects on anxiety symptoms of open recruitment trials and clinical service recruitment trials comparing internet-delivered cognitive behavioral therapy (iCBT) with face-to-face cognitive behavioral therapy (CBT). PD: panic disorder; SAD: social anxiety disorder.

Discussion

Principal findings

This meta-analysis showed that Internet-delivered CBT is more effective than WLC in reducing anxiety symptoms at posttreatment. We found no indication for differences in effect sizes between Internet-delivered CBT and face-to-face CBT. These outcomes confirm the results of previous meta-analyses, which found moderate to large effect sizes for WLC comparator studies and small and nonsignificant effect sizes when comparing Internet-delivered CBT versus face-to-face CBT [1-4].

Our main research question was whether OR trials produce effects for anxiety symptoms similar to those of CSR trials. For studies with WLC comparators, recruitment method was significantly associated with anxiety treatment outcomes (Q=10.09; P=.001), indicating that effect sizes are higher in OR trials than in CSR trials.

We explored whether differences between characteristics of samples in OR trials and CSR trials might explain the gap between effects we found in favor of OR trials. Multivariate metaregression analysis revealed that the association between recruitment method and effect size may be partly explained by greater treatment adherence and the exclusion of severely depressed patients in OR trials.

For studies with face-to-face CBT comparators, we observed no difference in anxiety outcomes between OR trials and CSR trials (Q=0.82; P=.37). Possibly, the number of studies with face-to-face CBT comparators was too low, making these analyses underpowered to detect differences. Another explanation could be that studies with face-to-face CBT comparators resembled each other more on other criteria for clinical representativeness than studies with WLC comparators, as these studies are conducted in routine care. For example, in studies with face-to-face comparators, treatments are generally delivered by skilled clinicians and in clinically representative settings. These study characteristics are more varied in studies with WLC comparators, where treatments can also be delivered by researchers or graduate students and in a research setting such as a university laboratory [108].

Regarding depressive symptoms and quality of life, we observed no differences between OR trials and CSR trials for either comparator group.

The difference in results we found between OR and CSR trials for studies with WLC comparators is in line with a previous meta-analysis on effectiveness of face-to-face CBT for anxiety disorders by Stewart and Chambless [9]. The small but significant effect size (d=–0.08; P<.05) they found indicated smaller improvements in more clinically representative patient studies than in less clinically representative studies.

Our findings are partly in keeping with Andersson and Hedman's review on the effectiveness of Internet-delivered CBT for anxiety [21]. Results of that review suggested that effectiveness studies obtain similar effects to efficacy trials. Considering they only included studies comparing Internet-delivered CBT with face-to-face CBT, that conclusion corresponds to our results for Internet-delivered CBT compared with face-to-face CBT. However, it needs to be noted that Andersson and Hedman based their distinction between efficacy and

effectiveness on the setting in which Internet-delivered CBT was delivered and not on recruitment strategy.

Strengths and limitations

A major strength of this study is that it is, to our knowledge, the first meta-analysis of Internet-delivered CBT for anxiety disorders comparing treatment outcomes between OR and CSR for both WLC and face-to-face CBT comparators. Furthermore, the studies comparing Internet-delivered CBT versus face-to-face CBT were head-to-head comparisons, generating direct evidence.

Some limitations in this study warrant caution in interpretation. First, the number of trials was relatively low for studies with face-to-face CBT comparators. Hence, finding no difference may have been caused by underpowered analyses.

Second, clinical representativeness of studies is often rated based on a multitude of criteria, besides recruitment type, such as setting of treatment delivery, experience of therapists, and flexibility in treatment manuals [9,109]. This means that the differences we found may have been caused by predictors not assessed in this study. In future research, considering multiple criteria of efficacy and effectiveness would be helpful to more thoroughly determine clinical representativeness of the studies and the association between clinical representativeness and treatment outcomes.

Third, in 3 included trials a mixed recruitment strategy was applied. This contamination may have led to some bias. Any such bias will have decreased the difference between OR and CSR trials found in the meta-analysis. We decided to include these trials because they reported clearly on their recruitment method and also the portion of participants recruited through an OR method versus a CSR method.

Fourth, when interpreting the subgroup analyses and metaregression analyses, it is important to bear in mind that the results were only observational. Direct comparisons are required to verify the findings presented here.

Conclusions

This meta-analysis indicated that the effects of Internet-delivered CBT for anxiety disorders compared with WLC in CSR trials were smaller than effects found in OR trials. Hence, for patients with anxiety disorders in routine care, the impact of Internet-delivered CBT may not be as positive as for self-referred study participants recruited from the community. The difference between OR and CSR might be partly caused by a greater treatment adherence of self-referred patients and stricter exclusion criteria for severe depressive symptoms in studies with an OR method. A future challenge is to build a more robust body of evidence supporting the effectiveness of Internet-delivered CBT for anxiety disorders in routine care populations.

Conflicts of interest

Nick Titov is Executive Director of MindSpot, which is funded by the Australian Government to deliver Internet-delivered CBT to adults with anxiety and depression across Australia.

Abbreviations

BAI: Beck Anxiety Inventory
CBT: cognitive behavioral therapy
CSR: clinical service recruitment
DSM: Diagnostic and Statistical Manual of Mental Disorders
iCBT: Internet-delivered cognitive behavioral therapy
NNT: number needed to treat
OR: open recruitment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WLC: waitlist control

References

1. Olthuis JV, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. Cochrane Database Syst Rev 2016 Mar 12;3:CD011565. [doi: 10.1002/14651858.CD011565.pub2] [Medline: 26968204]
2. Adelman CB, Panza KE, Bartley CA, Bontempo A, Bloch MH. A meta-analysis of computerized cognitive-behavioral therapy for the treatment of DSM-5 anxiety disorders. J Clin Psychiatry 2014 Jul;75(7):e695-e704. [doi: 10.4088/JCP.13r08894] [Medline: 25093485]
3. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G. Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. Cogn Behav Ther 2009;38(2):66-82. [doi: 10.1080/16506070802694776] [Medline: 20183688]
4. Reger MA, Gahm GA. A meta-analysis of the effects of internet- and computer-based cognitive-behavioral treatments for anxiety. J Clin Psychol 2009 Jan;65(1):53-75. [doi: 10.1002/jclp.20536] [Medline: 19051274]
5. Andersson G, Rozental A, Shafran R, Carlbring P. Long-term effects of internet-supported cognitive behaviour therapy. Expert Rev Neurother 2018 Jan;18(1):21-28. [doi: 10.1080/14737175.2018.1400381] [Medline: 29094622]
6. Hedman E, El Alaoui S, Lindefors N, Andersson E, Rück C, Ghaderi A, et al. Clinical effectiveness and cost-effectiveness of internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. Behav Res Ther 2014 Aug; 59:20-29. [doi: 10.1016/j.brat.2014.05.010] [Medline: 24949908]
7. Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki A, Eriksson S, et al. Effectiveness and cost-effectiveness of individually tailored internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. Behav Res Ther 2014 Aug; 59:1-11 [doi: 10.1016/j.brat.2014.05.007] [Medline: 24933451]
8. Westen D, Morrison K. A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. J Consult Clin Psychol 2001 Dec;69(6):875-899. [Medline: 11777114]

9. Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. J Consult Clin Psychol 2009 Aug;77(4):595-606. [doi: 10.1037/a0016032] [Medline: 19634954]
10. Streiner DL. The 2 "Es" of research: efficacy and effectiveness trials. Can J Psychiatry 2002 Aug;47(6):552-556. [doi: 10.1177/070674370204700607] [Medline: 12211883]
11. Persons JB, Silberschatz G. Are results of randomized controlled trials useful to psychotherapists? J Consult Clin Psychol 1998 Feb;66(1):126-135. [Medline: 9489266]
12. Stirman SW, DeRubeis RJ, Crits-Christoph P, Brody PE. Are samples in randomized controlled trials of psychotherapy representative of community outpatients? A new methodology and initial findings. J Consult Clin Psychol 2003 Dec;71(6):963-972. [doi: 10.1037/0022-006X.71.6.963] [Medline: 14622071]
13. Titov N, Andrews G, Kemp A, Robinson E. Characteristics of adults with anxiety or depression treated at an internet clinic: comparison with a national survey and an outpatient clinic. PLoS One 2010;5(5):e10885 [doi: 10.1371/journal.pone.0010885] [Medline: 20526371]
14. Wilks CR, Zieve GG, Lessing HK. Are trials of computerized therapy generalizable? A multidimensional meta-analysis. Telemed J E Health 2016 May;22(5):450-457. [doi: 10.1089/tmj.2015.0129] [Medline: 26461235]
15. Dear BF, Zou JB, Ali S, Lorian CN, Johnston L, Terides MD, et al. Examining self-guided internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety and depression: Two feasibility open trials. Internet Interventions 2015 Mar;2(1):17-23. [doi: 10.1016/j.invent.2014.11.002]
16. Titov N, Dear BF, Staples LG, Bennett-Levy J, Klein B, Rapee RM, et al. The first 30 months of the MindSpot Clinic: evaluation of a national e-mental health service against project objectives. Aust N Z J Psychiatry 2017 Dec;51(12):1227-1239. [doi: 10.1177/0004867416671598] [Medline: 27733709]
17. Hadjistavropoulos HD, Pugh NE, Hesser H, Andersson G. Predicting response to therapist-assisted internet-delivered cognitive behavior therapy for depression or anxiety within an open dissemination trial. Behav Ther 2016 Mar;47(2):155-165. [doi: 10.1016/j.beth.2015.10.006] [Medline: 26956649]
18. Ruwaard J, Lange A, Schrieken B, Dolan CV, Emmelkamp P. The effectiveness of online cognitive behavioral treatment in routine clinical practice. PLoS One 2012;7(7):e40089 [doi: 10.1371/journal.pone.0040089] [Medline: 22792217]
19. Williams AD, O'Moore K, Mason E, Andrews G. The effectiveness of internet cognitive behaviour therapy (iCBT) for social anxiety disorder across two routine practice pathways. Internet Interv 2014 Oct;1(4):225-229. [doi: 10.1016/j.invent.2014.11.001]
20. Mathiasen K, Riper H, Andersen TE, Roessler KK. Guided internet-based cognitive behavioral therapy for adult depression and anxiety in routine secondary care: observational study. J Med Internet Res 2018 Nov 28;20(11):e10927 [doi: 10.2196/10927] [Medline: 30487118]
21. Andersson G, Hedman E. Effectiveness of guided Internet-based cognitive behavior

therapy in regular clinical settings. Verhaltenstherapie 2013;23(3):140-148. [doi: 10.1159/000354779]
22. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64. [Medline: 19622511]
23. Riper H, Ballegooijen WV, Kooistra L. Preventie & eMental-health. Onderzoek dat leidt, technologie die verleidt, preventie die bereikt en beklijft. Kennissynthese 2013 in opdracht van ZonMw. Amsterdam, the Netherlands: ZonMw; 2013.
24. Mahoney AEJ, Mackenzie A, Williams AD, Smith J, Andrews G. Internet cognitive behavioural treatment for obsessive compulsive disorder: a randomised controlled trial. Behav Res Ther 2014 Dec; 63:99-106. [doi: 10.1016/j.brat.2014.09.012] [Medline: 25461784]
25. Engel CC, Litz B, Magruder KM, Harper E, Gore K, Stein N, et al. Delivery of self training and education for stressful situations (DESTRESS-PC): a randomized trial of nurse assisted online self-management for PTSD in primary care. Gen Hosp Psychiatry 2015;37(4):323-328 [doi: 10.1016/j.genhosppsych.2015.04.007] [Medline: 25929985]
26. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive Therapy of Depression. New York, NY: Guilford Press; 1979.
27. Oromendia P, Orrego J, Bonillo A, Molinuevo B. Internet-based self-help treatment for panic disorder: a randomized controlled trial comparing mandatory versus optional complementary psychological support. Cogn Behav Ther 2016 Jun;45(4):270-286. [doi: 10.1080/16506073.2016.1163615] [Medline: 27007256]
28. Johnston L, Titov N, Andrews G, Spence J, Dear BF. A RCT of a transdiagnostic internet-delivered treatment for three anxiety disorders: examination of support roles and disorder-specific outcomes. PLoS One 2011;6(11):e28079 [doi: 10.1371/journal.pone.0028079] [Medline: 22132216]
29. Titov N, Dear BF, Schwencke G, Andrews G, Johnston L, Craske MG, et al. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. Behav Res Ther 2011 Aug;49(8):441-452. [doi: 10.1016/j.brat.2011.03.007] [Medline: 21679925]
30. Titov N, Andrews G, Johnston L, Robinson E, Spence J. Transdiagnostic Internet treatment for anxiety disorders: a randomized controlled trial. Behav Res Ther 2010 Sep;48(9):890-899. [doi: 10.1016/j.brat.2010.05.014] [Medline: 20561606]
31. Berger T, Urech A, Krieger T, Stolz T, Schulz A, Vincent A, et al. Effects of a transdiagnostic unguided Internet intervention ('velibra') for anxiety disorders in primary care: results of a randomized controlled trial. Psychol Med 2017 Jan;47(1):67-80. [doi: 10.1017/S0033291716002270] [Medline: 27655039]
32. Heading K, Kirkby KC, Martin F, Daniels BA, Gilroy LJ, Menzies RG. Controlled comparison of single-session treatments for spider phobia: live graded exposure alone versus computer-aided vicarious exposure. Behav Change 2012 Feb 22;18(02):103-113. [doi: 10.1375/bech.18.2.103]
33. Dear BF, Staples LG, Terides MD, Karin E, Zou J, Johnston L, et al. Transdiagnostic versus

disorder-specific and clinician-guided versus self-guided internet-delivered treatment for generalized anxiety disorder and comorbid disorders: a randomized controlled trial. J Anxiety Disord 2015 Dec; 36:63-77 [doi: 10.1016/j.janxdis.2015.09.003] [Medline: 26460536]

34. Titov N, Dear BF, Staples LG, Terides MD, Karin E, Sheehan J, et al. Disorder-specific versus transdiagnostic and clinician-guided versus self-guided treatment for major depressive disorder and comorbid anxiety disorders: a randomized controlled trial. J Anxiety Disord 2015 Oct; 35:88-102 [doi: 10.1016/j.janxdis.2015.08.002] [Medline: 26422822]
35. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988 Dec;56(6):893-897. [Medline: 3204199]
36. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. Sydney, Australia: Psychology Foundation of Australia; 1995.
37. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1970:1-23.
38. Taylor S, Cox B. Anxiety sensitivity: multiple dimensions and hierarchic structure. Behav Res Ther 1998 Jan;36(1):37-51. [Medline: 9613015]
39. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry 1987;22:141-173. [Medline: 2885745]
40. Heimberg R, Horner K, Juster H, Safren S, Brown E, Schneier F, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. Psychol Med 1999 Jan;29(1):199-212. [Medline: 10077308]
41. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther 1998 Apr;36(4):455-470. [Medline: 9670605]
42. Furmark T, Tillfors M, Everz P, Marteinsdottir I, Gefvert O, Fredrikson M. Social phobia in the general population: prevalence and sociodemographic profile. Soc Psychiatry Psychiatr Epidemiol 1999 Aug;34(8):416-424. [Medline: 10501711]
43. Leary M. A brief version of the Fear of Negative Evaluation Scale. Personal Soc Psychol Bull 1983;9(3):371-375. [Medline: 803973233]
44. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]
45. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther 1990;28(6):487-495. [Medline: 2076086]
46. Shear MK, Brown T, Barlow D, Money R, Sholomskas D, Woods S, et al. Multicenter collaborative panic disorder severity scale. Am J Psychiatry 1997 Nov;154(11):1571-1575. [doi: 10.1176/ajp.154.11.1571] [Medline: 9356566]
47. Chambless DL, Caputo GC, Bright P, Gallagher R. Assessment of fear of fear in agoraphobics: the body sensations questionnaire and the agoraphobic cognitions questionnaire. J Consult Clin Psychol 1984 Dec;52(6):1090-1097. [Medline: 6520279]

48. Bandelow B. Assessing the efficacy of treatments for panic disorder and agoraphobia. II. The Panic and Agoraphobia Scale. Int Clin Psychopharmacol 1995 Jun;10(2):73-81. [Medline: 7673659]
49. Van Zuuren FJ. The fear questionnaire. Some data on validity, reliability and layout. Br J Psychiatry 1988 Nov;153:659-662. [Medline: 3255455]
50. Kok R, van Straten A, Beekman A, Cuijpers P. Short-term effectiveness of web-based guided self-help for phobic outpatients: randomized controlled trial. J Med Internet Res 2014 Sep 29;16(9):e226 [doi: 10.2196/jmir.3429] [Medline: 25266929]
51. Bergström J, Andersson G, Ljótsson B, Rück C, Andréewitch S, Karlsson A, et al. Internet- versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. BMC Psychiatry 2010;10:54 [doi: 10.1186/1471-244X-10-54] [Medline: 20598127]
52. Gallego M, Gerardus EP, van der Kooij M, Mees H. The effects of a Dutch version of an internet-based treatment program for fear of public speaking: a controlled study. Int J Clin Heal Psychol 2011;11(3):459-472
53. Marks IM, Kenwright M, McDonough M, Whittaker M, Mataix-Cols D. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med 2004 Jan;34(1):9-17. [Medline: 14971623]
54. Nordgreen T, Haug T, Öst L, Andersson G, Carlbring P, Kvale G, et al. Stepped care versus direct face-to-face cognitive behavior therapy for social anxiety disorder and panic disorder: a randomized effectiveness trial. Behav Ther 2016 Mar;47(2):166-183. [doi: 10.1016/j.beth.2015.10.004] [Medline: 26956650]
55. Andersson G, Waara J, Jonsson U, Malmaeus F, Carlbring P, Ost L. Internet-based self-help versus one-session exposure in the treatment of spider phobia: a randomized controlled trial. Cogn Behav Ther 2009;38(2):114-120. [doi: 10.1080/16506070902931326] [Medline: 20183690]
56. Andersson G, Paxling B, Roch-Norlund P, Östman G, Norgren A, Almlöv J, et al. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. Psychother Psychosom 2012;81(6):344-355. [doi: 10.1159/000339371] [Medline: 22964540]
57. Andersson G, Waara J, Jonsson U, Malmaeus F, Carlbring P, Ost LG. Internet-based exposure treatment versus one-session exposure treatment of snake phobia: a randomized controlled trial. Cogn Behav Ther 2013;42(4):284-291. [doi: 10.1080/16506073.2013.844202] [Medline: 24245707]
58. Andersson G, Carlbring P, Holmström A, Sparthan E, Furmark T, Nilsson-Ihrfelt E, et al. Internet-based self-help with therapist feedback and in vivo group exposure for social phobia: a randomized controlled trial. J Consult Clin Psychol 2006 Aug;74(4):677-686. [doi: 10.1037/0022-006X.74.4.677] [Medline: 16881775]
59. Andersson G, Carlbring P, Furmark T, S. O. F. I. E. Research Group. Therapist experience and knowledge acquisition in internet-delivered CBT for social anxiety disorder: a randomized controlled trial. PLoS One 2012;7(5):e37411 [doi:

10.1371/journal.pone.0037411] [Medline: 22649526]
60. Berger T, Hohl E, Caspar F. Internet-based treatment for social phobia: a randomized controlled trial. J Clin Psychol 2009 Oct;65(10):1021-1035. [doi: 10.1002/jclp.20603] [Medline: 19437505]
61. Berger T, Boettcher J, Caspar F. Internet-based guided self-help for several anxiety disorders: a randomized controlled trial comparing a tailored with a standardized disorder-specific approach. Psychotherapy (Chic) 2014 Jun;51(2):207-219. [doi: 10.1037/a0032527] [Medline: 24041199]
62. Botella C, Gallego MJ, Garcia-Palacios A, Guillen V, Baños RM, Quero S, et al. An Internet-based self-help treatment for fear of public speaking: a controlled trial. Cyberpsychol Behav Soc Netw 2010 Aug;13(4):407-421. [doi: 10.1089/cyber.2009.0224] [Medline: 20712499]
63. Carlbring P, Westling BE, Ljungstrand P, Ekselius L, Andersson G. Treatment of panic disorder via the internet: a randomized trial of a self-help program. Behav Ther 2001;32(4):751-764. [doi: 10.1016/S0005-7894(01)80019-8]
64. Carlbring P, Nilsson-Ihrfelt E, Waara J, Kollenstam C, Buhrman M, Kaldo V, et al. Treatment of panic disorder: live therapy vs. self-help via the Internet. Behav Res Ther 2005 Oct;43(10):1321-1333. [doi: 10.1016/j.brat.2004.10.002] [Medline: 16086983]
65. Carlbring P, Bohman S, Brunt S, Buhrman M, Westling BE, Ekselius L, et al. Remote treatment of panic disorder: a randomized trial of internet-based cognitive behavior therapy supplemented with telephone calls. Am J Psychiatry 2006 Dec;163(12):2119-2125. [doi: 10.1176/appi.ajp.163.12.2119] [Medline: 17151163]
66. Carlbring P, Gunnarsdóttir M, Hedensjö L, Andersson G, Ekselius L, Furmark T. Treatment of social phobia: randomised trial of internet-delivered cognitive-behavioural therapy with telephone support. Br J Psychiatry 2007 Feb;190:123-128. [doi: 10.1192/bjp.bp.105.020107] [Medline: 17267928]
67. Carlbring P, Maurin L, Törngren C, Linna E, Eriksson T, Sparthan E, et al. Individually-tailored, Internet-based treatment for anxiety disorders: a randomized controlled trial. Behav Res Ther 2011 Jan;49(1):18-24. [doi: 10.1016/j.brat.2010.10.002] [Medline: 21047620]
68. Christensen H, Mackinnon A, Batterham P, O'Dea B, Guastella A, Griffiths K, et al. The effectiveness of an online e-health application compared to attention placebo or Sertraline in the treatment of Generalised Anxiety Disorder. Internet Interventions 2014 Oct;1(4):169-174. [doi: 10.1016/j.invent.2014.08.002]
69. Furmark T, Carlbring P, Hedman E, Sonnenstein A, Clevberger P, Bohman B, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. Br J Psychiatry 2009 Nov;195(5):440-447. [doi: 10.1192/bjp.bp.108.060996] [Medline: 19880935]
70. Kiropoulos LA, Klein B, Austin DW, Gilson K, Pier C, Mitchell J, et al. Is internet-based CBT for panic disorder and agoraphobia as effective as face-to-face CBT? J Anxiety Disord 2008 Dec;22(8):1273-1284. [doi: 10.1016/j.janxdis.2008.01.008] [Medline: 18289829]

71. Klein B, Richards JC, Austin DW. Efficacy of internet therapy for panic disorder. J Behav Ther Exp Psychiatry 2006 Sep;37(3):213-238. [doi: 10.1016/j.jbtep.2005.07.001] [Medline: 16126161]
72. Paxling B, Almlöv J, Dahlin M, Carlbring P, Breitholtz E, Eriksson T, et al. Guided internet-delivered cognitive behavior therapy for generalized anxiety disorder: a randomized controlled trial. Cogn Behav Ther 2011;40(3):159-173. [doi: 10.1080/16506073.2011.576699] [Medline: 21770848]
73. Richards JC, Klein B, Austin DW. Internet cognitive behavioural therapy for panic disorder: does the inclusion of stress management information improve end-state functioning? Clin Psychol 2006 Mar;10(1):2-15. [doi: 10.1080/13284200500378795]
74. Robinson E, Titov N, Andrews G, McIntyre K, Schwencke G, Solley K. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. PLoS One 2010;5(6):e10942 [doi: 10.1371/journal.pone.0010942] [Medline: 20532167]
75. Schulz A, Stolz T, Vincent A, Krieger T, Andersson G, Berger T. A sorrow shared is a sorrow halved? A three-arm randomized controlled trial comparing internet-based clinician-guided individual versus group treatment for social anxiety disorder. Behav Res Ther 2016 Sep;84:14-26. [doi: 10.1016/j.brat.2016.07.001] [Medline: 27423374]
76. Titov N, Andrews G, Schwencke G, Drobny J, Einstein D. Shyness 1: distance treatment of social phobia over the Internet. Aust N Z J Psychiatry 2008 Jul;42(7):585-594. [doi: 10.1080/00048670802119762] [Medline: 18612862]
77. Titov N, Andrews G, Schwencke G. Shyness 2: treating social phobia online: replication and extension. Aust N Z J Psychiatry 2008 Jul;42(7):595-605. [doi: 10.1080/00048670802119820] [Medline: 18612863]
78. Titov N, Andrews G, Choi I, Schwencke G, Mahoney A. Shyness 3: randomized controlled trial of guided versus unguided internet-based CBT for social phobia. Aust N Z J Psychiatry 2008 Dec;42(12):1030-1040. [doi: 10.1080/00048670802512107] [Medline: 19016091]
79. Titov N, Andrews G, Robinson E, Schwencke G, Johnston L, Solley K, et al. Clinician-Assisted Internet-Based Treatment is Effective for Generalized Anxiety Disorder: Randomized Controlled Trial. Aust N Z J Psychiatry 2009 Jan;43(10):905-912. [doi: 10.1080/00048670903179269]
80. Wims E, Titov N, Andrews G, Choi I. Clinician-assisted Internet-based treatment is effective for panic: a randomized controlled trial. Aust N Z J Psychiatry 2010 Jul;44(7):599-607. [doi: 10.3109/00048671003614171] [Medline: 20560847]
81. Andrews G, Davies M, Titov N. Effectiveness randomized controlled trial of face to face versus Internet cognitive behaviour therapy for social phobia. Aust N Z J Psychiatry 2011 Apr;45(4):337-340. [doi: 10.3109/00048674.2010.538840] [Medline: 21323490]
82. Bell C, Colhoun H, Carter F, Frampton C. Effectiveness of computerised cognitive behaviour therapy for anxiety disorders in secondary care. Aust N Z J Psychiatry 2012 Jul;46(7):630-640. [doi: 10.1177/0004867412437345] [Medline: 22327097]
83. Bruinsma A, Kampman M, Exterkate CC, Hendriks GJ. [An exploratory study of 'blended'

cognitive behavioural therapy (CBT) for patients with a panic disorder: results and patients' experiences]. Tijdschr Psychiatr 2016;58(5):361-370 [Medline: 27213635]
84. Hedman E, Andersson G, Ljótsson B, Andersson E, Rück C, Mörtberg E, et al. Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: a randomized controlled non-inferiority trial. PLoS One 2011;6(3):e18001 [doi: 10.1371/journal.pone.0018001] [Medline: 21483704]
85. Mathiasen K, Riper H, Ehlers L, Valentin J, Rosenberg N. Internet-based CBT for social phobia and panic disorder in a specialised anxiety clinic in routine care: results of a pilot randomised controlled trial. Internet Interv 2016 May;4:92-98 [doi: 10.1016/j.invent.2016.03.001] [Medline: 30135794]
86. Norberg M, Diefenbach G, Tolin D. Quality of life and anxiety and depressive disorder comorbidity. J Anxiety Disord 2008 Dec;22(8):1516-1522. [doi: 10.1016/j.janxdis.2008.03.005] [Medline: 18424062]
87. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961 Jun;4:561-571. [Medline: 13688369]
88. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. Acta Psychiatr Scand 1994 Jan;89(1):21-28. [Medline: 8140903]
89. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613 [Medline: 11556941]
90. Radloff LS. The CES-D Scale. Applied Psychological Measurement 2016 Jul 26;1(3):385-401. [doi: 10.1177/014662167700100306]
91. Frisch M, Cornell J, Villanueva M, Retzlaff P. Clinical validation of the Quality of Life Inventory. A measure of life satisfaction for use in treatment planning and outcome assessment. Psychological Assessment 1992;4(1):92-101. [doi: 10.1037/1040-3590.4.1.92]
92. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998 May;28(3):551-558. [Medline: 9626712]
93. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [Medline: 10109801]
94. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [Medline: 8628042]
95. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Intervention. Chichester, UK: Wiley-Blackwell Publishing Ltd; 2008.
96. Hedges LV, Olkin I. Statistical Methods For Meta-analysis. Orlando, FL: Academic Press; 1995.
97. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Hillsdale, NJ: Lawrence Erlbaum; 1988.
98. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560 [doi: 10.1136/bmj.327.7414.557] [Medline:

12958120]
99. Borenstein M, Higgins J, Hedges LV, Rothstein HR. Basics of meta-analysis: I is not an absolute measure of heterogeneity. Res Synth Methods 2017 Mar;8(1):5-18. [doi: 10.1002/jrsm.1230] [Medline: 28058794]
100. Orsini N, Bottai M, Higgins J, Buchan I. Heterogi: Stata Module to Quantify Heterogeneity in a Meta-Analysis. Chestnut Hill, MA: Department of Economics, Boston College; 2006.
101. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-Analysis. Oxford, UK: Wiley; 2009.
102. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997 Sep 13;315(7109):629-634 [Medline: 9310563]
103. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-463. [Medline: 10877304]
104. Allison P. Logistic Regression Using SAS: Theory And Application. 1st edition. Cary, NC: SAS Institute; 1999. 105.
105. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. Biol Psychiatry 2006 Jun 1;59(11):990-996. [doi: 10.1016/j.biopsych.2005.09.014] [Medline: 16368078]
106. Citrome L, Ketter T. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013 May;67(5):407-411. [doi: 10.1111/ijcp.12142] [Medline: 23574101]
107. Klein B, Richards JC. A brief internet-based treatment for panic disorder. Behav Cogn Psychother 2001 Mar 6;29(01):113-117. [doi: 10.1017/S1352465801001138]
108. Weisz J, Donenberg G, Han S, Weiss B. Bridging the gap between laboratory and clinic in child and adolescent psychotherapy. J Consult Clin Psychol 1995 Oct;63(5):688-701. [Medline: 7593861]
109. Shadish WR, Matt GE, Navarro AM, Siegle G, Crits-Christoph P, Hazelrigg MD, et al. Evidence that therapy works in clinically representative conditions. J Consult Clin Psychol 1997 Jun;65(3):355-365. [Medline: 9170759]

Appendix 1. Search string

"Anxiety Disorders"[Mesh] OR anxiety disorder* [tiab] OR generalized anxiety disorder* [tiab] OR generalised anxiety disorder* [tiab] OR GAS [tiab] OR anxiety state* [tiab] OR agoraphobi* [tiab] OR panic* [tiab] OR phobi* [tiab] OR obsessive-compulsive [tiab] OR OCD [tiab] OR post-traumatic* [tiab] OR posttraumatic* [tiab] OR traumatic* [tiab] OR acrophobi* [tiab] OR claustrophobi* [tiab] OR ophidiophobi* [tiab] OR acute stress disorder* [tiab] OR castration anxiet* [tiab] OR death anxiet* [tiab]

AND

"Telemedicine"[Mesh] OR econsult*[tiab] OR e-consult*[tiab] OR eHealth*[tiab] OR e-health*[tiab] OR mhealth*[tiab] OR m-health*[tiab] OR mobile health*[tiab] OR remote consult*[tiab] OR Teleconsult*[tiab] OR Tele-consult*[tiab] OR telehealth*[tiab] OR tele-health*[tiab] OR telemedicin*[tiab] OR tele-medicin*[tiab] OR telemonitor*[tiab] OR tele-monitor*[tiab] OR blended [tiab] OR blending [tiab] OR web-based [tiab] OR webbased [tiab] OR online intervention* [tiab] OR online therap* [tiab] OR “Mobile applications” [Mesh] OR internet-based [tiab] OR web intervention* [tiab] OR mobile application* [tiab] OR tablet based [tiab] OR computerised [tiab] OR computerized [tiab] OR internet delivered [tiab] OR computer delivered [tiab] OR internet treatment* [tiab] OR internet cbt [tiab] OR computer augmented [tiab] OR computer assisted therap* [tiab]

AND

Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized [tiab] OR placebo* [tiab] OR randomly[tiab] OR RCT [tiab] OR controlled trial* [tiab] OR clinical trial* [tiab] OR randomised [tiab]

Appendix 2. Order of rating scales

Specific anxiety symptoms rating scale	Depression rating scales	Quality of Life (QOL) rating scales
Social anxiety disorder - Liebowitz Social Anxiety Scale (LSAS; 39, 40) - Social Phobia Scale (SPS;41), - Social Interaction Anxiety Scale (SIAS; 41) - Social Phobia Screening Questionnaire (SPSQ; 42) - Brief version of the Fear of Negative Evaluation Scale (BFNE; 43) *Generalized anxiety disorder* - Generalized Anxiety Disorder -7 item scale (GAD-7; 44) - Penn State Worry Questionnaire (PSWQ; 45) *Panic disorder* - Panic Disorder Severity Scale (PDSS; 46) - Body Sensation Questionnaire (BSQ; 47) - Panic and Agoraphobia Scale (PAS; 48) *Phobia* - Fear Questionnaire (FQ; 49)	- Beck Depression Inventory (BDI; 35) and - Montgomery-Asberg Rating Scale (MADRS-S; 88) - Patient Health Questionnaire-9 item scale (PHQ-9; 89) - Centre of Epidemiological Studies-Depression scale (CES-D; 90) - Depression Anxiety Stress Scales (DASS; 36)	- Quality Of Life Inventory (QOLI; 91) - WHO Quality of Life Questionnaire (QOL; 92) - EuroQol visual analogue scale (EQ-VAS; 93) - Short-Form Health Survey-12 (SF-12; 94)

Appendix 3. Characteristics of included studies

Open recruitment studies

	Study & year	Diagnosis, % comorbidity	N total	Age & gender (% women)	% Employed (total/ fulltime)	Education (% college degree	iCBT (no. of sessions, duration, support)	Control	Treatment dose (no. completed sessions) & Treatment adherence	Primary outcome measure + baseline score (mean, SD) Secondary outcome measures	Inclusion criteria regarding 1) psychoactive medication & 2) comorbidity
1.	Andersson et al., 2006 [58]	SAD 12,5%	64	37.3 51.6%	71,9% total 65,5% ft	43,8%	9 online sessions & 2 group sessions, 9 weeks, clinical support	WLC: delayed treatment, 9 weeks	7.5 sessions 83,3%	• BAI iCBT: 13.6 (7.3) WLC: 13.2 (6.6) • MADRS-S • QOLI	1) stable dose 3 months 2) no psychosis or substance abuse; score < 31 on the MADRS-S
2.	Andersson et al., 2009 [55]	Spider phobia	27	25.6 84.8%		26%	5 online sessions, 4 weeks, clinical support	ftf CBT: 2 sessions and maintenance program, clinical support, 2 weeks		• BAI iCBT: 9.2 (5.4) ftf CBT: 9.1 (5.3) • BDI	1) stable dose 3 months 2) no other psychiatric problems requiring immediate treatment; no current depressive episode for >= 2 weeks in the last month
3.	Andersson et al., 2012a [56]	GAD	54	iCBT: 44.4 / 74.1% WLC: 39.6 / 77.8%	61% total		8 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 12 weeks	5.1 sessions 63.8%	• BAI iCBT: 24.3 (9.10) WLC: 23.7 (10.61) • BDI • QOLI	1) stable dose 6 weeks 2) not be severely depressed
4.	Andersson, et al., 2012b [59]	SAD	204	iCBT: 38.1 / 77.5% WLC: 38.4 / 60%	74% ft	48%	9 online sessions, 9 weeks, clinical support	WLC: delayed treatment and access to discussion forum, 9 weeks	6.8 sessions 75.6%	• BAI iCBT: 15.73 (7.98) WLC: 16.47 (9.14) • MADRS-S • QOLI	1) stable dose 3 months 2) no other serious or dominant disorder (e.g. psychosis, substance misuse) that could influence outcome of the study; score <31 on the MADRS-S
5.	Andersson et al., 2013 [57]	Snake phobia	26	27.2 84.6%		27%	4 online sessions, 4 weeks, clinical support	ftf CBT: 2 sessions, clinical support, 2 weeks		• BAI iCBT: 5.5 (3.7) ftf CBT: 6.8 (3.3) • BDI	2) no current depressive episode for >= 2 weeks in the last month

6.	Berger et al., 2009 [60]	SAD 26,9%	52	28.9 55.8%		42,3%	5 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	4.3 sessions 85%	• LSAS iCBT: 68.7 (16.9) WLC: 75.0 (17.4) • BDI	2) not currently meet diagnostic criteria for psychosis or borderline personality disorder
7.	Berger et al., 2014 [61]	SAD, GAD or PD(a)	132	35.1 56.1%	51,5% total 37,9% ft	59,8%	8 online sessions (tailored), 8 weeks, clinical support	WLC: delayed treatment, 8 weeks	7.3 sessions 90.6%	• BAI iCBT: 33.8 (9.1) WLC: 34.3 (8.4) • BDI	1) stable dose for 3 months
8.							8 online sessions (disorder-specific), 8 weeks, clinical support		7.1 sessions 89.3%	iCBT: 34.3 (9.1)	
9.	Berger et al., 2017 [31]	SAD, GAD or PD(a)	139	42 70.5%	59,8% total 35,3% ft	52,5%	6 online sessions, 9 weeks, self-help	WLC: delayed treatment, access to treatment-as-usual, 9 weeks	3.9 sessions 65%	• BAI iCBT: 34.9 (9.1) WLC: 33.3 (10.3) • BDI • SF-12	1) stable dose 1 month
10.	Botella et al., 2010 [62]	SAD	127	24.4 79.2%		94,8%	Online sessions until feared situations are overcome, 2 months, self-help	ftf CBT; session once or twice a week, two months, clinical support		• BFNE iCBT: 42.80 (9.32) ftf CBT: 44.14 (8.97) • BDI	2) not have a primary diagnosis of major depression; not be diagnosed for substance abuse or dependence, psychosis, or mental retardation
11.								WLC: delayed treatment, 4 weeks		WLC: 44.42 (9.99)	
12.	Carlbring et al., 2001 [63]	PD	41	34 70,7%			6 online sessions, 7-12 weeks, clinical support	WLC: delayed treatment, 7-12 weeks		• BAI iCBT: 19.3 (6.2) WLC: 21.5 (10.0) • BDI • QOLI	1) stable dose for 3 months 2) not suffer from any other psychiatric disorder in immediate need of treatment; score <21 on MADRS
13.	Carlbring et al., 2005 [64]	PD	49	35.0 71%			10 online sessions, 10 weeks, clinical support	ftf CBT: 10 sessions, 10 weeks, clinical support	7.4 sessions 74%	• BAI iCBT: 18.7 (10.3) ftf CBT: 24.5 (10.4) • BDI • QOLI	1) stable dose for 3 months 2) not suffer from any other psychiatric disorder in immediate need of treatment; score <21 on MADRS

14.	Carlbring et al., 2006 [65]	PD	60	36.7 60.0%		33%	10 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	8.9 sessions 89%	• BAI iCBT: 20.8 (10.0) WLC: 19.5 (9.4) • BDI • QOLI	1) stable dose for 3 months 2) not suffer from any other psychiatric disorder in immediate need of treatment; score of <21 on MADRS
15.	Carlbring et al., 2007 [66]	SAD	57	iCBT: 32.4 / 58.6% WLC: 32.9 / 71.4%		29,8%	9 online sessions, 9 weeks, clinical support	WLC: delayed treatment, 9 weeks		• BAI iCBT: 14.5 (8.1) WLC: 15.1 (8.8) • MADRS-S • QOLI	1) stable dose for 3 months 2) not currently meet diagnostic criteria for psychosis or substance misuse; score <31 on MADRS
16.	Carlbring et al., 2011 [67]	Anxiety disorder 50%	54	38.8 75.9%	56% total	41%	6-10 online sessions, 10 weeks, clinical support	WLC with attention control (online support group), 10 weeks	8 sessions 99.5%	• BAI iCBT: 24.41 (9.97) WLC: 21.00 (9.87) • MADRS-S • QOLI	1) stable dose for 3 months 2) score <31 on MADRS
17.	Christensen et al., 2014 [68]	GAD	21	iCBT: 25 / 75% WLC: 26 / 86%			10 online sessions, 7 ftf meetings with therapist/GP, 10 weeks, clinical support	WLC with attention control (website) and 7 ftf meetings with therapist/GP, 10 weeks		• GAD-7 iCBT: 11.5 (3.7) WLC: 11.7 (4.8) • CES-D	1) no prior treatment with Sertraline or monoamine oxidase inhibitors 2) no psychosis, bipolar disorder, primary diagnosis of depression
18.	Furmark et al., 2009 [69]	SAD	80	iCBT: 35 / 77.5% WLC: 35.7 / 65.0%	52,5% ft		9 online sessions, 9 weeks, clinical support	WLC: delayed treatment, 9 weeks	6.4 sessions 71.2%	• LSAS iCBT: 71.30 (22.4) WLC: 71.28 (24.93)	1) stable dose 3 months 2) score <31 on MADRS
19.	Gallego et al., 2011 [52]	SAD	41	39.3 68.3%		43,9%	Online sessions until feared situations are overcome, 2 months, self-help	WLC: delayed treatment		• BFNE iCBT: 39.41 (9.69) WLC: 41.00 (9.72)	2) not suffering from alcohol or drug dependence or psychosis
20.	Johnston et al., 2011 [28]	GAD, SAD or PD(a) 69,7%	131	41.6 58.8%	44,3% ft		8 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	7.1 sessions 88.6%	• GAD-7 iCBT: 11.63 (5.96) WLC: 12.50 (4.80) PHQ-9	1) no benzodiazepines, stable dose 3 months 2) no psychosis; no score >22 on the PHQ-9
21.							8 online sessions, 10 weeks, non-clinical support		7.6 sessions 94.6%	iCBT: 11.28 (5.18)	

22.	Kiropoulos et al., 2008 [70]	PD(a) 72,1%	86	39 iCBT: 71.7% ftf: 72.5%			6 online sessions, 12 weeks, clinical support	ftf CBT: 12 sessions, 12 weeks, clinical support		• DASS iCBT: 3.67 (1.26) ftf CBT: 3.68 (1.13) • DASS • QOL	1) stable dose 12 weeks 2) no schizophrenia, alcohol or drug dependency, personality disorder
23.	Klein et al., 2006 [71]	PD(a) 89,1%	37	range 18-70 80.0%			6 online sessions, 6 weeks, clinical support	WLC: information, 6 weeks		• DASS iCBT: 18.24 (8.5) WLC: 16.13 (8.6) • DASS	1) stable dose 4 weeks 2) no schizophrenia, alcohol or drug dependency, personality disorder
24.	Marks et al., 2004 [53]	PDa, SAD, specific phobia, agoraphobia	50	38 69%			9 steps in 6 blended sessions, 10 weeks, clinical support	ftf CBT; 6 sessions, 10 weeks, clinical support	4.2 sessions 70%	• FQ iCBT: 6.1 (1.3) ftf CBT: 6.7 (1.2)	1) no benzodiazepine or diazepam- equivalent dose of>5 mg/days; stable dose 4 weeks 2) no active psychotic illness
25.	Oromendia et al., 2016 [27]	PD(a)	77	40.7 68.8%			8 online sessions, 8 weeks, clinical support (non-scheduled)	WLC: delayed treatment, 8 weeks	3.5 session 44.3%	• BAI iCBT: 34.92 (8.60) WLC: 30.63 (9.53) • BDI	1) stable dose 3 months 2) score =<25 on the BDI
26.							8 online sessions, 8 weeks, clinical support (scheduled)		5.5 sessions 68.3%	iCBT: 34.29 (10.97)	
27.	Paxling et al., 2011 [72]	GAD	89	39.3 79.8%			8 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 8 weeks		• BAI iCBT: 20.61 (10.64) WLC: 20.98 (9.66) • BDI • QOLI	1) stable dose 1 month 2) score =<35 on MADRS-S, no severe mental illness such as active psychosis, alcohol abuse (as assessed by the AUDIT)
28.	Richards et al., 2006 [73]	PD(a)	32	36.6 68.6%			6 online sessions, 8 weeks, clinical support	WLC: information (online), 8 weeks		• DASS iCBT: 19.58 (9.5) WLC: 13.00 (7.4) • DASS • QOLI	1) stable dose 4 weeks 2) no schizophrenia, alcohol or drug dependency
29.							6 online sessions + 6 stress modules, 8 weeks, clinical support			iCBT: 21.09 (8.3)	
30.	Robinson et al., 2010 [74]	GAD	145	47 68.3%	43,4% ft		6 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 11 weeks		• PSWQ iCBT: 64.02 (9.27) WLC: 65.81 (10.24) • PHQ-9	1) stable dose 1 month 2) no psychotic mental illness (schizophrenia or bipolar disorder); no score >23 on the PHQ-9

31.							6 online sessions, 10 weeks, non-clinical support			iCBT: 63.12 (9.46)	
32.	Schulz et al., 2016 [75]	SAD 47,7%	149	35.4 53%	60,4% total 42,3% ft	42,3%	8 online sessions (individual), 12 weeks, clinical support	WLC: delayed treatment, 12 weeks	6.5 sessions 81.5%	• SPS iCBT: 39.32 (11.64) WLC: 37.35 (12.45) • BDI • SF-12	1) stable dose 1 month
33.							8 online sessions (group), 12 weeks, clinical support		6.4 sessions 79.4%	iCBT: 38.90 (14.04)	
34.	Titov et al., 2008a [76]	SAD	99	38.1 58.6%	55,6% ft		6 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	5.2 sessions 86.7%	• SPS iCBT: 34.02 (14.42) WLC: 36.08 (16.63) • PHQ-9 • WHODAS	1) stable dose 1 month 2) no psychotic mental illness, no score >19 on PHQ-9
35.	Titov et al., 2008b [77]	SAD	81	36.8 63%	54,3% ft		6 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	5.5 sessions 91.7%	• SPS iCBT: 34.15 (15.55) WLC: 36.68 (14.62) • PHQ-9 • WHODAS	1) stable dose 1 month 2) no psychotic mental illness, no score >19 on PHQ-9
36.	Titov et al., 2008c [78]	SAD	95	38 61%	58,1% ft		6 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	5.4 sessions 89.8%	• SPS iCBT: 34.71 (15.04) WLC: 34.38 (18.77) • PHQ-9	1) stable dose 1 month 2) no psychotic mental illness, no score >19 on PHQ-9
37.							6 online sessions, 10 weeks, self-help		4 sessions 66.2%	iCBT: 32.87 (17.02)	
38.	Titov et al., 2009 [79]	GAD	45	44 75.6%	40% ft		6 online sessions, 9 weeks, clinical support	WLC: delayed treatment, 9 weeks		• GAD-7 iCBT: 14.33 (4.50) WLC: 13.62 (3.51) • PHQ-9	1) stable dose 1 month 2) no psychotic mental illness, no score >23 on PHQ-9
39.	Titov et al., 2010 (GAD) [30]	GAD 75,6%	34	39.5 67.9%	33,3% ft		6 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 8 weeks		• PSWQ iCBT: 66.17 (8.77) WLC: 65.19 (9.78)	1) no benzodiazepines, stable dose 1 month 2) 2) no psychotic mental illness, no score >22 on PHQ-9

40.	Titov et al., 2010 (SAD) [30]	SAD 75,6%	23	39.5 67.9%	33,3%ft		6 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 8 weeks		• SPSQ iCBT: 20.0 (9.49) WLC: 18.45 (9.34)	1) no benzodiazepines, stable dose 1 month 2) no psychotic mental illness, no score >23 on PHQ-9
41.	Titov et al., 2010 (PD) [30]	PD 75,6%	21	39.5 67.9%	33,3%ft		6 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 8 weeks		• PDSS iCBT: 12.80 (6.55) WLC: 15.18 (5.67)	1) no benzodiazepines, stable dose 1 month 2) no psychotic mental illness, no score >23 on PHQ-9
42.	Titov et al., 2011 [29]	GAD, SAD or PD(a) 81%	36	43.9 73.0% (total sample	35% ft		8 online sessions, 10 weeks, clinical support	WLC: delayed treatment, 10 weeks	7.4 sessions 91.9%	• DASS iCBT: 60.63 (25.72) WLC: 45.76 (17.77) • PHQ-9	1) no benzodiazepines; stable dose 1 month 2) no psychotic mental illness, no score >23 on PHQ-9
43.	Wims et al., 2010 [80]	PDa	54	iCBT: 39.5 / 72.4% WLC: 45.1 / 80%	53,7% ft		6 online sessions, 8 weeks, clinical support	WLC: delayed treatment, 8 weeks		• PDSS iCBT: 17.10 (4.84) WLC: 16.44 (4.63) • PHQ-9	1) no benzodiazepines, stable dose 1 month 2) no psychotic mental illness, no score >23 on PHQ-9

Clinical service recruitment studies

44.	Andrews et al., 2011 [81]	SAD	37	31.9 40.5%			6 online sessions, 8 weeks, clinical support	ftf group CBT, 7 4hr- sessions, 7 weeks, clinical support		• SPS iCBT: 43.81 (20.7) ftf CBT: 40.93 (15.4) • WHODAS	
45.	Bell et al., 2012 [82]	GAD, SAD or PD(a) 47%	83	iCBT: 33.6 / 72.5% WLC: 36.9 / 62.8%	59% total		4 (GAD) or 6 (PD or SAD) online sessions, 12 weeks, guided by research assistant*	WLC: remained on wait-list *	2.3 sessions 57%	• BAI iCBT: 24.0 (SE: 1.91) WLC: 18.3 (SE: 1.72) • BDI	1) stable dose 6 weeks 2) no substance dependence, psychotic illness, bipolar I disorder
46.	Bergstrom et al., 2010 [51]	PD(a)	104	iCBT: 33.8 / 64.0% ftf: 34.6 / 59.3%			10 online sessions, 10 weeks, clinical support	ftf group CBT, 10 2hr-sessions, 10 weeks, clinical support	6.7 sessions 67%	• ASI iCBT: 32.5 (11.6) ftf CBT: 33.2 (12.4) • MADRS-S	1) stable dose 2 months 2) no severe depression
47.	Bruinsma et al., 2016 [83]	PD(a) 58,3%	36	iCBT: 36.6 ftf: 39.4 61.1%		27,8%	12 online sessions, 12 weeks, clinical support	ftf CBT, 12 sessions, 12 weeks		• PAS iCBT: 20.28 (9.31) ftf CBT: 19.06 (9.18)	1) stable dose 2 months
48.	Hedman et al., 2011 [84]	SAD	126	iCBT: 35.2 / 62.5% ftf: 35.5 / 66.1%	74% total		15 online sessions, 15 weeks, clinical support	ftf group CBT, 1 individual session and 14 group sessions, 15 weeks, clinical support	9.3 sessions 62.2%	• BAI iCBT: 18.7 (10.9) ftf CBT: 18.6 (10.8) • MADRS-S • QOLI	1) stable dose 2 months 2) no substance abuse; no score >20 on the MADRS; no personality disorders cluster A or B
49.	Kok et al., 2014 [50]	PDa, SAD, specific phobia, agoraphobia	212	34.6 61%		57,1%	5 online sessions, 5 weeks, clinical support*	WLC: remained on wait-list * control and received a self-help book	3 sessions 37.5%	• BAI iCBT: 45.01 (13.78) WLC: 44.57 (13.16) • CES-D	1) stable for duration of the intervention 2) no psychotic disorders
50.	Mathiasen et al., 2016 [85]	GAD, PD(a)	66	iCBT: 32.3 / 63.9% WLC: 29.2 / 60.0%			9 modules, 9 weeks (or longer), clinical support*	WLC: remained on wait-list *,	5.3 sessions 58.7%	• BAI iCBT: 22.86 (10.41) WLC: 22.23 (8.54) • BDI • EQ-VAS	2) no Axis II disorders other than cluster C, bipolar disorder or depressive psychotic features

51.	Nordgreen et al., 2016 (PD) [54]	PD(a) 62,4%	69	34.9 / 60.1%	57% total		ftf psychoeducation session, 10 online sessions (10 weeks) + 12 ftf sessions, clinical support	ftf CBT: 12 sessions, clinical support		51.	Nordgreen et al., 2016 (PD) [54]
52.	Nordgreen et al., 2016 (SAD) [54]	SAD 62,4%	104	31 / 46.2%	57% total		ftf psychoeducation session, 9 online sessions (9 weeks) + 12 ftf sessions, clinical support	ftf CBT: 12 sessions, clinical support		• SPS iCBT: 42.55 (15.61) ftf CBT: 43.83 (15.65) • BDI	1) stable dose 3 months 2) no current psychosis, substance dependency
53.	Nordgren et al., 2014 [7]	GAD, SAD, PD(a), anxiety NOS 58%	100	iCBT: 35 / 66.0% WLC: 36 / 60.0%	47% total	41%	7-10 online modules, 10 weeks, clinical support	WLC with attention control, 10 weeks	4.6 sessions 53.5%	• BAI iCBT: 21.18 (SE: 1.37) ftf CBT: 21.31 (SE: 1.37) • MADRS-S • QOLI	1) stable dose 12 weeks 2) no score >30 on the MADRS

SAD: Social Anxiety Disorder; GAD: Generalized Anxiety Disorder; PD: Panic Disorder; PD(a): Panic Disorders with agoraphobia; iCBT: Internet-based Cognitive Behavioral Therapy; ftf CBT: face-to-face Cognitive Behavioral Therapy; WLC: Wait List Control

* Participants in both groups were on a wait-list for intensive outpatient treatment

Appendix 4. Risk of bias assessment

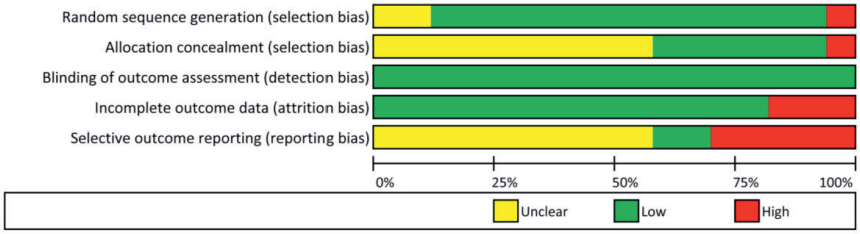
Risk of bias assessment OR trials per study

	sequence generation	allocation concealment	blinding outcome assessors	blinding participants / personnel	incomplete outcome data	selective outcome reporting
Andersson 2006	+	?	+	-	+	?
Andersson 2009	?	?	?	-	-	?
Andersson 2012a	+	+	+	-	+	+
Andersson 2012b	+	+	+	-	+	-
Andersson 2013	+	?	+	-	+	?
Berger 2009	+	?	+	-	+	?
Berger 2014	+	+	-	-	+	?
Berger 2017	+	+	+	-	+	-
Botella 2010	?	?	+	-	-	?
Carlbring 2001	?	?	+	-	+	?
Carlbring 2005	+	?	+	-	+	?
Carlbring 2006	+	?	+	-	+	?
Carlbring 2007	+	+	+	-	-	?
Carlbring 2011	+	+	+	-	+	?
Christensen 2014	+	?	+	-	+	?
Furmark 2009	+	+	+	-	+	?
Gallego 2011	-	?	?	-	-	?
Johnston 2011	+	+	+	-	+	-
Kiropoulos 2008	+	?	?	-	+	?
Klein 2006	-	-	-	-	+	?
Marks 2004	+	+	+	-	-	?
Oromendia 2016	+	+	+	-	+	+
Paxling 2011	+	+	+	-	+	?
Richards 2006	?	?	+	-	+	?
Robinson 2010	+	-	+	-	+	+
Schulz 2016	+	+	+	-	+	-
Titov 2008a	+	?	+	-	+	-
Titov 2008b	+	?	+	-	+	-
Titov 2008c	+	?	+	-	+	-
Titov 2009	+	?	+	-	-	+
Titov 2010	+	?	+	-	+	-
Titov 2011	+	?	+	-	+	-
Wims 2010	+	?	-	-	+	-

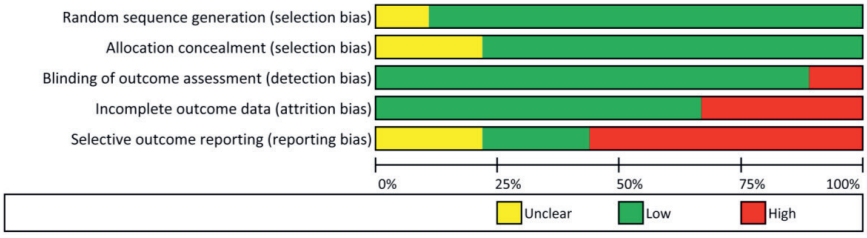
Risk of bias assessment CSR trials per study

	sequence generation	allocation concealment	blinding outcome assessors	blinding participants / personnel	incomplete outcome data	selective outcome reporting
Andrews 2011	?	?	+	-	+	-
Bell 2012	+	+	+	-	+	?
Bergström 2010	+	?	+	-	-	+
Bruinsma 2016	+	?	-	-	-	?
Hedman 2011	+	+	+	-	+	-
Kok 2014	+	+	+	-	-	-
Mathiasen 2016	+	+	+	-	+	-
Nordgreen 2016	+	+	-	-	+	-
Nordgren 2014	+	+	+	-	+	+

Risk of bias graph OR trials



Risk of bias graph CSR trials



Appendix 5. Secondary outcomes

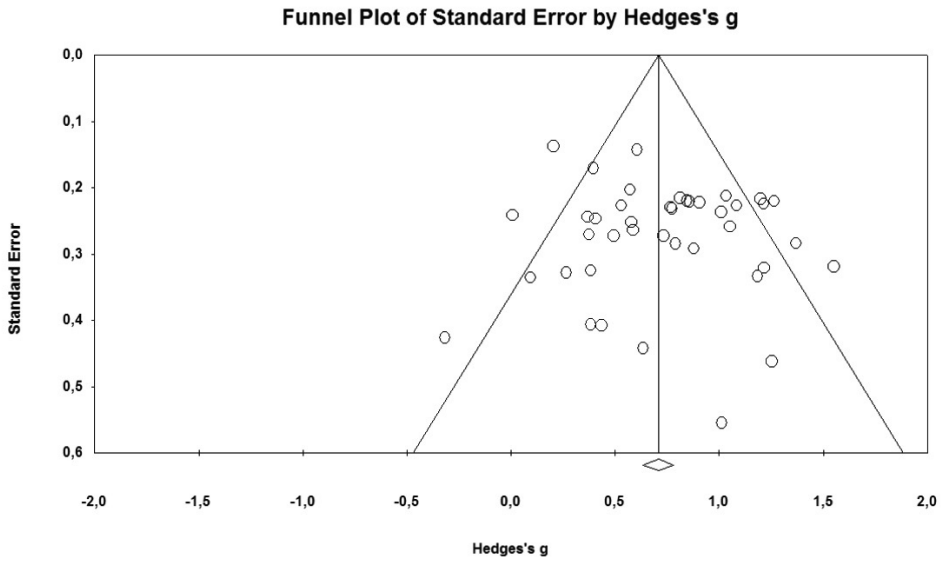
Main effects of OR trials and CSR trials comparing CBT to WLC and iCBT to ftf CBT at post-test, secondary outcomes

	N_{co}	N	g [95% CI]	*P-value*	I^2	NNT	Between-groups Q (*P-value*)
Depressive symptoms							
WLC control							
Open recruitment	32	2293	0.60 [0.51-0.68]	<.001	60	3	1.43 (.23)
Clinical recruitment	4	446	0.36 [0.17-0.54]	<.001	25	4	
Ftf CBT							
Open recruitment	5	286	-0.05 [-0.29-0.18]	.65	34	-35	0.85 (.36)
Clinical recruitment	4	392	0.12 [-0.08-0.31]	.25	0	14	
Quality of life							
WLC control							
Open recruitment	15	1167	0.43 [0.31-0.55]	<.001	0	4	0.05 (.83)
Clinical recruitment	2	167	0.47 [0.16-0.77]	.003	80	3	
Ftf CBT							
Open recruitment	2	298	0.09 [-0.24-0.43]	.59	0	19	0.48 (.49)
Clinical recruitment	2	163	0.25 [-0.06-0.56]	.11	0	7	

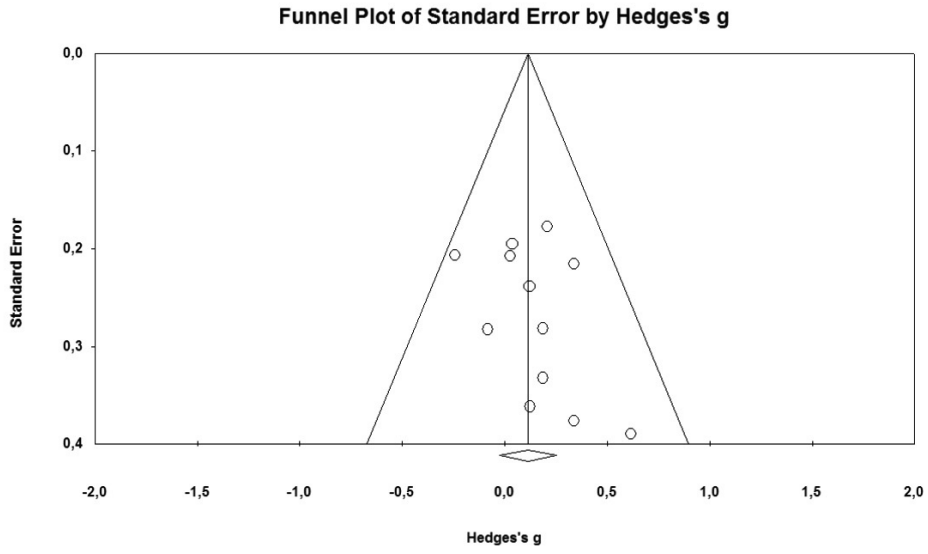
Note. WLC=wait list control; Ftf CBT=face-to-face cognitive behavioral therapy; Nco=number of comparisons; n=number of respondents;

Appendix 6. Funnel plot publication bias

iCBT compared to WLC



iCBT compared to face-to-face CBT



Appendix 7. Metaregression and subgroup analyses

Results of meta regression analyses with sample characteristics

	Association with effect size
Age	WLC: slope=0.02, *P*=.14 Ftf CBT: slope=0.00, *P*=.92
Gender	WLC: slope=-0.01, P=.22, Ftf CBT: slope=0.00, *P*=.37
Baseline BAI score	WLC: slope = -0.00, *P*=.69 Ftf CBT: slope=-0.02, *P*=.35
Baseline SPS score	WLC: slope= 0.03, *P*=.60
Treatment dose	WLC: slope=0.10, *P* =.003 Ftf CBT: slope=0.05, *P* =0.42
Treatment adherence	WLC: slope=0.01, *P* <.001 Ftf CBT: slope=-0.00, *P* =.81

Results of subgroup analysis based on exclusion of severely depressed patients

	N_{co}	**g [95% CI]**	***P-value***	**I^2**	**NNT**	**Between-groups Q (*P-value*)**
WLC						
Exclusion depressive patients						
No	16	0.50 [0.39-0.62]	<.001	46	3	8.06 (.005)
Yes	25	0.84 [0.75-0.94]	<.001	47	2	
Ftf CBT						
No	10	0.09 [-0.07-0.24]	.28	0	19	0.46 (.50)
Yes	2	0.20 [-0.09-0.50]	.18	0	8	

Chapter 3

Cost-effectiveness of blended versus face-to-face cognitive behavioral therapy for severe anxiety disorders: study protocol of a randomized controlled trial

Published as:
Romijn G, Riper H, Kok R, Donker T, Goorden M, van Roijen LH, Kooistra L, van Balkom A, Koning J (2015). Cost-effectiveness of blended vs. face-to-face cognitive behavioural therapy for severe anxiety disorders: study protocol of a randomized controlled trial.
BMC Psychiatry 15: 311.

Abstract

Background: Anxiety disorders are among the most prevalent psychiatric conditions, and are associated with poor quality of life and substantial economic burden. Cognitive behavioral therapy is an effective treatment to reduce anxiety symptoms, but is also costly and labour intensive. Cost-effectiveness could possibly be improved by delivering cognitive behavioral therapy in a blended format, where face-to-face sessions are partially replaced by online sessions. The aim of this trial is to determine the cost-effectiveness of blended cognitive behavioral therapy for adults with anxiety disorders, i.e. panic disorder, social phobia or generalized anxiety disorder, in specialized mental health care settings compared to face-to-face cognitive behavioral therapy. In this paper, we present the study protocol. It is hypothesized that blended cognitive behavioral therapy for anxiety disorders is clinically as effective as face-to-face cognitive behavioral therapy, but that intervention costs may be reduced. We thus hypothesize that blended cognitive behavioral therapy is more cost-effective than face-to-face cognitive behavioral therapy.

Methods: In a randomized controlled trial 156 patients will be included (n=78 in blended cognitive behavioral therapy, n=78 in face-to-face cognitive behavioral therapy) based on a power of 0.80, calculated by using a formula to estimate the power of a cost-effectiveness analysis: $n = \frac{2(z_\alpha + z_\beta)^2\left(sd^2 + (W^2 sd^2) - (2W\rho\, sd_c sd_q)\right)}{(WE - C)^2}$. Measurements will take place at baseline, midway treatment (7 weeks), immediately after treatment (15 weeks) and 12-month follow-up). At baseline a diagnostic interview will be administered. Primary clinical outcomes are changes in anxiety symptom severity as measured with the Beck Anxiety Inventory. An incremental cost-effectiveness ratio will be calculated to obtain the costs per quality-adjusted life years (QALYs) measured by the EQ-5D (5-level version). Health-economic outcomes will be explored from a societal and health care perspective.

Discussion: This trial will be one of the first to provide information on the cost-effectiveness of blended cognitive behavioral therapy for anxiety disorders in routine specialized mental health care settings, both from a societal and a health care perspective.

Trial registration: Netherlands Trial Register NTR4912. Registered 5 January 2015

Keywords: Anxiety disorders, Panic disorders, Generalized anxiety disorder, Social phobia, Internet-based treatment, Blended CBT, Cognitive behavioral therapy, Cost-effectiveness, Specialized mental health care, Randomized controlled trial

Background

Anxiety disorders are among the most prevalent psychiatric disorders worldwide [1]. They are associated with poor quality of life and a substantial economic burden [2-4]. Estimates of annual health care costs associated with anxiety disorders in the U.S. lie between $42 billion [5] and $47 billion [6]. A measure of overall disease burden is the disability-adjusted life year (DALY), expressed as the number of years lost due to ill health, disability or early death. The total global disease burden caused by anxiety disorders was 390 DALYs per 100,000 persons in 2010, being the sixth leading cause of disability [7]. In the Netherlands, annual health care

costs are estimated at €286 million. In 2007, anxiety disorders accounted for 202,000 DALYs in the Netherlands, being third in the top ten list of medical disorders and having a higher cost impact than depression, diabetes mellitus or lung cancer [3].

Appropriate and efficient treatments are essential to reduce the impact of severe anxiety disorders on public health. These disorders can be treated effectively with cognitive-behavioral therapies (CBT), whether or not combined with pharmacotherapy. CBT is regarded as one of the preferred treatments for anxiety disorders in the Netherlands, set out in the multidisciplinary guidelines for anxiety [8] and international treatment guidelines [9-10]. However, less than half of the patients with anxiety disorders receive appropriate treatment [11], due to anxiety-related avoidance behavior, stigmatisation, waiting lists, costs of therapy and distance from service locations [12-14].

In recent years effort has been put in making less expensive and easily accessible interventions available for anxiety disorders while ensuring clinical effectiveness. These include self-help interventions. Studies indicate that these interventions did significantly better than waiting lists in terms of reducing anxiety symptoms [15]. Another important strategy for lowering treatment costs and improving accessibility are Internet interventions for mental disorders such as depression, anxiety disorders and problem drinking. Several meta-analyses have demonstrated that anxiety treatment delivered via Internet is more effective than non-intervening and that it can be as effective as face-to-face treatment [15-23]. Reger and Gahm [21], for example, showed that Internet- and computer-based treatments for anxiety disorders were superior to waitlist and that effects were equal to therapist-delivered treatment. Cuijpers et al. [18] investigated the effects of guided self-help on depression and anxiety compared to face-to-face psychotherapies and found no differences between the effects of both interventions. Andersson et al. [16] investigated the efficacy of guided Internet-based CBT in direct comparison to face-to-face CBT for psychiatric and somatic disorders. They concluded that both treatments produce equivalent effects.

Increasing emphasis is placed on cost-effectiveness of health care programmes, because of pressure on health care resources across the globe. In general, Internet interventions may be more cost-effective than face-to-face treatment. This has been confirmed in a recent systematic review by Donker et al. [24], in which 16 studies with economic evaluations of Internet interventions for anxiety, depression, smoking cessation and alcohol consumption were included. Nordgren et al. [25], for example, compared Internet-delivered CBT to an active waiting list control condition and found it to be cost-effective for primary-care patients with anxiety disorders with an ICER of −$1824, indicating lower costs and larger clinical effects in Internet-delivered CBT at post-test

A rather new treatment approach combines face-to-face treatment with Internet components into one integrated treatment protocol [27]. This is called blended treatment [20]. Using this approach, part of the face-to-face treatment is replaced by Internet components, while the traditional face-to-face relationship between therapist and patient is retained. Blended treatment could possibly lower the number of face-to-face contacts, increase self-management competencies of patients and thereby reduce the overall (direct)

treatment costs. This approach could also have a positive effect on waitlist periods, as it is expected that therapists can take on more patients, thereby reducing the number of patients that are waitlisted [27]. Therefore, blended treatments appear an attractive alternative for treatment as usual. However, little is known about the clinical outcome and cost-effectiveness of these treatments. In a recent study, Volker et al. [28] investigated the effectiveness of a blended intervention versus treatment as usual for sick-listed employees with common mental disorders, such as depression, anxiety and somatization disorders. Results demonstrated that the group receiving the blended intervention returned to work faster (27 days earlier on average) and had a greater chance of achieving remission than the group receiving treatment as usual. As far as we know there is no study yet investigating the cost-effectiveness of blended treatment for anxiety disorders.

We therefore aimed to investigate the cost-effectiveness of blended CBT for severe anxiety disorders. This refers to the group of patients with an anxiety disorder (panic disorder, social phobia or generalized anxiety disorder) who are referred to outpatient specialized mental health care. Treating these patients in primary care settings is not intensive enough given the severity of their disorders, for example due to pervasive avoidance behavior leading to functional disabilities, or because of comorbidities that hamper treatment in primary care. We hypothesized that blended CBT is equally as effective as regular face- to-face CBT, but that intervention costs for blended CBT will be reduced.

Methods/design

Study design

The study is designed as a parallel-group randomized controlled equivalence trial (N=156), in which patients with panic disorder, social phobia or generalized anxiety disorder are randomly allocated to either blended CBT (N=78) or face-to-face CBT (N=78).

The protocol for this study has been approved by the Medical Ethics Committee of the VU University Medical Centre, Amsterdam (registration number 2015.073). Written informed consent will be obtained from all participants. Figure 1 displays the flowchart of the study design, in accordance with the CONSORT guidelines [29-30].

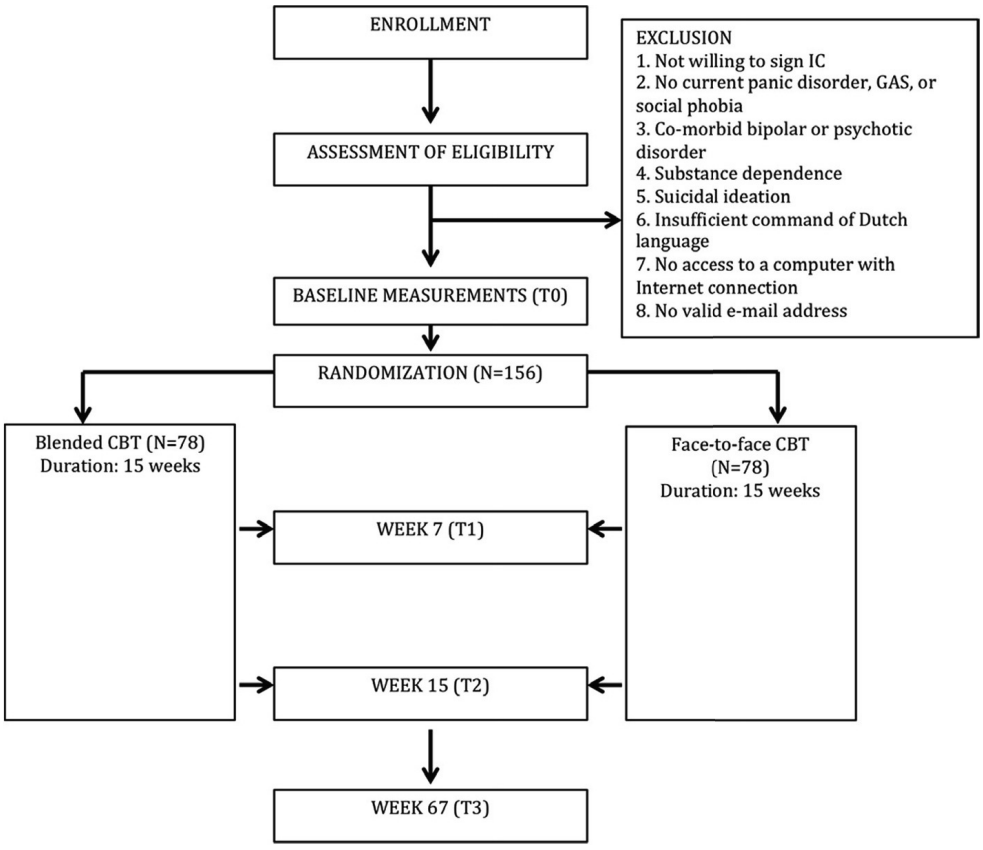


Figure 1. Flowchart of the study design

Measurements

Measurements are taken at baseline (T0) and at three fixed intervals after the first treatment session; at week 7 (T1), 15 (T2) and 67 (T3). Questionnaires are self-administered online. The diagnostic interviews will be administered by a trained researcher face-to-face at the mental health care location. Table 1 provides an overview of the measures that are used at each time point.

Table 1. Overview of measures administered at each assessment interval

Questionnaire	Aim	Baseline (T0)	Week 7 (T1)	Week 15 (T2)	Week 67 (T3)
Primary outcomes					
BAI	*Anxiety severity*	x	x	x	x
SCID-I/MINI-plus	*Diagnostic interview*	x			
EQ-5D-5L	*General well-being*	x	x	x	x
TiC-P	*Health-care utilization*	x		x	x
Other variables of interest					
General patient characteristics		x			
A priori treatment preference		x			
BDI	*Depression*	x	x	x	x
WSAS	*Work and social adjustment*	x	x	x	x
BSI	*General psychopathology*	x	x	x	x
CSQ	*Satisfaction*			x	
Mastery Scale	*Locus of control*	x	x	x	x
WAI	*Therapeutic alliance*		x		
SUS (bCBT only)	*System usability*			x	

BAI: Beck Anxiety Inventory; SCID: Structured Clinical Interview for DMS disorders axis I; MINI plus: Mini International Neuropsychiatric Interview Plus; EQ-5D-5L: EuroQol; iC-P: Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness; BDI: Beck Depression Inventory; WSAS: Work and Social Adjustment Scale; BSI: Brief Symptom Inventory; CSQ: Client Satisfaction Questionnaire; WAI: Work Alliance Inventory; SUS: System Usability Scale ; bCBT: blended Cognitive Behavioral Therapy

Participants

Inclusion criteria

Patients aged 18 years and older are eligible to participate if they meet the criteria for a DSM-V diagnosis of a severe anxiety disorder (social phobia, panic disorder with or without agoraphobia and generalized anxiety disorder). The Structured Clinical Interview for DSM disorders axis I (SCID-I) [31] or the MINI international Neuropsychiatric Interview plus (MINI plus) [32-33] will be performed face-to-face by a trained researcher to assess these inclusion criteria.

Exclusion criteria

Patients are excluded from the study if they i) do not have adequate proficiency in the Dutch language, both verbal and written, ii) do not have a valid e-mail address and a computer with Internet access, iii) suffer from one or more of the following disorders: a psychotic disorder, bipolar disorder and/or substance dependence, iv) are identified to be at high risk for suicide. The SCID-I [31] or the MINI plus [32-33] will be used to assess whether the exclusion criteria

iii) and iv) apply. Comorbid disorders other than psychotic and bipolar disorders are allowed, as is psychopharmacological treatment. Excluded participants will be offered one of the regular treatment options within the participating specialized mental health care centre. For respondents with a heightened suicide risk, the principal investigator will inform the professional responsible for treatment immediately via telephone and e-mail.

Recruitment

Patients will be recruited at the anxiety disorder departments of three large scale specialized mental health care centres in the Netherlands. All newly registered patients undergo an intake interview by an experienced clinician, after which diagnosis and treatment is established and discussed with the patient. Subsequently, eligible patients are informed about the study by the researcher. Interested patients will then receive an information brochure and an informed consent form via e-mail and will be invited to take the baseline diagnostic interview. During this interview, a trained researcher will confirm the primary diagnosis of panic disorder, social phobia or generalized anxiety disorder and assess comorbidity. If patients are willing and eligible to participate, written informed consent will be requested.

Randomization and blinding

Participants will be randomly assigned to either blended CBT or face-to-face CBT by an independent researcher, based on a computer-generated block randomization table [29]. Randomization will be stratified by research site to control for the differences between centres. Group allocation cannot be blinded to patients and therapists because they will obviously notice whether they perform or receive blended CBT or face-to-face CBT.

Interventions

Blended cognitive behavioral therapy

Blended CBT is a protocolized manualized treatment consisting of 15 sessions, with weekly alternating 45-minute face-to-face sessions and online sessions (approximately 50%-50%) with online feedback from the therapist. Online sessions are accessible in a secure web-based environment (Minddistrict; www.minddistrict.com). Patients and therapists access this platform with a personalized login. Performing an online session will take patients approximately 45 minutes, and providing online feedback will take therapists approximately 15 minutes per patient per session. Feedback messages are sent on the online platform to ensure secure communication.

The blended protocol is based on evidence-based protocols for treatment of anxiety disorders and recommendations in national and international treatment guidelines [8-10]. The protocol was developed in collaboration with patients, therapists and experts through organized focus groups during the development phase of the blended intervention, who provided feedback on the content and presentation.

Key elements of blended CBT are psycho-education (explanation of the treatment

rationale and the general procedures in cognitive therapy), cognitive therapy (examining relationships between thoughts, emotions and behavior), interoceptive exposure and exposure in vivo (exposure to feared situations) and relapse prevention (identifying and adopting strategies to prevent anxiety symptoms from re-occuring). After a face-to-face introduction session with an explanation of blended CBT, the treatment starts with a face-to-face session and it also ends with a face-to-face session.

The online sessions have a fixed structure that starts with therapy information, followed by multiple exercises and homework assignments. The sessions contain text boxes with information and testimonials from fictional patients and videos in which a therapist explains the theory. Patients get online feedback from their therapist on finished exercises at a fixed day and time. Homework assignments are discussed in the subsequent face-to-face session.

On completion of treatment, patients can continue to access the online treatment platform in order to reread information and look up homework exercises, such as the relapse prevention plan.

Face-to-face cognitive behavioral therapy

The face-to-face CBT entails fifteen weekly 45-minute face-to-face sessions with psycho-education, cognitive therapy, interoceptive exposure, exposure in vivo and relapse prevention. Therapists follow a protocol with the same content as the blended CBT protocol.

Therapists

All participating therapists are experienced clinicians and will be trained in the blended CBT protocol and the face-to-face cbt protocol prior to the study. During the training they are informed about the content and the structure of the protocol and they receive instructions about how to work with the online platform. Therapists work with both treatment groups. During the trial, therapists will attend peer group supervision meetings every other week. The supervision meetings are guided by the head researcher at the centre (an experienced psychologist) and the research coordinator.

Clinical outcome measures

Severity of anxiety symptoms

The Beck Anxiety Inventory (BAI) [34] will be used to measure the severity of anxiety symptoms at every assessment moment (T0-T3). The BAI is a reliable and well-validated measure of somatic anxiety symptoms found across the anxiety disorders [36]. It consists of twenty-one questions about how the subject has been feeling in the last week, expressed as common symptoms of anxiety (such as numbness and tingling, sweating not due to heat, and fear of the worst happening). Each question has the same set of four possible answer options, which are arranged in columns and are answered by marking the appropriate one with an X. The BAI has a maximum score of 63. For this study, treatment response is defined as a

symptom reduction of the baseline BAI symptom severity score of at least 30% and remission a score reduction of at least 30% plus a total score <11, based on validation in The Netherlands Study of Depression and Anxiety (NESDA) [36-38].

Measures of quality adjusted life years

General well-being

The EQ-5D-5L [39-40] will be administered at all time points (T0-T3) to assess health related quality of life. This validated questionnaire consists of five questions that tap mobility, self-care, daily activities, pain and mood. Each item has five response categories. The labels for each of the dimensions are: no problems, slight problems, moderate problems, severe problems and incapacity/extreme problems. In addition to this, participants use a VAS scale to rate their health on a scale ranging from 0 (*worst possible health*) to 100 (*best possible health*). The answers to the five questions are combined in a number sequence that corresponds with the five answers. Each sequence corresponds to a certain health state. On these health states, a value (utility) has been placed [41], which in turn is used to determine the quality-adjusted life years (QALYs). To obtain a utility score per patient, the area-under-the curve method (AUC) will be applied [42]. This method consists of linearly interpolating between the different health states at the different time points. Subsequently, the area under the curve is calculated.

Cost calculations

The cost-effectiveness will be assessed taking a societal and health care perspective. Cost within health care, costs to the patient and productivity costs are taken into account. The Treatment Inventory of Costs in Psychiatric patients (TiC-P) will be applied to collect input data on costs. The TiC-P is a validated comprehensive questionnaire focused on establishing costs incurred within and outside the health care system as well as costs due to productivity losses [43].

Health care utilization costs and patient costs

Part 1 of the TiC-P is a validated instrument that measures the direct medical costs by calculating the number of contacts with health care services (general practitioner, psychiatrist, medical specialist, physiotherapist, alternative health practitioner, day care/hospital length of stay), during the last three months. Also, information about the number of contacts and time spent by the patient on the online part of the intervention will be collected. Additionally, patients' out-of-pocket costs, such as the costs of travelling to the health services and the patients' time costs of travelling are determined.

Apart from these costs, the costs of offering the treatments will be taken into account. For example, the costs of developing and maintaining the online part of the treatment, as well as the costs of weekly therapist online feedback. The costs are calculated by multiplying the volumes by the corresponding reference unit prices [44].

Productivity costs

The second part of the TiC-P contains the iPCQ. This part asks questions about productivity losses that are caused by absence (absenteeism), reduced efficiency at work (presenteeism) and difficulties in job performance. Sickness absence for less than one month is defined as short-term absence, and sickness absence for more than one month as long-term absence. If respondents indicated that they had been absent for the entire recall period, data were collected from the time when the period of long-term absence started. This additional information will be used to value the production losses according to the friction cost method [45]. This method takes into account the economic circumstances that limit the losses of productivity to society, which are related to the fact that a formerly unemployed person may replace a person who becomes disabled. Productivity losses were valued according to the average value added per worker by age and gender per day and per hour prices [44].

Other variables of interest

To further evaluate blended CBT compared to face-to-face CBT, a number of explorative measures are administered.

General patient characteristics and treatment preference

Demographic characteristics such as age, sex, education, employment and marital status will be collected with a general demographic questionnaire at baseline (T0). Additional questions are asked concerning clinical anxiety characteristics such as age of onset, number of months with an anxiety disorder in past 4 years, duration of current episode, somatic illnesses and treatment status. In addition, participants are asked about their computer use: number of hours spent at a computer and reasons for use. Finally, patients indicate their treatment preference (blended CBT or face-to-face CBT).

Depression

The Beck Depression Inventory-II (BDI-II) [46] is a 21-question multiple choice self-report inventory of the most widely used instruments for measuring the severity of depression and assesses the presence and severity of depressive symptoms. The BSI-II has been validated in Dutch [47]. It will be used at every time point (T0-T3).

Work and social adjustment

The Work and Social Adjustment Scale (WSAS) [48] is a 5-item patient self-report measure, which assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships at all time points (T0-T3). The WSAS is used for all patients with depression or anxiety as well as phobic disorders. It is a reliable and valid measure [48].

General psychopathology

The Brief Symptom Inventory (BSI) [49] is a 53-item, self-report symptom inventory designed to evaluate general psychopathology at every time point (T0-T3). It is a brief form of the SCL-90 and is designed to provide a multidimensional symptom measurement in about 10 minutes. The questionnaire has been validated in Dutch [50].

Locus of control

The five-item version of The Mastery Scale [51] is administered at each assessment moment (T0-T3) to assess changes in *locus of control*. Locus of control could potentially mediate treatment effect and facilitate relapse prevention. The questionnaire consists of five questions, which are scored on a five-point Likert-scale, ranging from 1 (*totally disagree*) to 5 (*totally agree*). The total score ranges from 5 to 30, with higher scores being indicative of a higher level of experienced control. The scale has good psychometric properties [51].

Therapeutic alliance

The Revised Short Version of the Work Alliance Inventory (WAI-SR) [52-53] is used to let patients rate the *quality of the work alliance* between patient and therapist at T1 (week 10). The questionnaire is administered to investigate whether the blended treatment has an effect on the quality of the work alliance. The questionnaire consists of 12 items, which are scored on a five-point Likert-scale, ranging from 1 (seldom or never) to 5 (always). The raw scores range from 12 to 60, with higher scores being indicative of a better alliance between therapist and patient. The questionnaire has satisfactory psychometric properties [52].

Treatment evaluation

The Client Satisfaction Questionnaire-8 (CSQ-8) [54] will be administered at week 15 (T2). The CSQ consists of 8 questions with item-specific response categories. The total score ranges from 8 to 32, with higher scores being indicative of higher *levels of client satisfaction*. The CSQ-8 has a high internal consistency [55].

The System Usability Scale (SUS) [56] will be administered at week 15 (T2) amongst the participants randomized to the blended CBT group. The SUS consists of 10 questions with 5 response options, ranging from 0 (strongly disagree) to 4 (strongly agree). The total scores are converted to a scale ranging from 0 to 100. Higher scores are indicative of higher usability of the online platform that is used for blended CBT. It has been found to be a reliable questionnaire [57].

Process data

Data for process analyses are obtained from the administration of the participating mental health care institutions and through usage statistics of the online platform. We will consider the following aspects:

- Recruitment: time required for the recruitment of patients

- Treatment adherence: percentage of dropout during therapy, number of completed sessions, reasons for treatment dropout, number of face-to-face contacts and number of cancellations, homework adherence
- Time investment: by both the patient and the therapist

Sample size

In economic evaluations we are calculating the power to estimate the joint distribution of costs and treatment effects. Subsequently, we need more information for estimating power compared to clinical trials, namely expected costs of treatments, expected covariance of treatment effects/costs, and the maximum willingness to pay for the treatment effect. To incorporate this information, the formula of Glick et al. [58] can be used. A goal of sample size and power calculation for cost-effectiveness analysis is to identify the likelihood that an experiment will allow us to be confident that a therapy is acceptable or not when we adopt a particular willingness to pay.

For this study a sample size of 156 is based on a formula to estimate the power of a cost-effectiveness analyses.

$$n = \frac{2(z_\alpha + z_{\beta)})^2 \left(sd^2 + (W^2 sd^2) - \left(2W\rho\, sd_c sd_q\right)\right)}{(WE - C)^2}$$

Where:

N = sample size/group

z α = z statistic for alpha

z β = z statistic for beta

sdc = Expected standard deviation costs

sde = Expected standard deviation effects

W = Willingness to pay

C = Expected differences in costs

E = Expected differences in effects

ρ =correlation between differences in costs and effects

(zα=1,96; zβ=0,84; sdc=800; sde=0,02; W=80,000; C=832; E=0,02 ρ=0,1)

Based on the literature of the similar effectiveness of Internet-based CBT compared to face-to-face CBT, we will conduct an equivalence study to show that blended CBT and face-to-face CBT do not differ significantly in their short- and long-term effectiveness (expected between-groups effect-size *d* of 0.2). The sample size in this equivalence study is based on an applied equivalence limit difference ES of 0.4, as this range of small to moderate difference in effect size will not result in clinically important differences. The power of this study that both treatments are similar is set at 0.80 with an alpha of 0.05 to calculate sample size and resulted in the inclusion of 78 patients per condition (total n = 156). This was supported by the estimates based on the formula.

Statistical analysis

Primary analysis

A cost-effectiveness analysis (CEA) will be conducted from the societal perspective. In addition, a budget impact analysis (BIA) will be based on a health-economic modelling study in accordance with Mauskopf's recommendations [59], i.e. from the perspective of the health care decision maker.

Cost-effectiveness analysis

Costs will be assessed at pre-, post-treatment and at one-year follow up. As the TIC-P cost date covers a period of three months, all costs will be extrapolated to a 12-month period, assuming stability of costs during the time frame. A multilevel model (to correct for correlation between measurements) with a link function (as cost-data will not be normally distributed) is used to obtain parameter estimates, likelihood and p-values for the costs and effects. The fitted estimates will be bootstrapped to assess confidence intervals [60]. An incremental cost-effectiveness ratio (costs per case response or remission) will be calculated (ICER = (mean costs blended CBT treatment-mean costs face-to-face CBT)/(mean blended CBT - mean face-to-face CBT). The mean costs, including all costs, of the patients in the blended CBT condition will be subtracted from the mean costs of the patients in the face-to-face CBT condition. This difference will then be divided by the subtracted effects (case of response or remission on the BAI) and an estimation of the blended CBT treatment groups' incremental costs in relation to their incremental health benefit will be generated. Additionally, an incremental cost-utility ratio (costs per QALY) will be calculated; this procedure is identical to the cost-effectiveness ratio with the exception that instead of the cost per QALY, the cost per case of response or remission, is calculated. Finally, to test the robustness of the results, we will conduct sensitivity analyses, to investigate how sensitive the ICERs will be to changes of cost estimates (for example difference in costs per blended CBT contact, type of psychologists and number of sessions). For decision-making purposes, the ICER acceptability curve will be plotted for various willingness-to-pay (WTP) ceilings, which helps in making judgments about whether the blended intervention offers good value for money, relative to treatment as usual. One-way sensitivity analyses directed at uncertainty in the main cost drivers will be performed to gauge the robustness of our findings across a range of likely values for those parameters.

Budget impact analysis

To assess how health care budgets are changed by offering blended CBT for anxiety compared to face-to-face CBT, a *budget impact analysis* (BIA) will be conducted as outlined in Mauskopf et al. [59]. The BIA will include 1) the perspective of the public purse (in Dutch: Budgettair Kader Zorg), and 2) the perspective of the health care decision makers. We consider costs when 10%, 20%, 30% and 100% of the target group receive blended CBT compared to face-to-face CBT. These scenarios will be compared with the base-case scenario, reflecting current care, where 0% of the target group is offered blended CBT. The BIA will be conducted taking

account of the perspectives of health care decision makers. For this, the average remuneration rates of the Dutch Health Authority will be used (NZa). The Budget Impact Analysis (BIA) will be conducted using a health economic (Markov cohort) simulation model.

Explorative analyses

Outcomes on continuous clinical outcome variables, such anxiety symptoms, at T1, T2 and T3 (week 7, 15, and 67) are estimated for descriptive purposes through mixed-model analyses (MM), with participants as random effects, and time (T1-T3), group (blended vs. face-to-face treatment) and time x group as fixed effects, with baseline scores as a single covariate. Missing data will be imputed statistically. To assess the magnitude of treatment effects, Cohen's *d* effect sizes [61] for each time point are calculated by dividing MM parameter estimates of fixed effects at each post-treatment assessment by the pooled standard deviation of outcome measurements at baseline (T0).

Discussion

The study described is a randomized controlled trial in which the health care efficiency of blended CBT for adults with panic disorder, social phobia or generalized anxiety disorder in outpatient specialized mental health care is examined. The main goal is to assess the cost-effectiveness of blended CBT in comparison to face-to-face CBT, from a societal and a health care perspective.

Both national and international studies have shown that the costs of anxiety disorders are substantial. This is reflected in health care costs and loss of productivity. Blended CBT has the potential to increase the cost-effectiveness compared to face-to-face CBT, mainly due to its effectiveness combined with less therapist time needed and fewer patients' visits to therapist. Blended CBT may also increase patients' self-management; they have more control over time and frequency of treatment, because they can access the online platform as often and as long they want, in combination with therapist support. The fact that blended CBT may benefit patients and therapists and can be executed quite easily and possibly at less cost than conventional CBT, means that it is potentially very interesting for health care institutions to be able to deliver this type of treatment, and for health care insurance companies to include these treatments in their reimbursement programs.

However, clinical and economical evaluations of this type of treatment are still scarce. Several studies confirm the effectiveness and cost-effectiveness of Internet-based CBT for depression and anxiety disorders [24], but none of these studies investigated cost-effectiveness of blended CBT for anxiety disorders in specialized mental health care. By adopting a societal perspective in this study all relevant information that may be of interest for the decision-making process is incorporated in the analysis. Hence, in this study, patients´ time and productivity costs are part of the assessment.

A strong feature of the current trial is that therapy content of face-to-face CBT and blended CBT is similar, captured in a protocol for both conditions. Both interventions entail

clinical behavioral therapy and exposure, a daily routine treatment for anxiety disorders. In addition, the recruitment of patients and inclusion and exclusion criteria are similar to the usual procedures in mental health organizations, which enhances the external validity of the results that will be obtained.

The strength of high external validity is simultaneously a limitation with regard to internal validity. The study is designed to closely adhere to established procedures in routine practice in outpatient specialized mental health care, which can make it difficult to attribute clinical results to the blended treatment. However, with this study we want to gain insight into the cost-effectiveness of blended CBT, rather than its clinical effectiveness.

Furthermore, we aim to collect follow-up data after a year. Therefore, an inherent challenge to the study is retention. To minimize drop-out, reminders for filling in questionnaires will be sent by e-mail and if deemed necessary, participants will be called personally to remind them and possibly fill in the questionnaire together during the phone call. To handle missing data, we will impute missing values statistically.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JK (PI) and HR obtained funding for this study. All authors contributed to the design of the study. GR developed the intervention and coordinated the recruitment of patients and the data collection. HR, JK and TvB are responsible for the overall design and supervision. GR wrote the manuscript. All authors read, contributed and approved the final manuscript.

Acknowledgements

This study is funded by ZonMw (project number 837002505).

References

1. Kessler RC, Ruscio AM, Shear K, Wittchen H. Epidemiology of anxiety disorders: Behavioral neurobiology of anxiety and its treatment. Berlin: Springer; 2010. p. 21-35
2. Graaf R, ten Have M, van Dorsselear S, NEMESIS-2: opzet en eerste resultaten. Utrecht: Trimbos Instituut; 2010.
3. RIVM, 2013. Nationaal Kompas Volksgezondheid. http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/psychische-stoornissen/angststoornissen/. Accessed 19 January 2015
4. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: implications for curative and preventive psychiatry. The journal of mental health policy and economics. 2006; 9: 193-200.

5. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999; 60: 427–435.
6. DuPont RL, Rice DP, Miller LS, Shiraki SS, Rowland CR, Harwood HJ. Economic costs of anxiety. Anxiety. 1996; 2:167–172.
7. Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. Psychological Medicine. 2014; 44: 2363–2374.
8. Van Balkom ALJM, van Vliet IM, Emmelkamp PMG, Bockting CLH, Spijker J, Hermens MLM, Meeuwissen JAC. Multidisciplinaire richtlijn Angststoornissen (Derde revisie). Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een angststoornis. Utrecht: Trimbos-instituut; 2013
9. National Institute for Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary and community care. London: National Collaborating Centre for Mental Health; 2011
10. National Institute for Clinical Excellence. Social anxiety disorder: recognition, assessment and treatment. London: National Collaborating Centre for Mental Health; 2013
11. Bijl RV, de Graaf R, Hiripi E, Kessler RC. The prevalence of treated and untreated mental disorders in five countries. Health Aff (Millwood). 2003; 22:122-133.
12. Kohn R, Saxena S, Levav I, & Saraceno B. The treatment gap in mental health care. Bulletin of the World Health Organization. 2004; 82: 858-866.
13. Mohr DC, Ho J, Duffecy J, Baron KG, Lehman KA, Jin L, Reifler D. (2010). Perceived barriers to psychological treatments and their relationship to depression. Journal of Clinical Psychology. 2010; 66: 394-409.
14. Reger MA, Gahm GA. A meta-analysis of the effects of internet- and computer-based cognitive-behavioral treatments for anxiety. Journal of clinical psychology. 2009; 65:53-75.
15. Lewis C, Pearce J, Bisson JI. Efficacy, cost-effectiveness and acceptability of self-help interventions for anxiety disorders: systematic review. The British journal of psychiatry: the journal of mental science. 2012; 200:15-21.
16. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. Face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World psychiatry: official journal of the World Psychiatric Association. 2014; 13: 288-295.
17. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PloS one. 2010: 5; e13196.
18. Cuijpers P, Marks IM, van Straten A, Cavanagh K, Gega L, Andersson G. Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. Cognitive behaviour therapy. 2009; 38: 66-82.

19. Haug T, Nordgreen T, Ost LG, Havik OE. Self-help treatment of anxiety disorders: a meta-analysis and meta-regression of effects and potential moderators. Clinical psychology review. 2012; 32: 425-445.
20. Mayo-Wilson E, Montgomery P. Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults. The Cochrane database of systematic reviews. 2013; 9: CD005330.
21. Reger MA, Gahm GA. A meta-analysis of the effects of internet- and computer-based cognitive-behavioral treatments for anxiety. Journal of clinical psychology. 2009; 65: 53-75.
22. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychological medicine. 2007; 37: 319-328.
23. Olthuis JV, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. Cochrane Database of Systematic Reviews. 2015; 3: CD011565.
24. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, & Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychological Medicine. 2015; 1: 1–20.
25. Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki A, Eriksson S, Lindkvist E, Andersson G, Carlbring P. Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. Behaviour research and therapy. 2014; 59: 1-11.
26. Riper H, van Ballegooijen W, Kooistra L, de Wit J, Donker T: Preventie & eMental-Health - Prevention & eMental-Health. Amsterdam: Vrije Universiteit commissioned by ZonMw; 2013
27. Kooistra LC, Wiersma JE, Ruwaard JJ, van Oppen P, Smit F, Lokkerbol J, Cuijpers P, & Riper H (2014). Blended vs. face-to-face cognitive behavioural treatment for major depression in specialized mental health care: study protocol of a randomized controlled cost-effectiveness trial. BMC psychiatry 14, 290.
28. Volker D, Zijlstra-Vlasveld MC, Anema JR, Beekman ATF, Brouwers EPM, Emons WHM, van Lomwel AGC, van der Feltz-Cornelis CM. Effectiveness of a blended web-based intervention on return to work for sick-listed employees with common mental disorders: Results of a cluster randomized controlled trial. Journal of Medical Internet Research. 2015; 17: e116
29. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG: CONSORT: explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010; 340: c869.
30. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg.* 2011; 9:672-677.

31. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York: Biometrics Research, New York State Psychiatric Institute, 2002.
32. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM- IV and ICD-10. *J Clin Psychiatry.* 1998; 59: 34–57.
33. Van Vliet IM, De Beurs E. Het Mini Internationaal Neuropsychiatrisch Interview (MINI). Een kort gestructureerd diagnostisch psychiatrisch interview voor DSM-IV en ICD-10-stoornissen - The Mini International Neuropsychiatric Interview (MINI). A short structured diagnostic psychiatric interview for DSM-IV and ICS-10 disorders. Tijdschr Psychiatr. 2007; 49: 393–397.
34. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. Journal of consulting and clinical psychology. 1988; 56: 893-897.
35. Fydrich T, Dowdall D, Chambless DL. Reliability and validity of the Beck Anxiety Inventory. Journal of Anxiety Disorders. 1992; 6:55–61.
36. Lamers F, van Oppen P, Comijs HC, Smit JH, Spinhoven P, van Balkom AJ, Nolen WA, Zitman FG, Beekman AT, Penninx BW. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). Journal of Clinical Psychiatry. 2011; 72: 341-8.
37. Muntingh A, Van der Feltz-Cornelis C, Van Marwijk H, Spinhoven P, Assendelft W, De Waal M, Adèr H, Van Balkom A. Effectiveness of collaborative stepped care for anxiety disorders in primary care: a pragmatic cluster randomised controlled trial. Psychother Psychosom. 2014; 83: 37–44.
38. Muntingh ADT, van der Feltz-Cornelis CM, van Marwijk HWJ, Spinhoven P, Penninx BW, van Balkom AJ. Is the Beck Anxiety Inventory a good tool to assess severity of anxiety? A primary care study in the Netherlands Study of Depression and Anxiety. BMC Family Practice. 2011; 12: 66.
39. Group EQ: EuroQol – a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16:199–208.
40. Lamers LM, Stalmeier PFM, McDonnell J, Krabbe PFM, van Busschbach JJ. Kwaliteit van leven in economische evaluaties: het Nederlands EQ-5D tarief. Nederlandse Tijdschrift voor Geneeskunde, 2005; 149: 5.
41. Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJV: The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ.* 2006; 15: 1121-1132.
42. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990; 300: 230-235.
43. Bouwmans C, de Jong K, Timman R, Zijlstra-Vlasveld M, van der Feltz-Cornelis C, Tan Swan S, Hakkaart-van Roijen, L. Feasibility, reliability and validity of a questionnaire on

healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res. 2013; 13: 217.
44. Hakkaart van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kosten onderzoek, in: CVZ (Ed.). Medical Technology Assessment. Rotterdam: Erasmus Universiteit; 2010.
45. Koopmanschap MA, Rutten FFH, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. Journal of Health Economics. 1995; 14: 171-189.
46. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
47. Van der Does AJW. BDI–II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory—2nd edition [BDI–II-NL: The Dutch version of the Beck Depression Inventory—2nd edition]. Lisse: Harcourt Test Publishers, 2002
48. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. The British journal of psychiatry: the journal of mental science. 2002; 180: 461-464.
49. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychological medicine. 1983; 13: 595-605.
50. De Beurs E. Brief Symptom Inventory. Handleiding. Leiden: PITS; 2006.
51. Pearlin LI, Schooler C. The structure of coping. Journal of health and social behaviour. 1978; 19: 2-21.
52. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. *Psychother Res.* 2006; 16:12–25.
53. Stinckens N, Ulburghs A, Claes L. De werkalliantie als sleutelelement in het therapiegebeuren: Meting met behulp van de WAV-12, de Nederlandstalige versie van de Working Alliance Inventory - The working alliance as a key element in therapy: Measurement using the WAV-12, the Dutch shortened version of the Working Alliance Inventory. *Tijdschr voor Klin Psychol.* 2009; 39: 44–60.
54. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: development of a general scale. Evaluation and program planning. 1979; 2: 197-207.
55. De Brey H. A cross-national validation of the Client Satisfaction Questionnaire: the Dutch experience. *Eval Program Plann.* 1983; 6:395–400.
56. Brooke J. SUS: a quick and dirty usability scale. In: Jordan PW, Thomas B, Weerdmeester BA, McClelland IL, editors. Usability Evaluation in Industry. London: Taylor & Francis Ltd, 1996. P. 189-194.
57. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the System Usability Scale. Int J Hum Comput Interact. 2008; 24: 574–594.
58. Glick HA. Sample size and power for cost-effectiveness analysis (part 1). Pharmacoeconomics. 2011; 29: 189-198.
59. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, Orlewska E, Watkins J, Trueman P. Principles of good practice for budget impact analysis: report of the ISPOR

Task Force on good research practices-budget impact analysis. Value Health. 2007; 10: 336-347.

60. Efron B, Tibshirani RJ. (1993). An Introduction to the Bootstrap. New York: Chapman & Hall; 1993.
61. Cohen J. Statistical Power Analysis for the Behavioral Sciences (revised Edition). Hillsdale, New Jersey: Lawrence Erlbaum Associates, Inc; 1988.


4

Chapter 4

Acceptability, effectiveness and cost-effectiveness of blended versus face-to-face cognitive behavioral therapy for anxiety disorders in specialized mental health care: A 15-week randomized controlled trial with 1-year follow-up

Published as:
Romijn G, Batelaan N, Koning J, Balkom A Van, Leeuw A de, Benning F, Hakkaart van Roijen L, Riper H (2021). Acceptability, effectiveness and cost-effectiveness of blended cognitive-behavioural therapy (bCBT) versus face-to-face CBT (ftfCBT) for anxiety disorders in specialised mental health care: A 15- week randomised controlled trial with 1-year follow-up.
PLoS ONE 16 (11): e0259493

Abstract

Background: Anxiety disorders are highly prevalent and cause substantial economic burden. Blended cognitive behavioral therapy, which integrates Internet-based CBT and face-to-face CBT, is an attractive and potentially cost-saving treatment alternative to conventional CBT for patients with anxiety disorders in specialized mental health care. However, little is known about the effectiveness of blended CBT in routine care. We examined the acceptability, effectiveness and cost-effectiveness of blended CBT versus face-to-face CBT in outpatient specialized care to patients with panic disorder, social anxiety disorder and generalized anxiety disorder.

Methods and findings: Patients with anxiety disorders were randomized to blended CBT (n = 52) or face-to-face CBT (n = 62). Acceptability of blended CBT and face-to-face CBT were evaluated by assessing treatment preference, adherence, satisfaction and therapeutic alliance. Costs and effects were assessed at post-treatment and one-year follow-up. Primary outcome measure was the Beck Anxiety Inventory (BAI). Secondary outcomes were depressive symptoms, general psychopathology, work and social adjustment, quality of life and mastery. Incremental cost-effectiveness ratios (ICERs) were computed from societal and healthcare perspectives by calculating the incremental costs per incremental quality-adjusted life year (QALY). No significant differences between blended CBT and face-to-face CBT were found on acceptability or effectiveness measures at post-treatment (Cohen's d between-group effect size on BAI = 0.15, 95% CI −0.30 to 0.60) or at one-year follow-up (d = −0.38, 95% CI −0.84 to 0.09). The modelled point estimates of societal costs (blended CBT €10945, face-to-face CBT €10937) were higher and modelled point estimates of direct medical costs (blended CBT €3748, face-to-face CBT €3841) were lower in blended CBT. The acceptability curves showed that blended CBT was expected to be a cost-effective intervention. Results should be carefully interpreted due to the small sample size.

Conclusions: Blended CBT appears an acceptable, clinically effective and potentially cost-saving alternative option for treating patients with anxiety disorders. Trials with larger samples are needed to further investigate cost-effectiveness.

Trial registration: Netherlands Trial Register: NTR4912.

Background

Anxiety disorders are highly prevalent, and they are associated with considerable individual suffering and a high economic burden [1–4]. The disorders can be treated effectively with cognitive behavioral therapy (CBT) [5,6]. Despite the demonstrated effectiveness of CBT, fewer than half of the people with anxiety disorders receive appropriate treatment [7]. Reasons for undertreatment include stigmatisation, lack of trained therapists and the costs of therapy [8].

One strategy to expand access to evidence-based therapy while lowering treatment costs could be Internet-delivered CBT. Patients receiving Internet-delivered CBT usually work their way through an online modularised programme, with or without online therapist assistance [9]. Internet-delivered CBT has been found effective for several anxiety disorders

[10–13], and there are indications for its cost-effectiveness [14]. However, most evidence thus far derives from research outside routine clinical care settings. It has not been established that the promising results from those effectiveness studies can be extrapolated to samples in routine care. For example, in a recent meta-analysis [12], a large effect size (g = 0.79) was found for anxiety symptom reduction by Internet-delivered CBT as compared with waitlisted controls in samples recruited from the community, while a small effect size (g = 0.28) was found in the same comparison in routine care populations. A possible explanation for the discrepancy was the greater treatment adherence in self-referred samples recruited from the community and the stricter exclusion criteria in studies with such samples.

The low uptake of Internet-delivered CBT in routine care complicates the investigation of effectiveness in real-world settings. Reported reasons for therapists' reluctance to use Internet-delivered CBT are their concerns about the therapeutic relationship [15] and low treatment adherence, especially in patients with high symptom severity [16,17]. Blended CBT combines Internet-delivered CBT and face-to-face CBT into a single standardised treatment protocol [18] and could potentially alleviate some of the aforementioned limitations associated with Internet-delivered CBT, while partly or fully preserving the ad-vantages. It could help provide an attractive, and potentially cost-saving, treatment alternative for use in conventional mental health care settings. For one thing, blended CBT has been found to be better received by both providers and patients than Internet-delivered CBT, because the face-to-face contact in the blended format makes the treatment more personal, better addresses the needs of patients with complex symptomatology, and may help improve adherence rates [15,19–21]. A further possible advantage is that online components can be integrated into routine practice more gradually [22], making the blended format easier than Internet-delivered CBT to adopt for application in routine care.

Although blended CBT thus seems a promising alternative to both Internet-delivered CBT and face-to-face CBT, little is known so far about the clinical and cost benefits of blended interventions for anxiety disorders. In a feasibility randomized controlled trial (RCT) comparing blended CBT (n = 18) with face-to-face CBT (n = 18) for panic disorder, no difference was found between blended CBT and face-to-face CBT in reducing anxiety symptoms [23].

As blended CBT could possibly reduce therapist time [24] and improve self-management competencies of patients in comparison with face-to-face CBT, providing blended CBT to patients with severe anxiety disorders in specialized mental health care might lead to equal clinical effectiveness results at lower treatment costs. We thus hypothesised that blended CBT is more cost-effective than face-to-face CBT. We undertook a randomized controlled trial to investigate the acceptability and the clinical and cost-effectiveness of blended CBT for patients with panic disorder (PD), social anxiety disorder (SAD) and generalized anxiety disorder (GAD) in outpatient specialized mental health care. The current paper describes the acceptability, the post-treatment and 12-month clinical effectiveness, and the 12-month cost-effectiveness of blended CBT versus face-to-face CBT from both a societal and a healthcare perspective.

Methods

Study design and participants

The study design was a parallel-group randomized controlled trial. The purpose was to assess acceptability, effectiveness and cost-effectiveness of blended CBT compared with face-to-face CBT in patients with panic disorder, social phobia or generalized anxiety disorder in routine specialized mental health care. Assessments took place at post-treatment and at one-year follow-up, respectively 15 and 52 weeks after baseline. Patients who are referred to specialized mental health care in the Netherlands are suffering from serious mental disorders [25]. Hence, participants were likely to have received psychological treatment within primary care before they were enrolled in this trial. Patients in both treatment conditions were allowed to receive other supporting therapy after the intervention.

Participant inclusion criteria were (i) age 18 or older and (ii) satisfaction of the DSM-IV criteria for panic disorder (with or without agoraphobia), social anxiety disorder or generalized anxiety disorder, as diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [26], or the Mini-International Neuropsychiatric Interview, Plus version (MINI-Plus) [27,28]. Exclusion criteria were (i) inadequate proficiency in Dutch, (ii) lack of e-mail address or computer with Internet access and (iii) presence of a psychotic or bipolar disorder, substance dependence or a high risk for suicide. Psychotropic medication use was al-lowed.

A detailed study protocol has been published elsewhere [29]. The protocol was approved by the Medical Ethics Committee of the Vrije Universiteit Medical Centre, Amsterdam (registration number 2015.073), and registered in the Netherlands Trial Register (NTR4912). The study protocol and supporting CONSORT checklist and CHEERS checklist for this trial are available as supporting information.

Recruitment

Recruitment took place between November 2015 and July 2017 at outpatient departments of four specialized mental health care centres in the Netherlands. Mental health professionals who conducted the therapy intake session requested feasible patients' permission to be contacted by one of the researchers. The researcher briefed interested patients about the study, sent them all relevant information on the trial, and invited them for the baseline diagnostic interview (face-to-face or by telephone). For study inclusion, the primary diagnosis was to be confirmed in that interview by a research assistant using the MINI-Plus or SCID-I. Any comorbid DSM-IV diagnoses were also assessed with the MINI-Plus or SCID-I. Written informed consent was obtained from all participants before baseline assessment and randomization.

Randomization

After the baseline assessment, the included participants were randomly allocated to either blended CBT or face-to-face CBT by an independent researcher using a computer-generated

block randomization table. Randomization was stratified across the four research sites. Due to the nature of the intervention, patients and therapists could not be blinded to treatment allocation.

Interventions

Cognitive-behavioral therapy (CBT) was provided in both treatment conditions, including evidence-based components for treatment of anxiety disorders: psychoeducation, cognitive therapy, exposure and relapse prevention [5,6,25]. The treatment protocols were based on the standard Dutch treatment protocols [30]. For the blended variants, face-to-face and online sessions were integrated into a single blended treatment protocol for each disorder.
Therapists taking part in the study delivered therapy to patients in both treatment conditions. All therapists had formal training and experience in delivering CBT and had received training in the delivery of the blended format.

For the three primary diagnoses, three different treatment protocols were used. In the event of comorbid anxiety disorders, the protocol of choice was based on the patient's most prominent disorder, as established during the therapy intake session. The treatment sessions contained psychoeducation (explanation of treatment rationale and general procedures in cognitive therapy), cognitive therapy (examination of relationships between thoughts, emotions and behavior), exposure tasks (graded exposure to feared situations) and relapse prevention (identification and adoption of strategies to prevent anxiety symptoms from reoccurring). Cognitive therapy for PD and SAD focused on reinterpreting the causes and consequences of anxiety symptoms. The protocol for GAD consisted of metacognitive therapy, which identifies underlying metabeliefs about worrying and develops more adaptive meta-beliefs, since GAD is known to respond only modestly to conventional CBT [31].

The blended CBT delivery consisted of 15 weekly alternating face-to-face sessions (8) and online sessions with asynchronous therapeutic feedback (7). Online sessions were provided on a web-based treatment platform (Minddistrict, www.minddistrict.com), accessible through password-protected accounts. Online sessions contained text-based information and videos in which a therapist explained the theory, followed by exercises and homework assignments with examples from fictional patients. Feedback involved text-based messages from the therapist about the content of the online exercises performed by the patient and about treatment progress. face-to-face CBT entailed 15 weekly face-to-face sessions with similar content to the sessions of the blended CBT protocol.

Measures

Online questionnaires were administered at baseline, at week 7 (mid-treatment), at week 15 (post-treatment) and at one-year follow-up (see Appendix 1 for an overview of measures administered at each assessment interval). All questionnaires were self-administered, except for the diagnostic interview at baseline. The Dutch versions of the questionnaires were used. Our original study protocol specified that follow-up data would be collected after 67 weeks, one year after the post-treatment assessment, but for pragmatic reasons (funder

requirements in terms of final deadline), the time frame was adjusted to 52 weeks. Furthermore, to reduce burden on participants, quality of life was measured only by the EuroQol (EQ-5D-5L) [32] and not by the Short Form Health Survey (SF-36) [33] as well as both measure quality of life and anxiety severity was measured only by the Beck Anxiety Inventory (BAI) and not by the disorder-specific questionnaires as the overall sample size would be too small for robust subgroup-analyses. That means the Short Form Health Survey (SF-36) and the disorder-specific questionnaires were not administered. These changes were made prior to trial commencement (see our published study protocol [29]).

Demographic characteristics such as age, gender, education and employment were collected at baseline. Diagnoses were assessed at baseline with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [26] or the Mini-International Neuropsychiatric Inter-view, Plus version (MINI-Plus) [27,28].

Acceptability

We distinguished four aspects of acceptability: treatment preference, treatment adherence, therapeutic working alliance and treatment satisfaction. Treatment preference was assessed by asking participants to indicate their preference for blended CBT or face-to-face CBT at baseline, prior to randomization. Treatment adherence concerns the extent to which participants were exposed to the content of the interventions, as measured in three ways: (i) the percentage of completed prescribed sessions; (ii) the percentage of participants that finished treatment, defined as completing at least 15 sessions as described in the protocol or drop-ping out due to remission; and (iii) the duration of treatment in weeks.

The Revised Short Version of the Working Alliance Inventory (WAI-SR) [34,35] was administered halfway through treatment to both patients and therapists to rate the quality of the therapeutic alliance. The WAI-SR has excellent psychometric properties [35]. To evaluate treatment satisfaction at post-treatment, we administered the Client Satisfaction Ques-tionnaire-8 (CSQ-8) [36,37] and, additionally for the participants randomized to blended CBT, the System Usability Scale (SUS) [38,39]. Both the CSQ-8 and the SUS scales have demonstrated reliability and validity [37,39].

Effectiveness

Clinical outcome variables were assessed at baseline, at post-treatment (15 weeks) and at one-year follow-up 52 weeks after baseline. The primary clinical outcome was presence and severity of anxiety symptoms, as assessed with the Beck Anxiety Inventory (BAI) [40]. It contains 21 questions and total scores range between 0 and 63, with higher scores indicating more anxiety. The BAI is a reliable and well validated self-rated measure of anxiety symptoms [41].

Secondary clinical outcome variables included depressive symptoms, general psychopathology, mastery, social and work functioning, and quality of life, likewise assessed at baseline, post-treatment and follow-up. Presence and severity of depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II) [42,43], which has highly

acceptable psychometric properties [42]. Severity of general psychopathology was evaluated by the Brief Symptom Inventory (BSI) [44,45], whose psychometric properties are good [45]. The five-item version of the Mastery Scale [46] was administered to assess perceived control of a person's own life; it is a psychometrically valid instrument [46]. The Work and Social Adjustment Scale (WSAS), with adequate psychometric properties [47], is a measure of impaired functioning; it assesses the impact of a person's mental health problems on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships.

Quality of life

To estimate utilities the EuroQol (EQ-5D-5L) was administered [32]. We applied the Dutch tariff [48] to calculate the utilities. The EuroQol consists of five questions that gauge mobility, self-care, daily activities, pain and mood. It is the preference-based generic instrument for measuring health-related quality of life (HR-QoL) that is recommended by the Dutch guidelines for economic evaluations in healthcare and it has good psychometric properties [49]. Quality-adjusted life-years (QALYs) were calculated using the area-under-the-curve method (AUC) [50]. The health state descriptions were linked to empirical valuations of the Dutch general public, allowing utilities to be computed.

Costs

Costs were assessed at baseline, post-treatment and one-year follow-up using the Treatment Inventory Cost in Psychiatric Patients instrument (TiC-P) [51]. Costs can be determined from several perspectives. In this study we calculated costs for both the healthcare perspective (including direct medical costs) and the societal perspective (including direct medical costs, patient costs and productivity costs). Direct medical costs consist of costs for the use of healthcare services; patient costs consist of travel costs; productivity costs include costs arising from absenteeism and presenteeism.

In the TIC-P, a maximum recall period of 15 weeks was used and cumulative costs over the one-year study period were estimated using linear interpolation. In accordance with the TiC-P manual, a specific item on the service use accountable to the blended CBT intervention was added to the default TiC-P. Direct medical costs, patient costs and productivity costs were val-ued using Dutch indexed standard reference prices of 2018 (see Appendix 2) [52]. The friction cost method was applied to estimate productivity losses in paid work [53].

Sample size and power

The trial was powered to investigate the joint distribution of costs and treatment effects [29]. We aimed to include 156 participants, with 78 in each condition, based on a power of 0.80 calculated by using the formula of Glick [54].

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences version 24.0 (IBM Corporation, Somers, NY, USA) and Excel (2013). The descriptive characteristics of the blended CBT and face-to-face CBT groups and differences between study dropouts and study completers were compared using t-test for continuous variables and chi-square test for pro-portions.

Acceptability

Acceptability outcomes (treatment preference, treatment adherence, therapeutic working alliance, treatment satisfaction) were compared using t-test for continuous variables and chi-square test for proportions.

Effectiveness

Clinical outcomes were analysed on the basis of the intention-to-treat (ITT) principle. Linear mixed model (LMM) analyses with restricted maximum likelihood (REML) were conducted to evaluate differences in symptom reduction between the blended CBT and face-to-face CBT groups at post-treatment and one-year follow-up. The linear mixed models were adjusted for baseline scores, because using analysis of covariance the estimate of the intervention effect is not affected by baseline differences and more statistical power to detect a treatment effect is achieved [55]. The LMM approach has the ability to handle missing data, as it uses all available data to estimate parameters for missing values and can account for the correlation between repeated measures [56]. A separate model was estimated for each of the out-come measures. A Bonferroni-Holm correction was applied to adjust for repeated comparisons, yielding a significance level of p = .01 (.05 / 5) [57].

Effect sizes (Cohen's d) were calculated both within and between groups from estimated means and observed pooled standard deviations. The within-group effect size was computed as d = Meandiff / SDdiff, where Meandiff is the mean difference between the values at pre-test and at post-test or follow-up and SDdiff = √(SD2pre + SD2post − 2rSDpreSDpost), with r being the correlation between the pre-test and the post-test or follow-up values. The between-group effect size was computed as d = Meandiff / SDpooled, where Meandiff is the mean difference between blended CBT scores and face-to-face CBT scores.

Cost-effectiveness

Yearly costs and QALYs were modelled using generalized linear models (GLM), that can manage skewness of data [58]. Missing utility values and costs at each time point were imputed using multiple imputation by predictive mean matching [59,60]. For the estimation of costs, a log link and gamma family were used adjusting for age and baseline costs. For the estimation of QALYs a log link and gaussian family were used adjusting for age and baseline utility. The cost-effectiveness analysis was conducted by calculating the incremental costs per incremental QALY over the one-year follow-up period, resulting in the incremental cost-effectiveness ratio (ICER). The formula (C1-C2)/(E1-E2) was used, where (C1-C2) is the

difference in costs between blended CBT and face-to-face CBT, and (E1-E2) is the difference of the average effectiveness of blended CBT and face-to-face CBT [61].

The ICER was estimated from a healthcare and societal perspective. The latter included the direct medical costs, patient costs and productivity costs, while the healthcare perspective is limited to the direct medical costs. Costs and effects are not discounted as the time-horizon of the current study did not exceeded 12 months follow-up.

Standard errors around the GLM coefficients were used to explore the uncertainty of the ICER. For this purpose, 10,000 populations were simulated using non-parametric bootstrap-ping. Cholesky decomposition [62] was used to retain the correlations between the parameters. The simulated results were plotted in a CE-plane [63], on which uncertainty around incremental costs and incremental effects was displayed graphically by the scatter of ICERs. From a cost-effectiveness perspective, the southeast quadrant indicates superior treatment effects and lower costs for blended CBT in comparison with face-to-face CBT. If the ICER falls into this quadrant this indicates dominance of blended CBT over face-to-face CBT and should lead to a positive reimbursement decision. The northwest indicates reduced treatment effects and higher costs for blended CBT, thus leading to a negative reimbursement decision. ICERs in the two remaining quadrants indicate either that blended CBT is less expensive but also less effective (southwest quadrant) or more effective but also more expensive (northeast quadrant). The cost-effectiveness of the latter depends on the threshold of the cost-effectiveness ratio. For the Netherlands the threshold is €20,000 to €80,000 depending on the severity of the disease. The uncertainty in the cost-effectiveness analysis was assessed using bootstrapping in Excel, with 10,000 iterations. This was expressed in a cost-effectiveness acceptability curve. The acceptability curve illustrates the probability that the cost-effectiveness ratio will be accepted for different cost limits [64].

Results

Study sample and attrition

A total of 281 participants were assessed by mental health professionals during the intake procedure; 129 eligible candidates were invited for a diagnostic interview and 114 were randomized to either blended CBT (n = 52) or face-to-face CBT (n = 62; for details, see Figure 1). Demographic data of the included participants are presented in Table 1. The mean age of participants was 36.3 years (SD 10.6, range 19 to 69) and 60.5% were female (n = 69). Most patients had panic disorder as primary diagnosis (54.4%).

The post-treatment assessments at 15 weeks were completed by 77 (67.5%) participants (blended CBT n = 34, face-to-face CBT n = 43) and the one-year follow-up assessments by 74 (64.9%) participants (blended CBT n = 34, face-to-face CBT n = 40). There was no significant difference in total study dropout between the two treatment groups, $\chi2$ (1) = 0.78, p = 0.781. We tested for significant differences in demographic variables, primary diagnosis or presence of comorbidity between those who completed all post-baseline

assessments and those who did not. Participants with missing data at one or more of those assessments (n = 51) were less likely to have a comorbid diagnosis, $\chi2$ (2) = 4.84, p = 0.028.

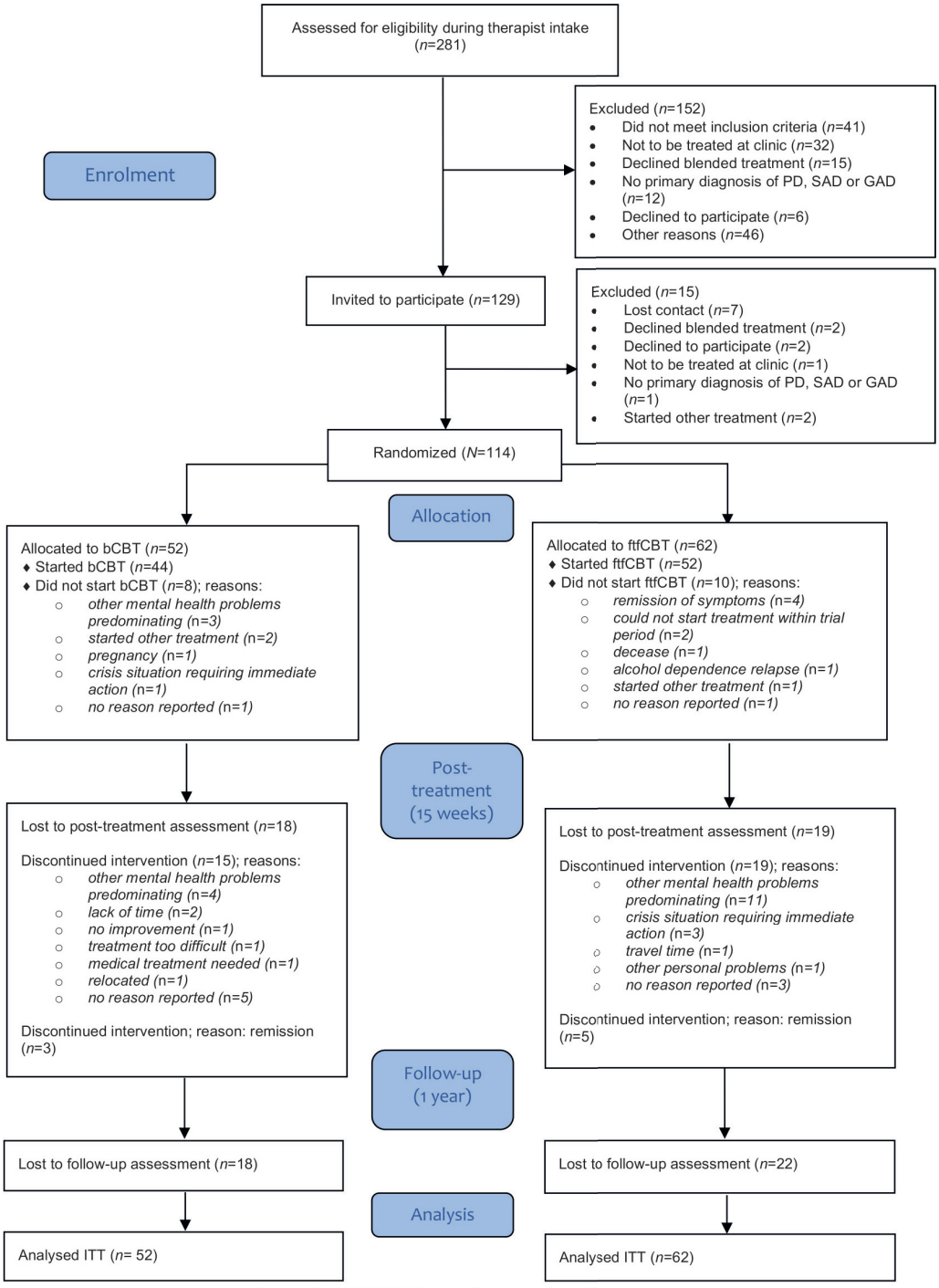


Figure 1. CONSORT flow diagram of participants

Table 1. Baseline characteristics of participants in blended CBT group and face-to-face CBT group

Characteristics	bCBT (*n*=52)	ftfCBT (*n*=62)	Total (*n*=114)
Demographics			
Age, mean (SD)	36.0 (10.4)	36.5 (10.9)	36.3 (10.6)
Female, n *(%)*	26 (50.0)	43 (69.4)	69 (60.5)
Higher education, [a] n *(%)*	16 (30.8)	14 (22.5)	30 (26.3)
Employed, n *(%)*	35 (67.3)	45 (72.6)	80 (70.2)
Student, n *(%)*	7 (13.5)	9 (14.5)	16 (14.0)
Born in Netherlands, n *(%)*	46 (88.5)	53 (85.5)	99 (86.8)
Taking psychotropic medication	29 (55.8)	38 (61.3)	67 (58.8)
Primary diagnosis, *n* (%)			
Panic disorder	27 (51.9)	35 (56.5)	62 (54.4)
Social anxiety disorder	12 (23.1)	13 (21.3)	25 (21.9)
Generalized anxiety disorder	13 (25.0)	14 (23.0)	27 (23.7)
Comorbidity, *n* (%)			
Any comorbid disorder	32 (61.5)	38 (61.3)	70 (61.4)
Anxiety disorders	16 (30.8)	15 (24.2)	31 (27.2)
Mood disorders	17 (32.7)	20 (32.3)	37 (32.5)
Other disorders	10 (19.2)	7 (11.3)	17 (14.9)

bCBT: blended cognitive-behavioral therapy; ftfCBT: face-to-face cognitive-behavioral therapy; comorbid anxiety disorders: social phobia, panic disorder, agoraphobia, generalized anxiety disorder; comorbid mood disorders: major depressive disorder, dysthymia; other comorbid disorders: posttraumatic stress disorder, obsessive-compulsive disorder, eating disorder. [a] Bachelor's equivalent or higher.

Acceptability

Queried prior to randomization, patients expressed a slight preference for blended CBT (54.4%) over face-to-face CBT (45.6%). The percentages with a blended CBT preference (56.5% in the face-to-face CBT treatment group, 51.9% in the blended CBT group) did not differ significantly between the groups, $\chi2$ (1) = 0.23, p = 0.629.

Adherence in terms of the percentage of completed prescribed sessions was slightly but not significantly higher in the blended CBT group, at 67.4% compared with 61.6% for the face-to-face CBT group (t = −0.515, p = 0.608). Thirty-one patients (59.6%) in the blended CBT group and 32 patients (51.6%) in the face-to-face CBT group completed treatment (t = −0.795, p = 0.428). Treatment duration was shorter in the blended CBT group, with an average of 14.4 weeks (range 0 to 56.4) com-pared with 16.1 weeks (range 0 to 67.7) for face-to-face CBT treatment (t = 0.796, p = 0.428).

The alliance assessment (WAI-SR) halfway through treatment was completed by 81 participants (71.1%) and 87 times (76.3%) by therapists. Participants in both groups reported high levels of working alliance on the WAI-SR, with a mean rating of 4.27 out of 5 (SD 0.69) in the blended CBT group and 4.25 (SD 0.51) in the face-to-face CBT group. Therapists' ratings were in a similar range, with scores of 4.32 (SD 0.37) in blended CBT and 4.24 (SD 0.56) in face-to-face CBT. We found no significant difference between blended CBT and face-to-face CBT in

terms of WAI patient ratings (t = −0.111, p = 0.912) nor WAI therapist ratings (t = −0.304, p = 0.762), indicating no difference in working alliance between groups.

On average, participants in both groups reported high levels of treatment satisfaction. The mean scores on the CSQ-8 were 25.61 out of 32 (SD 4.21, range 8 to 32) for the blended CBT group and 25.90 (SD 3.24) for the face-to-face CBT group, both lying between 'somewhat satisfied' (score 24) and 'very satisfied' (score 32). We found no significant difference between blended CBT and face-to-face CBT in treatment satisfaction (t = 0.320, p = 0.750).
The online treatment platform was evaluated by patients randomized to the blended condition at an 'above average' score of 69.11 (SD 19.32) on the SUS.

Effectiveness

Mean observed scores on primary and secondary clinical outcome measures at baseline, post-treatment and one-year follow-up are displayed in Table 2, accompanied by within-group and between-group effects. No statistically significant differences emerged between the blended CBT group and the face-to-face CBT group in terms of decreased anxiety severity, either at post-treatment (t = −0.715, p = 0.477) or at follow-up (t = 1.702, p = 0.093). Within-group effect sizes from baseline to post-treatment were d = 0.73 for blended CBT and d = 0.55 for face-to-face CBT and from baseline to follow-up d = 0.50 for blended CBT and d = 1.00 for face-to-face CBT.

Separate linear mixed model analyses revealed no significant effects of treatment condition at post-treatment or follow-up on secondary outcomes: depressive symptoms, general psychopathology, mastery, work and social functioning and quality of life. Within-group effect sizes at post-treatment and follow-up ranged from d = 0.13 to d = 0.98.

Table 2. Observed means and standard deviations for clinical outcome variables at baseline, post-treatment and one-year follow-up within each group, within-group effects and between-group effects based on estimated mean

		Blended CBT	Within-group effect size [a]		Face-to-face CBT	Within-group effect size [a]	Between-group comparison [b]	Between-group effect size [c]
Measure	***n***	**Mean (SD)**	**Cohen's *d* (95% CI)**	***n***	**Mean (SD)**	**Cohen's *d* (95% CI)**	***t* (*p*-value)**	**Cohen's *d* (95% CI)**
Primary outcome								
Anxiety (BAI)								
Baseline	51	27.90 (12.02)		62	27.15 (11.67)			
Post-treatment	34	17.18 (10.28)	0.73 (0.49, 0.97)	43	18.93 (11.55)	0.55 (0.34, 0.75)	−0.715 (0.477)	0.15 (−0.30, 0.60)
1-year follow-up	34	19.97 (13.12)	0.50 (0.25, 0.74)	40	14.28 (9.06)	1.00 (0.74, 1.26)	1.702 (0.093)	−0.38 (−0.84, 0.09)
Secondary outcomes								
Depression (BDI-II)								
Baseline	52	23.98 (12.17)		62	24.00 (10.26)			
Post-treatment	34	16.50 (11.63)	0.53 (0.30, 0.76)	42	18.69 (10.76)	0.42 (0.21, 0.62)	−0.801 (0.425)	0.16 (−0.30, 0.61)
1-year follow-up	32	15.69 (11.13)	0.72 (0.45, 0.98)	39	14.69 (9.44)	0.59 (0.36, 0.82)	0.203 (0.840)	−0.04 (−0.51, 0.43)
General psychopathology (BSI)								
Baseline	52	1.43 (0.72)		62	1.36 (0.67)			
Post-treatment	34	0.97 (0.63)	0.67 (0.44, 0.91)	42	0.95 (0.66)	0.50 (0.29, 0.70)	−0.130 (0.897)	0.02 (−0.43, 0.48)
1-year follow-up	32	1.00 (0.66)	0.63 (0.37, 0.89)	39	0.75 (0.61)	0.98 (0.72, 1.24)	1.339 (0.185)	−0.27 (−0.74, 0.20)
Mastery (Mastery Scale)								
Baseline	52	14.90 (4.45)		62	14.26 (4.39)			
Post-treatment	34	16.12 (4.20)	−0.26 (−0.48, −0.05)	42	16.05 (4.70)	−0.42 (−0.6, −0.22)	−0.290 (0.773)	0.05 (−0.40, 0.51)
1-year follow-up	32	15.56 (4.96)	−0.13 (−0.37, 0.10)	39	17.38 (4.78)	−0.63 (−0.86, −0.40)	−2.329 (0.023)	0.48 (0.01, 0.96)
Work and social adjustment (WSAS)								
Baseline	52	23.00 (10.22)		62	23.90 (9.11)			
Post-treatment	34	17.47 (9.61)	0.65 (0.41, 0.88)	42	18.95 (10.02)	0.35 (0.16, 0.55)	−0.751 (0.455)	0.15 (−0.31, 0.60)
1-year follow-up	32	16.34 (11.21)	0.66 (0.40, 0.92)	39	17.97 (10.77)	0.48 (0.26, 0.71)	−0.775 (0.441)	0.17 (−0.03, 0.64)
Quality of life (EQ-5D utility scores)								
Baseline	52	0.55 (0.28)		62	0.53 (0.26)			
Post-treatment	34	0.69 (0.20)	−0.47 (−0.69, −0.25)	43	0.61 (0.25)	−0.28 (−0.47, −0.08)	1.235 (0.220)	−0.24 (−0.69, 0.21)
1-year follow-up	34	0.69 (0.27)	−0.40 (−0.64, −0.16)	40	0.71 (0.25)	−0.60 (−0.83, −0.37)	−0.498 (0.620)	0.11 (−0.35, 0.56)

* Note, Bonferroni-Holm corrected significance level is $p = .01$

Abbreviations: bCBT: blended cognitive-behavioral therapy; ftfCBT: face-to-face cognitive-behavioral therapy; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II; BSI: Brief Symptom Inventory; WSAS: Work and Social Adjustment Scale; EQ-5D-5L: EuroQol.

[a] Within-group effect sizes were calculated based on estimated means from the linear mixed model using raw differences.

[b] Between-group comparisons were based on estimated means from the linear mixed model with baseline adjustment.

[c] Between-group effect sizes were calculated based on estimated means from the linear mixed model with baseline adjustment.

Cost-effectiveness

The results from the cost-effectiveness analyses are presented in Table 3. Multiple imputation (cost data: 35.1% imputed, QALY data: 32,7% imputed) followed by modelled simulations yielded average direct medical costs of €3758 for blended CBT and €3841 for face-to-face CBT over the one-year study period. Direct medical costs were statistically significantly lower in the blended CBT group (mean -83,78, 95% CI -96,96 to -70,61, p<0.001). Societal costs were €10945 for blended CBT and €10937 for face-to-face CBT. Differences were not statistically significant (mean 26,46, 95% CI -26,46 to 42,71, p>0.1). Total costs based on available data over the treatment period and the one-year follow-up period are included in Appendix 3. The average QALYs over the one-year study period were 0.66 for blended CBT and 0.62 for face-to-face CBT. QALYs were statistically significantly higher in the blended CBT group (mean 0.037, 95% CI 0.036 to 0.038, p<0.001). This resulted in a dominant ICER from the healthcare perspective (€-2257 per QALY) and an ICER of €219 per QALY from the societal perspective.

Table 3. Results of cost-effectiveness analyses

	Incremental costs, Eur, (95% CI)	**Incremental effects, quality-adjusted life year (95% CI)**	**ICER, mean**	**Distribution over the ICER plane (%)**			
				NE	NW	SE	SW
Healthcare perspective	€-83,78 (-96,96 to -70,61)	0.037 (0.036 to 0.038)	Dominant (€-2257)	37,6%	6,8%	46,6%	9,0%
Societal perspective	€8,13 (-26,46 to 42,71)	0.037 (0.036 to 0.038)	€219	41,8%	7,7%	42,3%	8,2%

* Note, ICER: incremental cost-effectiveness ratio. Plane distribution: NE: more expensive, more effective; NW: more expensive, less effective; SE: less expensive, more effective; SW: less expensive, less effective.

Uncertainty in cost and effect estimates is shown in cost-effectiveness planes (CE planes, Figures 2a and 2b). The CE planes show that the greatest numbers of ICERs were situated in the southeast quadrant of the CE plane, both in the healthcare perspective (46.6%) and in the societal perspective (42.3%), indicating lower costs for blended CBT as well as a superior effect in terms of quality of life. Another 37.6% were in the northeast quadrant from the healthcare perspective and 41.6% from the societal perspective respectively. From the health care perspective 6.8% and 9.0% of the estimates were in respectively in the north- and southwest quadrant. From the societal perspective these figures were 7.7% and 8.2%.

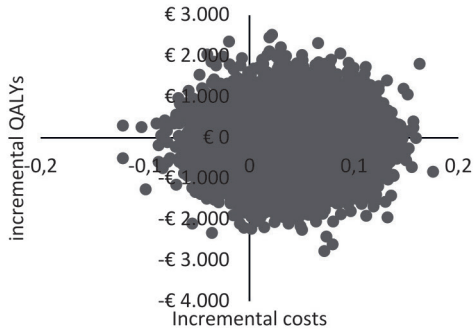


Figure 2a. CE plane for healthcare perspective

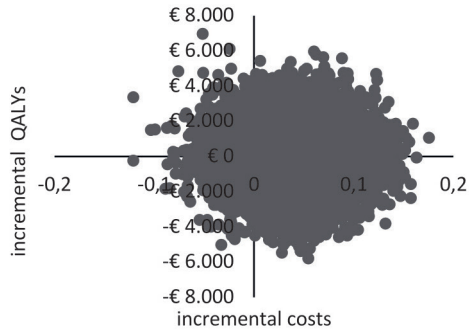


Figure 2b. CE plane for societal perspective

Determining the acceptability of the treatments, we calculated the proportion of ICERS that were below the threshold of 20,000 and 80,000 per QALY. The threshold is the willingness of society to pay and was varied as this is the common range for the Netherlands. The thresholds and the proportion of ICERS were subsequently plotted in the cost acceptability curve, see Figure 3. The figure shows that from a health care perspective, at a threshold of 20,000 Euro/QALY, the probability that the ratio is acceptable is more than 80%. Taking a societal perspective, the percentage that the intervention is acceptable was 67%. At a threshold of 80,000 Euro/QALY the intervention was acceptable more than 80% from both perspectives.

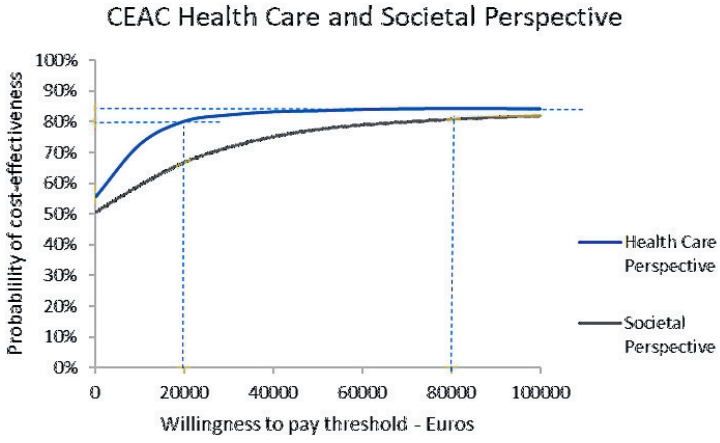


Figure 3. Cost acceptability curves from the societal perspective and health care perspective

Discussion

Blended treatment for anxiety disorders, which integrates face-to-face therapy and Internet-based therapy, has not yet been rigorously studied. To our knowledge, RCTs investigating effectiveness and costs are lacking. This study is the first to assess the acceptability, effectiveness and cost-effectiveness of blended CBT vis-à-vis face-to-face CBT in outpatients

receiving specialized mental health care who have been diagnosed with panic disorder, social anxiety disorder or generalized anxiety disorder.

Our findings on acceptability indicate that blended CBT is an acceptable treatment option for patients in specialized mental health care in terms of treatment preference, adherence, therapeutic alliance and treatment satisfaction. Over half (54.9%) of the participants would have preferred to start with blended CBT above face-to-face CBT. Although that is the treatment preference of patients who consented to take part in the current study, and hence not a fully representative finding for all patients in specialized mental health care, it does reveal that a considerable desire for the blended treatment format exists in that population. Therapeutic alliance and treatment satisfaction were high for both blended CBT and face-to-face CBT patients, and treatment adherence rates were comparable for both groups.

With regard to effectiveness in reducing anxiety symptoms, we found no significant differences between blended CBT and face-to-face CBT at post-treatment (t = −0.715, p = 0.477) nor at one-year follow-up (t = 1.702, p = 0.093). Both groups exhibited moderate to large within-group effect sizes (range of *d:* 0.50 to 1.00). Moreover, no significant differences between the groups were found in terms of effects on depressive symptoms, general psychopathology, sense of control (mastery), work and social functioning or quality of life, with within-group effect sizes ranging from small to large (range of *d:* 0.13 to 0.98).

In the current study online sessions partially replaced face-to-face sessions in the blended treatment. Other studies have investigated Internet-delivered CBT applied as an adjunctive to face-to-face CBT.

Our clinical findings appear to be in line with results from those studies. For example, Nordgreen and colleagues conducted an RCT (N = 173) whereby Internet-delivered CBT and face-to-face CBT for panic disorder and social anxiety disorder were combined in a stepped-care format, with a face-to-face psychoeducation session as first step, online treatment (9 or 10 sessions) as second step and face-to-face treatment (12 sessions) as final step [65]. The stepped-care variant was compared with face-to-face CBT (12 sessions). No significant differences in the reductions of anxiety symptoms and depressive symptoms were found between the groups at post-treatment and one-year follow-up, and within-group effect sizes were moderate to large. Comparability with our study is limited, however, as the stepped-care format consisted of Internet-delivered CBT as an add-on prior to face-to-face CBT. Moreover, treatment attrition in the stepped-care group was high (41.2%), with the majority dropping out before starting the face-to-face treatment, meaning that they only received online CBT. In a pilot study (N = 36) by Bruinsma and colleagues [23], a combination of 9 face-to-face CBT sessions supplemented with 3 Internet-delivered CBT sessions was compared with 12-session face-to-face CBT. They found no significant between-group differences at post-treatment in terms of improvement rates on panic-related symptoms and general functioning, with moderate to large within-group effect sizes.

Our cost analysis showed that societal costs were relatively larger than direct medical costs in both groups. This may be due to relatively low treatment costs and a large proportion

of patients of working age. This finding is in line with literature that showed that productivity costs are commonly responsible for the majority of the total costs [66,67]. These results highlight the substantial societal burden of anxiety disorders and the importance of making CBT for anxiety disorders more accessible. Further findings have shown that the costs for providing treatment would be compensated within two to five years by increased productivity resulting from the intervention [68].

The acceptability curves in the current study revealed that blended CBT was expected to be a cost-effective intervention. While blended CBT point estimates suggest slightly lower healthcare and slightly higher societal costs than face-to-face CBT over the one-year study period, the probabilistic results suggest a high probability of cost-effectiveness taking a threshold of €20.000 from both perspectives. In contrast, in a naturalistic study by Kenter and colleagues treatment time and costs increased for blended CBT relative to face-to-face CBT. In this study, no treatment protocol or clear guidelines on how to apply blended treatment were available and therapists turned out to have provided online sessions on top of face-to-face sessions resulting in longer treatment durations. This marked contrast to our trial possibly explains the difference in outcomes.

A strength of this study is that it is the first randomized controlled trial to explore acceptability, effectiveness and cost-effectiveness by comparing equal-intensity blended CBT and face-to-face CBT for anxiety disorders in routine outpatient specialized mental health care. In addition, participants in our study appear to be a clinically representative sample, in view of the large proportion of patients with comorbid disorders, lower education levels and severe anxiety symptoms at baseline, in comparison with self-referred samples recruited from the community [12]. Clinical representativeness is also reflected by the high productivity costs and the low scores on measurements of work, social functioning and quality of life; disability and decreased productivity are common among patients with severe anxiety disorders [70,71]. Although patients in both groups exhibited improvement on these scores at post-treatment and follow-up, the scores remained relatively low in comparison with those in the general healthy population [47,72]. That further demonstrates the severity and complexity of problems in the current study sample.

Some limitations are associated with the present study. First, because the sample size was smaller than expected, only initial indications of the cost-effectiveness of blended CBT in comparison with face-to-face CBT could be explored. Due to financial and time limits, only 114 participants rather than the intended 156 were included. However, it might be noted that such a sample size is considerable for routine specialized mental health care populations. Sample size and power challenges are common issues in trials investigating both clinical and cost-effectiveness [73]. In line with recommendations for dealing with such issues [74], the uncertainty was presented in cost-effectiveness planes. Another limitation lies in the substantial study dropout rate (35.1% at one-year follow-up), which was not considered in the power calculation. This dropout seems to reflect the reality of trials conducted in routine mental health care, as comparable rates were found in earlier clinical trials comparing Internet-delivered CBT with face-to-face CBT [65,75–78]; it could not be prevented by our e-

mail and telephone reminders. To handle missing data, a linear mixed model was used to analyse clinical effectiveness, and imputations were used for the cost-effectiveness analyses.

In addition, participants and therapists could not be blinded to treatment allocation. That was inevitable given the nature of this trial, but it may have affected results. For example, participants who know they are in the 'experimental condition' are more likely to provide biased effectiveness assessments than blinded participants; blinded therapists are less likely than unblinded therapists to provide additional treatment interventions [79].

Finally, we used the EQ-5D for measuring quality of life. In recent years, the usefulness of the EQ-5D to measure mental health related quality of life has been questioned [80,81]. Other questionnaires are available that include more dimensions of quality of life relevant to populations of people with mental health problems. For example, the more recently developed Assessment of Quality of Life – Eight Dimension Scale (AQoL-8D) [82] might serve as an alternative for the EQ-5D. However, validity of this instrument has not been tested in the Dutch population, which is one of the reasons that the EQ-5D is the recommended questionnaire for economic evaluations in the Dutch context [82]. Furthermore, the EQ-5D is reasonably responsive in patients with anxiety disorders [84] and thus seems suitable in the current study. Nevertheless, other available instruments to evaluate mental health related quality of life should be considered in future research, especially when research is focusing on mental disorders such as schizophrenia and bipolar disorder [85], and validation of the AQoL-8D for the Dutch population would be desirable.

In sum, our results suggest that blended CBT is an acceptable approach for patients with anxiety disorders in specialized mental health care settings. We found no indications that its clinical effectiveness differs from that of face-to-face CBT. Moreover, blended CBT is expected to be a cost-effective alternative to face-to-face CBT.

Acknowledgements

We are very grateful for the contribution of all research assistants and therapists to this study, and for the cooperation of the trial participants and the participating outpatient clinics: Altrecht, GGZ inGeest, GGZ Oost-Brabant and GGZ Noord-Holland-Noord. We also thank Robin Kok for his advice on the study protocol and Adriaan Hoogendoorn for his advice on the data analysis. Finally, we would like to thank Tim Kanters for his support on the cost-effectiveness analyses.

References

1. Kessler RC, Ruscio AM, Shear K, Wittchen HU. Epidemiology of anxiety disorders. Curr Top Behav Neurosci. 2010;2: 21–35. doi:10.1007/7854_2009_9
2. Mendlowicz M V. Quality of Life in Individuals With Anxiety Disorders. Am J Psychiatry. 2000;157: 669–682. doi:10.1176/appi.ajp.157.5.669

3. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: Implications for curative and preventive psychiatry. J Ment Health Policy Econ. 2006;9: 193–200.
4. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21: 655–679. doi:10.1016/j.euroneuro.2011.07.018
5. NICE. Generalised anxiety disorder and panic disorder in adults. Natl Inst Heal Clin Excell. 2011.
6. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. Clinical guideline 159. Available: http:// guidance.nice.org.uk/cg159. 2013. doi:10.1016/S0140-6736(08)60488-2 [doi]
7. Bijl R V, de Graaf R, Hiripi E, Kessler RC, Kohn R, Offord DR, et al. The prevalence of untreated mental disorders in five countries. Health Aff. 2003;22: 122–133. doi:10.1377/hlthaff.22.3.122
8. Andrade LH, Alonso J, Mneimneh Z, Wells JE, Al-Hamzawi A, Borges G, et al. Barriers to mental health treatment: Results from the WHO World Mental Health surveys. Psychol Med. 2014;44: 1303–1317. doi:10.1017/S0033291713001943
9. Riper H, Andersson G, Christensen H, Cuijpers P, Lange A, Eysenbach G. Theme issue on E-mental health: A growing field in internet research. Journal of Medical Internet Research. 2010. doi:10.2196/jmir.1713
10. Olthuis J V, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. Cochrane database Syst Rev. 2015;3: CD011565. doi:10.1002/14651858.CD011565
11. Adelman CB, Panza KE, Bartley CA, Bontempo A, Bloch MH. A meta-analysis of computerized cognitive-behavioral therapy for the treatment of DSM-5 anxiety disorders. J Clin Psychiatry. 2014;75: e695-704. doi:10.4088/JCP.13r08894
12. Romijn G, Batelaan N, Kok R, Koning J, van Balkom A, Titov N, et al. Internet-Delivered Cognitive Behavioral Therapy for Anxiety Disorders in Open Community Versus Clinical Service Recruitment: Meta-Analysis. J Med Internet Res. 2019;21: e11706. doi:10.2196/11706
13. Emmelkamp PMG. Technological innovations in clinical assessment and psychotherapy. Psychother Psychosom. 2005;74: 336–343. doi:10.1159/000087780
14. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med. 2015; 1–20. doi:10.1017/S0033291715001427
15. Topooco N, Riper H, Araya R, Berking M, Brunn M, Chevreul K, et al. Attitudes towards digital treatment for depression: A European stakeholder survey. Internet Interv. 2017;8: 1–9. doi:10.1016/j.invent.2017.01.001
16. Christensen H, Griffiths KM, Farrer L. Adherence in Internet intervention for anxiety and depression: Systematic review. J Med Internet Res. 2009;11: 1–16. doi:10.2196/jmir.1194

17. Kok RN, Beekman ATF, Cuijpers P, van Straten A. Adherence to a web-based pre-treatment for phobias in outpatient clinics. Internet Interv. 2017;9: 38–45. doi:10.1016/j.invent.2017.05.004
18. Riper H, Ballegooijen W Van, Kooistra L. Preventie & eMental-health. Onderzoek dat leidt, technologie die verleidt, preventie die bereikt en beklijft. Kennissynthese 2013 in opdracht van ZonMw. Amsterdam; 2013.
19. Titzler I, Saruhanjan K, Berking M, Riper H, Ebert DD. Barriers and facilitators for the implementation of blended psychotherapy for depression: A qualitative pilot study of therapists' perspective. Internet Interv. 2018;12: 150–164. doi:10.1016/j.invent.2018.01.002
20. Schuster R, Pokorny R, Berger T, Topooco N, Laireiter AR. The Advantages and Disadvantages of Online and Blended Therapy: Survey Study Amongst Licensed Psychotherapists in Austria. J Med Internet Res. 2018;20: e11007. doi:10.2196/11007
21. Erbe D, Psych D, Eichert HC, Riper H, Ebert DD. Blending face-to-face and internet-based interventions for the treatment of mental disorders in adults: Systematic review. J Med Internet Res. 2017;19. doi:10.2196/jmir.6588
22. van der Vaart R, Witting M, Riper H, Kooistra L, Bohlmeijer ET, van Gemert-Pijnen LJEWC. Blending online therapy into regular face-to-face therapy for depression: Content, ratio and preconditions according to patients and therapists using a Delphi study. BMC Psychiatry. 2014;14: 1–10. doi:10.1186/s12888-014-0355-z
23. Bruinsma A, Kampman M, Exterkate CC, Hendriks GJ. An exploratory study of 'blended' cognitive behavioural therapy (CBT) for patients with a panic disorder: results and patients' experiences. Tijdschr Psychiatr. 2016;58: 361–370.
24. Kaltenthaler E, Brazier J, Nigris E De, Tumur I, Ferriter M, Beverley C, et al. Computerised cognitive behaviour therapy for depression and anxiety update. 2006;10.
25. Dutch mental health guidelines (GGZ Richtlijnen) website. [cited 22 Dec 2018]. Available: http://www.ggzrichtlijnen.nl/angststoornissen
26. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York State Psychiatric Institute. 2002.
27. Sheehan D V., Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998. pp. 22–33. doi:10.1016/S0924-9338(99)80239-9
28. Van Vliet IM, De Beurs E. Het Mini Internationaal Neuropsychiatrisch Interview (MINI): Een kort gestructureerd diagnostisch psychiatrisch interview voor DSM-IV-en ICD-10-stoornissen. Tijdschr Psychiatr. 2007;49: 393–397.
29. Romijn G, Riper H, Kok R, Donker T, Goorden M, van Roijen LH, et al. Cost-effectiveness of blended vs. face-to-face cognitive behavioural therapy for severe anxiety disorders: study protocol of a randomized controlled trial. BMC Psychiatry. 2015;15: 311. doi:10.1186/s12888-015-0697-1

30. Keijsers GPJ, Minnen A van, Hoogduin CAL. Protocollaire behandelingen voor volwassenen met psychische klachten. Deel 1. [Manualized treatments for adults with psychological disorders, part 1]. 2010.
31. Durham RC, Allan T. Psychological treatment of generalised anxiety disorder. A review of the clinical significance of results in outcome studies since 1980. Br J Psychiatry. 1993. doi:10.1192/bjp.163.1.19
32. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16: 199–208. doi:10109801
33. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. J Clin Epidemiol. 1998. doi:10.1016/S0895-4356(98)00109-7
34. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the Working Alliance Inventory. Psychother Res. 2006;16: 12–25. doi:10.1080/10503300500352500
35. Stinckens N, Ulburghs A, Claes L. De werkalliantie als sleutelelement in het therapiegebeuren Meting met behulp van de WAV-12 , de Nederlandstalige verkorte versie van de Working Alliance Inventory. Tijdschr Klin Psychol. 2009;39: 44–60.
36. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: Development of a general scale. Eval Program Plann. 1979;2: 197–207. doi:10.1016/0149-7189(79)90094-6
37. De Brey H. A cross-national validation of the Client Satisfaction Questionnaire: The Dutch experience. Eval Program Plann. 1983;6: 395–400. doi:10.1016/0149-7189(83)90018-6
38. Brooke J. SUS - A quick and dirty usability scale. Usability Eval Ind. 1996;189: 4–7. doi:10.1002/hbm.20701
39. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. Int J Hum Comput Interact. 2008;24: 574–594. doi:10.1080/10447310802205776
40. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol. 1988;56: 893–897. doi:10.1037/0022-006X.56.6.893
41. Fydrich T, Dowdall D, Chambless DL. Reliability and validity of the beck anxiety inventory. J Anxiety Disord. 1992;6: 55–61. doi:10.1016/0887-6185(92)90026-4
42. Van der Does W. BDI-II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory-2nd edition. Lisse; 2002.
43. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev. 1988. doi:10.1016/0272-7358(88)90050-5
44. Derogatis LR. The Brief Symptom Inventory: An Introductory Report. Psychol Med. 1983;13: 595–605. doi:10.1017/S0033291700048017
45. Beurs EDE, Zitman FG. De Brief Symptom Inventory. Maandbl Geestelijke Volksgezond. 2006;61: 120–141.

46. Pearlin LI, Schooler C. The Structure of Coping. J Health Soc Behav. 1978;19: 2. doi:10.2307/2136319
47. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: A simple measure of impairment in functioning. Br J Psychiatry. 2002;180: 461–464. doi:10.1192/bjp.180.5.461
48. Versteegh M, M. Vermeulen K, M. A. A. Evers S, de Wit GA, Prenger R, A. Stolk E. Dutch Tariff for the Five-Level Version of EQ-5D. Value Heal. 2016;19: 343–352. doi:10.1016/j.jval.2016.01.003
49. Zorginstituut Nederland. Richtlijnen voor economische evaluatie. In: https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie.
50. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ. 1990.
51. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld MC, van der Feltz-Cornelis C, Tan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). Occup Environ Med. 2013;13: 217. doi:10.1136/oem.2004.013896
52. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Ned. 2015.
53. Koopmanschap MA, Rutten FFH, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ. 1995. doi:10.1016/0167-6296(94)00044-5
54. Glick HA. Sample size and power for cost-effectiveness analysis (Part 1). Pharmacoeconomics. 2011. doi:10.2165/11585070-000000000-00000
55. Vickers AJ, Altman DG, Vickers AJ, Altaian DG. Statistics Notes : Analysing Controlled Trials With Baseline And Follow Up Measurements Stable URL : https://www.jstor.org/stable/25227028 Linked references are available on JSTOR for this article : Statistics Notes Analysing controlled trials with baseli. 2001;323: 1123–1124.
56. Gueorguieva. Move over ANOVA? Arch Gen Psychiatry. 2011;61: 310–317.
57. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979.
58. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. Economic Evaluation in Clinical Trials. 2014. doi:10.1093/med/9780199685028.001.0001
59. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. Pharmacoeconomics. 2014. doi:10.1007/s40273-014-0193-3
60. MacNeil Vroomen J, Eekhout I, Dijkgraaf MG, van Hout H, de Rooij SE, Heymans MW, et al. Multiple imputation strategies for zero-inflated cost data in economic evaluations: which method works best? Eur J Heal Econ. 2016. doi:10.1007/s10198-015-0734-5

61. Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Methods for the Economic Evaluation of Health Care Programmes. 2005.
62. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford University Press, editor. New York; 2006. doi:10.1136/jech.2007.059576
63. Black WC. The CE Plane: A Graphic Representation of Cost-Effectiveness. Med Decis Mak. 1990. doi:10.1177/0272989X9001000308
64. Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: An example using data from a trial of management strategies for atrial fibrillation. BMC Health Serv Res. 2006;6: 1–8. doi:10.1186/1472-6963-6-52
65. Nordgreen T, Haug T, Ost L-G, Andersson G, Carlbring P, Kvale G, et al. Stepped Care Versus Direct Face-to-Face Cognitive Behavior Therapy for Social Anxiety Disorder and Panic Disorder: A Randomized Effectiveness Trial. Behav Ther. 2016;47: 166–183. doi:10.1016/j.beth.2015.10.004
66. Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do Productivity Costs Matter? Costs of Interventions Targeted at Depressive Disorders. Pharmoeconomics. 2011;29: 601–619.
67. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: Implications for curative and preventive psychiatry. J Ment Health Policy Econ. 2006.
68. Layard R, Clark DM, Knapp M, Mayraz G. Cost-benefit analysis of psychological therapy. Natl Inst Econ Rev. 2007;202: 90–98.
69. Kenter RMF, van de Ven PM, Cuijpers P, Koole G, Niamat S, Gerrits RS, et al. Costs and effects of Internet cognitive behavioral treatment blended with face-to-face treatment: Results from a naturalistic study. Internet Interv. 2015;2: 77–83. doi:10.1016/j.invent.2015.01.001
70. Hendriks SM, Spijker J, Licht CMM, Beekman ATF, Hardeveld F, De Graaf R, et al. Disability in anxiety disorders. J Affect Disord. 2014;166: 227–233. doi:10.1016/j.jad.2014.05.006
71. Dewa CS, Lin E. Chronic physical illness, psychiatric disorder and disability in the workplace. Soc Sci Med. 2000;51: 41–50. doi:10.1016/S0277-9536(99)00431-1
72. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy (New York). 1990;16: 199–208. doi:10.1016/0168-8510(90)90421-9
73. Briggs A. Economic evaluation and clinical trials: size matters. Bmj. 2002;321: 1362–1363. doi:10.1136/bmj.321.7273.1362
74. Briggs AH. Handling Uncertainty in Cost-Effectiveness Models. Pharmacoeconomics. 2000;17: 479–500. doi:10.2165/00019053-200017050-00006
75. Bergstrom J, Andersson G, Ljotsson B, Ruck C, Andreewitch S, Karlsson A, et al. Internet- versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. BMC Psychiatry. 2010;10: 54. doi:10.1186/1471-244X-10-54
76. Botella C, Gallego MJ, Garcia-Palacios A, Guillen V, Banos RM, Quero S, et al. An Internet-based self-help treatment for fear of public speaking: a controlled trial. Cyberpsychol Behav Soc Netw. 2010;13: 407–421. doi:10.1089/cyber.2009.0224

77. Kiropoulos LA, Klein B, Austin DW, Gilson K, Pier C, Mitchell J, et al. Is internet-based CBT for panic disorder and agoraphobia as effective as face-to-face CBT? J Anxiety Disord. 2008;22: 1273–1284. doi:10.1016/j.janxdis.2008.01.008
78. Marks IM, Kenwright M, McDonough M, Whittaker M, Mataix-Cols D. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med. 2004;34: 9–17. doi:10.1017/S003329170300878X
79. Schulz KF, Grimes DA. Epidemiology series Blinding in randomised trials: hiding who got what. 2002;359: 696–700.
80. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ. 2004;13: 873–884. doi:10.1002/hec.866
81. Mihalopoulos C, Chen G, Iezzi A, Khan MA, Richardson J. Assessing outcomes for cost-utility analysis in depression: Comparison of five multi-attribute utility instruments with two depression-specific outcome measures. Br J Psychiatry. 2014;205: 390–397. doi:10.1192/bjp.bp.113.136036
82. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the assessment of quality of life (AQoL)-8D multi-attribute utility instrument. Patient. 2014. doi:10.1007/s40271-013-0036-x
83. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Dutch Natl Heal Care Inst. 2016; 1–73.
84. König HH, Born A, Günther O, Matschinger H, Heinrich S, Riedel-Heller SG, et al. Validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with anxiety disorders. Health Qual Life Outcomes. 2010;8: 1–9. doi:10.1186/1477-7525-8-47
85. Brazier J. Is the EQ-5D fit for purpose in mental health? Br J Psychiatry. 2010;197: 348–349. doi:10.1192/bjp.bp.110.082453

Appendix 1. Overview of measures administered at each assessment interval including mode of assessment

Assessment point	Assessments	Mode of administration
Baseline	SCID-I or MINI-Plus BAI, BDI, BSI, Mastery Scale, WSAS, EQ-5D-5L, Tic-P	Ftf or telephone interview* Self-administered
Week 7 (mid-treatment)	WAI-SR patient version, WAI-SR therapist version	Self-administered
Week 15 (post-treatment)	BAI, BDI, BSI, Mastery Scale, WSAS, EQ-5D-5L, Tic-P, CSQ-8, SUS	Self-administered
Week 52 (1-year follow-up)	BAI, BDI, BSI, Mastery Scale, WSAS, EQ-5D-5L, Tic-P	Self-administered

* Based on patient preference

Appendix 2. Unit costs used in the cost-effectiveness analysis

Description	Cost per visit
Direct medical costs	
Visits to specialized mental healthcare centre	€ 115.00
Visit to independent psychologist	€ 96.00
Online sessions	€ 57.50
GP visits	€ 34.00
Social worker visits	€ 67.00
Physiotherapist visits	€ 34.00
Visits to alternative healers	€ 34.00
Visits to addiction services	€ 96.00
Visits to self-help groups	€ 16.38
Visits to company doctors	€ 74.80
Direct non-medical costs	€ 0.19 per km travel
	€ 3.00 parking costs
Productivity costs	
Short absence from work	€ 35.55 per h
Long absence from work	€ 35.55 per h
Presenteeism	€ 35.55 per h
Productivity loss in unpaid work	€ 14.32 per h

All unit costs were derived from the most recent Dutch guideline for economic evaluations. (Hakkaart-van Roijen et al., 2015)

Appendix 3. Total costs based on observed means and standard deviations

Costs		Blended CBT Post-treatment		Face-to-face CBT Post-treatment		Blended CBT 1-year follow-up		Face-to-face CBT 1-year follow-up
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Direct medical costs		**€1358**		**€1588**		**€2343**		**€2290**
Visits to psychologist or psychiatrist	34	€815 (€645)	43	€1369 (€1457)	32	€1649 (€2942)	39	€1836 (€3662)
Online sessions	34	€331 (€162)	43	€7 (€44)	32	€111(€395)	39	€50 (€240)
GP visits	34	€32 (€38)	43	€58 (€56)	32	€144 (€193)	40	€105 (€134)
Social worker visits	34	€39 (€140)	43	€34 (€141)	32	€161 (€180)	40	€21 (€102)
Physiotherapist visits	33	€75 (€205)	43	€29 (€87)	32	€190 (€372)	40	€160 (€315)
Visits to alternative healers	34	€14 (€38)	43	€28 (€140)	32	€3 (€19)	40	€16 (€99)
Visits to addiction services	34	€0 (€0)	43	€9 (€59)	32	€0 (€0)	39	€15 (€66)
Visits to self-help groups	34	€0 (€0)	43	€6 (€31)	32	€6 (€25)	39	€28 (€125)
Visits to company doctors	34	€52 (€92	43	€48 (€84)	32	€79 (€180)	40	€59 (€146)
Travel costs	33	**€28 (€40)**	43	**€59 (€64)**	32	**€42 (€79)**	39	**€87** (€233)
Productivity costs		**€3129**		**€2364**		**€4493**		**€4397**
Short absence from work	34	€491 (€1804)	43	€729 (€2886)	33	€1395 (€6399)	39	€864 (€2204)
Long absence from work	34	€0 (€0)	43	€176 (€894)	32	€0 (€0)	39	€183 (€1010)
Presenteeism	34	€1432 (€3000)	43	€1055 (€3112)	33	€2006 (€6089)	39	€1907 (€3714)
Productivity loss in unpaid work	34	€1206 (€4061)	43	€404 (€898)	31	€1092 (€2646)	39	€1443 (€3289)
Total		**€4515**		**€4011**		**€6878**		**€6774**

Chapter 5

Does it blend? Exploring therapist fidelity in blended cognitive behavioral therapy for anxiety disorders

Published as:
Romijn G, Provoost S, Batelaan N, Koning J, van Balkom A, Riper, H (2021).
Does it blend? Exploring therapist fidelity in blended CBT for anxiety disorders.
Internet Interventions 25, 100418

Abstract

Background: Blended cognitive behavioral therapy combines face-to-face CBT and Internet-based CBT into one integrated treatment protocol, opening up new ways to deliver therapy, increase cost-effectiveness and resolve scarcity of therapist availability. When traditional therapy is transformed into a new format, there is a need to evaluate whether principles of the new protocol are consistently applied.

Methods: This study aimed to explore therapist fidelity to blended CBT protocols for anxiety disorders in specialized mental health care and to assess whether fidelity is related to patient characteristics. Adult patients (N = 44) received blended CBT within a randomized controlled trial. Ratio of face-to-face to online sessions, session frequency and therapist adherence to instructions were assessed.

Results: Overall therapist fidelity with regard to ratio of blending, session frequency and instructions was high. Correlations were found between patients' share of online sessions and both session frequency ($r = .373$, $p = .013$), as well as patient computer experience ($r = .314$, $p = .038$). Adherence to instructions in face-to-face sessions was based on a subset of patients (n=23) and should therefore be interpreted with caution.

Conclusion: The blended approach was generally delivered as intended, indicating that the format is feasible in specialized mental health.

Introduction

Cognitive behavioral therapy (CBT) is an effective psychological treatment for anxiety disorders [1]. Internet-based CBT, where treatment is offered on an online platform, has the potential to maximize cost-effectiveness by reducing the burden of travel and reducing therapist hours. The uptake of Internet-delivered CBT in routine care is low, however, possibly because Internet-delivered CBT is not considered suitable for all patients; for example, providing web-based treatment without face-to-face contact may not be deemed acceptable for patients with severe symptoms [2]. A more recent approach, blended cognitive behavioral therapy, combines face-to-face CBT and Internet-based CBT, partially replacing face-to-face sessions with online sessions. Such a treatment format could address the limitations related to Internet-delivered CBT and may also fit better into current routine practice. In a previously conducted randomized controlled trial (RCT) [12] we evaluated the acceptability and effectiveness of blended CBT (n = 52) in comparison with face-to-face CBT (n = 62) for anxiety disorders in specialized mental health care and found promising results. Patients in both groups reported high levels of treatment satisfaction, and both conditions yielded large within-group effect sizes at posttest and at one-year follow-up. A small RCT (N = 36) of blended CBT for panic disorders by another research group achieved results in line with our findings regarding acceptability and effectiveness, with medium to high effect sizes in both treatment groups and no differences in treatment satisfaction between the groups [3].

Blended interventions appear increasingly popular as treatment protocols for blended therapy become more widely available [4–8]. However, little is known about therapist fidelity to such protocols. Therapist fidelity is defined as the extent to which treatment is carried out

as outlined in the treatment manual [9]. A lack of adequate evaluation of fidelity to blended treatment protocols can lead to incorrect conclusions about their clinical effectiveness [10], because there is no way of knowing what exactly took place during the therapy. A further aim of blended CBT is to improve cost-effectiveness through reduced therapist time, replacing a portion of the face-to-face sessions with online sessions. However, no clear indications for savings in terms of time or costs have been found up to now [3,11,12]. Whether or not blended CBT has been applied as designed is a key question for cost-effectiveness analysis, as it has important implications for the interpretation of cost outcomes. Suboptimal blended CBT implementation may actually lead to less effective ways of treating patients. For example, in a naturalistic study by Kenter and colleagues [11], which evaluated the use of blended treatment for anxiety and depression in routine mental health care settings, treatment time and costs increased for blended CBT relative to face-to-face CBT, because therapists delivered the online treatment on top of the face-to-face sessions.

The degree of treatment fidelity is important not only for understanding effectiveness and cost outcomes, but it also provides essential input for developing therapist guidelines on how to use blended CBT [13]. In a recent qualitative study by Mol and colleagues [14], therapists (N = 36) pointed to a lack of clear guidelines on incorporating online sessions as a major barrier to providing blended CBT.

Protocol use in face-to-face CBT for anxiety disorders has been evaluated, and results generally indicate high fidelity to treatment protocols [15, 16]. In these studies, audio-taped sessions (N = 495) [15] or video-taped sessions (N = 39) [16] were rated in terms of therapist adherence to the CBT protocol, with mean scores emerging of 85% on a 0%-to-100% scale (SD = 10.4) and 6.18 (SD = 0.51) on a 1-to-7 scale. Concerning Internet-based CBT, Hadjistavropoulos and colleagues [17] investigated adherence to feedback instructions in online feedback messages. They rated 706 messages for absence or presence of recommended therapist behaviors and found that adherence was generally high: seven out of nine behaviors were identified as present in 72–100% of messages. In a study by Mol and colleagues [18] therapist adherence to 219 written feedback instructions in online sessions within blended CBT was investigated in patients with depressive disorder on a 0%-to-100% scale. They concluded that therapists adhered to most of the instructions relating to issues like structure (87.7%), readability (68%), writing style (93.6%) and communication skills (69.4%).

Although fidelity to face-to-face CBT and Internet-delivered CBT has been studied separately, no research on fidelity to blended CBT has been conducted that takes both treatment modalities of the package into account. Blended CBT differs from face-to-face CBT and Internet-based CBT in that it requires therapists not only to apply therapeutic skills in both face-to-face and online sessions, but also to combine the two modalities into a single treatment. Several studies have shown that this integration of modalities can be challenging for therapists. In the naturalistic study by Kenter et al. [11] for example, only a minority (18%) of therapists (n=250) trained and equipped to use blended CBT actually offered a treatment containing both face-to-face CBT and Internet-based CBT to their patients. Furthermore, they

used Internet-based CBT as an add-on rather than a replacement of face-to-face sessions. In a qualitative study on barriers and facilitators of blended CBT [19] therapists (n=5) stated that they lacked knowledge on how to integrate online components in face-to-face therapy and in a study on patient experiences with blended CBT (n=15), a deficiency in the interplay between face-to-face and online components and a lack of therapist awareness of patient activities in online sessions was found to be a cause of patient dissatisfaction [20]. To improve the application of blended CBT as intended, a key recommendation is to provide therapists with more guidelines on how to use blended CBT [14].

The present study builds on the research reported by Romijn et al. [12], in which therapists were provided with a blended CBT protocol and clear guidelines on how to use blended CBT. To explore whether this enables therapists to conduct a blended treatment as intended, we assess fidelity to (i) the blended format of the treatment (distribution and frequency of face-to-face and online sessions) and (ii) the instructions pertaining to the interplay between face-to-face and online sessions (such as the explanation of the format to patients, the assisted login to the online platform during the first face-to-face session, and the provision of CBT-specific feedback in response to each online session). In addition, we assess the relationship between blended treatment fidelity and specific patient characteristics which therapists reportedly perceive as making patients better suited for blended therapy: younger age, employment, computer skills, higher cognitive capacities, mild-to-moderate and less complex symptoms, and preference for blended CBT over face-to-face CBT [14].

Methods

Design

Data were collected within an RCT assessing the clinical and cost-effectiveness of blended CBT in comparison with face-to-face CBT [12]. In that trial, 114 adult patients diagnosed with panic disorder, social anxiety disorder or generalized anxiety disorder were randomized to either blended CBT (n = 52) or face-to-face CBT (n = 62) in one of four Dutch outpatient clinics for specialized mental health care between November 2015 and July 2017. Written informed consent was obtained from all participants before baseline assessment and randomization. Participants were informed that participation in the trial was not contingent upon agreeing to be audio-recorded. A separate consent document for permission to record was obtained. A total of 45 patients started the blended CBT treatment. Since one patient dropped out after the first session, our study of treatment fidelity analyses data from the 44 participants who actually received blended CBT. The trial was approved by the Medical Ethics Committee of the Amsterdam University Medical Centers, location VU University Medical Center (registration number 2015.073) and registered in the Netherlands Trial Register (NTR4912).

Intervention

Separate manualised blended CBT protocols were developed for patients with panic disorder, social anxiety disorder and generalized anxiety disorder [8]. Their content was based on

protocols for face-to-face CBT [21], which contain evidence-based elements for the treatment of anxiety disorders, such as cognitive therapy and exposure [22,23] (see Appendix 1). In all blended treatments, both face-to-face and online sessions involved therapeutic guidance by qualified psychologists. The treatment consisted of 15 weekly sessions, with 8 face-to-face sessions alternating with 7 online sessions that were followed up by scheduled online feedback from the therapist. Every course of treatment began with a face-to-face session. Online sessions were accessible in a secure web-based environment (Minddistrict; www.minddistrict.com). Patients and therapists accessed this platform with a personalised login. The online sessions offered information (videos and text), testimonials from fictional patients, assignments (e.g., challenging negative thoughts) and homework exercises (e.g., monitoring activities, feelings, thoughts and behavior). Therapists provided feedback on assignments and homework exercises. Default text templates for feedback and instructions were supplied for every online session as a therapist aid for providing feedback as intended. Therapists were free to tailor these texts to the specific needs of their clients. The online treatment platform also offered the option of repeating an online session. Therapists could decide on that if they deemed it beneficial, for example if the patient had not fully comprehended the content of an online session or had greatly benefited from a specific exercise in it.

Table 1 shows the protocol components for the face-to-face sessions and the online sessions. These contained instructions for the blended format, which were used to rate the extent of therapist fidelity.

Table 1. Protocol components with instructions regarding the blended format

Face-to-face sessions		
Protocol component	**Session**	**Instructions**
Psychoeducation: explanation of anxiety disorder, treatment and blended approach	1	▪ Provide explanation of treatment format: alternating FtF and online sessions ▪ Log in to online platform together with patient to provide a technical introduction
Discussing previous online session	3–15	▪ Discuss homework and assignments from previous online session
Preparing upcoming online session	1–13	▪ Discuss homework and content of next online session ▪ Schedule appointment for providing feedback on next online session
Online sessions		
Generic therapeutic feedback	2–14	Provide feedback containing therapist behavior that would be used in any psychotherapy intervention, such as ▪ encouraging and motivating ▪ normalising ▪ empathising ▪ confirming by summarising
CBT-specific feedback	2–14	Provide CBT-driven feedback, such as ▪ helping patient identify and test automatic thoughts ▪ helping patient identify and modify core beliefs ▪ helping patient plan and conduct behavioral experiments
Scheduling upcoming FtF session	2–12	Schedule an appointment for next FtF session or remind patient of the already scheduled appointment

FtF: face-to-face

Patients

Patients were invited for study participation if they (i) were aged 18 or older and (ii) met the DSM-IV criteria for panic disorder with or without agoraphobia, social anxiety disorder or generalized anxiety disorder, as diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I [24]) or the Mini-International Neuropsychiatric Interview, Plus Version (MINI-Plus [25,26]). Exclusion criteria were (i) inadequate proficiency in Dutch, (ii) lack of e-mail address or computer with Internet access and (iii) presence of a psychotic or bipolar disorder, substance dependence or a high risk for suicide.

Therapists

Therapists were trained and experienced in delivering CBT. Prior to treating patients in the trial, all therapists received a 2-hour training course in the delivery of the blended treatment protocol, provided by researcher GR. During the training, therapists received instructions on how to apply the blended format, and were shown the main sections and functionalities of the online platform such as the start page of the therapist portal and entry point to other sections of the platform, treatment modules, homework area, feedback templates and messaging function. They also had the chance to practise with a fictitious patient. In addition,

discussion sessions were organised by the research team in which therapists could exchange their experiences with blended CBT.

Measures

Information on patient characteristics was obtained via an online self-report questionnaire at baseline. Primary diagnosis and comorbid disorders were established by a diagnostic interview (SCID-I [24] or MINI-Plus [25,26]). Data on the dose and timing of face-to-face sessions were extracted from electronic medical records. Data on the dose and timing of online sessions were collected through the online treatment platform. Face-to-face sessions were audio-recorded if participants consented, and these were transcribed verbatim. Feedback messages sent by therapists after online sessions were obtained from the online platform. All data were entered into Microsoft Office Excel (2016) spreadsheets.

Fidelity to ratio of blending

The ratio of blending for each course of treatment was calculated as the distribution of face-to-face and online sessions in percentages (ratio of blending = % face-to-face sessions / % online sessions).

Fidelity to session frequency

The blended CBT protocol prescribed weekly sessions. Session frequency was determined by dividing the total number of completed face-to-face and online sessions by the total therapy duration in weeks (session frequency = (number of completed face-to-face sessions + number of completed online sessions) / duration therapy in weeks)).

Fidelity to blended protocol instructions

To assess fidelity to the blended protocol in the face-to-face sessions and the online sessions, we developed a checklist based on the treatment protocol, containing the mandatory blended protocol components (Table 1; see Appendix 2 for the complete checklist). Transcripts of treatment recordings and online written feedback messages were evaluated by two independent raters (GR, SP), who quantified the extent of therapist fidelity to the blended protocol instructions. One of the raters was a researcher involved in developing the treatment and conducting the trial, and one was an independent researcher not involved in the trial or in developing the treatment. Rating results were discussed until agreement was established. Interrater reliability was measured with intraclass correlation coefficients (ICC). The ICC for fidelity ratings of the face-to-face protocol components was .90 ($p < .001$, 95% CI 0.86–0.93) and for online components .90 ($p < .001$, 95% CI 0.88–0.91), indicating good agreement between the raters with respect to both face-to-face and online sessions.

Analysis

Descriptive statistics (means, standard deviations, percentages) were used to describe the sample and the observed fidelity. The relationships between fidelity scores and patient

characteristics were assessed with Pearson correlations. Analyses were undertaken using SPSS, version 23 (IBM Inc., USA).

Results

Patient and therapist characteristics

A total of 44 patients were given blended CBT by 28 therapists. Baseline demographics and clinical characteristics of the patient sample can be found in Table 2. Of the 28 therapists 24 were female (86%), most were licensed health care psychologists (54%, 15/28). Others were psychologists in training for health care psychologist and under supervision (46%, 13/28).

Table 2. Patient characteristics (*N* = 44)

Age in years, mean (SD; range)	36.7 (11.0; 19–62)
Gender female, *n* (%)	23 (52)
Higher education*, *n* (%)	12 (27)
Employment, *n* (%)	28 (63.2)
Primary diagnosis, *n* (%)	
Panic disorder	23 (52.3)
Social anxiety disorder	11 (25.0)
Generalized anxiety disorder	10 (22.7)
BAI score at baseline, mean (SD)	28.2 (11.6)
Comorbid disorder**, *n* (%)	25 (57)
Preference for bCBT over FtFCBT, *n* (%)	24 (55)
Weekly hours of computer use, mean (SD)	20.5 (18.4)

SD: standard deviation; BAI: Beck Anxiety Inventory (Beck et al., 1988; Fydrich et al., 1992) ; bCBT: blended cognitive-behavioral therapy; FtFCBT: face-to-face cognitive-behavioral therapy

* Bachelor's equivalent or higher

** Comorbid disorders: social phobia, panic disorder, agoraphobia, generalized anxiety disorder, major depressive disorder, dysthymia, posttraumatic stress disorder, obsessive-compulsive disorder, eating disorder

Blending ratio and session frequency

The mean treatment duration was 12.6 sessions (SD: 5.2), with 6.7 face-to-face sessions (SD: 2.6) and 6.0 online sessions (SD: 2.9) in 15.6 weeks (SD: 8.7). The mean percentage of Face-to-face sessions in the 44 courses of blended treatment (55%) was almost equal to the prescribed 53%. Most courses of treatment (64%, n = 29) contained 50% to 60% face-to-face sessions. In fourteen cases (32%), the share of face-to-face sessions was either 40% to 50% (18%, n = 8) or 60% to 70% (14%, n = 6); in two cases (5%) it was higher than 70% (75% and 80%).

The mean session frequency was 0.89 sessions per week (SD: 0.26), slightly lower than the 1.0 sessions per week as prescribed. Five courses of treatment (11%) had a frequency of

exactly 1 session per week, in 13 cases (30%) frequency was higher (range: 1.1-1.4) and in 26 cases (59%) frequency was lower (range: 0.3-0.9).

Session frequency was higher (0.98 sessions/week, SD: 0.17) when the ratio of online to face-to-face sessions was positive than when the ratio of face-to-face to online sessions was positive (0.85 sessions/week, SD: 0.28). The correlation between session frequency and the face-to-face-to-online ratio was significant ($r = .373$, $p = .013$), suggesting that patients who received a larger share of online sessions were likely to have higher-frequency treatment than those receiving more face-to-face sessions.

Fidelity to the blended protocol in face-to-face sessions

A total of 293 face-to-face sessions were conducted. Recordings were available for 74 (25%) sessions received by 23 patients. There were no significant differences in baseline characteristics (age, gender, education level, employment, primary diagnosis, baseline symptom scores, comorbidity, treatment preference and computer experience) between the patient sample that consented with recordings and the patient sample that did not consent with recordings. The recorded sessions were provided by 17 therapists, of whom 15 were female (88%), 10 (59%) were licensed health care psychologists and 7 (41%) were supervised psychologists in training for health care psychologists. Reasons for non-availability of recordings included: participants not consenting to be recorded (n=21, 130 sessions), therapists forgetting to record sessions, poor recording quality and low battery of the recording device. Forty-six (62%) recorded sessions were conducted in full accordance with the blended instructions in the protocol, while in 28 sessions (38%) some deviations to the protocol occurred (see Table 3 for adherence to the specific protocol components).

Table 3. Adherence to protocol instructions in face-to-face sessions (n=74 recorded sessions)

Protocol component	Protocol instruction for blended approach	Adherence	Deviations from protocol
Psychoeducation (*n* = 8)	Explain treatment format: alternating FtF* and online sessions, and login to online platform together with patient	Full adherence: 7 Partial adherence: 1 Non-adherence: 0	- Therapist did not mention the alternating FtF and online sessions (1)
Discussing previous online session (*n* = 66)	Discuss homework and assignment(s) from previous online session	Full adherence: 61 Partial adherence: 4 Non-adherence: 1	- Session was mentioned, but with little or no discussion of homework and assignments (4) - Previous online session was not mentioned at all (1)
Preparing upcoming online session (*n* = 66)	Discuss homework for next online session and schedule time for feedback provision	Full adherence: 44 Partial adherence: 21 Non-adherence: 1	- No time for providing feedback was scheduled (20) - Homework for upcoming online session was not discussed (1) - Upcoming online session was not mentioned at all (1)

FtF: face-to-face

Blended protocol instructions for the psychoeducation component, which compared to the other two components only occurred in the first session, were adhered to in 7 of 8 recorded sessions (see Appendix 3, Box 1 for an example). All therapists assisted the patient in logging into the platform during the first session to introduce the online treatment programme, but in one session the therapist did not mention the alternation of face-to-face and online sessions in the blended treatment.

In 5 of 66 recorded sessions (7%), therapists deviated from the protocol where the previous online session should have been discussed (Boxes 2a and 2b). In one case the online session was not mentioned at all; in other cases therapists did refer to it, but there was little or no discussion of homework and assignments.

Most deviations from the protocol occurred when the upcoming online session was to be discussed (Box 3). In 22 of 66 sessions (33%), therapists deviated from the instructions, mostly by not scheduling an appointment for providing feedback on the next online session

(30%, n = 20). In the other two cases, therapists did not discuss the homework for the upcoming online session.

Fidelity to the blended protocol in online sessions

Therapists provided a total of 257 feedback messages on 257 online sessions (see Table 4 for adherence to specific protocol components). In 167 messages (65%), blended protocol instructions were fully adhered to, meaning that the therapist had provided both generic therapeutic and CBT-specific feedback, and had scheduled the appointment for the next face-to-face session (see Appendix 3, Boxes 4a and 4b for examples). Generic therapeutic feedback was provided in 232 messages (90%), CBT-specific feedback in 184 messages (72%) and an appointment for the upcoming face-to-face session was scheduled in 208 messages (81%).
Thirty-four (13%) of the 257 online sessions were repeated. Feedback messages on repeated sessions were usually short and practical in nature (Boxes 5a to 5c) and usually did not contain CBT-specific feedback (31 of 34 messages).

Table 4. Adherence to protocol instruction in online sessions (n=257 sessions)

Protocol component	Online sessions with full adherence to instructions
Generic therapeutic feedback	*n* = 232 (90%)
CBT-specific feedback	*n* = 184 (72%)
Scheduling upcoming FtF session	*n* = 208 (81%)

CBT: cognitive behavioral therapy; FtF: face-to-face

Correlations of patient characteristics with treatment fidelity outcomes

Table 5 shows correlations between patient characteristics and fidelity outcomes. There was a significant association between the ratio of face-to-face to online sessions and a patient experience with the use of computers ($r = -.314$, $p = .038$), indicating that the treatment of patients more experienced with computers was likely to contain a larger percentage of online sessions. No significant associations between other patient characteristics and fidelity outcomes were found.

Table 5. Correlations of patient characteristics with treatment fidelity outcomes (n=44, Pearson's *r*)

Patient characteristics	Blending ratio	Session frequency	FtF fidelity score (*n* = 23)	Online fidelity score
Age	.213	.163	−.083	.244
Higher education	−.104	.159	−.340	−.111
Employed	.016	.130	−.110	−.157
Baseline BAI score	.238	−.290	−.024	.114
Comorbid disorder	−.227	−.023	.080	−.275
Preference for bCBT	.161	.092	.228	−.132
Weekly computer hours	−.314*	.140	.024	−.159

BAI: Beck Anxiety Inventory; bCBT: blended cognitive-behavioral therapy; FtFCBT: face-to-face cognitive-behavioral therapy

* $p < .05$

Discussion

Principal findings

The aim of this paper was to explore therapist fidelity to blended CBT protocols for anxiety disorders in specialized mental health care, considering insights in the actual application of blended treatment are lacking. Additionally, we wanted to gauge the influence of patient characteristics on blended CBT fidelity, since therapists believe some patients are better suited for blended CBT than others [14].

Overall, therapist adherence to the instructions in the blended treatment protocol was high. The mean session frequency was 0.89 sessions per week (SD: 0.26), slightly lower than the 1.0 sessions per week as prescribed. The ratio of face-to-face to online sessions was negatively associated with session frequency, suggesting that a larger share of online sessions enables a higher treatment frequency. This may be relevant in the light of meta-analytic findings by Cuijpers and colleagues [27] showing the importance of treatment frequency: they found that an increase from one to two sessions per week in psychotherapy for depression boosted the effect size g by 0.45, with the total number of sessions held constant.

Our inspection of patient characteristics showed a significant association between the ratio of blending and patient experience with the use of computers, indicating that those with more computer experience were more likely to receive a higher share of online sessions. Other patient characteristics, such as pre-treatment anxiety severity or comorbidity, were not associated with fidelity outcomes. This finding is in line with previous findings for face-to-face therapy [15,16] and refutes therapists believe that patients with mild-to-moderate and less complex symptoms are better suited for blended CBT [14].

Strengths and limitations

Evaluating fidelity is a time-consuming process, and it becomes even more complex when two treatment modalities are integrated into one treatment protocol. For this reason, treatment fidelity is often not examined in intervention studies, and had not yet been evaluated for blended treatment at all, even though it is essential to the interpretation of treatment outcomes and to successful implementation of a blended format. As this study was an investigation of therapist fidelity to a blended treatment protocol assessing both the face-to-face and the online elements of the treatment, we were able to examine what actually happened during blended treatment: did it blend?

It should be taken into account that the current analyses into fidelity were explorative in nature and should be seen as one of the first steps in unravelling the application of blended treatment. Although findings on blending ratio, session frequency and adherence to protocol instructions in online sessions were based on the full patient sample, results regarding the adherence to instructions in face-to-face sessions were based on a subsample of patients and a subset of therapy sessions. Even though characteristics of this subsample of patients resembled the full sample, we cannot be sure whether the recorded sessions were representative of all face-to-face sessions, which is a clear limitation of the study.

Furthermore, comparing our results to other studies, and comparing outcomes on treatment fidelity in general, is complicated by the lack of uniformity in the definition of fidelity used by different authors. One general definition is: 'the degree to which a treatment is implemented as it was intended in the original protocol'; however, more specified definitions vary across studies and varying interpretations of the concept hinder shared understanding of findings [28]. The current study was the first to target fidelity assessment to the instructions aiming to achieve the blended format and interplay between face-to-face and online sessions. This limits generalizability to studies that take a broader view in defining fidelity and which were different in nature as they did not entail an Internet component as part of the treatment. However, the operationalisation of 'fidelity' applied in our study may be used as an indicator for other studies investigating fidelity in blended interventions and thus offers a helpful starting point to further unravel the black box of blended treatment.

Clinical and research implications

Opportunities to improve therapist fidelity to the blended treatment format appear to lie in enhancing therapist recognition of face-to-face and online sessions as equally important elements of treatment. If that is not acknowledged, online sessions cannot adequately replace face-to-face sessions. In the current study, therapists often did not set a date to provide feedback on online sessions, which could be an indication that a therapist sees those sessions as merely supportive to the face-to-face sessions and this idea can unconsciously be transferred to the patient. This requires attention in training therapist. Furthermore, if an appointment calendar function were added to the online platform, that might improve fidelity to this protocol component and heighten therapists' awareness of the importance of online elements in blended treatment.

Previously, a lack of clear guidelines has been identified as a barrier to the use of blended CBT [14,19]. In some cases in the current study, treatment frequency was higher than the intended one session per week, and that higher frequency was sometimes caused by a lack of clarity about how to integrate the online element into the treatment. This points to the need for clear instructions about online communication (such as how to deal with flexible, on-demand online contact opportunities and how much therapist time is available for online activities) and to the necessity of more intensive therapist training, which can prevent blended CBT from becoming too demanding for therapists or too costly.

One benefit of a blended format, as found in earlier studies, is that it can enhance therapists' adherence to the treatment protocol [14,19]. In the current study, we indeed found high therapist fidelity in most cases. The overall variability in ratio of blending and session frequency, however, was quite high. This could be an indication that some therapists feel the need for a more flexible protocol to be able to adapt to patient preferences and needs. The character of online sessions facilitates flexibility in shortening or expanding (the online part of) treatment or vary in therapy frequency. Offering a customisable blended protocol has been suggested before [19, 29–31], and future research should further explore this option and investigate what degree of flexibility might be feasible.

Finally, an interesting topic for subsequent research would be whether therapist variables are associated with the degree of treatment fidelity. Identifying therapist characteristics that predict fidelity to blended CBT could assist mental health care services in the selection and training of professionals.

Conclusions

Our findings suggest that the blended treatment was generally conducted as intended, indicating that delivery of blended CBT in the applied format is feasible for therapists in specialized mental health care. This enhances confidence in the findings on effectiveness and cost-effectiveness of blended CBT reported elsewhere [12]: high treatment fidelity improves internal validity (participants in the experiment group actually received the treatment variable as intended) and external validity (the treatment can be replicated because the protocol was followed) [32]. The results should, however, be interpreted with some level of caution, given that the findings on fidelity in face-to-face sessions were not based on the full patient sample. The current study was conducted prior to the coronavirus crisis. The outbreak of a pandemic disease highlights the relevance of online treatment as an important element of routine care practice [33]. Blended interventions are likely to be of critical importance in post-corona mental health care.

Acknowledgements

We are very grateful for the contribution of all research assistants and therapists to this study, and for the cooperation of the trial participants and the participating outpatient clinics: Altrecht, GGZ inGeest, GGZ Oost-Brabant and GGZ Noord-Holland-Noord.

Disclosure Statement

The authors report no conflicts of interest related to this publication.

References

1. Stewart RE, Chambless DL. Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies. J Consult Clin Psychol. 2009;77: 595–606. doi:10.1037/a0016032
2. Gun SY, Titov N, Andrews G. Acceptability of internet treatment of anxiety and depression. Australas Psychiatry. 2011;19: 259–264. doi:10.3109/10398562.2011.562295
3. Bruinsma A, Kampman M, Exterkate CC, Hendriks GJ. An exploratory study of 'blended' cognitive behavioural therapy (CBT) for patients with a panic disorder: results and patients' experiences. Tijdschr Psychiatr. 2016;58: 361–370.
4. Kemmeren LL, van Schaik DJF, Riper H, Kleiboer AM, Bosmans JE, Smit JH. Effectiveness of blended depression treatment for adults in specialised mental healthcare: study protocol for a randomised controlled trial. BMC Psychiatry. 2016;16: 113. doi:10.1186/s12888-016-0818-5
5. Kleiboer A, Smit J, Bosmans J, Ruwaard J, Andersson G, Topooco N, et al. European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED): Study protocol for a randomized controlled, non-inferiority trial in eight European countries. Trials. 2016;17: 1–10. doi:10.1186/s13063-016-1511-1
6. Kooistra LC, Wiersma JE, Ruwaard J, van Oppen P, Smit F, Lokkerbol J, et al. Blended vs. Face-to-face cognitive behavioural treatment for major depression in specialized mental health care: Study protocol of a randomized controlled cost-effectiveness trial. BMC Psychiatry. 2014;14: 1–11. doi:10.1186/s12888-014-0290-z
7. Nakao S, Nakagawa A, Oguchi Y, Mitsuda D, Kato N, Nakagawa Y, et al. Web-based cognitive behavioral therapy blended with face-to-face sessions for major depression: Randomized controlled trial. J Med Internet Res. 2018;20: 1–15. doi:10.2196/10743
8. Romijn G, Riper H, Kok R, Donker T, Goorden M, van Roijen LH, et al. Cost-effectiveness of blended vs. face-to-face cognitive behavioural therapy for severe anxiety disorders: study protocol of a randomized controlled trial. BMC Psychiatry. 2015;15: 311. doi:10.1186/s12888-015-0697-1
9. Waltz J, Addis ME, Koerner K, Jacobson NS. Testing the Integrity of a Psychotherapy Protocol: Assessment of Adherence and Competence. J Consult Clin Psychol. 1993;61: 620–630. doi:10.1037/0022-006X.61.4.620
10. Prowse PT. A Meta-Evaluation: The Role of Treatment Fidelity within Psychosocial Interventions during the Last Decade. J Psychiatry. 2015;18. doi:10.4172/Psychiatry.1000251
11. Kenter RMF, van de Ven PM, Cuijpers P, Koole G, Niamat S, Gerrits RS, et al. Costs and effects of Internet cognitive behavioral treatment blended with face-to-face

treatment: Results from a naturalistic study. Internet Interv. 2015;2: 77–83. doi:10.1016/j.invent.2015.01.001

12. Romijn G, Batelaan N, Koning J, Balkom A Van, Leeuw A de, Benning F, et al. Acceptability, effectiveness and cost-effectiveness of blended cognitive-behavioural therapy (bCBT) versus face-to-face CBT (ftfCBT) for anxiety disorders in specialised mental health care: A 15- week randomised controlled trial with 1-year follow-up. PLoS ONE 16 (11): e0259493. doi.org/10.1371/journal.pone.0259493
13. Bellg AJ, Resnick B, Minicucci DS, Ogedegbe G, Ernst D, Borrelli B, et al. Enhancing treatment fidelity in health behavior change studies: Best practices and recommendations from the NIH Behavior Change Consortium. Heal Psychol. 2004;23: 443–451. doi:10.1037/0278-6133.23.5.443
14. Mol M, van Genugten C, Dozeman E, van Schaik DJF, Draisma S, Riper H, et al. Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A Qualitative Study on Therapists' Perspectives. J Clin Med. 2019;9: 91. doi:10.3390/jcm9010091
15. Boswell JF, Gallagher MW, Sauer-Zavala SE, Bullis J, Gorman JM, Shear MK, et al. Patient characteristics and variability in adherence and competence in cognitive-behavioral therapy for panic disorder. J Consult Clin Psychol. 2013;81: 443–454. doi:10.1037/a0031437
16. Zickgraf HF, Chambless DL, McCarthy KS, Gallop R, Sharpless BA, Milrod BL, et al. Interpersonal Factors Are Associated with Lower Therapist Adherence in Cognitive-Behavioural Therapy for Panic Disorder. Clin Psychol Psychother. 2016;23: 272–284. doi:10.1002/cpp.1955
17. Hadjistavropoulos HD, Schneider LH, Klassen K, Dear BF, Titov N. Development and evaluation of a scale assessing therapist fidelity to guidelines for delivering therapist-assisted Internet-delivered cognitive behaviour therapy. Cogn Behav Ther. 2018;47: 447–461. doi:10.1080/16506073.2018.1457079
18. Mol M, Dozeman E, Provoost S, Van Schaik A, Riper H, Smit JH. Behind the scenes of online therapeutic feedback in blended therapy for depression: Mixed-methods observational study. J Med Internet Res. 2018;20: 2–3. doi:10.2196/jmir.9890
19. Titzler I, Saruhanjan K, Berking M, Riper H, Ebert DD. Barriers and facilitators for the implementation of blended psychotherapy for depression: A qualitative pilot study of therapists' perspective. Internet Interv. 2018;12: 150–164. doi:10.1016/j.invent.2018.01.002
20. Urech A, Krieger T, Möseneder L, Biaggi A, Vincent A, Poppe C, et al. A patient post hoc perspective on advantages and disadvantages of blended cognitive behaviour therapy for depression: A qualitative content analysis. Psychother Res. 2018;3307: 1–13. doi:10.1080/10503307.2018.1430910
21. Keijsers GPJ, Minnen A van, Hoogduin CAL. Protocollaire behandelingen voor volwassenen met psychische klachten. Deel 1. [Manualized treatments for adults with psychological disorders, part 1]. 2010.

22. NICE. Generalised anxiety disorder and panic disorder in adults. Natl Inst Heal Clin Excell. 2011.
23. National Institute for Health and Care Excellence. Social anxiety disorder: recognition, assessment and treatment. Clinical guideline 159. Available: http://guidance.nice.org.uk/cg159. 2013. doi:10.1016/S0140-6736(08)60488-2 [doi]
24. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York State Psychiatric Institute. 2002.
25. Sheehan D V., Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998. pp. 22–33. doi:10.1016/S0924-9338(99)80239-9
26. Van Vliet IM, De Beurs E. Het Mini Internationaal Neuropsychiatrisch Interview (MINI): Een kort gestructureerd diagnostisch psychiatrisch interview voor DSM-IV-en ICD-10-stoornissen. Tijdschr Psychiatr. 2007;49: 393–397.
27. Cuijpers P, Huibers M, Daniel Ebert D, Koole SL, Andersson G. How much psychotherapy is needed to treat depression? A metaregression analysis. J Affect Disord. 2013;149: 1–13. doi:10.1016/j.jad.2013.02.030
28. Gearing RE, El-Bassel N, Ghesquiere A, Baldwin S, Gillies J, Ngeow E. Major ingredients of fidelity: A review and scientific guide to improving quality of intervention research implementation. Clin Psychol Rev. 2011;31: 79–88. doi:10.1016/j.cpr.2010.09.007
29. Kemmeren LL, Van Schaik DJF, Smit JH, Ruwaard J, Rocha A, Henriques MR, et al. Unraveling the black box: Exploring usage patterns of a blended treatment for depression in a multicenter study. J Med Internet Res. 2019;21. doi:10.2196/12707
30. Van der Vaart R, Witting M, Riper H, Kooistra L, Bohlmeijer ET, van Gemert-Pijnen LJEWC. Blending online therapy into regular face-to-face therapy for depression: Content, ratio and preconditions according to patients and therapists using a Delphi study. BMC Psychiatry. 2014;14: 1–10. doi:10.1186/s12888-014-0355-z
31. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JEWC. Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. JMIR Ment Heal. 2016;3: e9. doi:10.2196/mental.4534
32. Borrelli B. The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. J Public Health Dent. 2011;71. doi:10.1111/j.1752-7325.2011.00233.x
33. Wind TR, Rijkeboer M, Andersson G, Riper H. The COVID-19 pandemic: The 'black swan' for mental health care and a turning point for e-health. Internet Interv. 2020; 100317. doi:10.1016/j.invent.2020.100317

Appendix 1. Content of the sessions in the blended CBT protocol

Session (modality)	**Content and exercises**
Panic disorder	
1 (FtF)	Introduction, psychoeducation
2 (online)	Treatment rationale, treatment motivation and expectation, worry diary
3 (FtF)	Explanation of exposure, instructions regarding interoceptive exposure, panic diary
4 (online)	Interoceptive exposure exercises, exposure diary
5 (FtF)	Explanation of interoceptive exposure and exposure in vivo, exposure exercise, exposure diary
6 (online)	Identifying automatic thoughts, challenging unhelpful thoughts, exposure diary
7 (FtF)	Explanation of behavioral experiments, treatment evaluation, exposure diary
8 (online)	Identifying cognitive distortions, behavioral experiment, exposure diary
9 (FtF)	Behavioral experiment, exposure diary
10 (online)	Exposure exercises, behavioral experiments
11 (FtF)	Exposure exercises, behavioral experiments
12 (online)	Exposure exercises, behavioral experiments
13 (FtF)	Exposure exercises, behavioral experiments
14 (online)	Explanation of relapse prevention, relapse prevention plan
15 (FtF)	Relapse prevention plan, recapitulation, treatment evaluation
Social anxiety disorder	
1 (FtF)	Introduction, psychoeducation
2 (online)	Treatment rationale, treatment motivation and expectation, worry diary
3 (FtF)	Explanation of selective attention, explanation and instructions regarding exposure, social anxiety diary
4 (online)	Identifying automatic thoughts, challenging unhelpful thoughts, social anxiety diary

5 (FtF)	Identifying automatic thoughts, challenging unhelpful thoughts, social anxiety diary
6 (online)	Identifying cognitive distortions, social anxiety diary
7 (FtF)	Explanation of behavioral experiments, treatment evaluation
8 (online)	Behavioral experiments, social anxiety diary
9 (FtF)	Behavioral experiments, social anxiety diary
10 (online)	Behavioral experiments, social anxiety diary
11 (FtF)	Behavioral experiments, social anxiety diary
12 (online)	Behavioral experiments, social anxiety diary
13 (FtF)	Behavioral experiments, social anxiety diary
14 (online)	Explanation of relapse prevention, relapse prevention plan
15 (FtF)	Relapse prevention plan, recapitulation, treatment evaluation
Generalized anxiety disorder	
1 (FtF)	Introduction, psychoeducation
2 (online)	Treatment rationale, treatment motivation and expectation, worry diary
3 (FtF)	Explanation and instructions regarding exposure, challenging unhelpful thoughts, explanation of metacognitions
4 (online)	Exploring metacognitions, worry exposure exercises
5 (FtF)	Exploring uncontrollability of worrying
6 (online)	Worry experiment regarding uncontrollability
7 (FtF)	Exploring the danger of worrying, treatment evaluation
8 (online)	Worry experiment regarding danger of worrying
9 (FtF)	Exploring positive beliefs about worrying
10 (online)	Worry experiment regarding positive beliefs
11 (FtF)	Explanation of selective attention

12 (online)	Learning to shift attention
13 (FtF)	Learning to shift attention
14 (online)	Explanation of relapse prevention, relapse prevention plan
15 (FtF)	Relapse prevention plan, recapitulation, treatment evaluation

Appendix 2: Checklist for fidelity to blended CBT treatment protocol (including examples)

Face-to-face sessions

Protocol component	**Checklist** Full adherence: score 2, partial adherence: score 1, non-adherence: score 0	**Examples from transcripts**
Psychoeducation	**Adherence**: therapist gives a clear explanation of the blended format and logs into the online platform with the patient	Session 1 (panic disorder, PD) **Therapist***: This treatment will last 15 weeks and FtF sessions will alternate with online sessions.* ... **Therapist***: Let's take a look at the online platform.* **Patient***: Okay.* **Therapist***: It's really easy, so you'll be fine. Here you see the sessions and your progress, so you know where to start when you log in again. Now we'll have a look at the introduction session together.* **Patient***: Yes, I can see that in Tasks.* **Therapist***: That's right, you can see the introduction sessions there. And here you see what the content of the session is.* **Patient***: I see.*
	Partial adherence: therapist does not give a clear explanation of the blended format *or* does not log into the online platform with patient	
	Non-adherence: therapist does not give a clear explanation of the blended format *and* does not log into the online platform with patient	
Discussing previous online session	**Adherence**: content of homework and exercises in the previous online session is discussed	Session 5 (PD) **Therapist***: I gave you some feedback on the online session. You had made a list of exposure activities and described your catastrophic thought. You described what happens when you get into your car very clearly. You think: "Oh no, I will stop at the next petrol station."* **Patient***: That's right.* **Therapist***: I think those are reactions to your catastrophic thought. It's not that thought that makes you feel anxious and that makes you want to stop driving the car. Because ... what might happen if you keep driving? What's the most catastrophic thing that could happen?*

	Partial adherence: reference is made to the online sessions, but content of homework and exercises is not discussed	Session 3 (PD) **Therapist***: First I want to briefly discuss the online session. How did that go?* **Patient***: I recognised some things, some of these exercises I've done before. And um ... I found it difficult to describe my own situation.* **Therapist***: Yes.* **Patient***: That's still difficult for me. The rest of it was clear. When you start working on it, you start thinking about your situation. That's good, I think....* **Therapist***: I read it and gave you feedback. How did you feel about that?* **Patient***: I found it supportive.* **Therapist***: Good.*
	Non-adherence: homework and exercises in the previous online sessions are not discussed	
Preparing upcoming online session	**Adherence**: homework for the upcoming online session is discussed and an appointment for providing feedback is made	Session 3 (PD) **Therapist***: This week you'll keep your panic diary; you can do that online. That means you describe every panic attack in your diary. For example, if you have trouble breathing again and that makes you feel anxious.* ... **Therapist***: I'll send you feedback on the online session next Monday, in the morning. Is that okay?* **Patient***: Yes.*
	Partial adherence: homework for the upcoming online session is not discussed *or* no appointment for providing feedback on the online sessions is made	Session 5 (PD) **Therapist***: We'll see each other again on Wednesday in two weeks' time.* **Patient***: Yes, that means I can do the exposure activity at least five times.* **Therapist***: That's good, you can practise a lot.* → An appointment for the next FtF session is made, but not one for providing feedback on the online session.
	Non-adherence: homework for the upcoming online sessions is not discussed *and* no appointment for providing feedback on the online sessions is made	

Online sessions

Protocol component	**Checklist** Presence of protocol component: score 1, non-presence of component: score 0	**Examples from feedback messages**
Generic therapeutic feedback	Encouraging and motivating	- *I see that you worked very hard!* - *Good job!* - *Well done!*
	Normalising and empathising	- *I can imagine that made you sad and anxious.* - *I understand that it feels like a disappointment.* - *I can imagine that is not easy.* - *Simply put, people feel anxiety in their bodies sometimes, and especially people who are recovering from an anxiety disorder will regularly feel restless and anxious. That can't be prevented.* - *Be aware that you don't have to understand and be able to perform things perfectly at once. I've never met anyone who could (myself included), so it's completely fine if you want to reassure yourself or need more time.* - *The goal was not (yet) to sit on your bike without fear (or fearful sensations). Because indeed, as you write, it takes time to get used to it, also for your body and your mind.*
	Confirming by summarising	- *The most important part of the treatment is indeed to investigate your thoughts.*
	Guiding treatment progress	- *You can log your panic attacks in the panic diary.* - *This week's homework is that you will perform three activities from your exposure list.* - *Once you've completed an exercise, it's good to log that in the exposure diary.*

CBT-specific feedback	Explaining CBT theory (including exposure)	- *Often you start by feeling something in your body: your heart starts beating faster, you start hyperventilating, and then you start feeling light-headed. Because you feel light-headed, you start thinking something bad could happen, for example fainting or having a heart attack. Then the reasoning becomes: If my heart beats faster, I will start hyperventilating, I'll become light-headed, and then I'll faint or have a heart attack.* - *The fear of fear became stronger, which made you end up in the panic cycle: anxiety → catastrophic thoughts about anxiety → anxiety increases → catastrophic thoughts become stronger → anxiety increases etc.* - *With an alternative thought we mean a thought that is more realistic than a catastrophic thought – keeping calming thoughts in mind. You can use those as well, but then they are more like helpful thoughts.* - *A more realistic thought is a combination of your catastrophic thought and common sense: If I start feeling dizzy, and start having palpitations, that means I'm starting to have a hyperventilation or panic attack, and not that I'll get into an accident. Even though I think I'm losing control, this doesn't mean it will actually happen (the chance of me having or causing an accident is smaller than I think).*
	Guiding patients through CBT assignments (including exposure), for example by asking questions or providing information or suggestions	- *Is it correct that the believability of the catastrophic thought becomes weaker once the experiment has ended? So do you believe less strongly that you are becoming unwell?* - *I think that, based on what you told me earlier, perhaps we could think of other exercises. It's not so much about all the things you're afraid of doing, but about things you do differently because of your fear. That could be always making sure there is someone nearby that could help you. You can see that in the way you formulate your answers to the exercises: it is especially difficult to do things on your own.* - *The moment that you flee after all, or start measuring before the tension has gone down – that is no longer exposure, and it won't work either. Moreover, the anxiety will just increase. One solution, I think, is to think of achievable steps and of using things that can aid you, in such a way that you can follow through.* - *In the evaluation of your experiment you write that you tend to overestimate negative outcomes, so that situations can be scary beforehand. What can you do to reduce this fear? What exercises from the treatment can you use to do this?* - *Of course, it could happen that someone does get angry when you don't know something or say something wrong. How would you feel about that? Could you handle it? What could help you with that?*

Scheduling appointment for FtF session		- *We'll see each other on Thursday 26th November at 13:00, see you then!*
		Examples from feedback messages non-adherent to instructions
		- *We already discussed this session during our FtF session.* - *I will open the next session for you.* - *We will discuss the assignments when we see each other again.*

Appendix 3: Examples of full and partial adherence to blended instructions in face-to-face sessions and online feedback messages

Box 1. Example of adherence to blended instructions in FtF session, protocol component *Psychoeducation*

Therapist*: This treatment will last 15 weeks and face-to-face sessions will alternate with online sessions.*
(…)
Therapist*: Let's take a look at the online platform.*
Patient: *Okay.*
Therapist: *It's really easy, so you'll be fine. Here you see the sessions and your progress, so you know where to start when you log on again. Now we'll have a look at the introduction session together.*
Patient: *Yes, I can see that in Tasks.*
Therapist*: That's right, you can see the introduction sessions there. And here you see what the content of the session is.*

Box 2a. Example of adherence to blended instructions in FtF session, protocol component *Discussing Previous Online Session*

Therapist*: I gave you some feedback in the online session. You had made a list of exposure activities and described your catastrophic thought. You described what happens when you get into your car very clearly. You think: "Oh no, I will stop at the next petrol station."*
Patient*: That's right.*
Therapist*: I think those are reactions to your catastrophic thought. It's not that thought that makes you feel anxious and that makes you want to stop driving the car. Because ... what might happen if you keep on driving? What's the most catastrophic thing that could happen?*

Box 2b. Example of partial adherence to blended instructions in FtF session, protocol component *Discussing Previous Online Session*

Therapist*: First I want to briefly discuss the online session. How did that go?*
Patient*: I recognised some things, some of these exercises I've done before. And um... I found it difficult to describe my own situation.*
Therapist*: Yes.*
Patient*: That's still difficult for me. The rest of it was clear. When you start working on it, you start thinking about your situation. That's good, I think....*
Therapist*: I read it and I gave you feedback. How did you feel about that?*
Patient*: I found it supportive.*
Therapist*: Good.*

Box 3. Example of adherence to blended instructions in FtF session, protocol component *Preparing Upcoming Online Session*

Therapist*: This week you'll keep your panic diary, you can do that online. That means you describe every panic attack in your diary. For example, if you have trouble breathing again and that makes you feel anxious.*
…
Therapist*: I'll send you feedback on the online session next Monday in the morning. Is that okay?*
Patient*: Yes.*

Box 4a. Example of feedback message in online session adhering to blended instructions

Your answers in the exercises are very clear, nice! **(Generic therapeutic feedback)**

In the first exercise you described the panic attack clearly, and you notice that it helps to formulate alternative thoughts such as: Thousands of people take the bus, I used to do that as well, and that is normal behavior. What you're telling yourself is that it is not a dangerous situation, and that the sensations of fear are essentially unnecessary. Henceforth you'll see that the catastrophic thought "I am fainting" goes down from a believability of 80% to 25%, and that the alternative thought becomes more believable, and that because of this you will feel less anxious. **(CBT-specific feedback)**

Very good that you practised the "head shaking". Just as you indicate at the end: this is an uncomfortable feeling. But the question is whether that also means that you are going to faint/die. You notice that the catastrophic thought goes down from a believability of 85% to 20%. It is not necessary to be anxious about those sensations.
Concerning the exposure list, it may be useful to look at an activity that you could perform daily. That would make it easier to practise (or more often) and to lower the threshold. That is important, because for the next FtF session you will perform three activities from your exposure list. Don't forget to keep track of those activities in your exposure diary. **(Generic therapeutic feedback + CBT-specific feedback)**

We'll discuss how that went on Monday next week. Good luck and see you then! **(Scheduling appointment for FtF session)**

Box 4b. Example of feedback message in online session adhering to blended instructions

Thank you for doing the exercises. Things are looking good! I will once again give you some tips for each exercise: **(Generic therapeutic feedback)**

(4.1 Describe a panic attack). I see that you're getting better at describing that. Under the heading Thoughts, I'd like to know whether you have any more thoughts that arise. To bring automatic thoughts to the surface you can try to replay the event like a short movie and to ask yourself: what am I thinking now? Because what? And then? About the catastrophic thought: does that thought describe the essence of your feelings? I ask this because you indicate that you are scared, angry and sad. What is the essence of your anxiety? For example: the thoughts never go away, and then....
For the alternative thought: nice, and a positive description! What effect does that thought have on you? Would the feeling or behavior be different to when you think the catastrophic thought? **(CBT-specific feedback)**

(4.2 Interoceptive exposure) Well done, you already did 2 exercises! I also see that the believability of the catastrophic thought was strongly reduced after the exercise. So it's not necessary to be afraid of physical sensations. **(CBT-specific feedback)**

(4.3 Exposure list) Great that you already managed to fill in 10 activities. It's important that the activities give you the opportunity to investigate the catastrophic thought, for example, "The thoughts never end". If an activity is accompanied by a different catastrophic thought, then it's good to describe it as well (if possible in the diary).
It's important to hold on to the alternative thought, and how you would react and feel, in the back of your mind. That way you can really challenge the thoughts. Example: Hyperventilating 1 minute –
Catastrophic thought: I'm going to faint. Feeling: fear. Behavior: sitting down and breathing calmly.
Alternative thought: I have all these physical sensations, but do not faint. Feeling: fear. Behavior: continuing and enduring the hyperventilation **(CBT-specific feedback)**

For the next face-to-face session, you will perform three activities from your exposure list. Don't forget to keep track of those activities in your exposure diary. **(Generic therapeutic feedback)**

We will discuss how things went on the 18th of May. Good luck and see you then! **(Scheduling appointment for FTF session)**

Box 5a. Example of feedback message on a repeated session

I gave you feedback on the online session during the last FtF session. You can now proceed to the next online

Box 5b. Example of feedback message on a repeated session

We completed this session together, because you needed some help with it.

Box 5c. Example of feedback message on a repeated session

Thanks for completing this session, you can now proceed to the next session.

Chapter 6

General discussion

Despite proposed advantages and positive results from controlled studies for Internet-supported treatment targeting anxiety disorders, the application by routine practice is so far limited and evidence on the (cost-)effectiveness in regular outpatient clinics is scarce. This thesis aimed to extend upon the existing literature on Internet-supported CBT for anxiety disorders by investigating the generalizability of research findings to routine care settings and populations and to examine the effects and costs of blended CBT versus face-to-face CBT in outpatient specialized mental health care among patients diagnosed with panic disorder with or without agoraphobia, social anxiety disorder or generalized anxiety disorder. This final chapter discusses and integrates the main findings of this thesis.

Main findings and interpretations

Effects and costs

Since the start of the trial described in this thesis, the attention to research on the efficacy of Internet-supported CBT in routine care has increased and tentative indications for cost-effectiveness have begun to emerge beyond the results of our study [1–3]. However, evidence from randomized controlled studies in routine care remains scarce. This is illustrated by the findings from our meta-analysis, that not only taught us that Internet-supported CBT is effective in samples recruited in clinical practice but also highlight the gap between research and practice, since effects were smaller in routine care samples compared to open recruitment samples and that the first were based on a relatively small number of studies. Furthermore, we found that the difference might be partly explained by patients' greater therapy adherence in open recruitment trials (association with a small, positive slope) and the stricter exclusion of patients with severe comorbid depressive symptoms in these studies.

When interpreting the findings of our meta-analysis, it should be considered that the difference between recruitment strategies might be overestimated, because the open recruitment trials in our analysis had a considerably higher proportion of wait-list comparators (n=37) as opposed to face-to-face CBT comparators (n=6) than the clinical recruitment trials (n = 4 wait list comparators, n = 6 face-to-face CBT comparators). Wait list control groups can cause artificial inflation of effect sizes, because people on a waiting list have been noted to improve less than would be expected based on natural recovery [4,5]. This phenomenon is thought to be caused by the fact that waiting for therapy does not stimulate to use natural help-seeking behavior and problem coping strategies [4].

Nonetheless, this meta-analysis confirmed that a large part of the current body of evidence on Internet-supported anxiety treatment is based on the examination of samples that were recruited through an open recruitment method and it underlined the importance of conducting more studies with routine care populations to further validate effectiveness findings for clinical populations.

The results from our RCT, that was conducted in specialized mental health care clinics, revealed no significant differences regarding effectiveness in reducing anxiety symptoms

between blended CBT and face-to-face CBT at post-treatment (t = −0.715, p = 0.477) nor at one-year follow-up (t = 1.702, p = 0.093). Both groups exhibited moderate to large within-group effect sizes (range of *d:* 0.50 to 1.00). These findings suggest that blended CBT provides a good treatment alternative to face-to-face CBT and clinical effects can be retained while reducing the number of face-to-face sessions at the clinic and replacing these with online sessions.

Due to the relative paucity of data on anxiety routine care samples and the rather new blended treatment format in our trial, there are few studies with which we can directly compare our results. Furthermore, comparability between studies on blended treatment is complicated because of the variety of formats that exists. A blended treatment format that was quite similar to the one employed in our RCT, was investigated in a pilot study (n=36) by Bruinsma and colleagues [2]. The study focused on patients with panic disorder in regular outpatient clinics providing primary and specialized mental healthcare. It compared conventional 12-session face-to-face CBT with 12-session blended CBT consisting of 9 face-to-face sessions and 3 Internet-based sessions based on a structured treatment protocol. Improvement rates on panic-related symptoms and general functioning were assessed with the Panic and Agoraphobia Scale [6] and the Outcome Questionnaire OQ-45 [7]. Results resembled those found in our trial [8] and showed no significant between-group differences at post-treatment and moderate to large within-group effect sizes. It needs to be noted though, that the small sample size in that pilot study did not allow for small differences between treatment groups to be detected.

In other variants of blended treatments, online elements may be used as adjunct to face-to-face therapy. Promising clinical trial results for this format have been found for treating depression [9,10]. Another variant is the arrangement of blended interventions as stepped care programs, where online elements are provided as one step within the sequence (e.g. prior to face-to-face treatment or as an aftercare intervention). Nordgreen and colleagues [11] found that clinical outcomes for such a blended stepped care approach (with Internet-delivered CBT prior to face-to-face CBT) were comparable to face-to-face CBT in a randomized controlled trial (n=173) on panic and social anxiety disorder. Moreover, the majority of the patients who recovered in the stepped care group, did so during Internet-delivered CBT, indicating the stepped care approach might be useful to improve accessibility of mental health care services. On the other hand, a large portion of patients dropped out during the Internet-based sessions, which might be a clue that this treatment step was not sufficiently responsive to them.

The economic analyses in this thesis revealed a dominant incremental cost-effectiveness ratio (ICER) from the healthcare perspective (including direct medical costs), meaning blended CBT is less costly and gains more quality-adjusted life years (QALYs) in comparison with face-to-face CBT. More specifically, one additional QALY was associated with €2257 lower costs. From the societal perspective (including direct medical costs, patient costs and productivity loss costs), €219 would have to be invested by society to gain one QALY. Based on these results, it

can be stated that cost-efficiency gains within a healthcare setting may be achieved by providing blended CBT instead of face-to-face CBT. If a broader, societal, view is taken and costs outside of healthcare are included, these gains seem to disappear as societal costs were comparable for both groups. Productivity loss costs appeared to have considerable impact on incremental costs and accounted for the majority of costs in both groups, possibly due to a large proportion of anxiety patients of working age. Furthermore, we found that most of productivity losses were caused by presenteeism, i.e. reduced productivity while at work, and not by absence from work. The influence of the inclusion of productivity loss costs is an important finding, considering these costs are often neglected in economic evaluations [12] or based on absenteeism only [23].

Decision makers who are responsible for resource allocation will mainly want to know how likely it is that blended CBT is cost-effective compared to face-to-face CBT. The cost-effectiveness acceptability curve (see figure 4 in chapter 5) addressed this question, by indicating that there is an 80% probability of blended CBT being cost-effective compared with face-to-face CBT from a healthcare perspective and a 67% probability from a societal perspective, using a willingness-to-pay threshold of €20,000. At a willingness–to–pay point of €80,000, this probability is more than 80% from both perspectives.

It is important to bear in mind, however, that effectiveness and cost estimates are inevitably associated with some degree of uncertainty. Guidelines on cost-effectiveness analyses emphasise the need for visualizing this uncertainty, for example in cost-effectiveness planes [14]. The scatter plot in these planes illustrate the uncertainty around the expected incremental costs (on the y-axis) and expected incremental effects (on the x-axis). In our study, values were scattered over all quadrants of the plane (see figure 2 and figure 3 in chapter 5). This indicates a high degree of uncertainty in results, especially regarding cost-savings since values were almost evenly distributed above and below the horizontal axis.

Results from our trial partly resemble initial findings in the field of blended CBT for depression from the Kooistra's et al RCT [15]. They found a probability of 85% from the healthcare perspective that blended CBT is cost-effective compared with face-to-face CBT, using a willingness-to-pay threshold of €10,000. The probability from a societal perspective was considerably lower compared to our findings, however, with only 2%. The low probability in the study on blended CBT for depression was mainly due to a difference in productivity loss costs, with higher productivity losses in the blended CBT group.

Other RCT's on cost-effectiveness of blended CBT for anxiety disorders are currently lacking. In the before-mentioned naturalistic study by Kenter and colleagues [16], therapist costs of blended CBT were compared to those of face-to-face CBT for patients with depression or anxiety disorders. Results showed that costs increased for blended CBT relative to face-to-face CBT. In that study, no treatment protocol was available for therapists and therapists turned out to have provided online sessions on top of face-to-face sessions resulting in longer treatment durations. This might imply that clear guidelines on how to apply blended treatment are a prerequisite to assess cost-effectiveness.

Our cost-effectiveness findings are promising and may indicate that providing blended CBT can reduce costs of anxiety treatments in specialized mental health care. Nevertheless, the considerable amount of uncertainty around incremental costs and incremental effects cripples the possibility of drawing firm conclusions regarding cost-effectiveness and serves as an encouragement to conduct studies with larger sample sizes in order to assess more stable cost and effect estimates. Further, because of the relatively new treatment format, most therapists had no experience in delivering blended CBT. It would be worthwhile to examine whether treatment costs can be further reduced when therapists' level of experience increases.

Acceptability

Besides clinical and cost-effectiveness, acceptability is a key determinant for the successful uptake of Internet-supported treatment in routine care. Acceptability refers to the degree to which people delivering or receiving an intervention are willing to use the intervention, actually use the intervention and are satisfied with the intervention [17]. This thesis addressed blended CBT acceptability from a patient perspective in terms of treatment preference, adherence, satisfaction and working alliance and acceptability from a therapist perspective in terms of treatment fidelity and working alliance.

Before the start of treatment, 54% of the patients in the trial in chapter 5 (62 of 114) indicated a preference of receiving blended CBT over for face-to-face CBT. Such a positive result was also found in a previous trial for patients with a depressive disorder in outpatient clinics, where 65% of participants preferred starting with blended CBT rather than face-to-face CBT [15]. Even though it stands to reason those patients who consented to take part in these trials are not a fully representative sample of the patient population in specialized mental health care when it comes to treatment preference, this result underlines that a desire for this treatment format exists in routine care, also in patients with more severe symptoms. It serves as an argument to assess the best treatment option individually for each patient, together with the patient, resulting in demand-driven mental health care instead of supply-driven care.

In terms of percentage of treatment completers, we found a high adherence rate in our trial in which 60% of patients completed blended CBT, and no difference in adherence compared to face-to-face CBT adherence. Kooistra and colleagues [15] also found a high rate of treatment completers (75%) for blended CBT for depression. This is an interesting finding, as it is often found to be difficult to encourage participants to continually engage with interventions in the field of Internet-based treatment [18]. For example, in two previous randomized controlled trials investigating guided Internet-based CBT targeting anxiety disorders [16,19], only about 13% of patients completed the treatment. Our findings on blended CBT adherence may be in indication that acceptability of Internet-based treatment modules can be improved by adding face-to-face sessions.

From the perspective of therapists, fidelity to treatment protocols can be an indicator for acceptability [20]. Prior studies have shown that clear instructions and guidelines are a

precondition to apply blended treatments as intended [16,21]. The RCT we conducted, provided us with an opportunity to examine therapist fidelity in a situation where this condition has been met. The high fidelity we found in terms of distribution and frequency of face-to-face and online sessions, session frequency and instructions regarding the interplay between face-to-face and online sessions seems to be an indication that the blended format is acceptable for therapists.

One other thing that might have an impact on acceptability, are concerns about establishing a therapeutic alliance in blended CBT [21–23] due to modifications in the amount and form of contact between therapist and patient as compared with face-to-face treatment. The role of the therapeutic alliance has been an area of interest in mental health care for many years and seems to be related to treatment outcome [24]. Therapeutic alliance is usually understood as one general factor with three different alliance components, which relate to the bond between patient and therapist, the agreement on the specific tasks in treatment, and the agreement on the therapeutic goals [25]. Evidence presented thus far has shown that the level of therapeutic alliance as rated by the patient is similar in Internet-based treatment and face-to-face treatment, but is mostly based on research outside regular clinical settings [26]. An initial evaluation on blended CBT for depressed patients in routine care showed that therapeutic alliance ratings by both patients and therapists were high and comparable to ratings in face-to-face CBT [15]. In our trial, we found similar results for blended CBT for anxiety, indicating that substitution of a portion of face-to-face sessions with online sessions has no negative effect on therapeutic alliance.

Finally, with regard to treatment satisfaction, patients expressed high levels of satisfaction with blended CBT. These findings are in line with earlier reported positive evaluations of blended CBT [27–29] and high treatment satisfaction [30].

In all, these aspects of acceptability indicate acceptance towards blended CBT in specialized regular clinical settings. This finding should be interpreted carefully, however, as results are expected to be biased because therapists and patients participating in the trial are most probably those who are open-minded toward a blended treatment format.

Blended treatment in routine mental health care

Overall, our findings in terms of acceptability, effectives and cost-effectiveness suggest that uptake of blended CBT in routine care may be feasible and a considerable portion of patients finds it desirable. Certain patient characteristics might give an indication in considering whether a blended treatment approach is suitable for specific patients. Therapists for example suspect that blended CBT is less suitable for patients suffering from personality disorder, trauma or complex symptoms [21]. Yet, no research has confirmed these assumptions. In fact, by now several studies have demonstrated positive treatment outcomes regarding post-traumatic stress disorder [31] and the development of evidence-based Internet-supported interventions targeting personality disorders has been recommended [32]. Regarding blended CBT for patients with anxiety disorders, it should be considered that avoidance behavior might be facilitated in a blended treatment approach since situations that evoke anxiety (e.g.

travelling or meeting new people) can be avoided when doing online sessions from home. On the other hand, blended treatment may lower the barrier to start therapy in the first place compared to face-to-face treatment for these patient groups. Moreover, online contact within a blended treatment can also be an advantage in exposure exercises, because the therapist can support and encourage the patient remotely in anxiety-provoking situations in daily life, such as a bus ride or a visit to the supermarket.

Uptake in routine care settings may be further accelerated due to the growing body of knowledge regarding barriers that have stalled implementation of Internet-supported treatment in routine care thus far, showing that key issues related to patients, therapists and health systems involve technical infrastructure and support, time and resources provided by organizations and knowledge and skills of therapists and patients [21,33,34]. Recently, the outbreak of the COVID-19 crisis has shown that these barriers can be overcome quickly if the situation calls for it [35] and researchers predict that mental health care delivery in post-COVID times will most likely have a more blended form [36]. Nevertheless, official uptake statistics are hard to come by and it is still unclear whether the increased adoption of online therapy is temporary or permanent. For example, a survey under 600 Dutch therapists shows that when COVID-related restrictions are being lifted, the large majority (85%) prefers to return to their old ways of working and provide regular face-to-face therapy at the clinic again [39]. On the other hand, in many instances patients and therapists reported positive experiences regarding online delivery of treatment during the COVID crisis [36,37].

In the RCT described in this dissertation, therapists received treatment protocols with guidelines on how to apply the blended format of the treatment and a training in the use of the blended CBT protocol. Given the positive fidelity results we found, this approach seems to better enable therapists to provide blended therapy as intended, which is in line with previous recommendations [16,21]. Developing treatment protocols and training programs for therapists in order to optimize implementation of blended therapy would therefore be worth the effort and can contribute to overcoming one of the main barriers in the uptake of blended CBT, namely a lack of knowledge on how to apply it [21].

However, although fidelity within the context of this trial was high, strict application of structured treatment protocols is not common in clinical practice [38]. Moreover, the possibility to customize treatment is often mentioned as an important advantage of a blended treatment approach [39]. The multitude of possibilities for tailoring blended treatment is also shown by the wide variety of blended formats that was discussed earlier in this chapter. This leads to the question: what is the right balance between the amount of flexibility and standardization in blended treatment protocols? Previous studies on blended treatment include various formats regarding the ratio between online and face-to-face sessions, and type of content in online versus face-to-face sessions [2,11,40]. A similarity between most blended formats is a face-to-face introduction and finalization of treatment. The positive treatment outcomes that were found for these different formats may be an indication that flexibility in these protocol components is feasible. In other words, it might be left to therapists and patients to decide on the distribution of and content in face-to-face versus

online sessions. However, further research is needed to explore how variations in ratio and type of content affect clinical outcomes. Moreover, based on the finding that a lack of guidelines on how to apply blended treatment results in longer treatment duration and subsequently higher costs [16], consequences of flexibility in these protocol components in terms of cost-effectiveness should be evaluated.

One blended protocol element that appears to be essential and thus leaves no room for flexibility, is the interchange between online sessions and face-to-face sessions. Establishing integration of online elements into treatment is necessary for blended treatment to be acceptable and meaningful for patients [21,41,42] . When therapists pay attention to and react on online patient activity, they play an active role in the integration process, which may prevent therapists from providing online sessions on top of face-to-face sessions and may warrant the contribution of the online sessions to treatment progress. The blended CBT protocol that was studied in this thesis, in which written feedback on all online sessions was provided and time was reserved to discuss the online activity in the face-to-face sessions, may serve as an example on how to establish integration.

All things considered, uptake of Internet–supported treatment can be valuable for mental health care organizations, alongside in person therapy services at the clinic, keeping in mind the fundamental precondition that both patients and therapists are able and willing to use it. In the near future, researchers will have to work closely together with mental health care organizations to explore in what way digital outpatient routine care has to be shaped to ensure sustainable uptake.

Strengths and limitations

The main strength of this dissertation is that research was conducted in a routine care setting and it thus makes a major contribution to bridge the gap between research and practice in the field of Internet-supported CBT targeting anxiety disorders. The included studies provide insight into how well these treatment formats work in real-world settings. Moreover, results offer valuable leads for further dissemination of blended treatment in daily clinical practice.

The previous sections of this thesis discussed several methodological considerations. Some important issues and limitations still deserve to be mentioned. First, as previously described, the number of included participants (n = 114) fell short from the intended number of participants (n = 156), while overrunning the planned time span and expanding enrolment to additional research sites. Therefore, uncertainty in the results should be taken into account. Low recruitment rates in randomized controlled trials in specialized mental health care services are common [43], and recruitment of patients with severe mental health issues in specialized mental health clinics seems to be even more complicated [1,15]. One method to increase chances of including larger sample sizes, would be to extend the duration of studies. However, in a field that must consider the pace of technological developments, this might not be a very pragmatic solution. Another approach to enhancing statistical power has been taken in the E-compared study [44]. In this large randomized controlled trial, data from eight

European countries will be pooled to obtain stable estimates of effects and costs of blended treatment for depressive disorders.

Second, treatment effects were assessed by exclusively using self-administered measures. The golden standard in psychiatric research to ascertain diagnoses and evaluate validity of self-rated questionnaires, is to conduct diagnostic interviews in person or over the phone (World Health Organization, WHO), 1997). In the RCT in this dissertation, the diagnosis anxiety disorder was established at baseline by the use of such an interview, but not in subsequent measurements. This increased validity of the trial, but it may have affected the reliability [45].

Lastly, concerning the calculation of medical costs, some costs associated with the blended treatment were not included. For example, costs of hosting and maintenance of the online treatment platform were not available. This has possibly led to an underestimation of medical costs of blended CBT. However, these fixed costs will decrease by scaling up blended treatment and are therefore expected not be a substantial part of total treatment costs per patient.

Future directions

Blended therapy as an alternative treatment option in routine mental health care warrants further studies in terms of acceptability, feasibility and cost-effectiveness based on the results of our studies. Here, relevant directions will be discussed.

A high-powered RCT comparing blended CBT to face-to-face CBT requires a sample size that was beyond the time frame and cost frame of the current explorative study. Nevertheless, the insights gained in our trial warrant future studies with larger sample sizes, such as the E-compared study on depressive disorders [44], to further examine cost-effectiveness of blended CBT for anxiety disorders.

With regard to blended treatment, it is still unclear how the different treatment components exactly work together and what optimal combinations of online and face-to-face treatment components are. RCT's are most frequently used in evaluations of clinical interventions, but other research designs are more suitable to investigate these types of research questions. For example, a factorial design allows for testing multiple intervention components and detecting interactions amongst components, without losing statistical power [46]. Greater use of such designs in research of Internet-supported and blended interventions is recommended.

Further, to further narrow the gap between research and practice, it is essential to focus more on sustainability of Internet-supported treatment in routine care. Sustainability is major challenge and depends on the complex interplay of individual, social, organizational, and economic factors. Variables such as intervention adaption, continual financial support and training seem to contribute to sustainability, but much more needs to be learned [46]. Additionally, the focus of therapist education is on providing in person face-to-face treatment nowadays. To sustain and normalize the use of Internet-supported treatment, skills regarding Internet-supported delivery must be given a more prominent place in therapist training and it

is advisable to monitor to which degree attention for these skills is growing in future education programs.

Finally, investigating acceptability of an intervention in the context of a randomized controlled trial is complicated due to the risk of selection bias. However, Dutch mental health care organizations are now shaping online outpatient routine care in a way that allows for large-scale observational research in order to evaluate the real-world need for and acceptability of Internet-supported treatments.

References

1. Kok RN, van Straten A, Beekman ATF, Cuijpers P. Short-term effectiveness of web-based guided self-help for phobic outpatients: randomized controlled trial. J Med Internet Res. 2014;16: e226. doi:10.2196/jmir.3429
2. Bruinsma A, Kampman M, Exterkate CC, Hendriks GJ. An exploratory study of “blended” cognitive behavioural therapy (CBT) for patients with a panic disorder: results and patients’ experiences. Tijdschr Psychiatr. 2016;58: 361–370.
3. Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki A, Eriksson S, et al. Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. Behav Res Ther. 2014;59: 1–11. doi:10.1016/j.brat.2014.05.007
4. Mohr DC, Spring B, Freedland KE, Beckner V, Arean P, Hollon SD, et al. The selection and design of control conditions for randomized controlled trials of psychological interventions. Psychother Psychosom. 2009;78: 275–284. doi:10.1159/000228248
5. Mohr DC, Ho J, Hart TL, Baron KG, Berendsen M, Beckner V, et al. Control condition design and implementation features in controlled trials: a meta-analysis of trials evaluating psychotherapy for depression. Transl Behav Med. 2014;4: 407–423. doi:10.1007/s13142-014-0262-3
6. Bandelow B. Assessing the efficacy of treatments for panic disorder and agoraphobia. II. The Panic and Agoraphobia Scale. Int Clin Psychopharmacol. 1995;10: 73–82. doi:10.1097/00004850-199506000-00003
7. Lambert M, Morton J, Hatfield D, Harmon C, Hamilton S, Shimokawa K. Administration and scoring manual for the OQ-45.2 (Outcome Questionnaire) (3e dr). Wilmington; 2004.
8. Romijn G, Batelaan N, Koning J, Balkom A Van, Leeuw A de, Benning F, et al. Acceptability, effectiveness and cost-effectiveness of blended cognitive-behavioural therapy (bCBT) versus face-to-face CBT (ftfCBT) for anxiety disorders in specialised mental health care: A 15- week randomised controlled trial with 1-year follow-up. PLoS ONE 16 (11): e0259493. doi.org/10.1371/journal.pone.0259493
9. Zwerenz R, Becker J, Knickenberg RJ, Siepmann M, Hagen K, Beutel ME. Online Self-Help as an Add-On to Inpatient Psychotherapy: Efficacy of a New Blended Treatment Approach. Psychother Psychosom. 2017;86: 341–350. doi:10.1159/000481177

10. Berger T, Krieger T, Sude K, Meyer B, Maercker A. Evaluating an e-mental health program ("deprexis") as adjunctive treatment tool in psychotherapy for depression: Results of a pragmatic randomized controlled trial. J Affect Disord. Elsevier B.V.; 2018;227: 455–462. doi:10.1016/j.jad.2017.11.021
11. Nordgreen T, Haug T, Ost L-G, Andersson G, Carlbring P, Kvale G, et al. Stepped Care Versus Direct Face-to-Face Cognitive Behavior Therapy for Social Anxiety Disorder and Panic Disorder: A Randomized Effectiveness Trial. Behav Ther. 2016;47: 166–183. doi:10.1016/j.beth.2015.10.004
12. Krol M, Papenburg J, Koopmanschap M, Brouwer W. Do Productivity Costs Matter? Costs of Interventions Targeted at Depressive Disorders. Pharmoeconomics. 2011;29: 601–619.
13. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Costs of nine common mental disorders: Implications for curative and preventive psychiatry. J Ment Health Policy Econ. 2006;
14. Black WC. The CE Plane: A Graphic Representation of Cost-Effectiveness. Med Decis Mak. 1990; doi:10.1177/0272989X9001000308
15. Kooistra LC, Wiersma JE, Ruwaard J, Neijenhuijs K, Lokkerbol J, Van Oppen P, et al. Cost and effectiveness of blended versus standard cognitive behavioral therapy for outpatients with depression in routine specialized mental health care: Pilot randomized controlled trial. J Med Internet Res. 2019;21. doi:10.2196/14261
16. Kenter RMF, van de Ven PM, Cuijpers P, Koole G, Niamat S, Gerrits RS, et al. Costs and effects of Internet cognitive behavioral treatment blended with face-to-face treatment: Results from a naturalistic study. Internet Interv. 2015;2: 77–83. doi:10.1016/j.invent.2015.01.001
17. Nadal C, Sas C, Doherty G. Technology acceptance in mobile health: Scoping review of definitions, models, and measurement. J Med Internet Res. 2020;22: 1–17. doi:10.2196/17256
18. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression. J Med Internet Res. H. Christensen, Centre for Mental Health Research, Australian National University, Canberra, ACT 0200, Australia; 2009;11. Available: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354703306
19. Kok RN, Beekman ATF, Cuijpers P, van Straten A. Adherence to a web-based pre-treatment for phobias in outpatient clinics. Internet Interv. Elsevier; 2017;9: 38–45. doi:10.1016/j.invent.2017.05.004
20. Sekhon M, Cartwright M, Francis JJ. Acceptability of health care interventions: A theoretical framework and proposed research agenda. Br J Health Psychol. 2018;23: 519–531. doi:10.1111/bjhp.12295
21. Mol M, van Genugten C, Dozeman E, van Schaik DJF, Draisma S, Riper H, et al. Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A

Qualitative Study on Therapists' Perspectives. J Clin Med. 2019;9: 91. doi:10.3390/jcm9010091

22. van der Vaart R, Witting M, Riper H, Kooistra L, Bohlmeijer ET, van Gemert-Pijnen LJEWC. Blending online therapy into regular face-to-face therapy for depression: Content, ratio and preconditions according to patients and therapists using a Delphi study. BMC Psychiatry. 2014;14: 1–10. doi:10.1186/s12888-014-0355-z
23. Topooco N, Riper H, Araya R, Berking M, Brunn M, Chevreul K, et al. Attitudes towards digital treatment for depression: A European stakeholder survey. Internet Interv. The Authors; 2017;8: 1–9. doi:10.1016/j.invent.2017.01.001
24. Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in Individual Psychotherapy. Psychotherapy. 2011;48: 9–16. doi:10.1037/a0022186
25. Bordin ES. The generalizability of the psychoanalytic concept of the working alliance. Psychother Theory, Res Pract. 1979;16: 909–912. doi:10.1016/B978-0-12-809324-5.05450-X
26. Berger T. The therapeutic alliance in internet interventions: A narrative review and suggestions for future research. Psychother Res. 2017;27: 511–524. doi:10.1080/10503307.2015.1119908
27. Hadjistavropoulos HD, Pugh NE, Nugent MM, Hesser H, Andersson G, Ivanov M, et al. Therapist-assisted Internet-delivered cognitive behavior therapy for depression and anxiety: Translating evidence into clinical practice. J Anxiety Disord. Elsevier Ltd; 2014;28: 884–893. doi:10.1016/j.janxdis.2014.09.018
28. Hoifodt RS, Strom C, Kolstrup N, Eisemann M, Waterloo K. Effectiveness of cognitive behavioural therapy in primary health care: a review. Fam Pract. England; 2011;28: 489–504. doi:10.1093/fampra/cmr017
29. Månsson KNT, Ruiz ES, Gervind E, Dahlin M, Andersson G. Development and initial evaluation of an internet-based support system for face-to-face cognitive behavior therapy: A proof of concept study. J Med Internet Res. 2013;15. doi:10.2196/jmir.3031
30. Kooistra LC, Ruwaard J, Wiersma JE, van Oppen P, van der Vaart R, van Gemert-Pijnen JEWC, et al. Development and initial evaluation of blended cognitive behavioural treatment for major depression in routine specialized mental health care. Internet Interv. 2016;4: 61–71. doi:10.1016/j.invent.2016.01.003
31. Bakker A, Riper H, Olff M. E-health applications in the field of traumatic stress. Eur J Psychotraumatol. Taylor & Francis; 2020;11. doi:10.1080/20008198.2020.1762317
32. Reis S, Matthews EL, Grenyer BFS. Characteristics of effective online interventions: Implications for adolescents with personality disorder during a global pandemic. Res Psychother Psychopathol Process Outcome. 2020;23: 256–278. doi:10.4081/RIPPPO.2020.488
33. Vis C, Mol M, Kleiboer A, Bührmann L, Finch T, Smit J, et al. Improving implementation of emental health for mood disorders in routine practice: Systematic review of barriers and facilitating factors. J Med Internet Res. 2018;20. doi:10.2196/mental.9769

34. Titzler I, Saruhanjan K, Berking M, Riper H, Ebert DD. Barriers and facilitators for the implementation of blended psychotherapy for depression: A qualitative pilot study of therapists' perspective. Internet Interv. Elsevier; 2018;12: 150–164. doi:10.1016/j.invent.2018.01.002
35. Wind TR, Rijkeboer M, Andersson G, Riper H. The COVID-19 pandemic: The 'black swan' for mental health care and a turning point for e-health. Internet Interv. Elsevier B.V; 2020; 100317. doi:10.1016/j.invent.2020.100317
36. Bierbooms JJPA, van Haaren M, IJsselsteijn WA, de Kort YAW, Feijt M, Bongers IMB. Integration of online treatment into the "new normal" in mental health care in post-COVID-19 times: Exploratory qualitative study. JMIR Form Res. 2020;4: 1–7. doi:10.2196/21344
37. Feijt M, De Kort Y, Bongers I, Bierbooms J, Westerink J, Ijsselsteijn W. Mental Health Care Goes Online: Practitioners' Experiences of Providing Mental Health Care during the COVID-19 Pandemic. Cyberpsychology, Behav Soc Netw. 2020;23: 860–864. doi:10.1089/cyber.2020.0370
38. Addis ME, Krasnow AD. A national survey of practicing psychologists' attitudes toward psychotherapy treatment manuals. J Consult Clin Psychol. 2000;68: 331–339. doi:10.1037/0022-006X.68.2.331
39. Urech A, Krieger T, Möseneder L, Biaggi A, Vincent A, Poppe C, et al. A patient post hoc perspective on advantages and disadvantages of blended cognitive behaviour therapy for depression: A qualitative content analysis. Psychother Res. 2018; 1–13. doi:10.1080/10503307.2018.1430910
40. Marks IM, Kenwright M, McDonough M, Whittaker M, Mataix-Cols D. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med. 2004;34: 9–17. doi:10.1017/S003329170300878X
41. Wentzel J, van der Vaart R, Bohlmeijer ET, van Gemert-Pijnen JEWC. Mixing Online and Face-to-Face Therapy: How to Benefit From Blended Care in Mental Health Care. JMIR Ment Heal. 2016;3: e9. doi:10.2196/mental.4534
42. Urech A, Krieger T, Möseneder L, Biaggi A, Vincent A, Poppe C, et al. A patient post hoc perspective on advantages and disadvantages of blended cognitive behaviour therapy for depression: A qualitative content analysis. Psychother Res. 2018;3307: 1–13. doi:10.1080/10503307.2018.1430910
43. Campbell MK, Snowdon C, Francis D, Elbourne DR, McDonald AM, Knight R, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STePS study. Health technology assessment (Winchester, England). 2007. pp. 11(48), iii, ix–105.
44. Kleiboer A, Smit J, Bosmans J, Ruwaard J, Andersson G, Topooco N, et al. European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED): Study protocol for a randomized controlled, non-

inferiority trial in eight European countries. Trials. 2016;17: 1–10. doi:10.1186/s13063-016-1511-1

45. Eaton WW, Neufeld K, Chen L-S, Cai G. A comparison of self-report and clinical diagnostic interviews for depression. Arch Gen Psychiatry. 2000;57: 222.

46. Baker TB, Gustafson DH, Shah D. How can research keep up with eHealth? Ten strategies for increasing the timeliness and usefulness of Ehealth research. J Med Internet Res. 2014;16: 1–10. doi:10.2196/jmir.2925

Chapter 7

Summary

Anxiety disorders are one of the most prevalent mental health problems. They are associated with considerable individual suffering and substantial economic burden. Cognitive behavioral therapy (CBT) is considered the golden standard in psychological treatment for anxiety disorders. Internet-supported CBT, that is delivered fully or partly via the Internet, is often discussed as a promising way to increase treatment availability and reduce treatment costs. Previous studies have shown the potential of Internet-supported CBT in research settings. Whether these results generalize to clinical populations, however, is unclear. The main purpose of the present thesis is to examine the acceptability, effectiveness, and cost-effectiveness of Internet-supported CBT for anxiety patients in routine outpatient clinics.

The meta-analysis in **chapter 2** encompasses the current state of knowledge of Internet-supported CBT for anxiety disorders. The main research question was whether trials that apply an open recruitment strategy, inviting individuals with anxiety symptoms from within the community to partake in the study, produce effects similar to those of trials with clinical service recruitment, inviting patients already seeking treatment in clinical practices to participate. Results showed smaller effect sizes for clinical service recruitment trials (g=0.28) than those found in trials with an open recruitment method (g=0.79) for studies with waitlist control comparators. Additional analyses revealed that the differences in effect sizes of open recruitment versus clinical service recruitment trials might be partly explained by patients' greater therapy adherence in open recruitment trials (association with a small, positive slope) and the stricter exclusion of patients with severe depressive symptoms in these studies. This meta-analysis showed novel meta-analytic evidence that Internet-supported CBT is effective in samples recruited in routine clinical practice. It also confirmed that a large part of the current body of evidence on Internet-supported anxiety treatment is based on the examination of samples that were recruited through an open recruitment method and thus underlined the importance of conducting more studies with routine care populations to further validate effectiveness findings for clinical populations.

Chapter 3 describes the protocol for a randomized controlled trial in routine specialized mental health care to explore the potential cost-effectiveness of blended CBT in comparison with face-to-face CBT and **chapter 4** reports the results of this trial. Blended CBT is a form of Internet-supported CBT in which part of the therapy is provided online and part face-to-face. Compared to fully Internet-based treatment, a blended format is thought to be more suitable to apply in routine care settings, because it may be more acceptable to patients who experience serious or complex symptoms and their therapists, and it may be less disruptive to the organization of care. The trial focused on acceptability, effectiveness and cost-effectiveness of blended CBT versus to face-to-face CBT in outpatient specialized mental health care services to patients with panic disorder with or without agoraphobia, social anxiety disorder and generalized anxiety disorder. Acceptability was evaluated by assessing treatment preference, adherence, satisfaction and therapeutic alliance. A total of n = 114 anxiety patients in four specialized mental health care services were included in the trial

(blended CBT n = 52; face-to-face CBT n = 62). Results show that blended CBT is an acceptable treatment option for patients in a clinical setting in terms of treatment preference, adherence, therapeutic alliance and treatment satisfaction. Of the patients who consented to participate in the trial, 54% would have preferred to start with blended CBT above face-to-face CBT. Therapeutic alliance and treatment satisfaction were high for both blended CBT and face-to-face CBT patients, and treatment adherence rates were comparable for both groups. With regard to effectiveness in reducing anxiety symptoms, linear mixed model analyses revealed no significant differences between blended CBT and face-to-face CBT at post-treatment (t = −0.715, p = 0.477) nor at one-year follow-up (t = 1.702, p = 0.093). Both groups exhibited moderate to large within-group effect sizes (range of *d:* 0.50 to 1.00). Moreover, no significant differences between the groups were found in terms of effects on depressive symptoms, general psychopathology, sense of control (mastery), work and social functioning or quality of life, with within-group effect sizes ranging from small to large (range of *d:* 0.13 to 0.98). When comparative costs and effects were combined in cost-effectiveness analyses, results showed that blended CBT had a high probability of cost-effectiveness from both the healthcare perspective and the societal perspective in terms of QALYs. The results of the study indicate that blended CBT may be an acceptable, clinically effective and potentially cost-saving alternative option for treating patients with anxiety disorders.

In **chapter 5** we zoomed in on therapist fidelity to the blended CBT protocol. Therapist fidelity is defined as the extent to which treatment is carried out as outlined in the treatment manual. In case of poor treatment fidelity, symptom changes cannot be attributed to the intervention, and consequently hampers replication and dissemination of a treatment. Fidelity is particularly important when comparing a novel treatment format like blended CBT to an existing treatment, because without evidence of treatment fidelity, it can be difficult to understand differences between treatments for example in terms of clinical outcome. In the RCT described in chapter 4, therapists received treatment protocols with guidelines on how to apply the blended format of the treatment and a training in the use of the blended CBT protocol. Results showed that overall therapist fidelity with regard to the blended format (ratio of blending and session frequency) and to the instructions pertaining to the interplay between face-to-face and online sessions was high, indicating that delivery of blended CBT in the applied format is feasible for therapists in specialized mental health care. In other words, one of the main barriers in the uptake of blended CBT (a lack of knowledge on how to apply blended therapy) might be overcome by providing therapists with clear instructions and guidelines on how to apply it. Moreover, the findings enhance confidence in the findings on effectiveness and cost-effectiveness of blended CBT reported in chapter 4.

Chapter 6 provides a general discussion of the research presented in this thesis, including the main findings, strengths, limitations, and implications, as well as suggestions for future research.

Chapter 8

Dankwoord

Het is zover, het is af! Wat in 2015 begon met een gesprek met Heleen Riper en Jeroen Koning ergens in een grijs en stoffig VU-kantoor, heeft uiteindelijk dan toch tot dit resultaat geleid: een heus proefschrift. De vergelijking tussen promoveren en een marathon lopen, ben ik de afgelopen jaren steeds beter gaan begrijpen. Onderweg heb ik veel geleerd, hard gelachen en enorm afgezien. En nu ik de finish gehaald heb, waan ik mij weer op de Coolsingel met een medaille om mijn nek en een koud biertje voor mijn neus. Proost!

Uiteraard wil ik Heleen, Ton, Neeltje en Jeroen bedanken voor hun begeleiding en hun vertrouwen in mij. Ik heb ontzettend veel van jullie geleerd. Over eHealth, angststoornissen, geestelijke gezondheidszorg en onderzoek. Op lastige momenten wisten jullie me te motiveren of voorzagen jullie me van nieuwe inzichten. Ook wil ik Robin bedanken, die me bij de start op de VU heeft opgevangen, nooit te beroerd was om mijn vele vragen te beantwoorden en me daarbij ook nog eens altijd aan het lachen wist te maken.

De leden van de beoordelingscommissie, prof. dr. Thomas Berger, prof. dr. Antoinette de Bont, prof. dr. Judith Bosmans, dr. Els Dozeman en dr. Tim Wind onder voorzitterschap van prof. dr. Marit Sijbrandij, wil ik bedanken voor het beoordelen van mijn proefschrift.

Dank aan alle collega's van de VU en Team Riper: Dilfa, Chani, Alyssa, Angel, Khadicha, Lisa, Mayke, Lise, Claudia, Felix, Joost, Niko, Christiaan, Wouter, Eirini, Anne, Metta, Marketa, Johan, Sherida, Deborah en van het Altrecht Academisch Angstcentrum: Sophie, Mathilde, Niels, Maartje, Suzy, Daniëlle, Aard.

Natuurlijk ook veel dank aan de GGZ-instellingen, alle patiënten en behandelaars die hebben meegewerkt aan de onderzoeken in dit proefschrift.

Collega's van de Digitale Poli van GGz Breburg - Annette, Priscilla, Fatos, Harvey, Jan, Sandra - wat een aangenaam avontuur om samen met jullie de praktijk van het online behandelen te verkennen. Bedankt voor jullie enthousiasme en de goede sfeer in ons team.

Mijn paranimfen verdienen ook zeker een alinea in dit dankwoord. Lieve Simon en Simone, zonder jullie waren de jaren waarin ik aan dit proefschrift heb gewerkt veel minder fijn geweest. Ik ben blij dat ik jullie op deze spannende dag aan mijn zijde heb. Dank jullie wel!

Daarnaast zijn er buiten mijn werk vele mensen die mijn leven een stuk leuker maken, onder meer door een gedeelde liefde voor festivals, sporten, eten en drinken. Bedankt dat jullie er zijn lieve vrienden: Mariska, Laurens, Thomas, Maartje, René, Robin, Marvin, Nick, Daphne, Ruud, Bart, Thomas, Marco, Mariska, Hans, Morgane, Ankie, Jeroen, Carianne, Mark, Rob, Tanja, loopmaatjes van Loopgroep Hank, dames van v.v. Be Ready, polonaisetoppers van C.V. NG&TN.

Dan heb ik ook nog een hele lieve (schoon)familie. Pim, René, Ben, Garda, Geert en Roos, wat fijn dat ik jullie om me heen heb. Maya, Yfke, Lobke, ik zou niet meer zonder de nichtjesclub kunnen! Janneke en Willemieke, ik ben zo trots op onze ijzersterke band, ondanks dat we drie totaal verschillende zussen zijn. Jullie zijn mijn rotsen in de branding. Allerliefste pa en ma, bedankt voor alles. Dankzij jullie ben ik wie ik ben.

Suus, met jou ben ik op mijn gelukkigst. Van suppen in de Biesbosch tot fietsen in Limburg, van meeblèren met Ferry van de Zaande tot nachten doorhalen op Lowlands, van bier drinken bij café ’t Sandoel tot negen gangen bij The Jane, van de IJslandse geisers en de Noorse fjorden tot de Italiaanse Dolomieten en Mount Cook in Nieuw-Zeeland. Ik hou van jou, wel 100 ($p<.05$).

Blending online and offline anxiety treatment in routine mental health care

Research on acceptability, effectiveness and cost-effectiveness of Internet-supported and blended cognitive behavioral therapy for patients with severe anxiety disorders

Geke Romijn