A mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy intervention for depression in a multinational randomised controlled trial in Europe

ASMAE DOUKANI

Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

2024

Department of Population Health
Faculty of Epidemiology and Population Health
LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

No funding received

Research group affiliation:
Centre for Global Mental Health

Primary Supervisor	Dr Ritsuko Kakuma Associate Professor Faculty of Epidemiology and Population London School of Hygiene and Tropical Medicine
Co-supervisors	Professor Caroline Free Professor of Primary Care and Epidemiology Faculty of Epidemiology and Population London School of Hygiene and Tropical Medicine
	Professor Ricardo Araya Professor of Global Mental Health Institute of Psychiatry King's College London
Advisory Committee	Dr Daniel Michelson Senior Lecturer Institute of Psychiatry King's College London
	Dr Matteo Quartagno Senior Research Fellow Institution of Clinical Trials and Methodology University College London
	Dr Francesco Sera Research Fellow Department of Statistics, Computer Science and Applications "G. Parenti" University of Florence

Declaration of own work

I, Asmae Doukani, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Date: 11th November 2024

Abstract

The client and therapist working alliance is widely considered as an important predictor of positive outcomes in face-to-face psychological therapies, but little is known about this concept in blended cognitive behavioural therapy (b-CBT) involving a digital programme and face-to-face sessions. My thesis evaluated the working alliance from client and therapist perspectives in b-CBT and when compared to face-to-face cognitive behavioural therapy (CBT) for depression in Europe.

My thesis was nested in a clinical trial investigating the effectiveness of different formats of b-CBT compared to usual care, for adults with depression in nine European countries. A mixed methods approach was adopted. Semi-structured interviews qualitatively explored client and therapist experiences of the working alliance in b-CBT in the UK. Secondary analysis of a subset of pooled data evaluated client (n=676) and therapist (n=616) working alliance scores using linear regression models to test the difference between b-CBT versus face-to-face CBT; determine if working alliance scores are associated with depression scores in b-CBT; and if programme system usability scores influence this association in b-CBT 3-months post-randomisation.

Client qualitative interviews (n=19) found a new working alliance dimension called 'digital heuristics', defined as a digital programmes' promotion of active engagement, self-discovery, and autonomous problem-solving. Therapist qualitative interviews (n=13) outlined barriers and facilitators to fostering the working alliance in relation to experiences of time in b-CBT, the functionality of the digital programme, ability to tailor b-CBT, and confidence in delivering b-CBT. Quantitative findings showed that working alliance scores were significantly higher in b-CBT compared to face-to-face CBT for client but not therapist scores. In b-CBT, higher client and therapist working alliance scores were associated with improvements in client depression scores, and were influenced by programme usability scores.

Collectively my thesis shows that b-CBT may enhance the quality of the working alliance when compared to face-to-face CBT. The digital programme should therefore be considered when assessing the working alliance in b-CBT for depression.

Acknowledgement

My PhD journey has been a long and winding road, filled with peaks and troughs, wins and losses, challenges, and personal growth. I have many people to thank and would like to express my gratitude to all of the people who supported me along the way.

First and foremost, I would like to thank my PhD supervisors Dr Ritsuko Kakuma and Professor Caroline Free for their continuous support, guidance, and input during my PhD, for which I am enormously grateful for. I also owe much gratitude to previous PhD supervisors, including Professor Ricardo Araya for giving me an opportunity to enroll as a staff PhD student alongside my research role; Dr Daniel Michelson who took over my supervision when Professor Araya left London School of Hygiene and Tropical Medicine (LSHTM), Professor Free for holding the fort while we searched for a new primary supervisor, and last but not least, Dr Kakuma who took over as my final primary supervisor following Dr Michelson's departure. I am also extremely grateful to Professor Araya and Dr Michelson for their continued support, and to my PhD advisors, Dr Matteo Quartagno and Dr Francesco Sera, who have been incredibly kind, supportive, and generous with their time, despite also moving institutions.

I am immensely grateful to Professor Heleen Riper and Dr Annett Kleiboer for granting me permission to use data from the E-COMPARED trial for my PhD, and for their responsiveness despite being incredibly busy. I am very much indebted to Dr Arlinda Cerga-Pashoja, my line manager, for her understanding and support during critical phases of my PhD, and for keeping me employed during much of my time at LSHTM, which is a requirement for completing a staff PhD. I would like to thank all of my colleagues at the Centre for Global Mental Health for their encouragement and support.

I thank Dr Sarah Smith for her support during the initial phases of my PhD, even though I was unable to use it in my thesis. I am also extremely grateful to Dr Nicki Thorogood for her kindness, support, and for helping me stay motivated while transitioning between supervisors.

Undertaking a staff PhD. is a privilege that I will always be grateful for, however, there have been many times when I have felt stuck, and disheartened while navigating through multiple hurdles, setbacks, and life's curve balls. I am immensely grateful to Dr Andrew Clarke for his mentorship, in which he provided motivation and direction through his shared wisdom, which marked a turning point in my PhD journey. I am also extremely grateful to Jon Acuff for writing the book 'Finish' that helped simplify the path to the finish line.

I am lucky to have received a tremendous amount of support from friends, which I am enormously grateful for. I would like to especially thank my dear friends, Linda and Theresa for their friendship and

support, and Elaine, Natasha, and Caroline for their encouragement and for being a joy to work with. I am extremely grateful to my friends Dr Azuzena Guzman and Dr Elaine Flores for reviewing my chapters, both of which helped me when I couldn't see the wood for the trees.

I would like to express my gratitude to the 11 patient advisors with lived experienced who took time out of their busy schedules to help with my PhD, including Abé Chekh-Dove El-Ghassani, Michael Clarke, Paul H Ware, Dr Sarah Markham, and Tibby Stodel (who have given me permission to name them). I would also like to thank Shamila Usmani for helping with the patient involvement meetings and Dr Jennifer Walke for her help in collecting data for the focus groups with therapists.

Lastly, I have no words to thank my parents and siblings for their unwavering encouragement, for always believing in me, and for getting me through the hard times.

Table of abbreviations

APA	American Psychological Association
b-CBT	Blended-Cognitive Behavioural Therapy
CBT	Cognitive Behavioural Therapy
COVID-19	Coronavirus disease
E-COMPARED	European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual
DMHIs	Digital mental health interventions
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder-IV
IAPT	Improving Access to Psychological Services
iCBT	Internet based cognitive behavioural therapy
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
MAR	Missing at random
MNAR	Missing not at random
M.I.N.I.	Mini-International Neuropsychiatric Interview
MDD	Major Depressive Disorder
PHQ-9	Patient Health Questionnaire-9
PWP	Psychological wellbeing practitioner
SUS-C	System Usability Scale - Client
SUS-T	System Usability Scale -Therapist
TAU	Treatment as usual
WAI-SR-C	Working Alliance Inventory-Short Revised-Client
WAI-SR-T	Working Alliance Inventory-Short Revised-Therapist
WHO	World Health Organization

Tables of contents

List of Appendices .....

Table of table

Table of figures

Chapter 1: Introduction

1.1 Introduction to chapter 1

This chapter provides a synopsis of my thesis, which is a mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy (b-CBT) intervention that involves both therapist and digital programmes sessions, when compared to usual care for depression, in a clinical trial in Europe. The chapter will begin by presenting a description of the working alliance and why it's important (see *Section 1.2)* and defining key terminology used throughout my thesis (*Section 1.3*). This chapter will then provide an overview of the rationale of my thesis (*Section 1.4*), the research, aims, objectives (*Section 1.5*), and significance of my thesis (*Sections 1.6*). Lastly, the introduction will also outline the context in which my research was conducted (*Section 1.7*), key information about my PhD journey and contributions (*Section 1.8*), and a brief summary of the chapters of my thesis (*Section 1.9*).

1.2 Introducing the working alliance

Depression is a highly prevalent and disabling condition that negatively effects peoples' ability to function across a range of life domains [1–3]. Cognitive behavioural therapy (CBT) for depression is a talking therapy that is recommended as a first-line psychological intervention. CBT aims to alleviate distress by helping clients develop adaptive thoughts and behaviours [4,5]. All psychological therapies, including CBT, are driven by common active ingredients that enable clients' to meaningfully engage in therapy, with the most prominent concept called the working alliance [6].

The working alliance is a component of a wider human-to-human relational framework that is considered to be an important mechanism of change in psychological therapies [6–8]. The working alliance has traditionally been conceptualised between the client seeking therapy, and their therapist in a face-to-face context [8]. The literature suggests that when clients' rate their working alliance with their therapist highly, and vice-versa, the client is more likely to experience positive treatment outcomes [8–10]. These findings hold true not only for CBT for depression, but across a range of psychological approaches, and mental health conditions [8–13]. This makes the working alliance an essential component in all psychological therapies, including novel and emerging therapeutic formats that include digital technologies [8,14].

This thesis adopts Edward Bordin's [6,7] tripartite theory of the working alliance, which is defined as the, (1) agreement between the client and the therapist on the therapeutic goals, (2) the tasks needed to

advance the client's goals, (3) and the emotional bond that helps to maintain a sense of partnership throughout treatment. More specifically, goals are defined as a collaborative effort between the client and the therapist to identify what the client wants to achieve through therapy. Task refers to an agreed-upon plan of action which specifies the means by which the clients' goal can be achieved. It also involves meaningful exchange between the client and their therapist to support the completion of the task. A bond is developed from shared activities and compatibility between the client and the therapist. Here, compatibility is expressed in terms of liking, trusting, and respecting one another. Figure 1.1, which was originally developed by Henson and colleagues [15: p.270] to depict the client-app alliance model, also conveys Bordin's [6,7] conceptualisation of the goals', task's, and bond's role in fostering a working alliance.

Figure 1.1. Working alliance dimensions goals, task and bond. This figure was developed by Henson and colleagues [15: p.270] to illustrate the patient-app alliance model

Bordin's [6,7] working alliance outlines common features that are found across all psychological therapies. However, he also posits that the building of the alliance is not separate from the intervention, in which different therapy approaches may place different demands on the working alliance. The American Psychological Association (APA) emphasised the importance of exploring such demands in novel psychological interventions that include digital technologies [6–8], highlighting scope to adapt the working alliance to consider the digital programme.

The working alliance is commonly measured using a self-report questionnaire [16–18], that capture clients' and therapists' ratings in relation to how they experienced goals, task, and bond [6,7]. Research

in this field has predominantly focused on understanding if the working alliance can predict treatment outcomes [8]. The working alliance is discussed in more detail in *Section 2.5*, in Chapter 2.

1.3 Explanation of terminology

This thesis uses several terms to describe the working alliance, the mental health practitioner, the digital mental health intervention (DMHI), and the level of support received by the client while completing DMHIs. This section will define and provide contextual information on how these terms are used in my thesis.

The working alliance is one of many terms used to describe client and therapist relationships in psychological therapies [8]. Other terms that are commonly used (although not limited to) include the therapeutic relationship, the therapeutic alliance, and the helping alliance [19]. While these concepts overlap considerably, they refer to distinct gradients of the client-therapist relationship, that are often rooted in different psychotherapeutic philosophies [20] and/or measurement scales [19] (distinctions are described under *Section 2.5.4* in Chapter 2). To honour these distinctions when describing other research studies, this thesis will apply the same term used within the source cited. However, the term *alliance* as a singular will be used when collectively describing multiple sources that use different labels.

DMHIs broadly refer to the use of digital technologies to support mental health systems at different levels including, service users, health care providers, health systems and data collection and management [21]. This thesis will use DMHIs to refer to a broad range of digital innovations that are used to support the mental health of *clients* and will apply the same term when citing a single source.

A broad range of mental health professionals support DMHIs. The term therapists will be adopted when summarising a body of literature used to describe different mental health professionals delivering or supporting psychological therapies, while the same term that is cited from a single source will be used. The same principles apply when referring to different components of my thesis that either focus on a specific cadre of staff in the UK called Psychological Wellbeing Practitioners (PWPs) or different types of therapists providing treatment across all E-COMPARED sites.

Internet-based CBT (iCBT) interventions are among the most common DMHIs [22]. iCBT is often supplemented with different levels of therapist support either through digital mediums (e.g., telephone, online) and/or in-person settings that are either unguided, guided, or blended [22]. Unguided interventions refer to receiving no support during the course of treatment; guided interventions refer to

receiving some support from a mental health practitioner, whereas blended treatments typically offer the highest level of clinical support, that is generally provided by a therapist within a clinical setting [22].

This thesis defines a b-CBT intervention as involving face-to-face CBT and an iCBT programme that is included in one treatment protocol [23]. The iCBT programmes evaluated in my thesis were accessed through a website, that included, CBT programme content, interactive activities, and limited feedback [23]. The iCBT programme was supplemented with an adjunct mobile-app that supported activities on the internet-based programme (e.g., mood monitoring, appointment reminders) [23]. My thesis will use the term 'digital programme' to refer to digital components (i.e., the iCBT programme and mobile app) of the blended intervention.

1.4 Rationale

According to the World Health Organization (WHO), depression is the leading cause of disability globally [1], and an estimated 25% of the population in the European region are effected by depression and anxiety [24]. Digital technologies are increasingly being deployed to support and expand mental health care, in aid of addressing the burden of mental illness [25,26]. Over the past decade, DMHIs have become increasingly popular, in which several tools have been adopted to support the mental health care of clients, most commonly through the use of internet-based CBT (iCBT) [15,27–30]. Growing evidence shows that internet or computer-based interventions can be effective in treating mild-to-moderate depression [31–33], however little is known about the role of the client-therapist alliance, which is critically important for enabling meaningful engagement and positive treatment outcomes in psychological therapies [8,20].

Few studies have explored the alliance in DMHIs at a conceptual level [34–36]. The available literature appears to indicate that the digital programme can lead to additional alliance related benefit such as greater client independence and autonomy [34–36]. While these studies have focused on unsupported digital programmes that were completed autonomously [34,35], or app-based interventions for severe mental health conditions [36], to my knowledge, no study has attempted to conceptually understand the working alliance needs of both clients and therapists, within the context of a b-CBT intervention for depression.

Between 2012-2020, four literature reviews examined the alliance in DMHIs for common mental disorders. DMHIs covered in these reviews largely involved text-exchange, email, telephone, guided/internet programme interventions, and guided smartphone interventions [37–40]. These studies found a dearth of research, in which only 0.36% and 9.5% (N=6, and N=11) of the studies focusing on

DMHIs, evaluated the working alliance [37,38]. While these reviews reported mixed and inconclusive results concerning the association between the alliance and treatment outcomes, there was evidence that higher alliance scores were associated with better treatment outcomes when DMHIs were supported by therapists [37,39,40].

More recently, three studies evaluated the working alliance in b-CBT for depression [41–43]. However, a significant effect for treatment condition was not found for client and therapist working alliance ratings [42,43]. A significant client-outcome association was found for therapists' rating of the working alliance, for one out of the three studies, and not for the remaining therapist and client correlations [41–43]. Notably, the study that found a significant alliance-outcome association employed the largest sample size (i.e., n=75) compared to studies that did not find an effect (i.e., n=38 and n=47) [42,43], which may indicate that the study was under sampled to detect an effect [41–43].

In summary, while there is growing interest in understanding and evaluating the working alliance, to my knowledge no study has explored client and therapist working alliance demands in b-CBT for depression conceptually. Moreover, quantitative evidence on the working alliance in b-CBT for depression is sparse, with existing studies utilising small sample sizes [42,43].

Considering the increased adoption of digital innovations in mental health care through guided and blended formats of therapy [8,15,29,30,44], evaluating the working alliance in a b-CBT environment is critical for optimising engagement, and enabling positive therapy outcomes. Not evaluating the working alliance in emerging psychotherapeutic approaches, may lead to inadequate preparedness in addressing clients' and therapists' needs, thus limiting opportunities to build a clinically meaningful working alliance.

1.5 Research aims and objectives

My thesis aims to build on the existing literature, to evaluate the working alliance from clients' and therapists' perspectives in a b-CBT intervention for depression, and when compared to usual care for depression on the E-COMPARED trial, in Europe.

The aim of my thesis will be addressed through the following objectives:

Objective 1: Qualitatively examine clients' working alliance demands in b-CBT to adapt Bordin's [6,7] working alliance theory for a b-CBT intervention for depression, in primary care services in the UK.

Objective 2: Qualitatively examine PWPs' experiences of the working alliance in a b-CBT intervention for depression, in primary care services in the UK.

Objective 3: Test the difference in client working alliance at 3-month (post randomisation) assessments between b-CBT versus face-to-face CBT in TAU for depression, using a subset of pooled E-COMPARED trial data.

Objective 4: Determine if client working alliance scores are associated with depression scores at 3-month assessments in b-CBT for depression using pooled E-COMPARED trial data.

Objective 5: Test for an interaction between client system usability and working alliance scores on the association between the client working alliance and depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

Objective 6: Test the difference in therapist working alliance scores at 3-month assessments between b-CBT versus face-to-face CBT in TAU for depression using a subset of pooled E-COMPARED trial data.

Objective 7: Determine if therapist working alliance scores are associated with client depression scores at 3-month assessments and when controlling for client working alliance scores in b-CBT for depression using pooled E-COMPARED trial data.

Objective 8: Test for an interaction between therapist system usability and client working alliance on the association between the therapist working alliance and depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

1.6 Research significance

The aims and objectives of my thesis contribute to the limited pool of evidence concerning mechanisms of change in DMHIs, especially in the context of b-CBT interventions [37–40]. The findings can also contribute towards informing guidance for clinical practice, delivery, and implementation, in aid of strengthening the working alliance and positively influencing clinical outcomes, in b-CBT for depression interventions.

1.7 Context

My PhD was nested in the UK country-site of the European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED) trial [ISRCTN registry, ISRCTN12388725, registered on 20 March 2015], which was funded by the European Commission, FP7-Health-2013-Innovation-1 programme (grant agreement number: 603098) [23]. E-COMPARED was a pragmatic randomised controlled non-inferiority study, including eight European countries: France, Germany, The Netherlands, Poland, Spain, Sweden, Switzerland, the UK [23], and Denmark which was added as a satellite recruitment site following the commencement of the study [45] (See Figure 1.2 for map of the recruitment sites on the E-COMPARED project). The principle aim of the trial was to evaluate if b-CBT is not inferior when compared to TAU which consisted of routine care for adults with major depression. The project hypothesised that both forms of treatment will lead to similar clinical improvements in clients, but that b-CBT can be offered at a significantly lower cost. Participants enrolled in the study were allocated to one of two treatment arms, b-CBT versus TAU. A b-CBT intervention is defined as the integration of an internet-based CBT programme and face-to-face CBT into one treatment protocol [23,46]. TAU consisted of psychological therapies, psychopharmacological interventions or a combination of both. The E-COMPARED study has yet to publish the main findings of the trial.

My PhD employed a mixed methods approach that involved both primary and secondary data collection on the E-COMPARED trial. Primary data collection involved conducting qualitative interviews with clients and therapists, in the UK country-site (for additional information on the UK trial country-site, see *Section 3.5.1 in* Chapter 3). Secondary data analysis utilised a locked and anonymised quantitative dataset from all country-sites of the E-COMPARED trial of the working alliance and other variables of interest.

1.8 Candidate's PhD journey and contributions

I undertook a part-time staff PhD, which involved completing my studies alongside paid employment between September 2015 and 2023. Staff PhD students at the London School of Hygiene and Tropical Medicine (LSHTM) have up to eight years to complete their studies, during which they are required to maintain continuous employment at LSHTM to be eligible to remain on this PhD track. My PhD was nested in the UK site of the E-COMPARED trial. My inception to the study was through my employment on the project as a Research Assistant, for which I was required to support research activities from the start to the close-out of the trial between November 2014 to July 2017. A staff PhD was negotiated upon being offered the Research Assistant role and later integrated into my employment

contract. I registered for a staff PhD in September 2015. I was responsible for designing all aspects of my PhD, with the guidance and support of my PhD supervisors and advisory team.

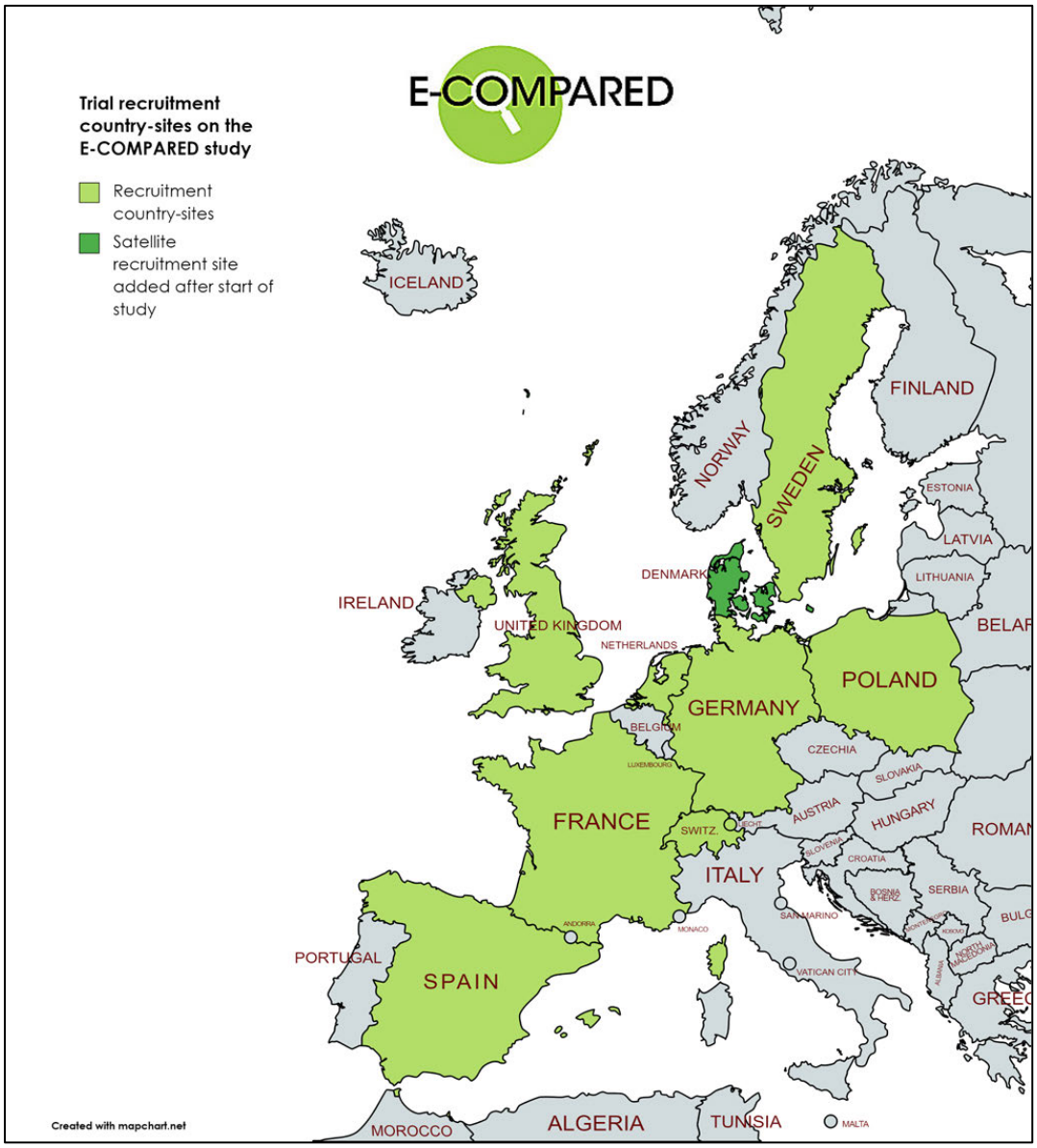


Figure 1.2. Map of E-COMPARED recruitment sites

My PhD consisted of primary and secondary data sources. Primary data collection involved conducting qualitative interviews with clients and therapists on the UK site of the E-COMPARED trial, which were not part of the original data collection plan within the trial. Qualitative data collection was integrated in the UK site's protocol (included in Appendix 1) and ethics applications, to accommodate for my PhD in the preparation phase of the trial, with the permission and help of Professor Ricardo Araya who was the Principal Investigator in the UK site and my primary PhD supervisor at the time, and Dr Arlinda Cerga-Pashoja who was the Trial Manager. I developed the information sheets, consent forms, and topic guides for the qualitative data collection. I conducted all individual interviews with clients and

therapists. Focus group discussions (FGDs) with therapists were conducted at the end of the trial to facilitate pragmatic data collection due to time constraints. A Research Fellow, Dr Jennifer Walke was hired at the end of the trial to assist with outstanding data collection efforts, which also included facilitating qualitative FGDs with therapists on their experience of the working alliance.

Secondary data were collected across all country-sites of the E-COMPARED trial [23]. Data were accessed following the end of data collection once data were collected in full, pooled, checked, cleaned and frozen in a data repository. An application to request permission to access and publish data was submitted online and later approved by the consortium. A pre-condition of the publication agreement was to invite a least two people from each country-site to co-author the papers. The research publication associated with the secondary analysis were only shared once a full, nearly ready to submit draft was prepared by myself, with the guidance and input of my supervisors and advisory group.

1.9 Style and structure of thesis

This thesis is written in research paper style and comprises of eight chapters. Four of the chapters are research papers, while the rest of the chapters provide a review of the background of the thesis, methodological overview and considerations, and a discussion and conclusion of the overall thesis. Each chapter is described below:

Chapter 1, the introduction chapter started by describing the working alliance and key terminology. It then outlined the rationale, aims, objectives and research significance of my thesis. Finally, this chapter presented, the context in which my PhD was conducted, reflections of my PhD journey, and contributions to my thesis. The remaining section will outline the chapters of my thesis.

Chapter 2 presents a background to the thesis, covering four key areas: (i) an overview of depression, the epidemiology of depression, and how it's treated; (ii) evidence associated with CBT and iCBT for mild-to-moderate depression; (iii) key literature around the working alliance in both face-to-face and internet-based CBT, and finally, (iv) a summary of the rationale, aims, objectives and research questions of my thesis.

Chapter 3 describes the research design and methodology adopted to address the aims and objectives of my thesis. This chapter will start by providing a foundational overview of the methods used in the research papers that make up my thesis, followed by a description of the E-COMPARED study. The chapter will then outline PhD specific methodological decisions, processes and considerations that were

made pre-data collection as well as specific methodological justifications concerning the qualitative and quantitative components of my thesis. This chapter will end by listing PhD related ethical approvals.

Chapter 4 (paper 1) is a published research paper entitled, 'Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study' [47]. This paper examined clients' working alliance demands, to adapt the working alliance theory for a low-intensity b-CBT intervention for depression. This paper addresses objective 1, as outlined in *Section 1.5* of this Chapter).

Chapter 5 (paper 2) is a published research paper entitled, 'Practitioners' experience of the working alliance in a blended cognitive–behavioural therapy intervention for depression: qualitative study of barriers and facilitators' [48]. This study aimed to examine the PWPs experience of the working alliance in b-CBT, that specifically focused on PWPs perceived facilitators and barriers in building a working alliance with clients. This paper addresses objective 2.

Chapter 6 (paper 3) presents the findings of a secondary analysis of client rated working alliance using pooled data, entitled, 'Comparison of the client working alliance in blended cognitive behavioural therapy and treatment as usual for depression in Europe: Secondary data analysis from the E-COMPARED randomised controlled trial'. The objectives of this paper are to: (i) investigate if there is a difference in client working alliance scores between b-CBT and face-to-face CBT in TAU; (ii) determine if there is an association between client working alliance, and client depressions scores in b-CBT; and (iii) test for an interaction between client system usability and client working alliance scores, on the association between the client working alliance and depression scores. This paper addresses objectives 3, 5 and 7.

Chapter 7 (paper 4) presents the findings of a secondary analysis of the therapist rated working alliance using pooled data, entitled, 'Comparison of the therapist working alliance in blended cognitive behavioural therapy and treatment as usual for depression in Europe: Secondary data analysis from the E-COMPARED randomised controlled trial'. Similarly to paper 3 (Chapter 6), the objectives of this paper are to: (i) investigate if there is a difference in therapist working alliance scores between b-CBT and face-to-face CBT in TAU; (ii) determine if there is an association between therapist working alliance, and client depression scores in b-CBT, and when controlling for client working alliance scores; and (iii) to test for an interaction between therapist system usability and therapist working alliance scores, on the association between the client working alliance and depression scores. This paper addresses objectives 4, 6 and 8.

Chapter 8 presents the discussion of this thesis. This chapter will provide an interpretation of the results, which delves into the meaning, importance and relevance of the findings presented across research papers 1-4 using a mixed methods approach. This chapter will also outline the implications, strengths and limitations of this thesis. Finally, this chapter will present clinical and research recommendations, and will end with a conclusion.

Chapter 2: Background to thesis

2.1 Introduction to chapter 2

Chapter 2 presents background information on key components of my PhD. First, *Section 2.2* provides an overview of depression, its epidemiology and how it's treated. *Section 2.3* will then provide a description of cognitive behavioural therapy (CBT) and synthesise associated evidence from face-to-face settings (see *Section 2.3*). *Section 2.4* will provide a brief introduction to digital technologies in mental health care, and the evidence for internet-based CBT (iCBT) for depression. *Section 2.5* presents a comprehensive overview of the working alliance that builds on *Chapter 1,* to describe and distinguish between different alliance theories, and to summarise the literature across both face-to-face and guided or blended iCBT. Finally, *Section 2.6* will conclude the chapter by tying together the threads from previous sections to present the rationale of my thesis. This section will also (re)state my thesis aims, research questions, and objectives.

2.2 Major Depressive Disorder

2.2.1 Clinical features, diagnosis, and classification of depression

Depression is a prevalent and often disabling mental health condition, that causes considerable emotional distress that interferes with daily functioning, and carries high societal and economic costs [49]. Major Depressive Disorder (MDD) is a common mental disorder, that is characterized by the presence of a persistent low mood and a loss of interest or enjoyment in activities [50]. Other symptoms include sleep disturbances, agitation or psychomotor problems, fatigue or loss of energy, feelings of worthlessness or excessive guilt, significant weight changes, diminished ability to concentrate, or indecisiveness, and recurrent thoughts of death.

According to the Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV), a person is diagnosed with MDD if they experience; (i) a persistent low mood and/or loss of interest or pleasure in life activities across a 2-week period; (ii) at least five other symptoms of MDD (as mentioned above) that cause significant impairment across social functioning, work, or other important areas of functioning, almost every day; and (iii) two or more major depressive episodes in their life-time [50].

There are multiple ways of determining the severity of MDD, including, the number of symptoms, severity of each symptom, and functional impairment. Four categories of severity are outlined in the

DSM-IV, including subthreshold depression (indicated by less than 5 symptoms, that are typically required for a diagnosis), mild depression (i.e., 5 symptoms or few in excess, which result in minor functional impairment), moderate depression (i.e., some symptoms in excess of 5, with mild-severe functional impairment), and severe depression (i.e., several symptoms in excess of 5, that rate higher on severity and that cause marked functional impairment) [50]. While there is evidence to suggest that severity correlates with functional impairment, individual cases may not always conform to the categories outlined [4].

The diagnosis of depression is made on the basis of a structured psychiatric assessment using a diagnostic criteria. On the E-COMPARED trial [23], a diagnosis of depression (was determined by Section C of the Mini-International Neuropsychiatric Interview (M.I.N.I.)) [51], which is a structured diagnostic interview based on the DSM-IV (see *Section 3.3* of Chapter 3 for more information about the recruitment procedure). To align with the populations and contexts associated with the E-COMPARED study [23], the remaining chapter will largely focus on mild-moderate depression and the epidemiology of depression in Europe and in the UK.

2.2.2 Aetiology of depression

The aetiology of depression is complex and is not well understood. Integrative models suggest that depression can be viewed through both biological and social variables. On one hand, the onset of depression can be influenced by genetic factors [52]. Findings from twin studies have found that the heritability rate of depression is around 37%, while family studies suggest that having depression can increase the risk of depression in first-degree offspring by two or three folds [52]. Nevertheless, specific genes for depression have yet to be identified [5].

A prominent etiological model in the field of psychology called the diathesis-stress model, proposes that a gene-environment interaction could increase susceptibility to developing depression [5,53,54]. The model suggests that environmental stressors such as stressful life events and chronic stress, may trigger depression based on pre-existing vulnerabilities as a result of both biological factors involved in emotional processing [5,53], and psychosocial factors (e.g., negative self-concept, rumination, negative emotionality, social support and adverse childhood experiences) [54].

2.2.3 Epidemiology of depression

Depression affects more than 264 million people, and is the leading cause of disability worldwide [1,2]. MDD is the most prevalent of all mental disorders with an estimated life prevalence as high as 27% [55] and a global prevalence of around 4.4% [2]. A notable symptom of MDD is suicidal ideation, with

higher symptom severity increasing the risk of death through suicide. [56]. According to the World Health Organization (WHO), around 700,000 people die due to suicide every year [1], increasing the burden of disease.

High rates of depression can also be observed in the European region and in the United Kingdom (UK). WHO have estimated that depression and anxiety affect around 25% of the population of the European region [24]. In the UK, the prevalence of depression is estimated around 4.5%, which sits higher than the prevalence of the WHO defined European region (4.2%), and the worldwide prevalence (4.4%) [57]. A more recent study on the prevalence of current depressive disorders that applied a wider definition of depression that includes clinically relevant depression and not just those who received an MDD diagnosis, found an overall prevalence of 6.4% across 27 European countries [58]. Notably, the prevalence of depression in the UK, Denmark, France, Germany, Poland and Sweden (corresponding with the recruitment sites on the E-COMPARED study [23]) were higher than the overall prevalence across 27 countries. Table 2.1 outlines the prevalence of current depressive disorders across these countries [58. p.e735].

Table 2.1. Prevalence of current depressive disorder in European countries [58. p.e735]

Countries	**Total population**	**Prevalence (95% CI)**
Denmark	5449	7·17% (6.45–7.89)
France	14 191	7·03% (6.54–7. 51)
Germany	24 404	9·24% (8.82–9.66)
Poland	22 076	4·31% (4.01–4.62)
Sweden	5737	8·75% (7.98–9.51)
UK	17 706	7·40% (6.90–7.89)

Note: Data are number of respondents without weighting and weighted prevalence with 95% CI in parentheses.

The rate of depression appears to be on the rise worldwide, increasing by 18.4% between 2005 and 2015 [59]. The emergence of the COVID-19 pandemic in the early months of 2020 has also resulted in an increase in cases of depression globally, estimated around 27.6% [60]. Collectively, this highlights the increasing burden of depression, which can lead to cumulative societal costs, if not effectively addressed.

2.2.4 Social and economic cost of depression

The burden of depression transcends clinical morbidity, incurring both economic and societal costs. MDD can have a negative impact on daily functioning, including aspects of work performance (e.g., productivity, task focus, days absent caused by sickness and having lower earnings), cognitive functioning, quality of life, and family and social relations (e.g., household strain, social irritability, lower marital quality, negative parenting behaviours and financial strain) [3]. MDD can also result in poor physical health, and has been associated with increased mortality due to suicide and a wide range of chronic disorders, such as the onset of coronary artery disease, heart attacks, diabetes, and some types of cancer [49,61,62]. It is important to note that while the adverse effects outlined are not directly impacted by MDD, explanatory models suggest that MDD has a causal impact on key mediators, and therefore carries a high level of burden [49].

Depression carries a large economic burden. The cost of untreated depression and anxiety is estimated around US$1trillion [63]. In Europe, around 50% of chronic sick leave is attributed to depression and/or anxiety [24]. Mood disorders and anxiety incur an annual cost of €170 billion [24], while the annual cost of depression in England is estimated around £20.2–£23.8 billion [64]. A global investment case for a scaled-up response to the public burden of depression and anxiety disorders, found that not scaling up treatment could lead to more than 12 billion days of lost productivity, which is attributed to an annual cost of around US$1trillion [63]. By contrast, scaling-up treatment for depression and anxiety disorders with a cost of US$147 billion, could lead to high productivity returns estimated at US$230 million for depression alone [63]. Despite such promising projections, the global median expenditure by governments worldwide is below 2%, and 5.1% in high-income countries [65–67].

2.2.5 Treatment gap for depression

In addition to the high burden and cost of depression, there is a significant gap between people who have a mental health condition, and those who receive care. A study investigating the extent of the treatment gap in mental health care, revealed that the median treatment gap for depression was 56.3% globally, and 45% in the WHO European region. Country specific data showed that rates of untreated depression were as high as 84% in the UK [68]. While the authors acknowledge that data used for analysis were limited, they also suggested that rates reported were likely to be underestimated. Although there are several factors that can impede access to care (e.g., preferring to resolve the issue alone, perceiving the treatment as unhelpful, not knowing where to seek help, not having money, among others) [69], with mental health stigma being a prominent barrier for treatment seeking behaviours [69–71].

2.2.6 Mental health workforce shortage

While mental health access presents one barrier to the treatment of depression, a shortage in mental health professionals may also pose yet another barrier to the timely treatment of clients. There is evidence to suggest that there is a misalignment between demands for mental health care access and the resources available to effectively provide care. For example a report by the British Medical Association that assessed the commitment by NHS England to support and expand the mental health workforce, found that while contact with mental health services increased between 2016 and 2019, some key mental health staff groups have either declined or stayed the same since 2009 [72]. The report also highlighted widespread workforce shortages in mental health care, in which 57% of clinical psychologists who responded to the survey on workforce pressures said there were shortages of one or more clinical psychologist on their last day or shift worked. Shortages in the mental health workforce was reported to negatively impact workload, morale, quality of work, and access to time for reflective practice [72].

These findings were also reflected in Europe. A survey by the EU compass for mental health and wellbeing, that involved, representatives from 22 member states, revealed that the highest perceived barriers in relation to accessing mental health care included, inadequate funding for mental health services, and inadequate availability of mental health professionals [73].

Considering the treatment gap [68], shortages in the mental health workforce [72,73], and the rise in depression rates in recent years [60,74], there is an increased need to develop innovative solutions to expand the workforce in mental health services.

2.2.7 Management of depression

Treatments for depression aim to eliminate symptoms, improve day-to-day functioning and quality of life [5]. Interventions for mild and moderate depression include, antidepressant medication, psychological therapies, while interventions for moderate presentations include a combination of antidepressant medication and psychological therapies [5].

Although antidepressants are considered to be evidence-based interventions for depression, their efficacy is increasingly debated [75–77]. Key areas of concern include, marginal benefits observed when compared to placebo that are often marked by less than a 2-point difference on self-report scales for depression [78], methodological flaws associated with measurement tools that don't primarily focus on mood (e.g., that also assess sleep and anxiety) [75,78], and ineffective blinding procedures that do not address the fact that antidepressants often make people feel markedly different (e.g. inducing a sedated feeling) [76]. It has been posited that the marginal gains from antidepressants could be due to

non-mood related symptoms [78], and having higher expectations of treatment after experiencing noticeable physiological change after taking the drug [76]. Moreover, a broader critique of antidepressants is that their effects may only offer short term relief, that are associated with a wide range of side effects such as drowsiness, lethargy, reduced sexual drive and emotional detachment or indifference. These side effects may negatively impact the person's ability to develop the skills and tools to address their problems [76], by contrast to psychological approaches such as CBT that provide an empirical approach to addressing negative emotions [79].

CBT is widely considered as a gold standard psychotherapeutic approach and has been recommended as a first-line intervention for a range of mental health conditions, by several international clinical guidelines for psychotherapeutic interventions [80,81]. A range of evidence-based supportive interventions have also been found to be effective in treating milder forms of depression including self-help books, yoga, relaxation training, and more notably internet-based interventions that have grown in popularity and garnered considerable interest and evidence in the past decade [5].

The following section will provide a description of CBT and the evidence associated with the psychological approach. This section will also provide an overview of digital psychological interventions, iCBT and the evidence associated with iCBT.

2.3 Overview and evidence for CBT

2.3.1 Overview of CBT

CBT is a psychological approach for managing mental health problems, that explores the links between thoughts, behaviours, and emotions in relation to a given situation as illustrated by the three component CBT model in Figure 2.1 which is based on Beck's cognitive model [82]. The approach aims to alleviate distress by helping clients develop more adaptive cognitions and behaviours [79,82]. Broadly speaking, sessions are structured, present-focused, time-limited and aim to transfer the knowledge and tools for managing symptoms, from the therapist to the client. The intervention is also goal-orientated, and takes a practical and empirical approach to problem-solving [79].

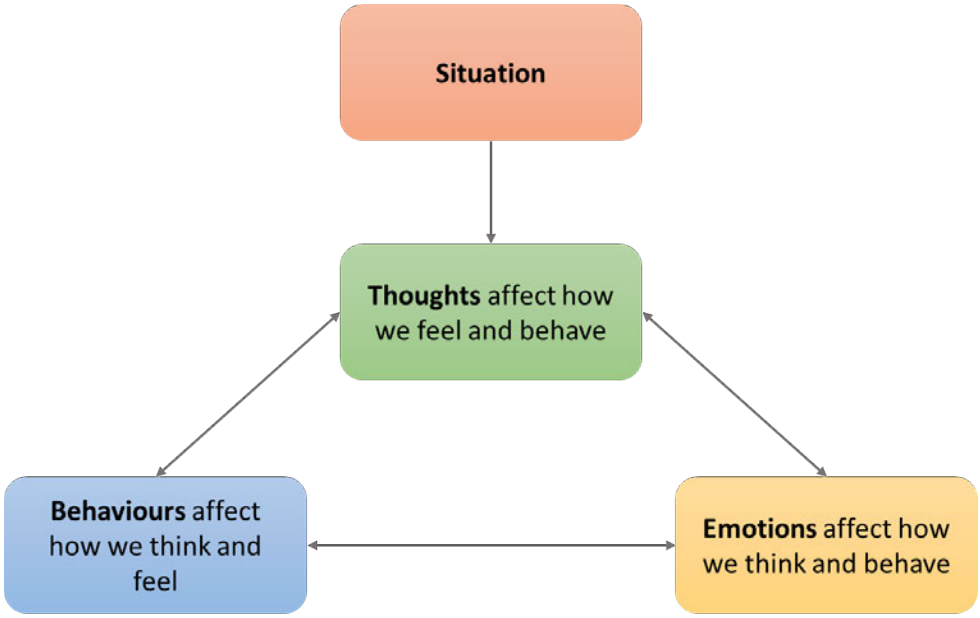


Figure 2.1. Three component cognitive behavioural therapy model

CBT is based on Aaron Beck's [82] cognitive model for depression that posits that people's emotions and behaviours are influenced by the way they 'perceive' a situation or event. As such, Beck [79,82] outlines three levels of cognitions, that include, (i) core beliefs, (ii) dysfunctional assumptions, and (iii) negative automatic thoughts. First, core beliefs refer to deeply held structures of thoughts and behaviours, that provide meaning to the experiences of a client, often referred to as schemas. Core beliefs, occur at three different levels, in which negative thoughts are generated in relation to oneself, the world, or the future. Second, dysfunctional assumptions are rigid, maladaptive, over-generalised, and/or conditional rules, that are often not realistic or reflect the reality of human experiences. Third, negative automatic thoughts are characterised by habitual and unhelpful thoughts that occur involuntarily [79].

CBT interventions use a range of techniques to help clients identify, evaluate and interrupt negative automatic thoughts and distortions, as well as behaviours that maintain and exacerbate feelings of distress [82]. Patterns of dysfunctional cognitions and maladaptive behaviours are corrected through a process of continual problems-solving and behavioural change [82]. CBT provides clients with the tools to understand and correct errors, distortions, and perceptions of automatic thoughts [82]

Key activities in CBT interventions include developing an individual formulation to guide treatment for each client, building a therapeutic relationship, setting goals, developing a treatment plan, and selecting therapeutic activities' [82]. There are a wide range of cognitive techniques that are used to question and

encourage the clients to break through rigid patterns of dysfunctional thinking and to gain new perspectives, that are summarised in the following section [83].

2.3.2 CBT techniques

Key CBT techniques used to address depression that aligned with the intervention arm of the E-COMPARED study [23], include (although not limited to) psychoeducation, behavioural activation, cognitive restructuring, and relapse prevention. CBT interventions for depression often start with psychoeducation [83]. This refers to a process in which the therapist provides their clients with information about the nature of depression, and typically uses cognitive models such as the diagram illustrated in Figure 2.1 [82,83]. Behavioural activation is a technique that aims to engage clients in valued behaviours and activities in order to improve their emotional state [83]. This can include using tools such as pleasant event scheduling, breaking down activities into smaller steps (e.g., graded task assignment), among others. Cognitive restructuring is a process of helping clients identify, challenge, and modify irrational beliefs and cognitive distortions using a range of tools [84]. This involves identifying cognitive errors (e.g., jumping to conclusions, polarized thinking, catastrophising etc.,), thought change records and generating rational alternatives. Treatment typically ends with a session on relapse prevention which is a procedure that aims to reduce the risk of relapse, by developing an action plan that can be used once treatment has ended [84].

2.3.3 Effectiveness of CBT

CBT is widely considered to be a gold standard psychotherapeutic approach that is recommended as a first-line intervention for mild-to-moderate depression, by several international clinical guidelines for psychotherapeutic interventions [4,5,80], including the National Health and Care Excellence guidelines (NICE) [4], and the American Psychological Association (APA) [81].

CBT for depression has been shown to be effective in addition to pharmacological interventions [85], and when compared to pharmacological placebo [86]. It has also demonstrated treatment outcomes that are comparable to antidepressants, especially for clients that present with milder symptoms [87]. Receiving CBT has been shown to reduce both relapse and the continued use of antidepressants [88–90]. Moreover, treating mild depression with psychotherapies such as CBT may reduce symptom progression to severe presentations of depression [91], and improve quality of life [92].

A systematic review and network meta-analysis on the process and delivery of CBT for depression in adults, found strong evidence that CBT could reduce symptoms of depression when compared to treatment as usual [93]. Another network analysis on the effectiveness and acceptability of CBT

delivery formats, found that individual, group, telephone, and guided self-help CBT were significantly more effective than waiting list controls (standardized mean differences [SMDs], 0.87-1.02), treatment as usual (SMDs, 0.47-0.72), and unguided self-help CBT (SMDs, 0.34-0.59) [32].

Over the past decade, the use of guided self-help such as CBT has increasingly been delivered through digital technologies [5]. The following section will introduce digital interventions for mental health and the evidence for internet-based CBT.

2.4 Digital mental health interventions and internet-based CBT

2.4.1 Digital mental health interventions

The expansive rate of technological growth and access to digital technologies such as mobile devices and the internet has resulted in the development of numerous tools that can be used to support health care systems and develop solutions to health care problems [21]. Digital health interventions adopt a range of tools that include internet connectivity, computers, mobile devices, wearables, software applications and associated technological functionalities. Such tools can be used to support different primary users, including, (a) clients, potential service-users, or caregivers; (b) health care providers; (c) health system or resource managers involved in the administration of public health systems; and, (d) intervention data services such as, data collection, management, usage, and exchange [21]. As such, this thesis will focus on digital mental health interventions (DMHIs) that target mental health service users.

2.4.2 Benefits and limitations of DMHIs

DMHIs have the potential to expand access to evidence-based mental health care, thereby offering a viable solution to addressing the mental health care-gap globally [21,94]. Unlike brick-and-mortar services, DMHIs are considered to be easier to scale-up and are perceived to be more cost-effective to implement [94]. They can also help address the stigma associated with seeking treatment from mental health services, by allowing clients to engage in treatments remotely [95]. Accessing mental health services digitally can allow clients to access treatment at a convenient time and location [96]. There are also opportunities to improve mental health care by, extending usual care beyond the clinic and offering tailored care that meets the needs and preferences of different clients [26,95,96].

However, while DMHIs are often commended for their potential in reaching vulnerable and marginalised groups (e.g., older adults, racial minorities and those experiencing high levels of mental health stigma), these populations are more likely to be affected by the digital divide, and as a result

experience lower levels of digital literacy and access to digital devices and the Internet [97]. It should also be noted that DMHIs that are unsupported often lead to lower levels of engagement [98–100], with some limited evidence suggesting worse treatment outcomes compared to supported DMHIs [101]. The use of digital technologies in mental health care is relatively new, and while research in this field is steadily increasing, mechanisms of change and therapeutic processes within digital interventions are not well understood [8]. It is for this reason that the therapeutic alliance was identified as a top ten priority for digital mental health research in a consensus study involving key stakeholders in the field [102].

2.4.3 Mode and functionality of DMHIs

Digital innovations that are targeted towards mental health clients are typically delivered through the internet or computer-based programmes, and mobile application [22]. These can be accessed through a wide range of devices such as computers or smart phones, and in conjunction with other technological tools such as wearables (e.g., smart watches or bracelets) [21,22]. Different interventions will use different functionalities to engage the client or end-user to the intervention, that broadly includes text-based information, interactive exercises and quizzes, audio and video content or feedback, gamification, avatars and artificial-intelligence driven chatbots, among others [22].

2.4.4 Clinical range, content, and format of DMHIs

DMHIs offer a wide range of interventions for the prevention, treatment, and management of symptoms of common mental health conditions [22]. While a range of psychological approaches are delivered through DMHIs (e.g., problem solving therapy, behavioural activation, interpersonal therapy, acceptance and commitment therapy, interpersonal therapy and mindfulness therapy, among others) [22], the vast majority of internet-based interventions apply CBT principles [103].

DMHIs can be supplemented with different levels of support, which range from no/minimal practitioner-support, to frequent face-to-face therapist sessions [22]. Generally, the level of support provided in DMHIs are grouped into three categories [22]. The first level is referred to as ‘unguided digital interventions’ in which the client completes treatment through a digital programme and without support from a practitioner. The second level is referred to as ‘guided digital interventions’, which is predominantly completed through a digital intervention, with some support from a mental health practitioner. The third level of support refers to ‘blended digital interventions’, in which the client received both in-person sessions with a therapist to equal or slightly varying degrees. Generally, but not always, digital interventions that provide a high level of support such as blended interventions, are guided by mental health clinicians and tend to be based within clinical settings [22]. On the other hand,

digital interventions that provide minimal support are typically guided by a non-specialist workforce and may also be accessible within the community-level as well as clinical settings [22].

2.4.5 Defining iCBT and blended CBT

A typical internet-based CBT intervention will be accessed through a website, and may include four components: CBT programme content, interactive activities, the use of multimedia choices (e.g., sound, video, text) and the provision of feedback and guidance [28,104].

While the literature distinguishes between three different levels of support (i.e., guided, unguided, and blended), the blended term can sometimes be used to refer to the use of different forms of delivery, including systems in which a patient receives the information via a digital platform but can contact a therapist remotely via synchronous approaches such as video conferencing, or asynchronous approaches, such as text-based communication. [37] Although there is no agreed upon definition for blended mental health interventions [22,46,105], my thesis will use the definition adopted by the E-COMPARED study [46,105] for a blended CBT (b-CBT) intervention which was defined as the integration of an internet-based programme and face-to-face interventions into one treatment protocol for CBT [46,105].

2.4.6 Evidence for iCBT for depression

Internet-based interventions for mild to moderate depression are also first-line treatments based on the NICE [4] and APA [81] guidelines. There is good evidence to suggest that guided internet-based CBT interventions are effective for treating depression. A meta-analysis that investigated the short-term and long-term efficacy of both guided and unguided iCBT for depression across 39 studies, showed that guided iCBT was associated with a high level of effectiveness compared to unguided iCBT (posttreatment patient health questionnaire-9 (PHQ-9) [106] scores mean difference, −0.8; 95% CI, −1.4 to −0.2) [33]. The review also found that the effects in guided iCBT were higher in participants with moderate-to-severe depression scoring greater than 9 on the PHQ-9, while those with mild/subthreshold depression (i.e., scoring between 5-9 on the PHQ-9) were associated with similar levels of effectiveness in unguided iCBT.

Another systematic review and meta-analysis on the effectiveness of internet-based CBT in the routine care of adults with depression and anxiety also showed promising findings [107]. Out of the 19 studies reviewed, individual effect sizes showed clinically relevant changes in depression (effect sizes ranging from Hedges' g=0.42-1.88), with a pooled effect of 1.78 for depression based on a mixture of outcome scales, that was largely measured through the PHQ-9 scale [106].

Finally, a systematic review and meta-analysis of 17 RCTs that aimed to evaluate the effects of therapist guided iCBT compared to face-to-face CBT found that therapist guided iCBT was more effective than face-to-face therapy in reducing the severity of depression symptoms (Standardized mean difference [SMD]: −1.73; 95% confidence interval [CI]: −2.72 to −0.74) across self-report measures of depressive symptoms [108]. The authors, however, noted that the high level of heterogeneity among the studies prevented definitive conclusions from being drawn.

2.4.7 Cost-effectiveness

Internet-based interventions for depression have been shown to be delivered at a lower cost. One study that examined the cost-effectiveness of internet-mediated CBT for mild-to-moderate depression in primary care settings when compared to treatment as usual found iCBT was just as cost-effective as treatment as usual (TAU) from a healthcare and societal perspective [109]. Another study that investigated the cost-effectiveness of iCBT and physical exercise compared to TAU, for mild-to-moderate depression found that iCBT was more cost-effective compared to TAU [110]. Similar findings were also found for guided iCBT for MDD [111], with evidence that guided internet-based intervention show greater cost-effectiveness [112].

2.4.8 Evidence for b-CBT for depression

The emerging evidence appears to suggest that guided iCBT might be more effective and cost-effective compared to unguided iCBT [23,45,112–115]. While most of the evidence has focused on guided and unguided iCBT, an increasing number of studies have adopted a blended approach [42,44].

A systematic review on blended face-to-face and internet-based interventions for the treatment of mental health conditions in adults, involving 44 studies of which 27 were RCTs, found that blended CBT showed benefits in relation to engaging clients to treatment, such as showing less dropout rates for some interventions compared to the control conditions with no treatment [44]. Few studies have investigated the effectiveness of b-CBT for depression. One example comes from a pilot study that investigated the effectiveness and cost-effectiveness of blended CBT compared with the usual treatment of face-to-face CBT for depressed clients in specialised mental health services [42]. The findings revealed that both groups led to a reduction of, symptom severity, the probability of a diagnosis of depression, and a higher quality of life. b-CBT was also found to have a higher probability of being cost-effective from the perspective of a health care provider.

2.4.9 Adherence to iCBT

iCBT has been found to be acceptable and effective in reducing the severity of depression, however engagement appears to vary depending on the level of support received, and in relation to whether data were collected in clinical trials or pragmatic clinical settings. [100,116,117]. Studies investigating adherence to unguided online psychological therapies found that as few as 1- 7% of clients completed all modules of unguided computer-based interventions [98,99]. These findings are supported by a pragmatic, multicentre RCTs evaluating the effectiveness of two commercially developed computerised CBT programmes [100]. The computerised-CBT interventions adopted in the trial were unguided, fully automated self-help programmes. The findings revealed that out of the 452 clients randomised to a digital programme, as little as 16-18% of clients completed treatment, and that on average only 1-2 session(s) were completed [100]. Moreover, Christensen and colleagues [118], conducted a systematic review on intervention adherence in randomised controlled trials of internet-based interventions for anxiety and depression and found that attrition ranged between 1-50%, compared to the literature on open access programmes, in which as little as 1% completed all treatment modules [98,118,119].

Adherence rates in iCBT appear to fluctuate between interventions [120]. For instance, a systematic review of real-world uptake and engagement of digital self-help programmes for depression and anxiety found high levels of variations between completion rates across studies (e.g., moderate use of programme ranged between 7% to 42%) [120]. However, there is some evidence to suggest that higher support may lead to better adherence [121], and treatment outcomes [101], compared to lower levels of support, although adherence levels were not directly compared.

Higher levels of access to a human therapist appear to positively enhance engagement. Van Ballegooijen and colleagues [122], conducted a meta-analysis that compared adherence between guided iCBT and individual face-to-face CBT for adults with depression. The study found that the percentage of completers was significantly higher for face-to-face CBT (84.7%) compared to guided iCBT (65.1%). While the review did not find papers that directly compared face-to-face and guided iCBT, the findings suggest that face-to-face contact in addition to iCBT may improve adherence. These findings appear to be supported by the wider literature. For example, a systematic review on adherence in internet interventions for anxiety and depression found that common reasons for dropping out of iCBT in clinical trials included, having a lack of face-to-face contact with a practitioner, among others [118]. Further to this, a study evaluating the therapeutic alliance in b-CBT for anxiety and depression found that lower levels of therapist contact were associated with lower ratings of the therapeutic alliance [123]. These findings also align with the supportive accountability model, which posits that human support is required to enhance adherence to digital health interventions [124].

Johansson and colleagues [125] explored qualitative experiences of non-adherence to iCBT for depression and anxiety and found that experiences of non-adherence were described as an interaction between patient factors and treatment factors. Treatment factors included, extensive content, complexity of material, negative psychological effects of treatment, having limited or no face-to-face contact, and a lack of understanding of what treatment would entail. On the other hand, personal factors that impacted adherence, included the inability to comprehend the content, psychological vulnerabilities that enhanced the negative effects, and the inability to assess suitability of the intervention.

A notable limitation concerning the adherence literature in DMHIs relates to how adherence is defined. For example, Sieverink and colleague [126], conducted a systematic review to describe how eHealth technologies are used, and how adherence is conceptualised. Across a total of 62 studies, over half (n=34) operationalised adherence as "the more use, the better", while the rest of the studies (n=28) described a threshold for intended use of the technology, although only 6 of these studies provided justifications concerning decisions around intended use. The findings revealed that the eHealth field was underdeveloped, leading to concerns that interventions were not being used properly and highlighted the need for a standardised definition of adherence in e-health intervention.

As well as standardising how adherence is measured, further research is required to compare adherence to iCBT across different formats and contexts directly. The emerging link between higher therapist contact and adherence, raises questions about the mechanisms of change that facilitate engagement to psychological interventions such as the working alliance and variations thereof.

The following section provides an overview of the mechanisms of change that have been found to influence treatment outcomes, specifically focusing on describing the working alliance and variations thereof. This section will also outline the available evidence concerning the working alliance in face-to-face and internet-based psychological interventions to understand, how the working alliance compares between treatment groups, and if working alliance scores positively influence treatment outcomes.

2.5 The working alliance

2.5.1 Mechanisms of change in psychological therapies

Several factors have been identified to facilitate positive therapeutic changes that are common across a range of different psychotherapeutic approaches, labelled as 'common factors in psychotherapy' [8,9]. A keystone review by Lambert [9] appraised and categorised the literature to develop four broad causal pathways that led to positive therapy outcomes [9]. Lambert's [9] review found that around 40% of the

variance of positive therapeutic outcomes were accounted for by spontaneous improvements that occurred without formal psychological interventions. Around 15% of the variance was accounted for by therapeutic expectancy (i.e., placebo effects), 15% for the techniques (i.e., psychological approach) [8,9], while 30% of the variance for positive therapy outcome was accounted for by the therapeutic relationship. See Figure 2.2 for a breakdown of the variance explained by the factors identified in the review [9].

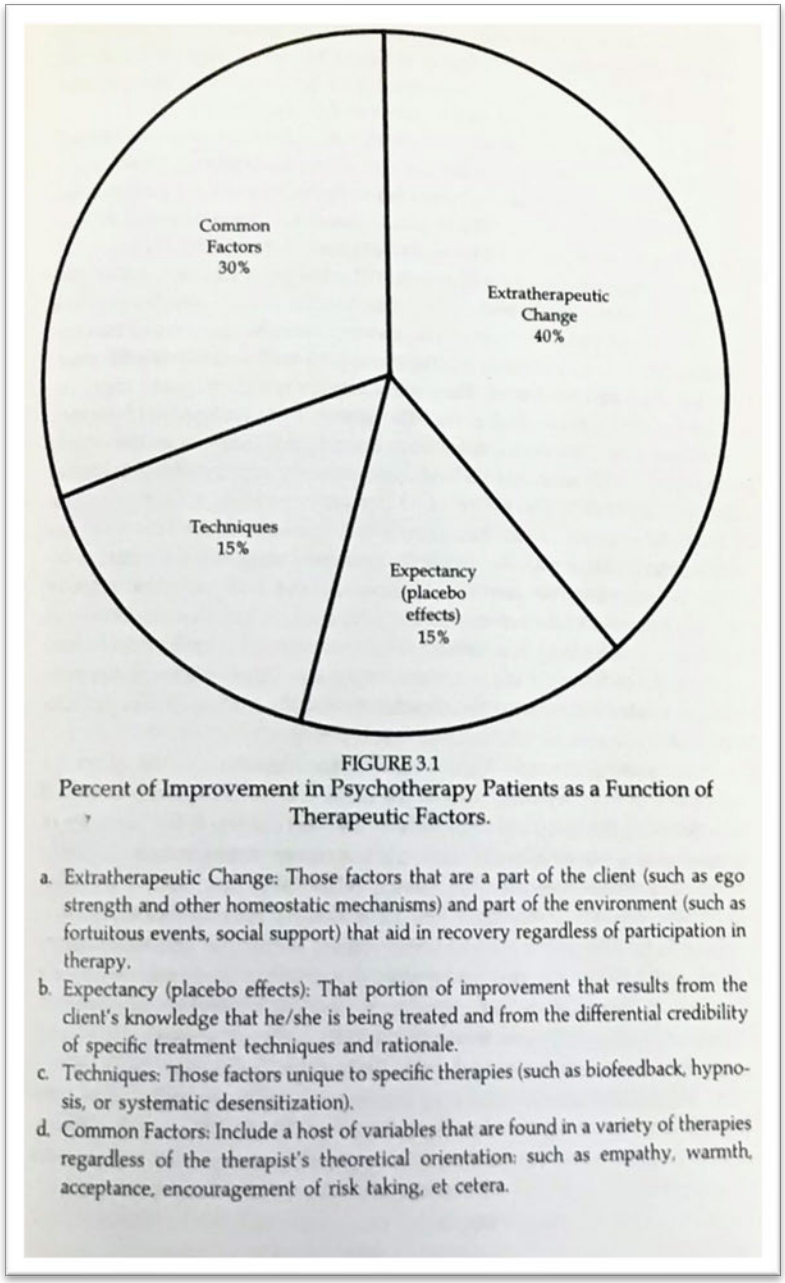


FIGURE 3.1
Percent of Improvement in Psychotherapy Patients as a Function of Therapeutic Factors.

a. Extratherapeutic Change: Those factors that are a part of the client (such as ego strength and other homeostatic mechanisms) and part of the environment (such as fortuitous events, social support) that aid in recovery regardless of participation in therapy.
b. Expectancy (placebo effects): That portion of improvement that results from the client's knowledge that he/she is being treated and from the differential credibility of specific treatment techniques and rationale.
c. Techniques: Those factors unique to specific therapies (such as biofeedback, hypnosis, or systematic desensitization).
d. Common Factors: Include a host of variables that are found in a variety of therapies regardless of the therapist's theoretical orientation: such as empathy, warmth, acceptance, encouragement of risk taking, et cetera.

Figure 2.2. Percentage of improvement in psychotherapy in clients as a function of therapeutic factors [9]

The findings of the review suggest that there are four factors that influence positive treatment outcomes, with varying levels of influence. Although the extra-therapeutic change factor accounts for the largest share of positive therapy outcomes, the 'spontaneous' nature of change that occurs in the client or in the client's environment, is beyond the influence of the therapist or therapeutic approach [9]. It can therefore be deduced that the therapeutic relationship is the largest predictor for in-therapeutic change. Wampold [127], proposed that there was a hierarchical structure between these factors. He theorised that the therapeutic alliance (one component of the relationship) has to be established first, in order for other pathways (e.g. technique and therapy expectancy) to be activated [127], demonstrating the therapeutic alliance's importance, to the chain of therapeutic change process.

2.5.2 A brief history of the therapeutic relationship

The working alliance is a component of a wider human-to-human relational framework called the therapeutic relationship. The origins of the therapeutic relationship is rooted in psychodynamic theory [20]. It was Sigmund Freud who first suggested that it was important for the therapist to maintain a 'serious interest' and 'sympathetic understanding' towards the client, to enable positive transference (i.e., a friendly and respectful feeling by the client towards the therapists) to occur [8,20]. Henceforth, the concept of the therapeutic relationship has taken root in various psychological approaches, leading to variations in the way the concept is defined [13].

A broad definition of the therapeutic relationship by Gelso and Carter [128] that applies to most, if not all theoretical approaches is: 'the feeling and attitude that the therapist and the client have towards one and other and the manner in which they are expressed' [p.4]. The therapeutic relationship is made of several interlocking elements (empathy, responsiveness, creating a safe place, and secure environment) that should be encompassed within psychological therapies. These elements have been described to be analogous to a diamond, composed of multiple, interconnected facets. Like a diamond, the concept of the therapeutic relationship is complex, reciprocal and multidimensional [8]. This has resulted in difficulty in developing clear and distinct taxonomies, while retaining the essence and meaning of the relationship. For this reason, many have focused on measuring the therapeutic alliance instead of the therapeutic relationship, to which Norcross and Lambert [8] stated that, "one way of conceptualising what has been achieved by the appropriate use of the therapeutic elements is to measure the therapeutic alliance" [p.5].

Following two decades of alliance research, a consensus started to emerge that the therapeutic alliance was not unique to a given therapeutic model, but one that existed across a range of different therapeutic approaches (i.e. a common factor) [8].

2.5.3 Edward Bordin's working alliance

Edward Bordin [7], attempted to unify the way the alliance was defined, by proposing a pan-theoretical conceptualisation called the working alliance, which he defined as:

> 'a client seeking change and the therapist offering to act as a change agent that [incorporates] a mutual understanding and agreement about change goals and the necessary tasks to move forward these goals along with the establishment of bonds to maintain the partners' work' (p.13)

Central to Bordin's [6,7] theory, was his emphasis on collaboration and consensus in building the three dimensions that form the foundation of the working alliance, namely 'goals', 'task', and 'bond', that are depicted in Figure 2.3 sourced from Doukani and colleagues [47: p.4].

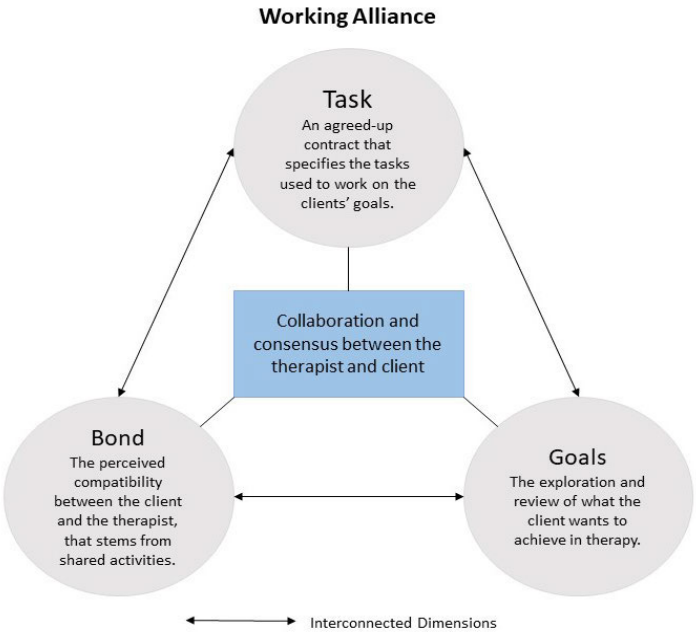


Figure 2.3. Bordin's theory of the working alliance. Source: Doukani and colleagues [47: p.4]

Here goals or goals setting involves a collaborative effort between the client and the therapist to identify what the client wants to achieve through therapy [6,7]. This requires the therapist to carefully explore the clients' story (e.g., struggles with pains and frustrations experienced) in order to establish suitable and relevant goals. Goals are typically developed at the start of therapy, and subsequently frame the activities carried out in treatment. However, they are also reviewed and fine-tuned throughout the course of therapy to ensure the goals remain relevant to the client.

The task refers to an agreed-upon contract that includes concrete exchanges, which specify the means by which the clients' goals can be achieved [6,7]. The selection of the therapeutic task involves both the client and the therapist. The collaboration stipulates that the client is actively involved in the selection process to ensure the task is relevant to their goals. However, the therapist is generally the major source of selection, considering their clinical knowledge and expertise.

A bond is developed from shared activities and compatibility between the client and the therapist [6,7]. Shared activities refers to the sense of common commitment and mutual understanding of the therapeutic activities. Compatibility is expressed in terms of liking, trusting, and respecting one another [6,7].

2.5.4 Distinguishing between client-therapist alliance labels

Apart from the working alliance, there are several labels for the alliance including the therapeutic alliance, the helping alliance, and the therapeutic relationship, among others [8,20]. While some of these labels are used interchangeably, these concepts differ with respect to their theoretical positions. Wampold [127] attempted to differentiate these terms by defining the therapeutic alliance as the, 'capacity of a therapist and a client to form a personal bond' [p.26], while he described the working alliance as 'the client's ability to align with the task of the analysis [i.e., therapeutic work]' [p.26]. In essence, while the therapeutic alliance and the helping alliance place emphasis on the 'bond', the working alliance places emphasis on the task.

A review on psychotherapy relationships, that was conducted by the APA, stated that interpersonal and instrumental elements of therapy should be considered as complementary [8]. They also proposed that the synergy between what the therapist delivers (intervention) and how they deliver it (relationship) should be collectively evaluated in respect to clinical outcomes. For this reason, the vast majority of the research in this field has focused on evaluating the association between self-reported alliance and clinical outcomes [8,20].

2.5.5 Alliance-outcome association in face-to-face psychological therapies

The findings of Lambert's [9] review on the association between the alliance and treatment outcomes, were reflected in more recent studies that found similar effects, showing that the alliance was a consistent predictor for treatment outcomes. The alliance can be measured from four perspectives, including the client, therapist, observer and other categories such as family members and partners [10].

A study that reviewed all ratings of the alliance, across 191 articles published between 1973 and 2009, found an alliance – outcome relationship of r =.275 (the 95% confidence interval of this aggregated effect size ranged from 0.249 to 0.301) [8]. These findings were consistent with another meta-analysis focusing on CBT interventions for depression (r = .26 [95% CI: .19 to .32]) [129]. A more recent review that included studies between 1979 and 2017 found that the alliance-outcome association for face-to-face psychotherapy was r = .278 (95% confidence intervals [0.256, 0.299], p < .0001; equivalent of d =.579) [10]. This review also provided a breakdown of the alliance-outcomes effect by the four categories of raters (i.e., clients, therapists, observers, and others) and showed that therapists' (radjusted .22, k = 40) and others' ratings (radjusted .25, k=48) did not differ from the clients' rating (radjusted .25, k =223), while observers' ratings (radjusted .22, k=66) showed smaller effects. Although the effect sizes are modest, these findings highlight the alliance as a reliable and consistent predictor of treatment outcomes.

The alliance between the client and the therapist is an integral feature of person-centred care [8,130,131]. The alliance is also regarded as a mutual investment by both the client and the therapist to promote meaningful engagement and commitment to treatment [8]. As such, the alliance has been integrated into practice guidance [27], including the treatment of depression through CBT [83].

2.5.6 Expanding the working alliance for DMHIs

The alliance has traditionally been captured between the client and their therapist, within in-person brick-and-mortar mental health services [8]. However, following the emergence of DMHIs, studies have increasingly evaluated the alliance in the context of guided and unguided, (although not limited to) internet-based interventions, mobile applications, and avatar therapy [38,132–134].

The concept of the alliance has undergone a number of transitions and developments to meet the diverse nature of different therapeutic approaches. Bordin [6,7] posits that the building of the alliance is not separate from the intervention. It is therefore the responsibility of the therapist or the service-provider to present the work in a way that effectively forges an alliance. Bordin [6,7] proposed that different therapies place different demands on the alliance. The ideal alliance *profile* is therefore likely to be different across therapeutic approaches [6–8]. Similarly, therapy that is mediated or delivered through an internet-based programme, requires an understanding of the alliance in relation to the mode of delivery. In support of this notion, Norcross and Lambert [8] stated the following:

> 'Both clinical and research evidence point to the complex, reciprocal interaction between the interpersonal relationship and the instrument methods. The therapist does not exist apart from

what the therapist does in terms of method, and we cannot imagine any treatment methods that would not have a relational impact'[p. 27].

It can therefore be inferred that the mode of treatment delivery, may have an impact on the working alliance. An APA [13] taskforce exploring elements of effective therapy concluded that, 'efforts to promulgate best practices of evidence based practice without including the therapeutic relationship are incomplete and potentially misleading' (p.423). They also extended their conclusion to therapies mediated by technology, in which the taskforce advised that the therapeutic relationship mattered in all forms of interventions, including therapies that are mediated by media, such as the telephone or the Internet [13]. In line with the task force recommendations, Kate Cavanagh and colleagues [14,34,135], have also called for evaluating the triadic relationship between the, client, therapist and programme.

Research concerning the working alliance in DMHIs have involved both qualitative and quantitative examinations . Qualitative evidence, although limited, has focused on understanding the alliance in digital innovations in mental health. The majority of evidence is quantitative evidence and has generally focus on evaluating the working alliance in clinical trials, that have compared the alliance between DMHIs and usual care, and/or examined the association between ratings of the working alliance and treatment outcomes.

2.5.7 Client qualitative accounts of the alliance in DMHIs

Barazzone and colleagues [34], were among the first to qualitatively explore the therapeutic relationship across three internet-based interventions. The study examined the extent to which the three digital programmes conveyed key features of the therapeutic relationship, as well as programmes related features that could contribute to the therapeutic relationship framework (e.g., design, multimedia, presentation, formatting, and quality and potency of features). The key features described were rated by the researcher, and evidence from the wider literature was used to validate observations. The findings revealed that while standalone programs were able to establish a therapeutic relationship (e.g., through conveying, empathy, warmth, negotiation of goals, collaboration, they were less effective at developing (e.g., a secure base, feedback, and responsiveness) and maintaining (e.g., repairing ruptures, maintaining flexibility and responsiveness) a therapeutic relationship. Findings also revealed that computerised therapies may provide clients with a higher level of flexibility and control over their treatment [34]. In line with sociological accounts of technology, novel digital technologies may mediate the construction of new social, personal or professional roles and identities [136]. This viewpoint takes us away from a position of using technology to 'emulate' traditional therapy between the client and the therapist, and steers us towards exploring the novel medium that technology can offer the psychotherapeutic process [14,34,135].

A narrative review of the therapeutic alliance in digital mental health interventions for serious mental illness found that the design and implementation of digital interventions may enhance the therapeutic alliance [36]. The review posited that technological features such as availability (e.g., how freely or conveniently accessible the digital intervention is), and interactivity (e.g., the degree to which personalisation and feedback based on how the user feels), may have an important role to play in building the therapeutic alliance.

A study investigating the therapeutic alliance in a fully automated phone and web-based interventions in a randomised controlled trial found that participants reported experiencing non-specific alliance features such as, empathy, acceptance, collaboration, and openness [35]. They also experienced other non-traditional alliance features, such as client initiative, availability, interactions, and responsiveness, indicating the programme's influence on the alliance.

These studies suggest that DMHIs may offer new alliance benefits in unguided CBT programmes [34–36]. My thesis will build on these studies to be the first to conceptually explore the working alliance in a b-CBT intervention for depression, in primary mental health services in the UK.

2.5.8 Therapist qualitative accounts of working alliance in DMHIs

In contrast to the qualitative literature on the working alliance from clients' perspective, to date, no other study has specifically explored this from therapists' perspective. Literature concerning the implementation of internet-based interventions, have touched on the topic of the working alliance. For example, a study that qualitatively explored the barriers and facilitators to implementing b-CBT in the German country-site of the E-COMPARED trial [23], found that therapists' perceptions of a 'one-size fits all' approach, a lack of autonomy of how b-CBT is used, and persistent technical issues that could not be solved, hindered the therapeutic alliance [137]. The same study reported that therapists' traits that facilitated the therapeutic alliance included, being empathic, persistent, having good written skills, having a high tolerance for frustration, and being able to cultivate the therapeutic alliance within a short space of time.

A systematic review on health professionals' perspectives of implementing internet-based therapy in routine mental health care involving 29 eligible qualitative articles, provided important insights on the barriers and facilitators that can impact the alliance [138]. The findings revealed that health professionals perceived the online therapy's flexibility in relation to time and location as advantageous, and that blended therapy facilitated the building of rapport and allowed the active monitoring and follow-up of clients. Health professionals perceived the therapeutic relationship as different from that

in face-to-face therapy but not necessarily worse and that online interventions extended the time needed to develop a therapeutic relationship. Moreover, they emphasized the need for targeted training and organisational support to manage changing workflows, in order to support their delivery of online interventions.

These findings appear to highlight unique alliance needs, limitations, and advantages to implementing online therapies, that my thesis will build on and explore in greater detail using Bordin's working alliance theory [6,7], within the context of a blended CBT intervention for depression.

2.5.9 The alliance in internet-based psychological therapies

Over the past decade, interest has centred on investigating the alliance in internet-based interventions. A systematic review examining the therapeutic relationship in internet-based therapy, found that only three out of the eleven studies reviewed, directly compared computerised therapy (including synchronous and asynchronous communication over email, chat with a trained therapist or psychologist) and face-to-face therapy [37]. The findings of these studies either reported no differences between online therapy and face-to-face therapy; higher alliance goals subscale scores for online therapy compared to face-to-face therapy; or higher composite working alliance scores for online therapy compared to face-to-face therapy, although the latter did not directly compare these treatment conditions. While this review is based on finite research in the field, the findings appear to indicate that the quality of the working alliance may be equal and/or better than traditional forms of face-to-face therapy.

In order to understand if the alliance impacts treatment outcomes, it is important to evaluate the alliance-outcome association [8]. In a systematic review of six studies evaluating the therapeutic alliance in guided-internet therapy programmes for depression and anxiety disorders, three studies found that the alliance was directly associated with treatment outcomes, with a higher therapeutic alliance leading to symptom improvement [38]. A narrative review of the therapeutic alliance in online therapy also found significant alliance-outcome associations for guided iCBT interventions [40]. The review also reported that most studies on guided iCBT found significant associations between the outcome and the tasks and goals, but not the bond subscale. The author proposed that goals and task may play more of an important role in forging the alliance in guided iCBT, and that client needs in relation to the bond subscale may not have been sufficiently met. Another systematic review that evaluated the therapeutic alliance in a range of technology-based interventions (e.g., email, telephone, internet-based programmes) for the treatment of depression found mixed results in relation to the alliance-outcome association [39].

While the findings across reviews appear to be mixed [38–40], there is also clear evidence that an alliance that influences treatment outcomes, can be established in guided iCBT. However, very few studies have examined the working alliance in a b-CBT intervention for depression.

2.5.10 Working alliance in b-CBT

To this end, only three other studies have examined the working alliance in b-CBT for depression, all of which were affiliated with the E-COMPARED study [23]. The first study was an uncontrolled study in Sweden which recruited a total of 73 participants to b-CBT from primary care services. The study found that while the therapist rated working alliance was predictive of subsequent changes in depression scores during treatment, the client-rated working alliance was not. These findings suggest that the therapist working alliance may play a pertinent role in predicting the trajectory of the client's outcome in a b-CBT intervention.

The second study was based in the Netherlands and recruited 102 participants from specialist care-services, in which participants either received a total of a 20-week intervention (10 face-to-face, and 10 online) (n=47), compared to 15-20 face-to-face CBT sessions (n=45) [42]. The study found no treatment group effects for both the client and therapist working alliance. An alliance-outcome association was found for clients allocated to face-to-face CBT; however, no effect was found in the b-CBT group. This led the authors to speculate that the digital component in b-CBT may have led participants to perceive the working alliance differently from those receiving face-to-face CBT [42].

The third study explored clients' and therapists' working alliance ratings in b-CBT compared to face-to-face CBT for depression in Denmark [43]. The b-CBT intervention consisted of six face-to-face sessions that were alternated with six to eight online modules of iCBT. The face-to-face CBT condition consisted of 12 face-to-face sessions. The study recruited 76 participants (38 participants were allocated to each group). The findings showed that both client and therapist had comparable working alliance ratings between treatment groups. However, clients' and therapists' ratings were not significantly associated with treatment outcomes, across both treatment conditions. Pooling client and therapist ratings across both conditions showed that only therapist ratings of the working alliance predicted treatment outcomes. This may suggest that the study did not have enough power to detect an effect for each treatment group.

While these studies were affiliated with the E-COMPARED trial [23], they appeared to use different datasets, that stemmed from, using a different depression outcome measure [42], utilising therapist working alliance ratings that were not made available in the locked E-COMPARED dataset [43], and measuring the working alliance at an earlier timepoint (i.e., after four weeks into therapy compared to

3-months-post randomisation in the main trial). Across these studies data only crossed over for 38 cases from the Denmark study [43], therefore the data used in my thesis was by and large unique.

2.6 Summary of literature and rationale

Depression is a prevalent mental health condition that affects more than 264 million people, and is the leading cause of disability worldwide [1,2]. In Europe, depression and anxiety affect around 25% of the population [24], while the prevalence of depression in the UK, Denmark, France, Germany, Poland and Sweden sit higher than the worldwide prevalence [57], and by comparison to other European countries [58].

Depression is often a disabling condition that can impair social and occupational functioning, and that can lead to high societal costs. For example, around 50% of chronic sick leave in Europe is attributed to depression and/or anxiety [24], while mood and anxiety disorders are estimated to cost €170 billion annually [24].

Despite the high economic burden of depression, around 45% of people who experience depression and require treatment, do not access mental health care, with countries such as the UK experiencing a treatment gap that is high as 84% [68]. The burden of depression is further compounded by reports of workforce shortages, and inadequate resources in mental health care [72,73]. This underscores the importance of developing cost-effective solutions to increasing access to evidenced-based interventions.

The use of DMHIs has been put forward as a potential solution for addressing the treatment gap and workforce shortages [21,94]. Unlike brick-and-mortar services, DMHIs generally offer access to mental health care remotely, and are therefore considered to be cost-saving, and easier to scale-up [94]. Remote access to treatment, can increase patient and provider convenience in respect to the time and location of sessions, and can also combat public stigma of mental health [95,96]. Associated benefits suggest that DMHIs may have the potential to increase access to mental health care, and expand the mental health workforce [72,73].

Evidence concerning DMHIs has largely centred on iCBT interventions. iCBT is an online programme that generally provides CBT content, interactive activities, multimedia choices, and offers some feedback and guidance [28,104]. These programmes are typically supplemented with three levels of support during treatment, that includes, no support from a mental health practitioner (i.e., referred to as unguided iCBT), minimal support from a mental health practitioner (i.e., guided iCBT), and therapist

support through face-to-face sessions that are integrated with a digital programme into one protocol (i.e., b-CBT) [22,23].

There is considerable evidence showing that guided iCBT can be effective in reducing symptom severity for depression, and can lead to cost-benefits to health care providers [42]. iCBT is also established as a first-line intervention for mild-to-moderate depression, based on the NICE [4] and APA [81] guidance. While blended formats of CBT are comparatively new and less researched, evidence suggests that blended CBT can improve adherence and treatment outcomes [44]. In general, receiving higher levels of therapy support has been found to lead to better adherence and clinical outcomes [101,121], while lower levels of support has been associated with lower ratings of the client-therapist alliance [123]. This raises important questions about traditional mechanisms of change that have been found to promote engagement and positive treatment outcomes in psychological therapies, with much interest being directed towards the concept of the alliance (working, therapeutic, etc.,). For example, the therapeutic alliance was identified as a research priority in digital mental health care by two consensus studies that involved multi-stakeholder and international interdisciplinary panels [26,102].

The working alliance is part of a larger relational framework that has been traditionally conceptualised between the client and their therapist [8]. This refers to the emotional 'bond' between the client and the therapist that maintains the partnership, the agreement between the client and therapist on the therapeutic 'goals', and the 'tasks' that address the client's goals [6,7].

The working alliance is an important pillar in psychological therapies that has been found to reliably predict positive treatment outcomes, across a range of psychological approaches and clinical presentations, albeit with a modest effect size [8–12,129]. A study comparing the alliance between different mental health presentations, found that while higher therapeutic alliance ratings were associated with better outcomes in people with emotional disorders, the implications appear to be greater for people with severe mental health presentations, in which this association was only found for people with positive treatment outcomes [139]. In line with these findings, a study investigating the therapeutic alliance in people with psychosis found a causal relationship that showed that a good therapeutic alliance led to better clinical outcomes, whereas a poor therapeutic alliance led to deteriorations in clinical symptoms [140]. This highlights the cost of not developing an adequate working alliance, and the need to investigate such costs, in highly prevalent mental health conditions such as depression [1,2]. The alliance is theorised to influence positive treatment outcomes by driving deeper levels of engagement in therapy [9,13,83,141]. It is regarded as a mutual investment by both the client and the therapist to promote meaningful engagement and commitment to therapy, respectively [8]. As such, the alliance has been integrated into practice guidance for psychological therapies [27], including CBT [83].

Evidence concerning the alliance in iCBT, has largely focused on: (a), comparing the alliance between iCBT and a control intervention, and (b) determining if the alliance is associated with treatment outcomes. Findings have largely shown the working alliance to be comparatively high and did not significantly differ across guided/ blended iCBT interventions and face-to-face CBT [37–43]. There is also evidence to suggest that higher alliance scores predicted better treatment outcomes in guided iCBT for depression, however it should be noted that literature reviews have largely reported mixed findings [37–40]. No effects were found between client ratings and treatment outcomes across the three studies that have assessed the working alliance in b-CBT for depression [41–43], while one study found a significant alliance-outcomes association based on therapist working alliance ratings [41]. Notably, having a comparatively bigger sample size (e.g., n=76 compared to n=38 and n=47) [34–36], and pooling data across conditions [43], appears to produce significant alliance-outcome associations. A possible explanation for the non-significant results could therefore be due to not having enough power to detect an effect.

On a conceptual level, the ideal alliance profile has been argued to differ across therapeutic approaches [6–8], with many calling for a better understanding of the alliance profile in relation to the digital programme [14,34,135]. Very few studies have explored the alliance conceptually in DMHIs, however, based on the limited evidence available, findings suggest that unguided digital programmes or mobile applications may produce novel alliance benefits, such as experiences of greater flexibility, control, autonomy, accessibility, interactivity and responsiveness [34]. In line with sociological accounts of technology, novel digital technologies may mediate the construction of new social, personal or professional roles and identities [36,136]. Moreover, a review on qualitative accounts of practitioners' experiences of delivering iCBT, showed that therapists perceived blended formats of therapy to facilitate the building of rapport with their clients and enable the active monitoring of their progress [138]. Therapists' also reported that online interventions extended the time needed to develop a therapeutic relationship [138]. While these studies emphasis the novel alliance profile in DMHIs, they have largely focused on unguided DMHIs [34–36], common mental disorders and severe mental illness [35,36], and have only briefly discussed the alliance when exploring therapists' experiences of DMHIs more broadly [138]. To my knowledge, the alliance in blended CBT has yet to be qualitatively examined. Blended interventions are particularly pertinent, considering that blended models of care are increasingly being recommended and adopted, especially following the COVID-19 pandemic in which the integration of digital solutions enabled health services to realise the benefits of DMHIs in care [26,142–144].

My thesis will build on the existing literature to conduct a mixed methods evaluation of the working alliance that aims to uncover the working alliance profile demanded by the b-CBT intervention. To my

knowledge, my thesis will be the first to exclusively explore the working alliance from clients and therapists' perspectives in a b-CBT intervention for depression. The quantitative component of the mixed methods approach will evaluate the working alliance in b-CBT and when compared to usual care in a large clinical trial (i.e., E-COMPARED study), investigating the effectiveness of b-CBT compared to TAU, for depression, across nine European countries [23]. It is anticipated that using a larger sample may address the limitations of previous studies, as it reduces the risk of type II error. While the quantitative measures [18,145] used in the E-COMPARED study [23] (see *Section 3.3* for additional information on the E-COMPARED study), only assessed the working alliance between clients' and therapists' in b-CBT, my thesis aims to address this limitation by investigating how the digital programmes' usability impacted the alliance-outcome association, to begin to explore the influence of the digital programme.

2.6.1 Thesis aims, research questions and research objectives

My thesis aims to evaluate the working alliance from clients' and therapists' perspectives in a b-CBT intervention for depression, and when compared to usual care for depression on the E-COMPARED trial, in Europe.

There are eight research questions (RQ) associated with the aim of my thesis:

- RQ1: What is the working alliance needs of clients with major depression in relation to a b-CBT intervention for depression in primary mental health services in the UK?
- RQ2: How was the working alliance experienced by therapists delivering b-CBT for depression in primary mental health services in the UK?
- RQ3: Does client working alliance scores at 3-months (post-randomisation) assessments differ between b-CBT versus face-to-face in TAU?
- RQ4: Are client working alliance scores associated with client depression scores at 3-month assessments in b-CBT?
- RQ5: Does client-rated system usability scores, influence the association between client working alliance and depression scores at 3-month assessments?
- RQ6: Does the therapist working alliance scores at 3-month assessments differ between b-CBT versus face-to-face in TAU?
- RQ7: Are therapist working alliance scores associated with client depression scores at 3-month assessments in b-CBT?
- RQ8: Does therapist-rated system usability scores, influence the association between therapist working alliance on client depression scores at 3-month assessments?

The associated thesis objectives are presented below:

- Objective 1: Qualitatively examine clients' working alliance demands in b-CBT to adapt Bordin's [6,7] working alliance theory for a b-CBT intervention for depression, in primary care services in the UK.
- Objective 2: Qualitatively examine PWPs' experience of the working alliance in a b-CBT intervention for depression, in primary care services in the UK.
- Objective 3: Test the difference in client working alliance scores at 3-month assessments between b-CBT versus face-to-face in TAU for depression, using a subset of pooled E-COMPARED trial data.
- Objective 4: Determine if client working alliance scores are associated with depression scores at 3-month assessments in b-CBT for depression using pooled E-COMPARED trial data.
- Objective 5: Test for an interaction between client system usability and working alliance scores on the association between the client working alliance and depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.
- Objective 6: Test the difference in therapist working alliance scores at 3-month assessments between b-CBT versus face-to-face in TAU for depression using a subset of pooled E-COMPARED trial data.
- Objective 7: Determine if therapist working alliance scores are associated with client depression scores at 3-month assessments and when controlling for client working alliance scores in b-CBT for depression using pooled E-COMPARED trial data.
- Objective 8: Test for an interaction between therapist system usability and working alliance scores on the association between the therapist working alliance and client depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

Chapter 3 provides a detailed description of the methodology adopted to address the aims and objectives of my thesis.

Chapter 3: Methodological overview and considerations

3.1 Introduction to chapter 3

This chapter describes and justifies the research methodology adopted in my thesis. This will start by providing a foundational overview of the methods used in the research papers that make up my thesis (*Section 3.2*), followed by a description of the E-COMPARED study at a consortium level and at the level of the UK country-site that my PhD was nested in (*Section 3.3*). The chapter will then outline PhD specific methodological decisions, processes and considerations that were made pre-data collection (*Section 3.4*), as well as specific methodological justifications concerning the qualitative (*Section 3.5*) and quantitative (*Section 3.6*) components of my thesis, pertaining to recruitment, data collection and data analysis. This chapter will end by listing PhD related ethical approvals (*Section 3.7*).

3.2 Methodological overview of thesis

My thesis evaluated the working alliance from clients' and therapists' perspectives in a blended cognitive behavioural therapy (b-CBT) intervention for depression, and when compared to usual care for depression on the E-COMPARED study [23], using a mixed methods approach [146]. Papers 1 and 2 employed a qualitative design to gain an in-depth conceptual understanding of the clients' and therapists' experiences of the working alliance in the UK country-site of the E-COMPARED trial, through primary data collection that was specifically for my PhD. Papers 3 and 4 were secondary analyses of pooled quantitative data from the E-COMPARED trial. The remaining section provides a summary of the methods used in each of the four research papers. Table 3.1 also provides a summary of the research questions, objectives, hypothesis (where relevant) and methods applied across the four research papers.

Paper 1 examined client working alliance demands in a b-CBT intervention for depression, to adapt Bordin's [6,7] working alliance for a b-CBT context [47]. Patient involvement was recruited to shape the design of the study ahead of data collection. Semi-structured interviews were carried out with participants on the UK E-COMPARED trial. Client participants that completed at least one module on the internet-based programme and one face-to-face session, in the b-CBT arm were invited to participate in the study. Participants (n=19) were recruited from four Improving Access to Psychological Therapies (IAPT) services in the UK (additional information on IAPT services can be found in *Section 3.3.2.3*). E-COMPARED trial participants with major depressive disorder, who engaged in at least one internet-based programme and face-to-face session in the b-CBT arm were recruited to the study. A constant

comparative method informed by grounded theory was used to gain higher level abstractions during data collection that involved comparing and contrasting newly collected data with previously collected data, to understand, similarities, differences and newly emerging information that can be explored in prospective interviews. A thematic analysis was used to analyse the data [147].

Paper 2 examined Psychological Wellbeing Practitioners' (PWPs) experiences of the working alliance in a b-CBT intervention for depression in the UK E-COMPARED trial (additional information on PWPs can be found in *Section 3.3.2.4)* [48]. Recruitment was conducted across six IAPT services in England. Semi-structured qualitative interviews (i.e., individual and focus group discussions) were conducted with 13 PWPs who delivered b-CBT on the trial. Thematic analysis was used to analyse the data to identify barriers and facilitators to fostering the working alliance with clients', in a b-CBT context [147].

Paper 3 investigated the client-rated working alliance in a b-CBT intervention versus face-to-face CBT in treatment as usual (TAU) for depression. The primary objectives were to test the difference in working alliance scores between b-CBT and face-to-face CBT in TAU and determine if working alliance scores are associated with depression scores in b-CBT, at 3-month assessments post-randomisation. The secondary objectives were to test for an interaction between system usability and client-rated working alliance, on the association between the client-rated working alliance and depression scores at 3-month assessments in b-CBT. Eligible participants (n=945) were aged 18 years or older, had a diagnosis of major depressive disorder and were either randomized to b-CBT (n=476) or TAU (n=467), however only a subset of data for countries offering face-to-face CBT in TAU were used (n=200). b-CBT consisted of 6-20 sessions, involving face-to-face sessions with a therapist and an internet-based programme with an adjunct mobile application. TAU consisted of usual care for depression. Primary outcomes were scores on working alliance, as measured by the Working Alliance Inventory-Short Revised-Client (WAI-SR-C) [145] and depressive symptoms, as measured by the Patient Health Questionnaire-9 (PHQ-9) [106], at 3-month assessments. System usability was a secondary scale, measured by the System Usability Scale-Client (SUS-C) [148], at 3-month assessments. Data were analysed using generalized linear regression models that adjusted for a set of baseline variables.

Paper 4 was a qualitative secondary data analysis of pool data from the E-COMPARED study investigating therapist-rated working alliance in a b-CBT intervention versus TAU, for depression. The primary objectives of the study were to test the difference in therapist-rated working alliance scores between b-CBT and face-to-face CBT in TAU and determine if working alliance scores were associated with PHQ-9 scores at 3-month post-randomisation assessments, and when controlling for client-rated working alliance in b-CBT. The secondary objective was to test for an interaction between system

usability and therapist working alliance, on the association between the therapist working alliance and depression scores at 3-months assessments in b-CBT. There were 883 cases that were either allocated to b-CBT (n=444) or TAU (n=439), however only a subset of data from TAU that only offered face-to-face CBT were used (n=172). Primary outcomes were scores on the working alliance, as measured by the Working Alliance Inventory-Short Revised-Therapist (WAI-SR-T) [18], and depressive symptoms as measured by the PHQ-9 [106], at 3-months. System usability scores were measured by System Usability Scale-Therapist (SUS-T) at 3-month assessments [148]. Data were analysed using generalized linear regression models, adjusted for a set of baseline variables.

A full description of the research design and the methodology for papers 1 to 4, are described across Chapters 5 to 7. It should be noted that duplicated description of the methodology will be presented in the papers, due to being nested in the same trial and due to the research paper format.

3.3 Background to the E-COMPARED trial

This section will describe the methods and design adopted within the E-COMPARED trial [23] both at the consortium level involving nine country-sites, and the UK country-site level (see Appendix 1 for the unpublished UK trial protocol).

3.3.1 Design

The E-COMPARED study is a two-arm, non-inferiority randomised controlled trial (RCT) investigating the effectiveness and cost-effectiveness of b-CBT compared to TAU across eight European countries [23]. A pragmatic trial design was used to evaluate the effectiveness of b-CBT in real-life routine care, that reflects client variations in clinical practice in aid of enabling greater generalisability [149,150]. A non-inferiority trial was used to test if b-CBT is not unacceptably worse than an active control treatment (i.e., TAU) that is already in use within services [151–153]. The trial was conducted in routine primary care, in Germany, Poland, Spain, Sweden and the United Kingdom, and specialised mental health care in France, The Netherlands and Switzerland [23]. An additional satellite site was added in specialised mental healthcare services in Denmark in 2016 to boost recruitment [45]. The trial's recruitment target was 1200, which was based on a power calculation [23]. Participants were assessed across four time points over 12 months (baseline – 0 month, 3-months, 6 months, and 12 months). Data was collected between April 2015 - June 2017 [23].

Table 3.1. Overview of research questions, objectives and hypothesis addressed by papers 1-4 and the research methodology applied in each paper

Papers	**Research questions (RQ)**	**Objectives(s)**	**Hypotheses**	**Research Data**
Paper 1: Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study [47].	RQ1: What is the working alliance needs of clients with major depression in relation to a b-CBT intervention for depression in primary mental health services in the UK?	Objective 1: Qualitatively examine clients' working alliance demands in b-CBT to adapt Bordin's [6,7] working alliance theory for a b-CBT intervention for depression, in primary care services in the UK.	n/a	Qualitative primary data from 19 clients with major depression in the UK country-site of the E-COMPARED trial.
Paper 2: Practitioners' experience of the working alliance in a blended cognitive-behavioural therapy intervention for depression: qualitative study of barriers and facilitators [48].	RQ2: How was the working alliance experienced by PWPs delivering b-CBT for depression in primary mental health services in the UK?	Objective 2: Qualitatively examine PWPs' experience of the working alliance in a b-CBT intervention for depression, in primary care services in the UK.	n/a	Qualitative primary data from 13 PWPs involved in delivering b-CBT in the UK country-site of the E-COMPARED trial.

Papers	Research questions (RQ)	Objectives(s)	Hypotheses	Research Data
Paper 3: Comparison of the working alliance in blended-cognitive behavioural therapy and treatment as usual for depression in Europe: Secondary data analysis from the E-COMPARED randomised controlled trial.	RQ3: Does client working alliance scores at 3-months (post-randomisation) assessments differ between b-CBT versus face-to-face CBT in TAU?	Objective 3: Test the difference in client working alliance scores at 3-month assessments between b-CBT versus face-to-face CBT in TAU for depression using a subset of pooled E-COMPARED trial data.	H1: Client working alliance scores at 3-month assessments will be higher in b-CBT compared to face-to-face CBT in TAU for depression.	Pooled secondary quantitative data from 943 clients with major depression participating in the E-COMPARED trial, across nine European countries: Germany, Sweden, Netherlands, France, United Kingdom, Spain, Poland, Switzerland, and Denmark.
	RQ4: Are client working alliance scores associated with client depression scores at 3-month assessments in b-CBT?	Objective 4: Determine if client working alliance scores are associated with depression scores at 3-month assessments in b-CBT for depression, using pooled E-COMPARED trial data.	H2: Higher client working alliance scores will be associated with lower depression scores at 3-month assessments in b-CBT.	
	RQ5: Does client-rated system usability scores, influence the association between client working	Objective 5: Test for an interaction between client system usability and working alliance scores on the	H3: There will be a significant interaction between client system usability and working alliance scores, on the	

Papers	Research questions (RQ)	Objectives(s)	Hypotheses	Research Data
	alliance and depression scores at 3-month assessments?	association between the client working alliance and depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.	association between the client working alliance scores and depression scores at 3-month assessments in b-CBT.	
Paper 4: Comparison of the therapist-rated working alliance in a blended cognitive behavioural therapy intervention for depression: A secondary data analysis from a multi-site randomised controlled trial in Europe.	RQ6: Does the therapist working alliance scores at 3-month assessments differ between b-CBT versus face-to-face CBT in TAU?	Objective 6: Test the difference in therapist working alliance scores at 3-month assessments between b-CBT versus face-to-face CBT in TAU for depression, using a subset of pooled E-COMPARED trial data.	H4: Therapist working alliance scores at 3-month assessments, will be higher in b-CBT compared to face-to-face CBT in TAU.	Pooled secondary quantitative data from 883 enrolled cases from eight country-sites on the E-COMPARED trial: Germany, Sweden, Netherlands, France, United Kingdom, Spain, Poland & Switzerland.
	RQ7: Are therapist working alliance scores associated with client depression scores at 3-month assessments in b-CBT?	Objective 7: Determine if therapist working alliance scores are associated with depression scores at 3-month assessments and when	H5: Higher therapist working alliance scores will be associated with lower depression scores at 3-month assessments in b-CBT.	

Papers	Research questions (RQ)	Objectives(s)	Hypotheses	Research Data
		controlling for client working alliance scores, in b-CBT for depression, using pooled E-COMPARED trial data.		
	RQ8: Does therapist-rated system usability scores, influence the association between therapist working alliance on client depression scores at 3-month assessments?	Objective 8: Test for an interaction between therapist system usability and working alliance scores on the association between the therapist working alliance and client depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.	H6: There will be a significant interaction between therapist system usability and working alliance scores on the association between the therapist working alliance and client depression scores at 3-month assessments in b-CBT.	

Abbreviations: b-CBT, blended cognitive behavioural therapy; PWP, Psychological Wellbeing Practitioner; TAU, treatment as usual.

3.3.2 Participants and recruitment

3.3.2.1 Consortium

Recruitment procedures differed in each country, but all sites enrolled new clients seeking help for depression that had a score of 5 or higher on the PHQ-9 [106], and who were referred to the study by a therapist or general practitioner (GP) [23]. See Table 3.2 for a breakdown of recruitment procedures across country-sites [23,43].

The study was explained to potential participants either face-to-face or over a telephone call [23]. Clients who agreed to take part in the study were invited to an initial appointment in which written informed consent was taken. The same inclusion and exclusion criteria were applied in all trial country-sites [23]. The inclusion criteria consisted of: being aged 18 years or older, scoring 5 or higher on the PHQ-9 screening questionnaire [106], and meeting diagnostic criteria for Major Depressive Disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), as confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) version 5.0 [51]. The exclusion criteria included: high risk of suicide, other psychiatric comorbidity (i.e., substance dependence, bipolar affective disorder, psychotic illness, or obsessive compulsive disorder) as established during the M.I.N.I. interview; receiving psychological treatment for depression in primary or specialised mental health care at the point of recruitment; being unable to comprehend the spoken and written language of the country where the study was conducted; not having access to a computer and or to a fast internet connection (i.e., broadband or comparable), and not having a smartphone or being unwilling to carry a smartphone if one was provided by the research team.

Once eligibility was established and baseline assessments were completed, participants were randomised to one of two treatment arms, b-CBT or TAU. Randomisation was pre-specified ahead of the trial by an independent administrator outside of the research team. Block randomisation took place at an individual level and was stratified by country [23]. Additional information about the randomisation process can be found in the unpublished E-COMPARED UK trial protocol in Appendix 1).

3.3.2.2 UK country-site

Potential participants accessing IAPT services were identified by low-intensity PWPs. Clients were referred to the research team if they scored 5 or higher on the PHQ-9 and were interested in taking part in the trial. The research team were responsible for screening, consenting, and assessing potential participants.

PWPs were involved in delivering the intervention across both conditions. In the UK, the ethics committee advised that PWPs should be considered as research participants. This was because PWPs were required to complete questionnaires on the trial regarding the working alliance, system usability, treatment fidelity as well as demographic information such as their gender, years of experience and highest level of qualification, that was not collected in other E-COMPARED country-sites [23,45]. As a result, both clients and PWPs were required to provide written consent, ahead of their participation, while therapists in other E-COMPARED country-sites were not consented [23].

Client participants seeking treatment in IAPT services were approached about the E-COMPARED trial by email, and telephone, while therapist participants were approached by email and in person. All participants were given at least 48 hours to contemplate information from the information sheet (see Appendix 2 and Appendix 4, for patient and therapist participant information sheets, respectively) and were provided with the opportunity to discuss and ask questions about their participation. Those who were interested in participating in the trial were booked for an appointment to take written consent, at a convenient time and place either at the London School of Hygiene and Tropical Medicine (LSHTM) or their respective clinic. The consent form was largely focused on their participation in the trial, however it also included an item asking if they were willing to participate in qualitative interviews which was optional (see Appendix 5 and Appendix 6 for client and therapist trial consent forms respectively).

Table 3.2. Overview of recruitment on the trial, b-CBT format and dosage, and treatments offered in TAU by trial country-site [23,45]

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
Country	Treatment setting	Recruitment procedure	Platform	Duration (weeks)	Online/ face-to face	[a]Sequencing	
France	Specialised mental health care	New or regular patients recruited by CBT therapists from 11 experts centres throughout France.	Moodbuster	16	8/8	Alternate	Face-to-face CBT
Germany	Primary care	Recruitment in the waiting room of GP clinics or during GP consultations.	Moodbuster	11-13	10/6	Alternate	[b]GP care (e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT)
Netherlands	Specialised mental health care	Recruited through mood disorder departments of three	Moodbuster	20	10/10	Alternate	[b]Face-to-face psychotherapy (mainly CBT, interpersonal

	Recruitment		b-CBT format and dosage				TAU allocation
		outpatient clinics in Amsterdam and Leiden.					psychotherapy, problem-solving therapy, antidepressant medication, or a combination of these).
Poland	Primary care	Recruited through primary care centres by CBT therapists (licenced and in training) in five major cities in Poland (Warsaw, Sopot, Poznan, Katowice, and Wroclaw).	Moodbuster	6-10	6/7	Alternate	Face-to-face CBT
Spain	Primary care	Recruitment through routine primary care from the Spanish National Health System in several cites	Smiling is fun	10	8/3	1-4-1-4-2	[b]Prescribed medication by the GP and/or received face-to-face CBT, interpersonal

	Recruitment		b-CBT format and dosage				TAU allocation
		(Valencia, Castellón, and Zamora).					psychotherapy or supportive therapy once a month
Sweden	Primary care	Recruitment through collaborating primary care clinics in three Swedish counties (Stockholm, Linköping, Västerås). Posters and leaflets were distributed in the waiting areas and/or were administered to GPs in clinics, who in turn referred potentially eligible participants.	Iterapi	10	6/4	Alternate	[b]Usual care paths in Sweden; including general practitioner care, e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT.
Switzerland	Specialised mental health care	Recruitment through two outpatient clinics (Bern and Zurich) and individual therapists.	Deprexis	18	9/9	Alternate	Face-to-face CBT

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
United Kingdom	Primary care	Recruited through a primary mental health programme that delivers psychological therapies to people with depression and anxiety disorders, in Northern and Southern England.	Moodbuster	11	5/6	Alternate	Face-to-face CBT
Denmark	Specialised mental health care	Recruited through Centre for Telepsychiatry in specialised mental health care at the Mental Health Services of the Region of Southern Denmark, where patients are referred to the study by clinicians. Initially patients are self-	NoDep	12	6-8/6	Alternate	Face-to-face CBT

	Recruitment		b-CBT format and dosage				TAU allocation
		referred to the Centre for Telepsychiatry.					

Abbreviations: b-CBT, blended cognitive behavioural therapy; CBT, cognitive behavioural therapy; GP, general practitioner; NHS, National Health Service; TAU, treatment as usual.

[a]Sequencing of face-to-face and online can include more than one session per week for either component.

[b]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites.

3.3.2.3 Description of IAPT services in the UK

IAPT services aim to systematically coordinate and improve access and delivery of evidence-based psychological therapies within the National Health Service (NHS) [154]. According to the IAPT manual, IAPT services were developed in response to high rates of depression and anxiety in England. The first wave of IAPT services were established in 2008, and later rolled out nationally in England [154].

IAPT services provide evidence-based interventions for common mental health disorders (e.g., depression, anxiety, co-morbid presentations), long-term physical conditions (e.g., chronic fatigue syndrome, irritable bowel syndrome), and medically unexplained symptoms [154]. IAPT services are defined by three principles, including, (i) the application of the appropriate dose of treatment to the mental health condition, as guided by the National Institute for Health and Care Excellence (NICE) guidelines; (ii) treatment that is delivered by a workforce that are trained to deliver interventions for the appropriate mental health problem and treatment dosage, and receive supervision from senior practitioners; and (iii) the routine monitoring of client outcomes session-by-session to provide the client and the practitioner with up-to-date information to guide the course of treatment, and contribute to broader service improvements and reporting [154].

IAPT services are appointed by local clinical commissioning groups and provide services across both primary and secondary care mental health services in England. Referral pathways within services, such as self-referral promote equality and access [154]. IAPT services use a stepped-care model [155], which offers the 'least intrusive intervention' that meets the clients' needs. Two main levels of treatments are offered, including low-intensity (step 2) and higher intensity treatment (step 3), which lie in a wider four-step model within the health care system (See Figure 3.1 for stepped care model) [155]. Low-intensity treatment is targeted at people with mild to moderate anxiety and depression [154]. For example, treatments offered for depression include individual guided self-help CBT, behavioural activation, structured group physical activity programmes, and internet-based CBT. Clients who have not fully recovered, are stepped up to high-intensity treatments. High intensity treatments are also offered to people with severe presentations of depression, social anxiety, and PTSD, who typically receive weekly face-to-face sessions with a trained therapist that offers a wide range of psychological approaches in addition to CBT.

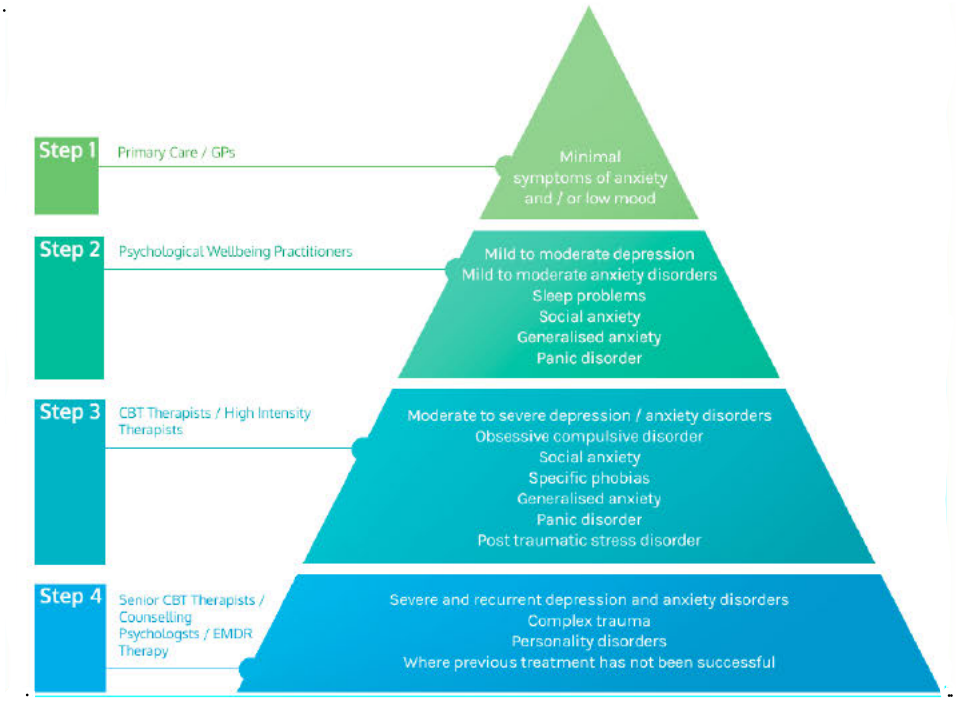


Figure 3.1. The stepped care model used by IAPT services to make clinical decisions about treatment allocation [155]

3.3.2.4 Description of PWP workforce in the UK

PWPs are a relatively new workforce associated with the introduction of the IAPT programme that was rolled out in 2008 [154]. The PWP workforce consist of low-intensity and high-intensity practitioners. Differences between the role of a low and high intensity PWP relate to their clients' symptom severity and their required treatment dosage [114]. Low-intensity PWPs generally offer treatment to clients with mild-to-moderate presentations, while high intensity PWPs typically offer treatment to clients with greater symptom severity. The low-intensity PWP workforce delivers 'step 2 intensity interventions' with clients with mild-to-moderate presentations of depression and anxiety [114]. This includes, short-term evidence-based treatments using cognitive–behavioural principles, self-help materials, and engaging in 6 hours or less of contact with clients, with each session expected to be around 30 minutes or less [114]. Practicing PWPs are required to either have completed a training course with an appropriate registration with a professional body or be in the process of completing their training. They are also expected to complete relevant continued professional development training [114].

3.3.3 Intervention

3.3.3.1 consortium

b-CBT

Client participants in the b-CBT group received CBT treatment for depression that was delivered by a therapist in a clinic setting, and a digital programme that was completed outside of the clinic [23]. Different internet-based programmes, blended formats, ratios, and sequencing of online and face-to-face therapy were adopted by different country-sites (see Table 3.2 for an overview of the blended interventions applied in each country-site [23,45]). Five different digital programmes were used in the trial, namely Smiling is fun (n=1), Iterapi (n=1), Deprexis (n=1), NoDep (n=1), with the remaining sites using Moodbuster (n=5). All digital programmes focused on treating depression and were based on CBT, which is an evidence-based intervention for depression [27]. Smiling is fun Iterapi, Deprexis, and NoDep were developed and/or affiliated with the Spanish, Swedish, Swiss, and Danish country-sites, respectively. Moodbuster was adopted by all other countries that were not affiliated with a digital programme [23,45].

All digital programmes included content on four mandatory modules that all trial participants had to complete, including psychological education, behavioural activation, cognitive restructuring, and relapse prevention [23] (see Section 2.3.2 in Chapter 2 for a description of these CBT approaches). Optional modules were also offered to participants, including physical exercise and problem solving through the Moodbuster digital programme, coping skills through Smiling is Fun, and mindfulness, interpersonal skills, positive psychology, emotion-focused therapy, and childhood experiences, through Deprexis [23,45]. The number of b-CBT sessions varied between 6 and 20, while the duration of the intervention was an average of 13 (SD=3.83) weeks, ranging between 8 to 20 weeks across all sites [23,45]. The ratio of face-to-face and programmes sessions varied across sites. The sequence of face-to-face and programmes session were predominantly alternated (n=8) [23,45]. Additional information on the Moodbuster digital programme is provided in *Section 3.3.3.2* of this Chapter. Detailed information of the digital programme for countries that did not use Moodbuster were not available to the rest of the consortium.

All digital programmes were supplemented with a mobile phone application that was either integrated to the Moodbuster digital programme or was used as a separate system, for sites that used other digital programmes [23]. The mobile application was used to monitor the mood of client participants, in which they were asked to rate their mood daily when prompted by the app, and complete ecological momentary assessments (e.g., on their mood, rumination, sleep and self-esteem) that were completed across two time-points within their treatment course (i.e., first and second week of treatment). The mobile applications that were integrated to the Moodbuster digital programme could also be used to access a messaging portal, appointment reminders with their therapist, and appointments booked in their behavioural activation calendar, for mobile apps that were integrated to the Moodbuster digital programme.

Information on the treatment and dosage offered in the TAU arm was not collected in the trial [23]. Interventions for depression that were typically offered in services recruited from included, psychopharmacological medication, psychotherapy and GP care, although the majority of the sites offered face-to-face CBT for depression [23]. Further information is provided in Table 3.2 [23,45].

Therapists across the consortium involved in the trial delivered the intervention across both treatment conditions (b-CBT and TAU) [23]. They were required to rate their working alliance with each of their clients across both treatment conditions. Therapists were also required to complete a one-off questionnaire on their experiences of the digital programme's usability (system usability), and treatment fidelity, in respect to sessions in the b-CBT group. No other data collection was required at a consortium level, therefore demographic information and other participant characteristics such as years of clinical experience were not available. Broadly speaking, therapists were either CBT therapists, or were engaged in a postgraduate CBT training programme. Considering that all therapists were trained to deliver CBT in routine practice, contamination between treatment groups was not perceived to be an issue. Blinding of therapists and clients was not possible, however assessors were blind to the treatment condition.

TAU

The TAU arm of the E-COMPARED trial consisted of usual care offered in primary and specialised mental health services that participants were recruited from. The treatments received by clients on the TAU arm were not collected in the trial, however treatments for depression offered in the recruitment sites that largely consisted of psychological and pharmacological interventions were provided (see Table 3.2 for a breakdown of interventions offered by country-site). Face-to-face CBT was the most common intervention offered across 5 of the 9 country-sites, that included the UK, Switzerland, Poland, France, and Denmark. In Germany watchful GP care was offered, while the Netherlands provided a mixture of psychotherapeutic care, that largely included interpersonal psychotherapy, problem-solving therapy, and/or antidepressant medication. Similarly, services in Spain offered a mixture of psychological therapies (e.g., face-to-face CBT, interpersonal psychotherapy, or supportive therapy) and pharmacological interventions offered by a GP. Finally, services in Sweden offered a wider range of services, including GP care, watchful waiting, medication prescription, referral to medical specialists or face-to-face CBT. None of the sites were permitted to offer internet-based psychological interventions in the TAU arm of the trial.

In light of the heterogeneity in TAU, the quantitative studies in my thesis (papers 3 and 4) only included country-sites that exclusively compared b-CBT with face-to-face CBT (i.e., France, United Kingdom, Switzerland, Poland, and Denmark) for analyses that compared the working alliance across treatment conditions. While other sites such as Spain and Sweden also offered face-to-face CBT in TAU, it was

not possible to specifically identify these cases as data were not collected in relation to the treatment received in the TAU arm.

3.3.3.2 UK site country-site

In the UK, the b-CBT intervention consisted of six face-to-face and five online CBT sessions, over an 11-week period. The b-CBT intervention consisted of an internet-based CBT (iCBT) programme, and an adjunct mobile application, both called Moodbuster. On the iCBT programme, client participants were required to complete an introductory module that introduces the online platform, which they typically go through with a clinical research officer after randomisation or with a PWP in their first session of therapy, respectively. Participants are then required to complete four mandatory modules (i.e., psychological education, behavioural activation, cognitive restructuring and relapse prevention), and are given the option to complete two other modules (i.e., physical exercise and/or problems solving).

Client participants were able to receive support from their therapists between face-to-face sessions, either via email or through scheduled sessions using the messaging function. There was an expectation to complete the modules sequentially and could not unlock more than two modules at a time in aid of promoting module completion. The final module, relapse prevention could only be unlocked by the therapists once other mandatory modules were completed. TAU in the UK consisted of face-to-face CBT for depression. See Figure 3.2 for images of the Moodbuster internet programme, and mobile application through the client portal.

Figure 3.2. Client portal for Moodbuster internet programme and mobile application. Source: Moodbuster manual

Legend: (a) Landing page of Moodbuster internet programme; (b) summary of completed exercises across all modules; (c) moodbuster mobile application used to rate mood and provide visualizations of mood ratings.

PWPs were required to access a therapist portal on the digital programme. This allowed them to review the clients' level of completion on each module, responses to exercises, and mood ratings. They were expected to review the therapist portal before each session (see Figure 3.3 for the therapists' landing page of the therapist's Moodbuster portal). PWPs were trained by the research team on how to use the digital programme and blend the face-to-face and digital component of the b-CBT intervention, using a training manual. Examples of the guidance provided included advising PWPs to, alternate face-to-face sessions with online sessions, to ensure that treatment started and ended with a face-to-face session, and to use face-to-face sessions to introduce online modules, review client progress and support clients with any problems that arise. PWPs were able to introduce techniques that are not included in moodbuster (e.g., relaxation) and address co-morbid presentations (i.e., anxiety) in face-to-face sessions. They were also encouraged to blend the intervention flexibly and in response to the client

needs. Clients were expected to report technical or usability problems to the PWP in the first instance. Issues that could not be resolved by the PWP were referred to the research team, who either addressed the problem or requested assistance from the technical support team. Resolutions were communicated by the research team to the therapists or clients directly.

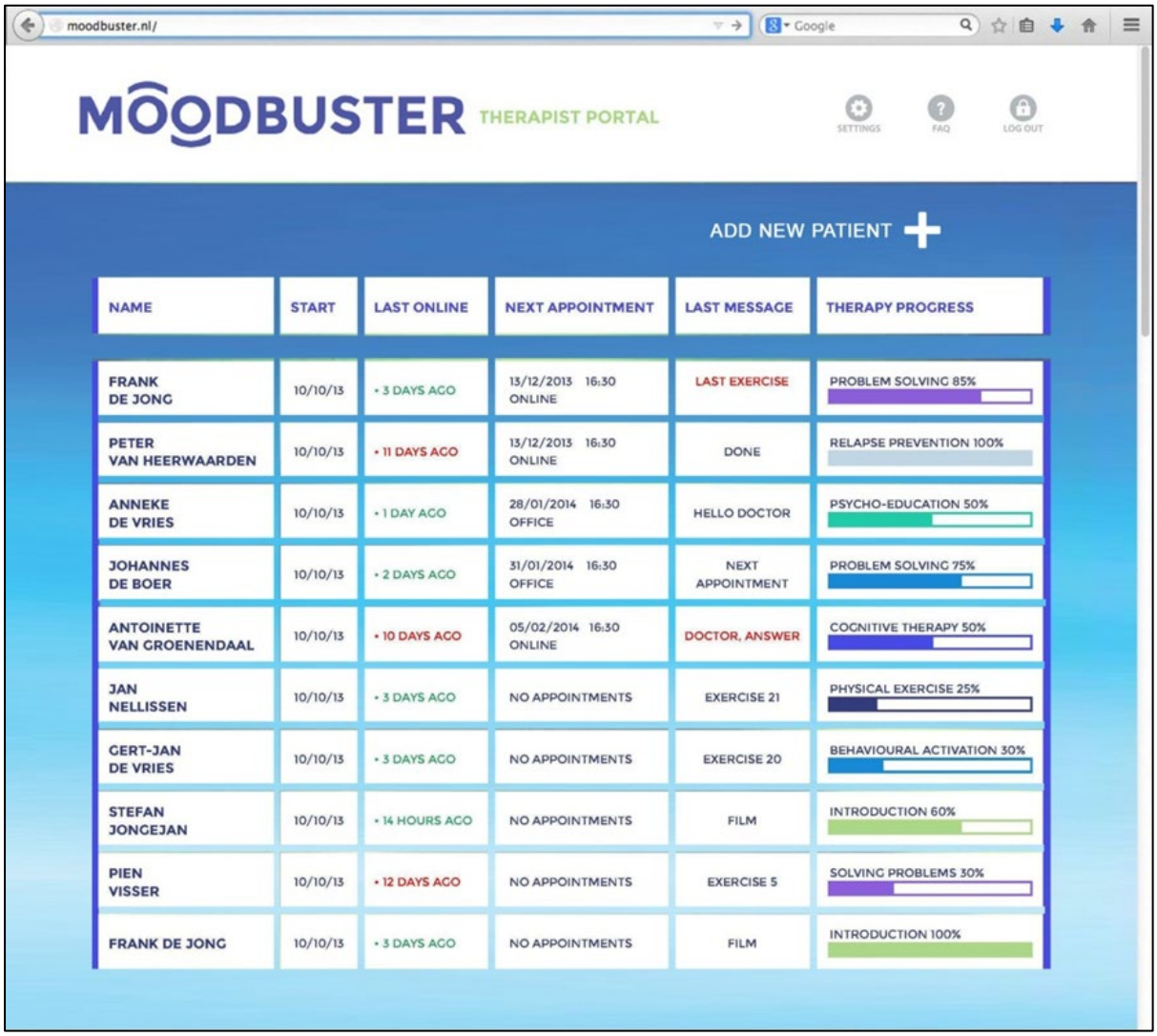


Figure 3.3. The landing page of the therapists' portal on the Moodbuster internet programme that summarises client progress. Source: Moodbuster manual

3.3.4 Outcome measures

Around 15 measures were administered on the E-COMPARED trial [23], however only measures used in my PhD are summarised in this section, namely concerning the working alliance, depression severity,

programme usability and demographic information . Further information about other measures administered on the trial can be found in the UK E-COMPARED protocol in Appendix 1[23].

3.3.4.1 Primary measures

The client working alliance was measured using the WAI-SR-C [145]. The 12 items are rated on a scale of, 1=Seldom, to 5= Always, with the total score ranging from 12-60. WAI-SR-C has demonstrated internal consistency. for all three factors, bond task and goals subscales (Cronbach's alpha = .92, .92, and .89, respectively) [19]. The inventory has been correlated with other therapeutic alliance scales such as the California Therapeutic Alliance Rating System [8,156] and the Helping Alliance Questionnaire-II [8,157]. The scale was administered at the 3-month follow-ups. The therapist working alliance was measured using WAI-SR-T [18], a 10-item self-report questionnaire incorporating a 5-point Likert scale from 1=Seldom to 5=Always. Both of the WAI-SR-C and WAI-SR-T scales are based on Bordin's [6,7] tripartite conceptualisation of the working alliance that consisted of the goals, task and bond. Higher scores indicate a better working alliance across both scales.

Depressive symptoms were measured using the PHQ-9 questionnaire [106]. The nine items are rated on a 4-point scale of, 0=Not at all, to 3= Nearly every day. Higher scores indicate greater symptom severity. PHQ-9 data were collected at multiple stages of the trial; however, data were only used for baseline and 3-month follow-up assessments [23]. The PHQ-9 is a widely used screening tool for depression, that has been shown to have good psychometric properties [158].

3.3.4.2 Secondary measures

Clients' and therapists' experiences of the digital programmes' (i.e., internet-based programme and/or mobile application) usability was measured through the System Usability Scale-Client (SUS-C) and System Usability Scale – Therapist (SUS-T), respectively [148]. Both scales are 10-item self-report questionnaires, that are measured on a 5-point scale, ranging from, 1=strongly disagree, to 5=strongly agree. Total SUS scores range between 10–50 to produce a global score. The scale has been found to be both psychometrically reliable and robust [148]. Higher scores indicate better system usability. The SUS was administered at 3-month follow-up assessments [23].

Client demographic information was collected at baseline assessments, and included: gender (i.e., male and female), age, educational attainment (i.e., low, middle, and high, corresponding to secondary school education or equivalent, college or equivalent, and university degree or higher, respectively), marital status (i.e., single, divorced, widowed, living together, and married) and country of birth. Only data used in my thesis were summarised in this section [23]. A copy of the above outlined primary and

secondary measures are included in Appendix 11. The number of sessions was not collected in TAU, or systematically collected in b-CBT.

3.3.5 Trial registration

Trial registration information for each country-site provided in the E-COMPARED trial protocol are as follows [23]:

> 'France: ClinicalTrials.gov NCT02542891. Registered on 4 September 2015; Germany: German Clinical Trials Register DRKS00006866. Registered on 2 December 2014; The Netherlands: Netherlands Trials Register NTR4962. Registered on 5 January 2015; Poland: ClinicalTrials.Gov NCT02389660. Registered on 18 February 2015; Spain: ClinicalTrials.gov NCT02361684. Registered on 8 January 2015; Sweden: ClinicalTrials.gov NCT02449447. Registered on 30 March 2015; Switzerland: ClinicalTrials.gov NCT02410616. Registered on 2 April 2015; United Kingdom: ISRCTN registry, ISRCTN12388725. Registered on 20 March 2015'. [p.2]

The trial in Denmark, which was a satellite recruitment site, was registered on 1st June 2016 (ClinicalTrials.gov NCT02796573) [45].

3.3.6 Ethical approvals

Ethical approvals to conduct the E-COMPARED trial locally are provided in the published protocol paper which have been copied below [23] :

> '(France: Comité de protection des personnes, Ile de France V; 15033-n° 2015-A00565-44; Germany: Ethik Kommison DGPsychologie, Universitat Trier; MB 102014; The Netherlands: METC VUMC; 2015.078; Poland: Komisja ds. Etyki Badan Naukowych; 10/2014; Spain: Comision Deontologica/Comite Etico de Investigacion en Humanos; H1414775276823; Sweden: Regionala etikprovningsnamnden; 2014/ 428-31; Switzerland: Kantonale Ethikkomission Bern; 001/2015; United Kingdom: NRES Committee London-Camden and King's Cross; 15/LO/0511).' [P.9]

Denmark received ethical approval from the Ethics Committee of the Region of Southern Denmark (registration number S-20150150) [45].

3.4 PhD methodological considerations pre-data collection

Prior to finalising the design and methodology of my PhD, several important considerations were required to assess the feasibility of evaluating the working alliance in digital mental health interventions (DMHIs). This will cover pre-data collection decisions that concern the selection of an appropriate guiding theory to measure the working alliance and concerning the feasibility of adapting the working alliance theory. This section will also present, justifications for using a mixed methods approach in my thesis and outline important consideration concerning design constraints imposed by the design of the E-COMPARED study.

3.4.1 Selection of a client-provider alliance theory

The first consideration involved identifying a guiding theory to evaluate the working alliance. The literature revealed that there were few theories concerning the alliance, however numerous attempts were made to understand the client-therapist alliance using measurement tools between 1978 and 1998 [8,19]. A common limitation of psychological measurement tools is that attempts are made to validate a theory through developing and testing a measurement scale, as opposed to the best practice of developing a theory that can then be developed into a measurement scale and tested [8,19].

A review and critical appraisal of the measures of therapist and client interactions in mental health settings identified 260 candidate measures [19]. Of these measures, around 30 scales specifically evaluated varied forms of the alliance. The approach to measuring alliance is often shaped by the psychological therapeutic approach adopted in treatment [8]. Common theoretical approaches used in the measurement of the alliance include psychoanalytic, psychodynamic, counselling, interpersonal, person-centred theories, with the most prominent approach being pan-theoretical [19]. Pan-theoretical approaches such as Bordin's [6,7] working alliance, draw on core structures that uphold the client-therapist alliance across all psychological approaches, including CBT [8,20,131].

This review highlighted four self-report questionnaires based on a pan-theoretical approach that had adequate reliability and validity [8,19]. These included the, Working Alliance Inventory [16], Session Rating Scale [159], the Helping Alliance Questionnaire [157], and the Agnew Relationship Measure [160].

The working alliance inventory (see *Section 3.3.4.1* for more information) [16,145], appeared to hold a number of advantages when compared to the other scales listed. First and foremost, the inventory is underpinned by Bordin's [6,7] theory of the working alliance, which offers the clearest description of the alliance, that explicitly covers the three dimensions, goals, task, and bond, compared to other

measures [8,20]. Second, the pan-theoretical nature of Bordin's [6,7] working alliance has been found to be compatible with CBT [16,145]. Raue and Goldfried [131] reported that the concept of the working alliance was central within CBT, stating that, 'successful cognitive-behavioural interventions are unlikely to occur unless there exists a good working alliance—a good therapeutic bond, and a mutual agreement on goals and therapeutic methods' (p.135). Third, the inventory [20] has consistently demonstrated evidence of reliability and validity [17,157,159].

To summarise, my thesis adopted Bordin's [6,7] working alliance conceptualisation to inform the qualitative interviews considering its compatibility with CBT and the opportunity to adapt the theory into a framework to meet intervention-specific needs. The working alliance inventory measure adopted on the E-COMPARED trial [23], is one of the few working alliance measures that is based on a theory [19] (i.e., Bordin's [6,7] working alliance) thereby increasing the validity of the measurement scale. Using a theory and measure that is underpinned by the same conceptualisation enables greater levels of comparability across the qualitative and quantitative studies in my thesis. Based on the most recent systematic review evaluating the working alliance in digital mental health interventions, the working alliance inventory emerged as a popular measure to evaluate the working alliance in DMHIs in which 5 of the 8 studies reviewed, utilised the inventory [39].

3.4.2 Expanding working alliance for DMHIs: Patient and public involvement

A second consideration was to explore if the working alliance can be expanded within a new psychotherapeutic context. A review of the literature suggested that the concept of the working alliance has undergone a number of transitions and developments to meet the diverse nature of different therapeutic approaches. As mentioned in *Section 2.5.6* in Chapter 2, Bordin's [6,7] working alliance proposes that the building of the alliance is not separate from the intervention, and that it's important for the work to be presented in a way that effectively forges a working alliance. However in order to do this, working alliance demands within the intervention should be explored [6–8].

In order to explore this further, PPI was enlisted to understand: (a) if the working alliance was relevant in an iCBT intervention; (b) if working alliance needs can be met through an unsupported iCBT programme? and (c) what impact the digital programme had on the working alliance in iCBT? To help address these questions PPI was invited to shape the design of my research ahead of data collection. A summary of the participatory process and the output, that was reported in a published paper concerning client qualitative interviews by Doukani and colleagues [47] is quoted below:

> 'Patient advisors were enlisted at a pre-research data collection stage to collaboratively examine WA in a c-CBT programme without human support. Patient advisors were not involved in the

recruitment of participants or of conducting the study. Patient involvement included 11 advisors with experience of mental health service-use for mild-to-moderate depression (n=7), anxiety (n=1) and severe mental health conditions (n=3). It should be noted that patient involvement was enlisted before the focus of the project was finalised, therefore people with a range of lived experiences were invited to be involved. Advisors attended two meetings in the summer of 2015. The first meeting consisted of a comprehensive pre-involvement preparation briefing, to provide advisors with the knowledge and skills that would enable optimal conditions for their involvement [161]. Advisors were also provided with access to a c-CBT programme for depression called Moodbuster (programme used on the E-COMPARED trial) [23], which they were encouraged to test and review in their own time to provide context for discussion [161]. Advisors voluntarily tested all components of the Moodbuster intervention between meetings. In the second meeting, advisors were split into three small focus group discussion interviews, to facilitate the sharing of personal experiences and enable a higher level of opportunities to participate [162]. Discussions attempted to address three broad objectives, including: (1) Is working alliance, as defined by Bordin [6,7] relevant in the context of digital psychological interventions? (2) What are the intrinsic working alliance demands of a client in relation to a digital provider? and (3) Can digital delivery offer new ways of building working alliance, above and beyond Bordin's [6,7] bond, goals and task? The three focus group discussions (FGDs) were audio-recorded using an Olympus digital voice recorder WS-852, transcribed and analysed to identify thematic patterns and themes. Patient involvement contribution was reported in line with V.2 of the Guidance for Reporting Involvement of Patients and the Public Short Form [163]. Patient advisors were thanked for their contribution after their involvement and also in the acknowledgements of this paper. The results of the study will be disseminated to patient advisors via a lay summary of the research, which will be supplemented with the peer-reviewed publication.

Patient involvement was instrumental in shaping the focus of the study and in guiding participant interviews in three different ways: First, patient advisors suggested that Bordin's [6,7] working alliance, as a function of enhancing engagement, was both relevant and important in the context of a digital psychological intervention. Second, the focus of the planned qualitative research changed from exploring working alliance within a c-CBT intervention without human support, to exploring working alliance in a b-CBT format. This was in response to advisors' unanimous feedback that some working alliance needs (especially bond and elements of task support) could not be satisfied without human facilitation. Third, we set out to extend Bordin's [6,7] WA theory as patient advisors fed back that the c-CBT programme could lead to additional alliance building and maintenance benefits' [p.2-3].

PPI was reported in relation to the Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2) Short Form [163] (Please see Appendix 16). While PPI interviews largely informed the design of paper 1, the learnings from the consultations also provided direction for the rest of the PhD, in which a decision was made to evaluate the working alliance in a blended context, instead of only focusing on the iCBT component of the b-CBT intervention.

Patient involvement included 11 advisors with experience of mental health service-use for mild-to-moderate depression (n=7), anxiety (n=1) and severe mental health conditions (n=3), of which 7 were women and 4 were male. No other advisor characteristics were collected. The PPI advisor roles were advertised via the National Service User Network (NSUN) and service user forums associated with the primary mental health services in London recruited from. Out of the 11 advisors, four people reported prior access to digital mental health interventions, however this information was not systematically collected and was based on feedback during group discussions. It should be noted that there was no requirement for advisors to have experience with a digital intervention, as the initial goal of the study was to capture feedback from a wide range of users, not just those that opted for digital interventions.

Several strengths were associated with the PPI process adopted in my thesis. First, advisors were prepared for their role, in two steps. The first step involved inviting advisors to a briefing session that provided key information about the project, including, the study aim, objectives, key activities, timelines, an introduction to Bordin's [6,7] working alliance framework, and an overview of what digital mental health interventions were. Second, advisors were provided with access to a digital mental health platform called Moodbuster [23], that they were introduced to during the briefing session, and were given access to review and experience before the advisory meetings. The steps taken to prepare advisors for their role aligns with best practice for involving people with lived experience in research [161]. Another strength is that advisory meetings were split into three small groups that involved 3-4 people, instead of meeting as a large group with 11 advisors. Working with smaller groups enabled opportunities to elicit in-depth insights, while still making it possible to gauge agreement [147,162]. Feedback was also captured using an audio recorder with the agreement of advisors, to ensure that feedback could be accurately captured and processed.

The process used to involve PPI also had limitations. The first limitation relates to the lack of remuneration provided for advisors. While travel costs were recompensed, and refreshments were provided during meetings, I was unable to pay advisors for their time and expertise, due to not having access to relevant funds. This meant that advisors could not be involved in other phases of the study, such as data collection, analysis and interpretation, limiting the level in which the design and findings can be grounded in user-experience [164].

A second limitation is that the lived experience of some advisors did not align with the focus of the study post-involvement. The pre-involvement aim was to develop a framework of the working alliance in relation to an iCBT programme that could be applicable to multiple mental health conditions. However, following PPI, the focus of the study changed to evaluate the working alliance in a b-CBT intervention for depression. While the majority of advisors had lived experience of common mental disorders (n=8), the feedback generated might have been less specific to a depressed population. We attempted to mitigate this limitation by adopting a partially inductive approach to client participant qualitative interviews, to ensure that topics that were not covered in Bordin's [6,7] framework or raised by PPI could still be explored. Interview guides were also developed iteratively which meant newly emerging themes could be integrated into topic guides and explored further in prospective interviews [47].

3.4.3 Mixed methods research

A mixed methods design, which employed both qualitative and quantitative data collection and analysis, was adopted in my thesis. This approach enabled my thesis to apply different research lenses to develop a more complete and comprehensive understanding of the working alliance in a b-CBT intervention for depression [165]. The quantitative approach allowed systematic measurement of the working alliance under controlled conditions to generate generalisable findings of the quality of the working alliance in b-CBT and when compared to TAU [166]. However, a notable limitation of the working alliance measurement scales [18,145] adopted on the trial [23], is that they were developed for an in-person context between the client and therapist, that does not consider the digital programmes' influence on the client-therapist working alliance in a b-CBT setting. Qualitative interviews were therefore critical for building a contextual, and conceptual understanding of the nature of the working alliance in a b-CBT intervention for depression [146,166]. Such insights were anticipated to help uncover blind-spots associated with using a self-report measurement scale that does not consider the impact of a novel multi-provider (i.e., therapist and digital programme) on the clients' and therapists' experience of the working alliance [146]. The use of a mixed methods design allowed for different levels of evidence and a wider range of data points to be generated, enabling a more complete understanding of the working alliance within a comparatively novel and little understood psychotherapeutic context [146].

Specifically, my thesis adopted a concurrent nested mixed methods design [146]. The quantitative data analysis used pooled secondary data from the E-COMPARED consortium, while qualitative interviews involved primary data collection that was nested in the UK E-COMPARED trial. Both qualitative and quantitative data were collected within the same time-period corresponding to post-treatment completion. The quantitative design and findings were given a marginally higher weighting compared to the qualitative design within the thesis [146]. This is because the quantitative analyses comprised of data collected across nine European countries, enabling greater generalisability to be inferred from the

findings [23]. On the other hand, qualitative data was only collected in the UK. As such, the findings may not be generalisable to other country settings.

The qualitative and quantitative data will be integrated using a staged approach that will involve reporting the findings of the four studies in a series of research papers, that are analysed and published separately [167]. Consequently, a discussion of the findings will be provided separately for each report. In addition to this, the findings from the quantitative and qualitative studies will be collectively described and interpreted in the 'discussion chapter' of my thesis [167].

3.4.4 Important considerations

Considering that my thesis was nested in a large RCT, my research was largely constrained within the design of the trial. As such, the measurement tools used, the time point that the data was collected, and the interventions offered, among other factors, were fixed, and could not be changed.

Another important consideration is that this thesis will use pooled data across all country-sites of the E-COMPARED trial [23] as my thesis is largely interested in understanding the working alliance across different types of b-CBT interventions in aid of increasing generalizability [151,168]. Moreover, several E-COMPARED country-sites requested to publish their own country specific data around the working alliance, thus, to avoid duplicating efforts I made a decision to not investigate country-specific effects.

It was not possible to conduct qualitative interviews with clients and therapists about their experience of the working alliance across all country-sites of the E-COMPARED trial [23]. This was due to not having the resources and permissions to coordinate interviews in different countries. Consequently, qualitative interviews were only conducted in the UK country-site of the E-COMPARED study. While this thesis aims to draw connections between the qualitative research in the UK and quantitative secondary data analysis that includes all country-sites in the trial, the findings of the qualitative studies in the UK may not be representative of other European countries involved in the trial.

It should be noted that both the primary (e.g., qualitative interviews with clients) and the secondary analysis of E-COMPARED trial data, included participants that both completed and did not complete treatment.

3.5 PhD methods: Qualitative research

The qualitative component of my PhD consisted of collecting primary qualitative data on clients' and therapists' experiences of the working alliance in the UK site of the E-COMPARED study. This section will outline recruitment, data collection and analysis, that will be described separately for client and therapist interviews. This section will also provide a reflexivity statement.

3.5.1 Recruitment

Client and therapist participants were recruited from four primary mental health services that lie under the umbrella of IAPT, offering treatment for anxiety and depression across west London (n=2) and the Tees, Esk, and Wear catchment areas (e.g., County Durham and Darlington, Teesside, North Yorkshire, York and Selby) (n=2). Participants who took part in the qualitative interviews were consented twice in the UK. For example, clients and therapists who consented to participate in the E-COMPARED trial were invited to take part in qualitative interviews if they: indicated that they wanted to participate in qualitative interviews in their first consent form, and if clients completed at least one online and face-to-face session in b-CBT, or if therapists delivered at least one session on the b-CBT arm of the trial. The re-consent procedure followed the same steps described in *Section 3.3.2.2* (See Appendix 7 and Appendix 8 for client and therapist information sheets, respectively, for qualitative interviews). Consent was taken ahead of participation in the trial (See Appendix 9 and Appendix 10 for client and therapist consent forms, respectively, for qualitative interviews).

3.5.2 Data collection and analysis

3.5.2.1 Client qualitative interviews (Paper 1)

In paper 1, data were collected from client participants through in-depth semi-structured individual qualitative interviews [47]. In-depth interviews were used to enable a detailed examination of participants' personal understanding, perspectives, motivations, within the context of their personal history and experience of receiving therapy [169]. A semi-structured interview method was used to achieve a balance between the need for consistency of questioning across participants, while enabling a greater depth, nuance, and opportunities for unanticipated topics to emerge [169]. Interviews were guided by topic guides (see Appendix 12 for client qualitative interview topic guide) that were developed based on the working alliance literature (i.e., Bordin's [6,7] conceptualisation of the working alliance theory [6,7], other closely related constructs concerning the client and therapist psychotherapeutic relationship [8,20], and the feedback provided through PPI consultations [47]. The topic guides were used to suggest areas of discussion and were not applied as a definitive framework to limit conversations during the interviews [169]. As data collection progressed, topic guides evolved iteratively based on emerging themes [170]. Subsequent interviews were therefore influenced by those that previously took place. The study involved elements of both inductive and deductive approaches,

which allowed the exploration of the working alliance in b-CBT (deductive approach), while remaining open to novel or unexpected findings (inductive approach) [169]. This approach is consistent with other qualitative work exploring user-experience of health technologies [171,172]. Interviews were audio recorded, anonymised, and sent for transcription to produce orthographic verbal verbatim and non-verbal (e.g., cough, um, ah) utterances, to facilitate the data collection process by allowing me (the analyst) to become closer to the data [169].

Preliminary qualitative data analyses took place alongside early interviews, allowing both the topic guide and framework to be adapted and progress iteratively [170]. Memos were written after each interview, to aid the preliminary analysis. A thematic approach that drew on the constant comparative method was used [147,170]. Thematic analysis was adopted due to its theoretical flexibility and practical benefits of being comparatively easy to carry out [147]. However, the simplicity of the approach did not compromise the quality of data, as it allowed for 'thick description of the dataset to be generated. The data analysis also incorporated constant comparative method from grounded theory, that enable the analyst to search for new theoretical models that are grounded in empirical data [170]. While grounded theory analysis is recommended for theory building, this approach was not used in its' entirety, because the theories pure inductive stance was not deemed suitable for adopting a deductive approach that would allow Bordin's working alliance [6,7] to be explored [147]. Adopting a deductive line of enquiry would therefore preclude the organic formation of inductive themes that is stipulated by a pure grounded theory approach [173].

3.5.2.2 Therapist qualitative interviews and data analysis (Paper 2)

In paper 2, data were collected from therapists delivering interventions across both treatment conditions in the UK country-site of the E-COMPARED trial, through semi-structured individual and FGD interviews (see Appendix 13 for therapist qualitative topic guides for individual interviews and FGDs) [97]. The topic guides employed deductive and inductive approaches, that were loosely guided by Bordin's working alliance [6,7] theory, and PPI consultations, while allowing for new information to emerge, respectively. Individual interviews were used to develop an in-depth understanding of therapists' experience of the working alliance when delivering b-CBT. FGDs were primarily used for pragmatic reasons to collect data at pace at the end of the trial [162]. However, the use of FDGs also expanded the scope of data collection. For example, FGDs provided opportunities to discuss topics collectively, drawing out a breadth of insights, while illuminating contrasting perspectives and levels of agreement on a given topic [162]. Using a combination of individual and FGD interviews enabled a better balance in relation to applying both 'deductive' and 'inductive' approaches to data collection [174]. Individual interviews provided the interviewer with higher levels of control on the direction and

dynamics of discussion, that is better suited for a deductive approach, while FGDs enabled the direction of conversation to be guided by FGD respondents, that is conducive to an inductive approach [174].

Data were analysed using a thematic data analysis approach, which aimed to understand therapist experiences, perceptions, and needs in relation to developing an effective working alliance with clients in the b-CBT arm [147]. The analysis primarily uses a latent approach to thematic analysis, to uncover underlying ideas and patterns [147]. The analysis was guided by Bordin's [6,7] working alliance theory, and the findings from paper 1 that found a newly emerging factor that impacted the working alliance in b-CBT called 'usability heuristics' [47].

3.5.3 Reflexivity statement for qualitative research

I conducted all client and therapist individual qualitative interviews and facilitated the first of three FGDs with therapist participants. Another member of the research team, Dr Jennifer Walke (JW) led data collection for all therapist FGDs. JW and I are both females. At the time of the interviews, I was a Research Assistant and a part-time PhD student on the E-COMPARED trial and my highest qualification was a Master of Science in *Research Methods in Psychology*. JW had a PhD and was a Research Fellow who was recruited to help with outstanding tasks at the end of the E-COMPARED trial. Prior to conducting qualitative interviews, I had acquired knowledge of qualitative methods through my Master's degree, which I further developed through enrolling on a qualitative research module at LSHTM. I gained practical experience of conducting focus groups on the E-COMPARED trial. As a Research Assistant, I had contact with all therapist and client participants throughout the study, in which I was responsible for recruiting and training PWPs, prompting client participants to complete their online surveys once they were enrolled to the study and allocating vouchers to client participants after they completed their follow-up assessments on the trial. I used the time spent before the start of interviews to build rapport with participants. Prior knowledge of the working alliance varied between client and therapist participants. Client participants were told that the research was focused on understanding their experience of b-CBT, with a particular interest on how they engaged with the intervention. Therapist participants were told that the qualitative interviews aimed to understand their experience of delivering b-CBT with a specific interest in the therapeutic relationship. Terms such as *engagement* and the *therapeutic relationship* were used because they were anticipated to be more accessible compared to the working alliance. Some therapist participants were aware that data collected were being used for my PhD. While JW conducted FGDs for pragmatic reasons, having a new member of staff who was not involved in the running of the study was anticipated to be helpful for reducing social desirability bias [175] that may stem from therapists providing responses perceived to be favourable to my PhD.

My interest in the concept of the working alliance was developed prior to joining LSHTM, after working in clinically orientated roles as a research assistant, assistant psychologist, and trial therapist that placed emphasis on building strong working relationships with clients. For example, the importance of developing trust, rapport, positive regard was particularly important for engaging people with schizophrenia and post-traumatic stress disorder, to diagnostic assessments for PTSD (which was often the first-time clients had spoken about their traumatic experience), as a research assistant; and when delivering CBT for non-cardiac chest pain (medically unexplained symptoms) to people who believed they had cardiac problems, as a trial therapist. After being employed on the E-COMPARED trial, I was curious to understand if and how the therapeutic relationship manifested in a digital intervention. This idea flourished to form the basis of my PhD.

3.6 PhD methods: Quantitative research

The quantitative component used secondary working alliance data from the E-COMPARED study [23]. The use of trial data was agreed ahead of data collection, and formally through an online publication intent form. Data was accessed at the end of the trial once the dataset had been cleaned, locked, and stored in a data repository.

Secondary data analysis included data for participant characteristics (measured at baseline assessments), client and therapist working alliance (3-month assessments post randomisation), system usability (3-month assessments) and client depression scores (baseline and 3-month assessments). 3-month assessment largely corresponded to post-treatment for 7 of the 9 country-sites (i.e., Germany, Sweden, UK, Spain, Switzerland, Poland, and Denmark) covering 78% of the sample.

A total of 943 cases were included in the dataset, of which 476 were allocated to b-CBT and 467 were allocated to TAU. It should be noted that the number of cases varied between paper 3 (n=943) that focused on the client working alliance and paper 4 (n=883) that focused on the therapist working alliance. Therapist working alliance data was not available for Denmark (n=60 cases). Working alliance data were also not available for clients (n=67) and therapists (n=67) in the TAU arm in Sweden (n=67). As a result, Swedish data across all variables were excluded for statistical analyses that focused on the TAU treatment condition. Due to the heterogeneity in TAU, papers 3 and 4 will only include country-sites that exclusively compared b-CBT with face-to-face CBT (i.e., France, United Kingdom, Switzerland, Poland, and Denmark) for the analysis investigating the effects of treatment condition on working alliance scores. This means that only a subset of the data was used for paper 3 (b-CBT=200, TAU=200) and paper 4 (b-CBT=168, TAU=172) for this analysis.

Considering that this is a secondary data analysis, this section will largely cover methodological consideration that are associated with the statistical analysis. Papers 3 and 4 explore almost identical aims and objectives, that only differed in relation to whether the working alliance is evaluated with respect to clients' or therapists' perspectives. As a result, the research methodology and statistical plans hold many similarities, and will therefore be described collectively. The following section will provide considerations around adopting the SUS scale, an overview of the statistical analyses, and justifications that cover the use of, an intention-to-treat population (ITT), multiple imputation (MI), fixed effects models, and covariates adopted for the secondary data analysis.

3.6.1. Methodological considerations

Clients' and therapists' experiences of the digital programme usability was measured through the SUS measure [148]. SUS is a widely adopted tool for quantifying the usability of a range of software and hardware products [148]. According to a scoping review from 2019, programme usability was largely measured via self-report questionnaires, with SUS being the most frequently adopted in respect to eHealth products [176]. SUS has been shown to be a valid and interpretable measure to assess the usability of internet-based interventions in mental healthcare within the context of Europe, demonstrating good reliability ($\omega = 0.91$) and convergent validity [177]. While the scale offered a reliable and pragmatic method of measuring usability, it is not clear if perceived system usability impacted actual programme use, which is an important pathway for engaging clients to the therapeutic task. While it would have been helpful to use programme use data (e.g., number of modules completed, frequency of access, time spent on programme etc.,), this information was not available for my PhD. Future research should consider expanding how system usability is measured to explore, (a) if there is a congruence between perceived system usability and programme use, and (b) if different levels of system use are associated with the working alliance and respective subscales (i.e., bond, task, and goals).

3.6.1 Statistical analysis overview

Fixed effects linear regression models were used to investigate, (a) treatment assignment as a predictor for working alliance scores, (b) the association between post-treatment depression scores and working alliance scores, and (c) the interaction between the working alliance and system usability scores on the association between the working alliance and depression scores. All analyses controlled for client baseline variables (more information is provided in *Section 3.6.5*). Missing data were addressed using multiple imputation via a chained equation approach [178]. Data were imputed separately for the analyses that included an interaction term in the regression model (i.e., analysis c), for which the Just Another Variable (JAV) approach was used [179]. Post-hoc sensitivity analyses were conducted to examine if the multiple imputation approach that was used to handle missing data, resulted in different conclusions when compared to a complete case analysis [180]. To address the heterogeneity of

interventions offered in TAU, a sub-group analysis was also conducted to explore the magnitude of treatment effects on the working alliance when using a subset of the sample, that compared b-CBT, with face-to-face CBT offered in the TAU arm across five country-sites (i.e., Denmark, France, Poland, Switzerland, and the UK) [180–183]. These analyses were conducted using client working alliance ratings in paper 3, and therapist working alliance ratings in paper 4, although data for Denmark were not available for the analyses for therapist rated working alliance (paper 4). The full statistical analysis can be found in *Section 6.6.5* of paper 3 (Chapter 6) and *Section 7.5.6* of paper 4 (Chapter 7).

3.6.2 ITT population

A decision was made to use an ITT population instead of using a per-protocol population, or a combination thereof, for the statistical analysis. An ITT approach involves the inclusion of all participants that were randomised, in the statistical analysis that may or may not have completed treatment [184]. Using this approach enables participants to retain their originally assigned group, regardless of whether they received or completed the treatment that they were assigned to. On the other hand, a per-protocol population includes all participants who completed their intervention, and adhered to it without deviating from the protocol [184,185].

A decision was made to use a pure ITT population to maintain the original treatment group composition achieved after the random allocation of trial participants, therefore minimising the risk of bias in the estimates of the treatment effects on the working alliance, when considering the effect of treatment recommendation, rather than administration [184]. This was particularly important for the analysis that investigated the effects of treatment allocation on the working alliance, in which randomisation enabled a causal interpretation of the findings. An ITT analysis as compared to the per-protocol analysis is also more suitable for pragmatic RCT designs evaluating the effectiveness of an intervention in routine care [184]. In this context clients may not start, complete, or continue with their treatment for a range of different valid reasons (e.g. interventions that are not accepted by clients).

While the ITT analysis is standard for RCTs, some experts argue that a per-protocol approach can be equally useful in pragmatic trials, due to concerns that a 'flawed trial' is likely to incorrectly demonstrate non-inferiority (i.e., a trial that loses the ability to distinguish any true differences between treatment groups that are present) [151]. However, others disagree with this opinion, suggesting that instead of using a per-protocol population as de facto, efforts are better placed in ensuring that a trial is well designed and carefully monitored [151]. To my knowledge, there is no indication that the E-COMPARED trial was flawed or poorly conducted, following the completion of data collection in 2017 [23].

A decision was made not to combine ITT and per-protocol approaches, because it was not possible to determine which participants completed treatment as intended or as per-protocol. In the E-COMPARED trial [23], therapists were only required to complete treatment fidelity forms for participants in the b-CBT but not the TAU arm. Moreover, the treatment fidelity form only covered the face-to-face sessions, and harmonized data on module completion across five different iCBT platforms were not available.

3.6.3 Multiple imputation approach for missing data

The fixed E-COMPARED dataset revealed considerable levels of missing data for the working alliance ratings (client: 20.7%; therapist: 40.77%), depression scores (client: 36.6%), and system usability scores (client: 27.7%; therapist; 33.3%)], that were all measured at 3-month follow-ups. The missingness for each variable are listed in Table 3.3 The highest levels of missing data were observed in the control condition.

Table 3.3. Missing data for WAI-SR-C, WAI-SR-T, PHQ-9, SUS-C and SUS-T scales across treatment conditions

Measures	Treatment conditions	
	b-CBT	Control
WAI-SR-C	153/467 (32.1%)	215/476 (46%)
WAI-SF-T	129/443 (27.2%)	231/439 (52.6%)
PHQ-9	153/467 (32.1%)	216/476 (46%)
SUS-C	133/476 (27.7%)	n/a
SUS-T	148 (33.3%)	n/a

Abbreviations: b-CBT, blended-cognitive behaviour therapy; PHQ-9, patient health questionnaire-9; SUS-C, system usability scale-client; SUS-T, system usability scale-therapist; TAU, treatment as usual; WAI-SR-C, working alliance inventory-short revised-client; WAI-SR-T, working alliance inventory-short revised-therapist.

MI was used to address missing data. Although MI is optimal when conducted on datasets that do not have high levels of missing data (e.g., above 40% as a general rule of thumb) [186], multiply imputing data is still more reliable than other approaches, at least under the missing at random assumption (MAR), and have been shown to produce unbiased estimates for missing data up to 90% during simulation models [186]. MAR is believed to be plausible because of the effects of country-site on missingness, that is highlighted in the method sections of papers 3 (*Section 6.6*) and 4 (*Section 7.5*), however it should be noted that this analysis cannot rule out data is missing not at random which is a limitation associated with my thesis [186].

MI was used to treat missing data under the MAR assumption, using a chained equation approach [178]. Data were imputed separately for the analyses that included an interaction term in the regression models, for which the Just Another Variable (JAV) approach was used [179]. While there are mixed views on if the JAV approach can give consistent estimates under the MAR condition [179,187], there is evidence to suggest that JAV performs better when compared to the 'passive imputation' and 'predictive means matching' approaches with continuous outcomes [187].

3.6.4 Fixed effects regression

A decision was made to employ a fixed effects regression model, instead of a mixed effects regression model for several reasons. First, the number of sites on the trial (n=9) was not adequately high enough for a random-effects approach to be effectively used. While the number of sites required is highly debated, the emerging consensus appears to suggest that having more sites (e.g., in excess of 20) is required to provide stable estimates [188,189]. On the other hand, a fixed effects model makes less distributional assumptions and only accounts for within-centre information [190], which is well suited for investigating the aims and objectives of papers 3 and 4. Second, the number of participants per country-site are relatively large, which is handled well in fixed effects models, whereas random effects models are better at handling a smaller sample size per cluster [188,189]. Third, while random effects is said to produce more efficient estimates for both within and between centre effects, this approach is also prone to limitations, one of which is that it's disposed to ecological bias that stems from within and between centre effects not being consistent [191]. Finally, papers 3 and 4 are only interested in single treatment effects and within-centre information valid across countries under the no-between-effects heterogeneity assumption [189]. Potential heterogeneity introduced by different country-sites was accounted for by adding 'country-site' as a covariate in all models.

3.6.5 Covariate variables considerations

All statistical analyses largely adjusted for the same covariates, that are independent variables that may or may not be associated with the outcome in a study or trial, but are not the focus of the study [192]. Covariates included in the statistical models were baseline variables including age, gender, marital status, educational attainment, country-site and depression severity. Categorical data that included more than one level (i.e., marital status, educational attainments and country-site) were dichotomised, using a reference group that had the highest frequency (i.e., being single, university educated or with an equivalent qualification, and the German country-site, respectively) [193]. Baseline covariates were adjusted for because there is some evidence to suggest that age [118,194–197], gender [118,194,195,198,199], level of education [194,195,200,201], and baseline severity [118,195,199,201], may influence treatment process factors such as engagement to treatment (e.g., dropout rates and treatment completion) and treatment outcomes in iCBT. While engagement levels may be linked to

experiences of the working alliance [135], further research is required to explore the impact of participant characteristics on the working alliance. Adjusting for baseline characteristics has been reported to increase statistical power, to detect an effect that is present, and reduce biased estimates [202].

A number of other covariates were also considered but could not be added to the model. The first was to adjust for the number of in-person sessions with a therapist, as measured by a treatment fidelity form that therapists were required to complete after each session. The treatment fidelity form outlined the session number and the time spent on each treatment components (e.g., psychological education, behavioural activation etc.,). However, as highlighted in *Section 3.3.2.2* the completion of the treatment fidelity form was only stipulated for clients seen in the b-CBT arm. Moreover, Sweden and Denmark did not collect this information from therapists. This pattern of missingness meant that data could not be multiply imputed in the treatment arm under the MAR assumption [203].

I also considered adding a set of covariates that adjusted for treatment differences with respect to the, iCBT platform, duration of intervention, online and face-to-face ratio, and the sequencing of the intervention. These components differed across trial country-sites to tailor the intervention to local mental health services, thereby mirroring real world settings in line with pragmatic design principles [149]. The high level of variability meant that grouping treatment components was less meaningful. A decision was therefore made to only adjust for country-site, that incapsulated site-specific variabilities in the b-CBT arm, as this was deemed to be more appropriate, and limited the risk of overfitting the model [204] with variables that might contain less beneficial information.

3.7 Ethical approvals for PhD

All procedures in this study comply with the Helsinki Declaration of 1975, as revised in 2008. Research activities associated with the primary data collection on papers 1 and 2 of my thesis were integrated to the UK E-COMPARED trial protocol and ethics applications. Ethical approval for the trial and qualitative interviews were obtained by the Health Research Authority's (HRA) Ethics Research Committee on 17 April 2015 (REC reference: 15/LO/0511) and LSHTM Research Ethics Committee on 9 June 2015 (Ethics Ref: 9409) (See Appendix 14 for local HRA and LSHTM ethics approvals). Ethical approval to conduct a secondary analysis for papers 3 and 4 was obtained from LSHTM Research Ethics Committee on 7th October 2019 (Ethics Ref: 17852) (see Appendix 15 for ethics approval from LSHTM).

Chapter 4: Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study (paper 1)

4.1 Introduction to chapter 4

This chapter will provide a comprehensive description of the first of two qualitative papers that conceptually examined the working alliance in a blended cognitive behavioural therapy (b-CBT) intervention for depression in the UK, that collected primary data. Client participants who experienced b-CBT in primary mental health services were invited to participate in qualitative interviews, to examine and understand their working alliance needs in b-CBT, and to adapt Bordin's [6,7] working alliance theory to reflect these needs [47]. This chapter will also outline the public and patient involvement used to shape the design of the study, qualitative interviews topic guides, and guide the direction of my thesis more broadly (that was also outlined in *Section 3.4.2* of Chapter 3).

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1407974	**Title**	Ms
First Name(s)	Asmae		
Surname/Family Name	Doukani		
Thesis Title	A mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy intervention for depression in a multinational randomised controlled trial in Europe		
Primary Supervisor	Dr Ritsuko Kakuma		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	23/09/202		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the concept of design for this paper. Patient involvement shaped the focus of the research. I was responsible for leading all aspects of patient involvement sessions, and in processing the information produced. I led the design of participant qualitative interviews and all aspects of data collection, analysis and interpretation. Professor Caroline Free and Dr Daniel Michelson analysed a portion of the data independently for cross-checking purposes. I produced the first draft of the manuscript for co-authors to review, and was responsible for addressing comments from co-authors, and from peer reviewers following the submission of the paper. PhD supervisors and advisors, provided guidance and feedback across all phases of research described. Co-authors provided feedback on successive drafts and approved the final version, ahead of submission.

SECTION E

Student Signature	[redacted]
Date	19/05/2023

Supervisor Signature	[redacted]
Date	[redacted]

BMJ Open

Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study

Asmae Doukani ,[1] Caroline Free,[1] Daniel Michelson,[2] Ricardo Araya,[3] Jesús Montero-Marin ,[4] Sarah Smith ,[5] Arlinda Cerga-Pashoja,[1] Ritsuko Kakuma[1]

To cite: Doukani A, Free C, Michelson D, *et al*. Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study. *BMJ Open* 2020;**10**:e036299. doi:10.1136/bmjopen-2019-036299

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-036299).

Received 17 December 2019
Revised 18 July 2020
Accepted 07 August 2020

For numbered affiliations see end of article.

Correspondence to
Asmae Doukani
Asmae.doukani@lshtm.ac.uk

ABSTRACT

Objectives To examine and adapt a conceptual framework of the working alliance (WA) in the context of a low-intensity blended (psychological well-being practitioner (PWP) plus computerised program) cognitive behavioural therapy intervention (b-CBT) for depression.

Design Patient involvement was enlisted to collaboratively shape the design of the project from the onset, before data collection. In-depth semi-structured interviews were carried out with participants who experienced b-CBT as part of the E-compared trial. A thematic analysis was conducted using a constant comparative method informed by grounded theory.

Setting Recruitment was carried out in four psychological primary care services across the UK.

Participants Nineteen trial participants with major depressive disorder who completed at least one computerised program and face-to-face session with a PWP in the b-CBT arm were recruited to the study.

Results Qualitative interviews that were guided by WA theory and patient involvement, revealed four themes: (1) a healthcare provider (PWP and computerised program) with good interpersonal competencies for building a working relationship with the client ('bond'); (2) collaborative efforts between the client and the provider to appropriately identify what the client hopes to achieve through therapy ('goals'); (3) the selection of acceptable therapeutic activities that address client goals and the availability of responsive support ('task') and (4) the promotion of active engagement and autonomous problem solving ('usability heuristics'). Participants described how the PWP and computerised program uniquely and collectively contributed to different WA needs.

Conclusions This study is the first to offer a preliminary conceptual framework of WA in b-CBT for depression, and how such demands can be addressed through blended PWP-computerised program delivery. These findings can be used to promote WA in technological design and clinical practice, thereby promoting engagement to b-CBT interventions and effective deployment of practitioner and program resources.

Trial registration number ISRCTN12388725.

Strengths and limitations of this study

- ► Patient involvement enabled the project aims to be grounded in the needs and interests of people who have experienced mental health service-use, in order to enhance the application of the findings.
- ► Bordin's theory was specifically selected to examine the working alliance (WA) in blended cognitive behavioural therapy, due to the theory's comprehensive description, pan-theoretical nature, and openness to adaptation to accommodate different therapeutic formats.
- ► The studies' sample is limited to 19 individuals with a primary diagnosis of mild-to-moderate depression, who mostly reporting moderate-to-high WA, and were largely male, British white and university educated individuals. This thereby restricts the generalisability of our findings.
- ► Exposure to only one type of digital program may have influenced participants' experience of WA (eg, a computerised platform that does not work adequately might generate more data on the importance of 'ease of use', than one that does), limiting the breadth of data collected on WA.
- ► Efforts were made to strengthen the conceptual framework through a topic guide that was informed by Bordin's WA theory, patient involvement input and a data analysis approach which avoided surface-level themes specific to technological design.

INTRODUCTION

Mental health conditions impact one in six people in Europe, resulting in an estimated economic burden of over □600 billion.[1] The treatment gap in the region remains high with 35%–50% of people experiencing mental health concerns not accessing treatment.[1] The wide disparity between mental healthcare needs and access to services prompted calls for the strategic deployment

of technology to facilitate and expand access to mental health services at a lower cost.[2 3] In the past decade, an increasing number of studies have investigated the efficacy of computerised cognitive behavioural therapy (c-CBT), a type of digital intervention that delivers CBT via interactive presentation features.[4] The implementation of c-CBT is generally either unguided (led by a computerised program with no external support), guided (led by a computerised program and typically supported by a non-specialist facilitator) or blended (led by a therapist, incorporating a c-CBT program, or led by a c-CBT program and supported by a therapist), with the latter approach offering the highest level of human support.[4 5] The evidence for c-CBT has demonstrated equal benefits to face-to-face CBT for a range of mental health conditions.[4] However, these findings largely hold true when digital psychotherapies are guided by a human facilitator. Higher support from a therapist or another human facilitator appears to be associated with better adherence and clinical outcomes.[6] The effects of human support on engagement with c-CBT raises important questions about mechanisms that support positive change. This has led scholars to consider the applicability of established mechanisms of change derived from conventional psychotherapies, to 'blended' formats. Particular interest has centred on the construct of the client-therapist alliance (the use of the 'alliance' as a singular, broadly refers to the client-therapist alliance, and not to a specific variation – eg, therapeutic alliance, working alliance, helping alliance etc – which have distinct theoretical underpinnings).[7 8] While the concept of the alliance has taken root in a number of psychotherapeutic approaches, Edward Bordin[9] drew on their commonalities to formulate a pan-theoretical theory called the working alliance (WA) defined as:

> a client seeking change and the therapist offering to act as a change agent that [incorporates] a mutual understanding and agreement about change goals and the necessary tasks to move forward these goals along with the establishment of bonds to maintain the partners' work.[10] (p. 13)

Here, the 'task' refers to an agreed-upon contract that specifies the activities used to work on the client's goals. 'Goals' entails the exploration and review of what the client wants to achieve in therapy, while the 'bond' relates to the perceived compatibility between the client and the therapist, and the partnership that stems from shared activities.[9 10] Central to Bordin's[9 10] conceptualisation is the collaboration and consensus between the therapist and the client, in order to promote meaningful engagement in therapy.

The alliance has consistently been found to predict positive therapeutic outcomes. A keystone meta-analytic review found that the therapeutic alliance accounted for more variance (30%) than the therapeutic technique (15%) and therapy expectancy (15%).[11] This alliance-outcome relationship finding was mirrored in recent meta-analyses, one of 191 varied therapeutic studies (r=0.28 (95% CI 0.25 to o.30)),[12] and another focusing on CBT interventions for depression (r=0.26 (95% CI 0.19 to o.32)).[13]

A growing body of literature appears to indicate that the quality of the alliance in guided internet-based psychotherapy programmes and blended (b)-CBT may be equal to or better than traditional formats of face-to-face therapy.[14–16] There is also evidence to suggest that the client-reported alliance in guided c-CBT is directly associated with treatment outcome.[17 18] However, some literature appears to suggest that c-CBT may place different demands on the alliance. A narrative review evaluating WA in supported c-CBT found that while significant associations were found between the task and goals subscales of WA and treatment outcome, none was found for the bond subscale.[18] Qualitative research on the alliance in unguided mental health interventions also indicate that c-CBT may offer additional alliance benefits such as higher control and autonomy.[19 20]

Taken together, these findings underscore the importance of developing a guiding framework for understanding the nature of WA in b-CBT, amid a gradual movement towards shared mental healthcare delivery between human practitioners and digital technology.[21] Our study therefore aims to examine the WA demands through patient involvement and participant qualitative interviews, to adapt Bordin's[9 10] conceptualisation of WA for a b-CBT intervention for depression.[22]

METHODS

Patient and public involvement

Patient advisors were enlisted at a preresearch data collection stage to collaboratively examine WA in a c-CBT program without human support. Patient advisors were not involved in the recruitment of participants or of conducting the study. Patient involvement included 11 advisors with experience of mental health service-use for mild-to-moderate depression (n=7), anxiety (n=1) and severe mental health conditions (n=3). It should be noted that patient involvement was enlisted before the focus of the project was finalised, therefore people with a range of lived experiences were invited to be involved. Advisors attended two meetings in the summer of 2015. The first meeting consisted of a comprehensive pre-involvement preparation briefing, to provide advisors with the knowledge and skills that would enable optimal conditions for their involvment.[23] Advisors were also provided with access to a c-CBT program for depression called Moodbuster (program used on the E-compared trial),[5] which they were encouraged to test and review in their own time to provide context for discussion.[23] Advisors voluntarily tested all components of the Moodbuster intervention between meetings. In the second meeting, advisors were split into three small focus group discussion interviews, to facilitate the sharing of personal experiences and enable a higher level of opportunities to participate.[24] Discussions

attempted to address three broad objectives, including: (1) Is WA, as defined by Bordin[9 10] relevant in the context of digital psychological interventions? (2) What are the intrinsic WA demands of a client in relation to a digital provider? and (3) Can digital delivery offer new ways of building WA, above and beyond Bordin's[9 10] bond, goals and task? The three focus group discussions were audio-recorded using an Olympus digital voice recorder WS-852, transcribed and analysed to identify thematic patterns and themes. Patient involvement contribution was reported in line with V.2 of the Guidance for Reporting Involvement of Patients and the Public Short Form.[25] Patient advisors were thanked for their contribution after their involvement and also in the acknowledgements of this paper. The results of the study will be disseminated to patient advisors via a lay summary of the research, which will be supplemented with the peer-reviewed publication.

Patient involvement was instrumental in shaping the focus of the study and in guiding participant interviews in three different ways: First, patient advisors suggested that Bordin's[9 10] WA, as a function of enhancing engagement, was both relevant and important in the context of a digital psychological intervention. Second, the focus of the planned qualitative research changed from exploring WA within a c-CBT intervention without human support, to exploring WA in a b-CBT format. This was in response to advisors' unanimous feedback that some WA needs (especially bond and elements of task support) could not be satisfied without human facilitation. Third, we set out to extend Bordin's[9 10] WA theory as patient advisors fed back that the c-CBT program could lead to additional alliance building and maintenance benefits.

Design

A qualitative methodology design was used to gain an in-depth understanding of participants' experience of WA in b-CBT on the E-compared trial.[5] E-compared is a non-inferiority, pragmatic trial that evaluated the cost-effectiveness of b-CBT for depression, when compared with usual care, across eight countries in the European region.[5] Potential participants from the UK were referred from primary care services by clinical staff, if they scored 4 points or higher on the Patient Health Questionnaire-9 (PHQ-9),[26] and if they were interested in receiving b-CBT for depression. The b-CBT intervention consisted of 11 blended low-intensity CBT sessions, six 30 minute sessions with a low-intensity psychological well-being practitioner (PWP), a workforce that typically provide short-term, evidenced-based treatment in line with National Institute for Health and Care Excellence (NICE) guidance in the UK, and at least five sessions at home via a synchronised computerised platform and mobile-application called Moodbuster. The treatment course spanned across 11 weeks. There were four mandatory core modules of CBT on the computerised platform (psychological education, behavioural activation, cognitive restructuring and relapse prevention) and two optional modules (physical exercise and problem solving) that were completed autonomously at home. The low-intensity PWP in the clinic encouraged participants to use the computerised program in different ways. The PWP could introduce modules, review the client's progress on the modules, or guide the client on the use of specific modules. Face-to-face sessions in the clinic were alternated with Moodbuster sessions away from the clinic, however there was flexibility in the sequence of the delivery mode and the order in which the modules were completed, including opportunities for the PWP to use bespoke tasks. Additional information about the trial and the b-CBT intervention can be accessed from the E-compared trial protocol by Kleiboer *et al*.[5]

Participants

E-compared participants from the UK were invited to take part in qualitative interviews. Trial participants aged 18 years or older with a clinical diagnosis of major depressive disorder were enrolled in the study.[5] People with substance abuse, suicidal tendencies, other severe psychiatric disorders, cognitive disability or people who had insufficient knowledge of English were excluded. Psychiatric diagnoses were confirmed by the MINI International Neuropsychiatric Interview V.5.0.[27] E-compared trial[5] participants who: (a) provided written consent to the qualitative interviews when they enrolled on the trial (n=101); (b) were randomised to the b-CBT arm (n=49) and (c) had completed at least one computerised module and face-to-face session (n=42) were purposively sampled to be representative of the b-CBT arm, in relation to their sex, age and recruitment site.[28] Altogether, 26 out of 42 people were invited to take part in the qualitative study, with 19 reconsenting to participate. Reasons for non-consent included scheduling conflicts (n=2) non-response to invitation (n=4), and change in eligibility status due to erroneous information about treatment arm allocation (n=1). This case was discovered during the interview, and corroborated with the E-compared UK trial manager after the interview. Data for this participant were not analysed.

Procedure

E-compared participants were invited to take part in face-to-face individual semi-structured qualitative interviews, at least 2 weeks after they completed their course of therapy on the trial. This was to provide participants with enough time to reflect on their experience of the b-CBT intervention. Potential participants were invited to take part in interviews about their experience of b-CBT, and were emailed a patient information sheet following their initial correspondence with the research team. Participants were provided with at least 48 hours to read and consolidate the information, before they were followed up and booked in for a qualitative interview at an acceptable time and place. Written consent for their participation, and permission to audio record interviews, were sought again prior to starting the interviews. Participants were also reminded of their right to withdraw at any time and without giving a reason. Data collection took place

until saturation was reached.[28] The study adopted Corbin and Strauss's definition of saturation, which is described as the point where further data collection becomes 'counterproductive', and where 'new' themes do not add anything to the overall narrative of the story.[28] Saturation was monitored through writing memos after each interview, in which information on both exisiting and novel emerging themes from the interview were noted.[28]

Measures

Data collected on self-reported WA and depression questionnaires on the E-compared trial[5] were reported to further describe participant characteristics (in addi- tion to sociodemographic data) to provide insights into the level WA and depression symptoms experienced by participants on this study. Self-reported WA was assessed through the Working Alliance Inventory Short Form-Client (WAI-SF-C).[29] Scores for the 12 items on WAI-SF-C range between 12 and 60. Scores were divided into three groups to produce a low-range (12–28), medium-range (29–44) and high-range (45–60) to indicate the level of WA reported by each participant. Higher scores indicate better WA. Self-reported depression was assessed through the PHQ-9.[26] Scores for the nine items on the PHQ-9 range between 0 and 27. Higher scores indicate more severe symptoms. Data were collected during the trial's 3 months follow-up assessments.[5]

Guiding framework

Our study adopted Edward Bordin's[9 10] theory to examine WA in the context of b-CBT for three reasons. The first relates to the generalisable nature of the theory. While the concept of the alliance stemmed from psychodynamic theory in 1912, it has since been incorporated in various therapeutic approaches, leading to heterogeneity in the way the concept is defined.[12] In 1979, Bordin[9 10] attempted to unify the way the alliance is defined, by proposing a pan-theoretical conceptualisation[9] that drew on the key features of all therapeutic approaches.[12] Second, Bordin's[9 10] theory is operationalised as task focused,[12] and therefore offers a suitable fit for task-orientated psychological approaches such as CBT.[30] Third, the theory is open to adaptation. Bordin[9 10] suggested that while a pan-theoretical approach allowed the basic measurement of the bond, goals and task to produce beneficial therapeutic change, he also suggested that the ideal alliance 'profile' is likely to be different across therapeutic approaches and interventions.[9 10 12]

Data collection

Data collection took place between October 2016 and July 2017 across four primary care mental health services in the UK. Qualitative interviews were adopted to enable a detailed examination of the participant's personal experiences and perspectives of WA within the context of receiving b-CBT. The study predominately included a deductive approach to exploring WA that was guided by Bordin's[9 10] theoretical framework, while remaining open to novel or unexpected new themes. On average, participant interviews lasted around 47 min. Interviews were conducted in a confidential setting within a university campus or the health service which the participant was recruited from. All interviews were audio-recorded using an Olympus digital voice recorder WS-852 and transcribed to produce orthographic verbal verbatim. AD (female) conducted the qualitative interviews, was a PhD candidate with experience of conducting and analysing qualitative data. Semi-structured interviews with a conversational technique were used to achieve a balance between the need for consistency of questioning across participants, and the ability to explore topics that are important to the participant. During interviews there was also scope to allow topics covered to evolve iteratively based on the emerging data.[28 31] The development of an interview topic guide was guided by patient involvement input and WA theory.[9 10] The initial topic guide was used to suggest topics of discussion, and not as a definitive framework to limit conversations. As the data collection progressed, the topic guides evolved iteratively based on emerging themes. Subsequent interviews were therefore influenced by interviews that previously took place, providing opportunities to validate and refute interpretations.[28]

Data analysis

A preliminary data analysis took place alongside early interviews, allowing subsequent interviews to progress iteratively.[28] Memos were written after each interview, to aid the preliminary analysis and iterative adaptation of the topic guide and to propose possible relationships between codes. Thematic analysis was adopted due to the theoretical flexibility, as well as the 'thick descriptions' afforded by the approach.[32] The data analysis incorporated a constant comparative method from grounded theory, to enable the analyst to search for new theoretical models that are grounded in empirical data and to enhance the trustworthiness of data.[28]

The lead analyst (AD) commenced the data analysis by reading through the transcripts, while listening to the audio-recording and reading the corresponding memos. The analyst then actively re-read the data, searching for meaning and noted down initial concepts. Data were coded line-by-line. Codes were generated by searching for interesting features across the entire dataset and collating data relevant to each code segments. The emerging codes were clustered into categories and labelled thematically. Once the data were initially coded and collated, the analyst commenced searching for themes that were compatible with Bordin's[9 10] WA theory and patient involvement input, while also searching for novel alliance concepts. Themes were located at a latent level, to delve beyond the semantic content of the data, to identify and examine underlying ideas, assumptions, conceptualisation and ideologies that theorise semantic content of the data.[32] The initial codes were gradually merged into broader categories through comparison across transcripts, to identify overarching themes. The themes were

then reviewed to ensure that the codes cohere together meaningfully, while maintaining a clear and identifiable distinction with no overlap between the themes. Finally, the themes were reviewed to consider their relationship to the overall thematic map. Once a thematic 'map' was identified, the findings were developed into a conceptual framework of WA in b-CBT.[32]

Two other members of the research team (CF and DM), who are highly familiar with qualitative methodologies and Bordin's[9 10] WA theory, read through 20% of all transcripts and reviewed all supporting quotes across all phases of the analysis, so that close to half of the transcripts were reviewed. Discrepancies were discussed and reconciled. The final framework was discussed and revised over eight meetings. The entire coding process was performed using the NVivo V.11 data analysis software package. Supporting quotes were anonymised to ensure that participants and their PWP could not be identified.

To ensure the final conceptual framework accurately reflected WA (a 'therapeutic process') was not confounded with early manifestations of 'treatment outcomes' we defined 'therapeutic processes' relevant to WA, and the 'treatment outcomes' associated with CBT.[29] 'Therapeutic process' was defined as *'actions, experiences and relatedness of the client and the therapist in therapy sessions…'*.[33] We a priori extended the use of the term 'therapy session' to include face-to-face and digital delivery in the context of blended therapy. Horvath *et al*[29] noted three ways of defining the outcome in psychotherapy including: (a) the core value attributed to the outcome by the client, (b) the importance of the outcome in the theoretical framework of the therapist, and (c) the utility of the outcome (eg, the technique) to promote other outcomes that are valued. We defined outcome in relation to definitions b and c to enable a standardised definition that does not vary from client-to-client (ie, definition a). We a priori defined the outcomes of CBT as the alleviation of distress (b) through helping the client to develop more adaptive cognitions and behaviours (c).[30] The final conceptual framework was reviewed in light of the aforementioned definitions by members of the research team. Themes and subthemes that were judged to correspond with the definition of 'treatment outcome' were removed. We used the Standards for Reporting Qualitative Research checklist when reporting our findings.[34]

RESULTS

Description of sample

An exploration of WA in b-CBT was undertaken through 19 qualitative interviews with participants who experienced b-CBT in the treatment arm of the E-compared trial.[5] Participants were aged between 19 and 67 years (mean=34.47 years, SD=14.44 years), were largely male (n=13), white British or white other (n=12) and university educated (n=12) (full sample characteristics are presented in table 1). All interviews were conducted face-to-face apart from one, which was completed by phone.

Table 1 Sample characteristics of participants who took part in the qualitative interviews (n=19)

Characteristics	Mean (SD) or percentage (n)
Age in years	34.47 (14.44), range 19–67 years
Gender (male)	69% (13)
Marital status	
Divorced	5% (1)
Living together	11% (2)
Single	63% (12)
Married	21% (4)
Highest educational level completed	
Secondary school, equivalent	11% (2)
Colleague, equivalent	26% (5)
University degree or higher	63% (12)
Ethnicity	
British white or white other	63.1% (12)
Black/African/Caribbean/Black British	5.3% (1)
Asian or Asian British (any other Asian)	21% (4)
Mixed or multiple ethnic group	5.3% (1)
Other	5.3% (1)
Intervention completion level*	
Completed course of b-CBT	63.2% (12)
Incomplete course of b-CBT	36.8% (7)
WAI-SF-C†	46.29 (SD=10.21), score range 27–60 (17)
High WAI-SF-C	Score range 47–60 (10)
Medium WAI-SF-C	Score range 31–41 (6)
Low WAI-SF-C	Score 27 (1)
No score	(4)
PHQ-9	7.8 (6.87), score range 1–22 (n=18)

*Intervention completion level: a complete course of b-CBT refers to the completion of four mandatory Moodbuster modules (psychological education, behavioural activation, cognitive restructuring and relapse prevention), while an incomplete course of b-CBT course refers to the non-completion of the four mandatory Moodbuster modules.
†Four participants did not provide data for this questionnaire during their 3-month follow-up assessment.
b-CBT, blended plus cognitive behavioural therapy; PHQ-9, Patient Health Questionnaire-9; WAI-SF-C, Working Alliance Inventory Short Form-Client.

Saturation appeared to be reached by the 16th interview. Another three interviews were carried out to ensure that the selected saturation cut-off point had been accurately identified and to further validate interpretations. tables 2–4 show that the main themes were endorsed by 89%–100% of participants, indicating that the selected saturation cut-off point was sufficient.

Table 2 Theme 1, bond subtheme descriptions and supporting quotes

Theme, percentage of sample endorsed (*n*) and description	Supporting quotes
Theme 1: bond, 89%, (17)	
1.1 Feeling understood, 74% (14) The PWP's ability to make the client feel understood. This requires the PWP to closely listen to the client, comprehend what is being said and demonstrate empathic awareness and insight into the client's concerns.	*P12, high-range WAI-SF-C score:* "My therapist did make a real effort to try and get to know me, try to maybe get to know what made me tick and why I was feeling how I did, rather than just assuming this is what you need without … taking into account maybe what I as a person, personally needed".
1.2 Genuineness, 32% (6) The PWP's efforts to help the client, that are perceived as genuine and authentic, as opposed to procedural or routine.	*P9, low WAI-SF-C score:* "To be honest, I kind of felt like she (PWP) was very fake…Every time I'd say something there would be an, ahh, it just felt not genuine at all, that she was just saying it because she thought I felt down…"
1.3. Partnership, 74% (14) The ability of the client and PWP to achieve a working relationship that is akin to a friendship. Such a partnership is characterised by trust, empathy, feeling liked and feeling cared for.	*P12, high-range WAI-SF-C score:* "I feel like she, as I said earlier, took the time to get to know me and … what I was currently doing, so it did feel like she kind of knew me on an individual level, rather than just being the patient".

PWP, psychological well-being practitioner; WAI-SF-C, Working Alliance Inventory Short Form-Client.

Conceptual framework of WA in b-CBT

A thematic analysis with a constant comparative method[32] revealed multifaceted WA demands which show that the work of building WA in b-CBT involved a symbiotic effort by the PWP and the digital program, to actively engage the client to meaningful therapeutic activities and to promote self-discovery and commitment to the intervention. Such demands can be grouped into four overarching WA themes, (1) 'bond', (2) 'goals', (3) 'task' (in line with Bordin's[9 10] WA theory categories)[9 10] and (4) 'usability heuristics' (a newly emerging theme) (see figure 1 for a summary of the main themes and subthemes).

Theme 1: bond

The 'bond' is defined as a set of mental healthcare provider (including both the PWP and computerised program) competencies that enable a working relationship to be established and maintained with a client. Participants unanimously reported that a human therapist was the most important facilitator for building the bond in a b-CBT context. This was because participants valued qualities of 'humanity' and 'responsiveness' attributed to a human therapist. Through a process in which participants appeared to compare and contrast the strengths of the digital program with the PWP, most participants questioned the 'meaningfulness' of interacting with a digital platform that was incapable of understanding or responding to a client's needs as demonstrated by the following quote:

> an app is like a machine, it's not personal at all. I think it's good to have some element[s] of talking to a human about this kind of thing because I think you want reassurance as well, which you wouldn't get from an app and if you did it would just be responses built in. (P8, low-range WAI-SF-C)

Data from participant interviews revealed three broad PWP attributes considered to be important for the bond building process, namely the mental health providers' ability to effectively demonstrate their understanding of their client's struggles and needs (subtheme 1.1); convey that they are genuine in their endeavours towards the client (subtheme 1.2) and forge a working partnership founded on friendliness, feeling cared for, empathy and trust (subtheme 1.3) (see table 2 for subtheme descriptions and supporting quotes). Some participants elaborated on these concepts further to unearth granular insights of what it means to be in the presence of a PWP. Visually observing a PWP's non-verbal cues was reported to be especially important for gauging abstract relational concepts such as empathic understanding (subtheme 1.1), and genuineness (subtheme 1.2). The recognition of positive non-verbal cues appeared to increase congruence between the PWP and the client (subtheme 1.3) throughout the course of therapy:

> [During telephone therapy] he was like 'mm hm, go on…so how do you feel?' I can't see his face. I don't know what he was thinking. I can't feel him. But during face-to-face [sessions] I think when I talk about something I can notice, his or her like facial expression. I know he's listening …That make[s] me feel like talk[ing] more. (P14, WAI-SF-C score not available [WAI-SF-C scores are unavailable for participants who did not complete their online 3-month follow-up assessments on the E-compared trial])

Theme 2: goals

'Goals' refers to the collaborative work between the PWP, the client and the digital program, to appropriately identify what the client hopes to achieve through therapy (68% of sample endorsed the 'goals' theme, n=13). While 'goals' emerged as a distinct factor, it also appears to be interrelated with the 'task', thereby playing a fundamental

Table 3 Theme 3, task subtheme descriptions and supporting quotes

Theme, percentage of sample endorsed (*n*) and description	Supporting quotes
Theme 3: task 100%, (19)	
Activity-based task, 100% (19)	
3.1. Personalisation, 95% (18) The level at which a client is able to tailor the therapeutic task to their individual needs. A non-personalised digital intervention was reported to negatively impact engagement. The *PWP* in blended-therapy can play an important role in making a generic intervention (ie, computerised CBT) as more personalised.	*P12, high-range WAI-SF-C Score:* "I think it's a bit more personalised, because I would say while the E-Compared is good, it is still, it is to an extent generic, because it can't kind of know every single person that's watching the video, so whereas the therapists can kind of get an idea of you, your story, your journey, what's maybe led you to kind of this maybe relapse, or for you to be feeling the way you are, and you can't maybe get that from a computer…Whereas if I'm hearing it from the person, I'm going to take a bit more notice, but then if I'm just hearing it from the computer, where it will say that to everyone watching the video".
3.2. Usefulness, 95% (18) A useful task was defined as one that promotes new learning, reflection and is effective in creating desired change in the client's life.	*P4, medium-range WAI-S-C score:* "But like the modules themselves, feelings-wise they were often quite helpful for clarifying stuff. Like I usually came out the other end feeling better or more kind of composed…it would kind of shape how I was seeing things. So like if I, you know learnt about thought distortions, I'd kind of go in with that knowledge and be able to kind of talk about it…"
3.3. Complementary, 84% (16) The ability to experience complementary tasks in face-to-face therapy and on the digital platform as continuous and cohesive, as opposed to stilted and disjoint. Knowing what to expect from the respective components of blended therapy was reported to help the client optimise the benefits sought from different components of therapy.	*P16, medium working alliance:* "I was finding it really hard to leave the house so that whole thought of going to therapy was quite difficult in the very beginning, so it did take me a couple of sessions to really start talking to (therapist) and opening up but because I had this online support I found it easier to open up to (therapist) so maybe instead of you know, two sessions it would have taken four or five".
Responsive support task, 100% (19)	
3.4. Accountability, 79% (15) The availability of a figure of authority that the client can (positively) feel responsible towards, as a means of garnering motivation to work on therapeutic activities. For the process of accountability to positively impact the client's motivation, a PWP is required to demonstrate their knowledge of the client's progress and provide feedback accordingly.	P19, medium-range WAI-S-C score: " *Well, to me, I saw it like homework, you've got to get it done otherwise you get into trouble, not that I would have got in trouble, but do you know what I mean, you're sort of motivated that way. And there is the other, the embarrassment of going in and saying 'oh yeah, I didn't do the modules' and then you feel really about that big and you know, someone's trying to help you and you haven't bothered to do your bit kind of thing. So that was a motivation in itself*".
3.5. Guidance, 89% (17) The provision of guidance and reassurance on the therapeutic tasks by a *PWP*. The PWP's intuition, expertise, interpretation and foresight is especially considered as helpful in addressing salient issues that would not have otherwise been communicated by the client.	*P10, high-range WAI-SF-C score:* "When you speak to your therapist, obviously she's had a lot of different scenarios with a lot of different people, she's got the experience and the know-how, and then obviously how I'm looking at it thinking the module's really working like this, she then says, 'That's really brilliant, but to then add onto that and to support you, how about if you think about that?"
3.6. Expression of feelings 100% (19) The client's expressed need to speak to another human being, in order to communicate issues that are pertinent to their treatment journey. In order for the client to optimally benefit, clients require the *PWP* to dedicate a sufficient amount of time for the activity. The amount of time required by each person appears to vary in relation to pretherapy expectations and symptom severity.	*P14, WAI-SF-C score unavailable:* "I think it's nice to have someone to talk to. It's kind of, I think it's important for me to express my feelings like in a private situation. Because sometimes I have, kind of I live with my partner but, you know, some(times), you can't talk to her".

PWP, psychological well-being practitioner; WAI-SF-C, Working Alliance Inventory Short Form-Client.

Table 4 Theme 4, usability heuristics, subtheme descriptions and supporting quotes

Theme, percentage of sample endorsed (*n*) and description	Supporting quotes
Theme 4: usability heuristics, 100% (19)	
4.1. Accessibility, 95% (18) The ability of a client to access the digital intervention at a time and place of convenience. Higher accessibility provides opportunities for the client to review and reflect on what has been learnt at a deeper level.	*P10, high-range WAI-SF-C score:* "Being on your own you know, in your own time and in your own safe place, your blanket, whatever you call it just allowed me personally just to open up and look at it, and then going from the start of the process to the end, … thinking positively, looking at your behaviours, looking at adding little things in and then the exercise at the end, rewarding yourself for just achieving things what I felt at the time were trivial made everything different".
4.2. Interactivity, 63% (12) An interactive digital program that is able to react to the clients input, to produce feedback. Interactive activities were perceived as more enjoyable, and promoted a degree of accountability.	*P6, high working alliance:* "One thing immediately comes to mind, it has to be a bit more interactive I think. The client shall we say, as well I feel should be given more feedback, the results, you know when you're scoring yourself on those, what that's about you know, how do they interpret that score, when you're putting your mood in on the smartphone, what's that about you know, who's looking at that, who's interpreting that".
4.3. Ease of use, 63% (12) The ease of use of the digital interface is described as a well-functioning, intuitive, digital interface which enables optimal access to the therapeutic task.	*P2, high-range WAI-SF-C score:* "It was really nice, I thought it was really, well very well presented I would say, and everything was just there, like for easy viewing, so you didn't have to like go through like folders or like go deeper into the website, like it was just there, and you know, I could just easily click on what I needed to do and just follow the instructions set out on the exercises".
4.4. Aesthetic appeal, 21% (4) The appearance or appeal of the digital interface is a factor that clients use to judge the credibility of the digital intervention and which could impact their engagement to the therapeutic task.	*P13, medium-range WAI-SF-C score*: "Yeah, and actually it became quite a bit of work just keeping up with the calendar, sort of, I found it a bit clunky, but then I worked in I.T for sixteen years…"
4.5. Self-directed, 79% (15) The process of taking responsibility for one's own behaviour and well-being, appears to instil clients with a sense of independence and control.	*P3, medium-range WAI-SF-C score:* "Other times it was good kind of to do a time and also independence, kind of learning to do stuff without a therapist there…I quite liked that I could, I don't know for me because it, I suppose it ties back into the independence thing, but because I was doing it on my own I almost proved I could do it on my own…because I feel like sometimes with a therapist you almost become like dependent on them or, it's like being taught something, when you're like dependent on the teacher".

WAI-SF-C, Working Alliance Inventory Short Form-Client.

role in framing activity-based tasks and maintaining the client's motivation to work towards creating change.

> The goal setting actually was something that I spoke to [the PWP] quite a bit about in the session […] I was then like 'God well what are my goals? […] what, where am I exactly going? (P5, higher-range WAI-SF-C score)

Theme 3: task

The 'task' refers to the careful selection and acceptability of the therapeutic activities prescribed to address the client's presenting symptoms ('activity-based task'), and the degree to which the support received by the health-care provider on these activities is responsive ('responsive support').

The defining features of 'activity-based task' refers to the client's ability to work on tasks that are: personalised and acceptable for addressing the client's therapy goals (subtheme 3.1); useful in promoting new learning, insights and reflection (subtheme 3.2) and are complimentary across both modes of delivery (subtheme 3.3). The defining features of 'responsive support' relate to the provider's (largely referring to the PWP's role) ability to appropriately respond to a range of clients' expressed and unexpressed needs to maintain accountability (subtheme 3.4); provide activity-based guidance (subtheme 3.5) and a safe-space for clients to express their feelings and emotions (subtheme 3.6) (see table 3 for subtheme descriptions, and supporting quotes).

The majority of participants noted the importance of experiencing the therapeutic activity as complementary across modes of delivery (subtheme 3.3). Some participants elaborated that an initial step to achieving an effective symbiotic delivery was to provide the client with an understanding of how the PWP and digital delivery contributed towards their treatment both distinctively and collectively.

Our findings also suggested that c-CBT appeared to positively impact the client-PWP WA, through increased

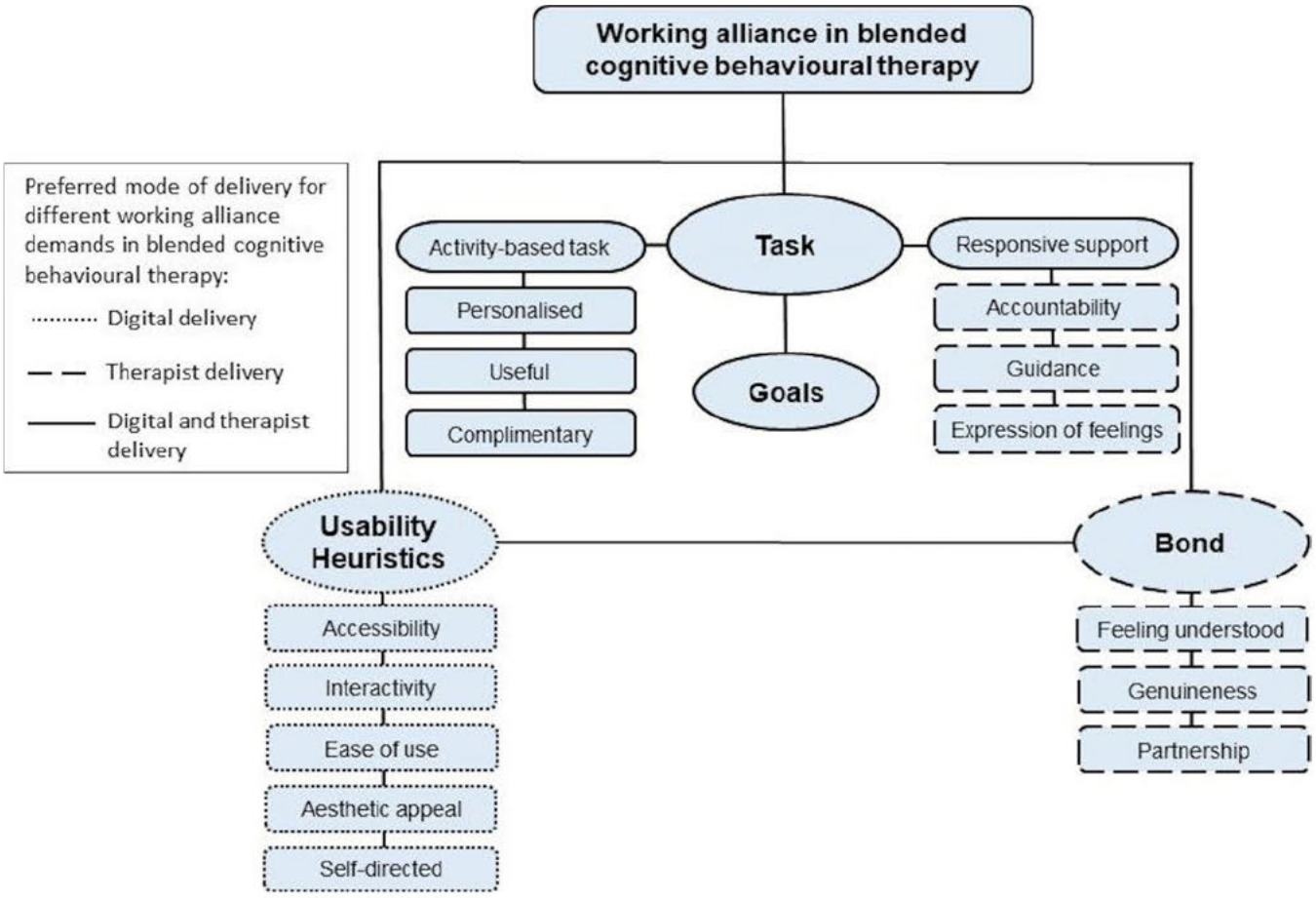


Figure 1 Participant reported working alliance demands in a blended cognitive behavioural therapy intervention.

opportunities to reinforce what was learnt through the digital platform, with a PWP, and vice versa, for instance:

> Well I think it gave you something to do over and above the face-to-face… having the modules to go through, it reinforces what you're talking about face-to-face and makes it easier to understand. It's, that repetition thing isn't it where you learn by repetition basically and that's how I saw it working. (P17, WAI-SF-C score not available)

Theme 4: usability heuristics

The final alliance building theme identified is, 'usability heuristics', which refers to the process of predominantly using digital technologies to promote active engagement, self-discovery and autonomous problem solving in b-CBT. This category is a novel component to Bordin's[9 10] theory. Features that enable 'usability heuristics' include ubiquitous digital technologies that: increase access and immediacy to the therapeutic task (subtheme 4.1), appropriately respond to the client's input (subtheme 4.2), are easy to use (subtheme 4.3) have aesthetic appeal (subtheme 4.4) and promotes self-directed therapy (subtheme 4.5) (see table 4 for subtheme descriptions and supporting quotes).

While PWP competencies emerged as the most important facilitator for building the alliance, almost all participants expressed that they preferred blended CBT to face-to-face alone. Some participants elaborated that their ability to access the intervention at a time and place of convenience (subthemes 4.1) further bolstered their engagement to therapeutic activities (theme 2). Participants who reported a high technological affinity suggested that the appearance (subtheme 4.4) and ease of use (subtheme 4.3) of the interface impacted their perceptions of the digital program's credibility and therefore, their desire to engage in treatment activities.

Almost all participants reported that the digital program provided them with the tools to initiate treatment independently (subtheme 4.5), with some participants noting that they continued to use the digital program as a means of maintaining therapeutic gains once their therapy course had ended. Here, autonomous completion of the therapeutic task was described as a secure-base that allowed clients to progressively explore self-directed therapy:

> it kind of reminds me of Winnicott and the Secure Base in Attachment theory in psychology, that you know, children become securely attached if they have a secure base in terms of the home and the parents

> that they can come back to, so they can go off and explore the world confidently in the knowledge that they can come back to security, and that, that helps them to develop—and it's kind of like that, I feel, with having that Moodbuster resource (digital program) there, that you can keep coming back to it … there is a lot in there and you can keep going back and it's a sort of source of strength really. (P10, higher-range WAI-SF-C score)

Participants suggested that the blended approach prepared the client to engage in autonomous self-directed therapy, through a process of supervised autonomy.

DISCUSSION

Statement of principal findings

The results of the study present a preliminary conceptual framework of WA in b-CBT. It can be seen that Bordin's[9 10] 'bond', 'goals' and 'task' appear to be relevant in b-CBT, however the priorities of WA demands have shifted to meet the client needs within a blended format. Moreover, an entirely new category 'usability heuristics', emerged as a novel means of promoting WA through a process of self-directed discovery and autonomous problem solving. Participants also explained that different WA demands were met by the PWP (eg, client-provider bond, responsive support) and the digital program (eg, upholding goals, task and promoting usability heuristics).

Strengths and limitations of the study

To our knowledge, this study is the first to provide an account of WA in b-CBT, and insights into how different delivery roles within a blended format are used to meet different WA demands. This is especially important given that digital technologies are increasingly being used to treat mental health conditions,[4] and that WA plays an important role in promoting positive therapeutic change.[12] The design of our study had two key strengths. First, we used the most comprehensive and commonly used theory of the alliance .[35] Second, involving patient involvement enabled the project to be grounded on the needs and interests of people who have experienced mental health conditions and service-use, thereby enhancing the application of our findings.[23] There are also several limitations to be noted. Our study does not include the PWP's perspective, which may have provided additional insights on WA in b-CBT,[18] however, this will be explored in a separate paper. Our sample was limited to 19 individuals with a primary diagnosis of mild-to-moderate depression and who mostly reported moderate-to-high WA, were largely male, British white or white other and university educated. This thereby limits the representativeness of people seeking treatment in the UK[36] and restricts the generalisability of our findings. Exposure to only one type of digital program, may have influenced participant's experience of WA. For instance, a computerised platform that does not work adequately might generate more data on the importance of 'ease of use' than one that does. Some of these issues were pre-empted ahead of the study. Efforts were made to strengthen the conceptual framework in two ways. First, emerging participant data were guided by key literature on the alliance and patient involvement input. Second, our qualitative data analysis avoided the use of surface-level themes, such as specific technological design. Instead, latent thematic analysis was used to unearth underlying psychological processes.[32]

Strengths and weaknesses in relation to other studies, discussing important differences in results

Participants reported that, while it was essential for therapeutic activities to be complimentary between modes of delivery, they also suggested that modes of delivery can uniquely meet different WA needs. For instance, participants unanimously fed back that the PWP played an essential role in establishing the 'bond'. The importance of the practitioner's role in supporting digital interventions is well documented in the literature.[6] A 2018 study evaluating the relationship between the client, the human provider and their c-CBT program found that participants rated their overall treatment approach higher when they experienced c-CBT that was guided by a human provider compared with c-CBT that was unguided.[7] Another study evaluating the expectations of clients and practitioners in a c-CBT intervention for depression found that personalised interactions with a therapist were key for engagement.[37] When attempts were made to unpack the importance of the therapist's role, participants suggested that the PWP's physical presence facilitated the PWP's propensity to convey important features of the bond (subthemes 1.1–1.3) through verbal and non-verbal communication. This aligns with early psychotherapy research by Karl Rogers,[38] who proposed that a therapist's ability to display active listening (empathic understanding, unconditional positive regard and congruent behaviour) was important for positively changing the impressions of the client's perceived negative experiences. Neuroscientific research evaluating the impact of active listening, suggested that the participant's recognition of active listening behaviour in another, can positively change the appraisal of an emotional episode and increased positive impressions of the active-listener.[39] These findings appear to be unique to human-to-human interactions. One study assessing the therapeutic alliance in a digital mental health mobile application for psychosis found that the anthropomorphizing of digital devices was not accepted by clients or mental health practitioners.[20] Given that little gains have been made to effectively deploy emotional artificial intelligence, a tool that is required for the effective biomimicry of human beings in the digital space,[40] the exclusion or non-effective deployment of a human provider in digital psychological interventions may therefore compromise the quality of WA.

On the other hand, participants reported that while the PWP was essential for the effective delivery of CBT, they

preferred blended delivery compared with PWP delivery alone. Almost all participants reported WA benefits, in the form of engagement through desired opportunities to engage in self-directed therapy (ie, 'usability heuristics'). Our findings are echoed in the digital mental health user-experience and the alliance literature, which indicate that digital psychotherapy can enhance the client's perceived control, autonomy and feelings of empowerment, when sufficient human support is provided.[20 41] The findings of our study suggest that the impact of digital delivery cannot be removed from the formation of the WA. For example, a digital program that was perceived as non-interactive appeared to limit engagement with 'activity-based task'. Given that the program plays an important role in delivering and engaging the client to 'activity-based task', we argue that the inclusion of program factors that uphold existing alliance structures should therefore be accounted for in the WA framework. Our findings align with Bordin's[9 10] conceptualisation of WA, in which he proposed that the therapeutic tool cannot be disentangled from the means in which the alliance is built. This therefore suggests that the client-program WA may have an impact on the client-PWP WA, and vice-versa, contrary to research suggesting that the contribution of a digital program to WA is independent and additive.[7]

The 'task' appears to play a central role in b-CBT, as initially theorised by Bordin.[9 10] Our findings address Bordin's[10] call to distinguish between the task that is in service of 'building WA' (responsive support) and the task in the service of 'change' (activity-based task). While many of the 'task' subthemes appear to be novel to Bordin's[9 10] theory, with the exception of complementary tasks (subtheme 3.3), all other 'task' subthemes are in fact implicit in his broad conceptualisation. The integration of technology in psychotherapy has prompted a re-evaluation of the demands placed on WA by a blended psychotherapeutic format. For example, the concept of accountability is implicit and forms one of many appendages associated with the PWP's role in building and maintaining WA. However, this concept has been propelled to the forefront as an essential ingredient for maintaining the alliance in b-CBT, in line with the 'supportive accountability' model for e-health proposed by Mohr *et al*.[42]

While 'bond', 'goal', 'task' and 'usability heuristic' emerged as distinct themes, the 'goals' theme appears to be interlinked with 'task'. The data from the qualitative interviews indicated that the 'goals' theme was grounded in goal-setting activities. This however diverges from Bordin's[9 10] description of the 'goals', which appears to move further, to address the PWP's efforts to unearth the core struggles that have bought the client to psychotherapy in great detail.[10] One possible reason for our findings may be explained by the time-lag between the assessment and the first therapy session, which may have led participants to only focus on their course of b-CBT and not the proceeding assessment where more in-depth explorations of the client's struggles and goals *may* have taken place. On the other hand, our study is not the first to question the operational distinctiveness of 'goals' and 'task'. The psychometric evaluation of the Working Alliance Inventory (based on Bordin's[9 10] WA) suggested that these concepts were highly interrelated,[29] while a more recent psychometric evaluation found that goals and task did not emerge as distinct factors.[43]

Box 1 Top 10 research priorities for digital technology in mental healthcare, identified by the priority setting partnerships[7]

Q1. What are the benefits and risks of delivering mental healthcare through technology instead of face-to-face and what impact does the removal of face-to-face human interaction have?
Q3. How can treatment outcomes be maximised by combining existing treatment options (medication, psychological therapies, etc) with digital mental health interventions.
Q8. Can the common elements of therapy (eg, empathy, gestures, non-verbal cues) that come from person-to-person interactions be maintained with digital technology interventions?

Meaning of the study: possible explanations and implications for clinicians and policymakers

Our findings address, at least in part, 3 of the 10 clinical and research priorities of digital technology in mental healthcare identified by people with lived experience of mental health conditions, carers and health and social care practitioners (see box 1).[8] WA, a common element of psychotherapy appears to be both relevant and important in a b-CBT intervention for depression. Human delivery was reported as central to the maintenance of empathy, gestures and non-verbal cues, in which the PWP's role in b-CBT may be especially helpful in establishing the bond, and developing and maintaining the client's engagement through responsive support (Q8). Participants noted that both modes of delivery collaboratively contributed to the building of the alliance through distinctive pathways. While human support is perceived as 'responsive' and 'meaningful', digital delivery appears to promote autonomy and self-directed discovery (eg, accessibility and self-directed) which may be important for maintaining WA across 'goal' and 'task' activities (eg, ease of use, interactivity of digital program and aesthetic appeal). Our findings suggest that the removal of human support, may increase the risk of therapeutic ruptures and disengagement (Q1 and Q3). The findings of our study can be used to promote WA in technological design and clinical practice, thereby promoting engagement to b-CBT interventions for depression, and guiding the effective deployment of PWP and digital program resources.

Unanswered questions and future research

We propose four directions for future research. First, while our findings outline WA demands in b-CBT, it is unknown if fulfilling such demands will lead to positive clinical change. Future research should aim to investigate if self-reported WA as defined by our conceptual framework, predicts psychotherapy outcome. Second, WA

should be further explored across different computerised programs, clinical groups, higher-intensity interventions and other digital technologies (eg, virtual experiences, gamification and text-based interventions) intended for use within a blended format, especially in relation to understanding how the demands of different digital technologies shape 'usability heuristics'. Third, our findings can be used to inform the design of behavioural intervention technology theories, as a means of enhancing engagement and adherence to digital components of blended interventions for mental health conditions. Fourth, given that digital technologies hold significant potential for bridging the gap in mental healthcare in low-resource settings,[44] future research should examine WA in digital mental health interventions in non-Western cultures and settings.

Author affiliations
[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[2]School of Psychology, University of Sussex, Brighton, UK
[3]Health Service and Population Research Department, King's College London, London, UK
[4]Department of Psychiatry, Oxford University, Oxford, UK
[5]Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK

Twitter Asmae Doukani @asmae.doukani

Acknowledgements The authors would like to thank the E-compared trial for supporting the study and the 11 patient advisors whose input shaped the methodology of the project, including Abé Chekh-Dove El-Ghassani, Michael Clarke, Paul H Ware, Dr Sarah Markham and Tibby Stodel. The authors would like to thank Dr Thomas Kabir from the McPin Foundation for his guidance on involving patient advisors, Dr Nicki Thorogood who provided guidance on the participant qualitative interviews methodology and to Shumaila Usmani who helped facilitate and transcribe the patient involvement focus group interviews.

Contributors AD developed the concept of the work. Patient involvement shaped the focus of the research. AD led all aspects of patient involvement. AC-P and SS assisted with the patient involvement focus groups. The design and analysis of the patient involvement focus groups was contributed to by SS, JM-M, CF and RA. AD, CF and SS significantly contributed to the design of the qualitative participant interview. AD led all aspects of data collection, analysis and interpretation. CF and DM analysed a portion of the data independently. The iterative development of the conceptual framework was led by AD, overseen by DM and RK and contributed to by CF, RA, and AC-P. AD prepared all iterations of the manuscript, with significant contributions from RK, CF, DM, RA, JM-M, SS and AC-P.

Funding This work was supported by the E-compared trial, which was funded by the European Commission's Seventh Framework Programme (Health), grant agreement number 603098. JM-M is supported by the Wellcome Trust Grant (104908/Z/14/Z).

Competing interests None declared

Patient consent for publication Not required.

Ethics approval The project was approved by the Health Research Authority's Ethics Committee on 17 April 2015 (REC reference: 15/LO/0511) and the London School of Hygiene and Tropical Medicine Research Ethics Committee on 9 June 2015 (Ethics Ref: 9409).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Asmae Doukani http://orcid.org/0000-0001-8629-2953
Jesús Montero-Marin http://orcid.org/0000-0001-5677-1662
Sarah Smith http://orcid.org/0000-0002-2013-6963

REFERENCES

1 OECD/EU. *Health at a glance: Europe 2018: state of health in the EU cycle*. Paris: OECD Publishing, 2018. https://doi.org/10.1787/health_glance_eur-2018-en%0Ahttps://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2018_health_glance_eur-2018-en
2 WHO. *Mental health: new understanding, new hope [online]*. Geneva: World Health Organization, 2001. https://www.who.int/whr/2001/en/
3 WHO. *Services and deinstitutionalization [online]*. World Health Organization, 2019. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/priority-areas/services-and-deinstitutionalization
4 Fairburn CG, Patel V. The impact of digital technology on psychological treatments and their dissemination. *Behav Res Ther* 2017;88:25
5 Kleiboer A, Smit J, Bosmans J, *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;17:387.
6 van Ballegooijen W, Cuijpers P, van Straten A, *et al*. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One* 2014;9:e100674.
7 Cavanagh K, Herbeck Belnap B, Rothenberger SD, *et al*. My care manager, my computer therapy and me: the relationship triangle in computerized cognitive behavioural therapy. *Internet Interv* 2018;11:11–19.
8 Hollis C, Sampson S, Simons L, *et al*. Identifying research priorities for digital technology in mental health care: results of the James Lind alliance priority setting partnership. *Lancet Psychiatry* 2018;5:845–54.
9 Bordin ES. The generalizability of the psychoanalytic concept of the working alliance. *Psychother Res Practice* 1979;16:252–60.
10 Bordin ES. Theory and research on the theraputic working alliance: New directions. In: Horvath AO, Greenberg Leslie S, eds. *The working alliance: theory, research, and practice*. New York: John Wiley & Sons, 1994: 13–37.
11 Lambert MJ. Psychotherapy outcome research: implications for integrative and eclectic therapists. In: Norcross JC, Goldfried MR, eds. *Handbook of psychotherapy intergration*. 1st edn. New York: Basic Books, 1992.
12 Norcross JC, Lambert MJ. Psychotherapy relationships that work II. *Psychotherapy* 2010;48:4–8.
13 Cameron SK, Rodgers J, Dagnan D. The relationship between the therapeutic alliance and clinical outcomes in cognitive behaviour therapy for adults with depression: a meta-analytic review. *Clin Psychol Psychother* 2018;25:446–56.
14 Sucala M, Schnur JB, Constantino MJ, *et al*. The therapeutic relationship in e-therapy for mental health: a systematic review. *J Med Internet Res* 2012;14:e110.
15 Vernmark K, Hesser H, Topooco N, *et al*. Working alliance as a predictor of change in depression during blended cognitive behaviour therapy. *Cogn Behav Ther* 2019;48:299
16 Kooistra L, Ruwaard J, Wiersma J, *et al*. Working alliance in blended versus face-to-face cognitive behavioral treatment for patients with depression in specialized mental health care. *J Clin Med* 2020;9:347.
17 Pihlaja S, Stenberg J-H, Joutsenniemi K, *et al*. Therapeutic alliance in guided internet therapy programs for depression and anxiety disorders - a systematic review. *Internet Interv* 2018;11:1–10.
18 Berger T. The therapeutic alliance in Internet interventions: a narrative review and suggestions for future research. *Psychother Res* 2017;27:511–24.
19 Barazzone N, Cavanagh K, Richards DA. Computerized cognitive behavioural therapy and the therapeutic alliance: a qualitative enquiry. *Br J Clin Psychol* 2012;51:396–417.
20 Berry K, Salter A, Morris R, *et al*. Assessing therapeutic alliance in the context of mHealth interventions for mental health problems: development of the mobile Agnew relationship measure (mARM) questionnaire. *J Med Internet Res* 2018;20:e90.

1 Torous J, Jän Myrick K, Rauseo-Ricupero N, *et al*. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. *JMIR Ment Health* 2020;7:e18848.
2 Warraich HJ, Califf RM, Krumholz HM. The digital transformation of medicine can revitalize the patient-clinician relationship. *NPJ Digit Med* 2018;1:49.
3 Hayes H, Buckland S, Tarpey M. *Briefing notes for researchers: public involvement in NHS: public health and social care research*, 2012. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Briefing+notes+for+researchers:+public+involvement+in+NHS,+public+health+and+social+care+research#2
4 Krueger RA. *Focus groups : a practical guide for applied research*. 2nd edn. London: Sage, 1994.
5 Staniszewska S, Brett J, Simera I, *et al*. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ* 2017;358:j3453.
6 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
7 Lecrubier Y, Sheehan DV, Weiller E, *et al*. The mini international neuropsychiatric interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *Eur psychiatr* 1997;12:224–31.
8 Corbin J, Strauss A. *Basics of qualitative research: techniques and procedures for developing grounded theory*. 4th edn. London: SAGE Publications, 2008.
9 Horvath AO, Greenberg LS. Development and validation of the working alliance inventory. *J Couns Psychol* 1989;36:223–33.
10 Beck Institute. What is cognitive behavior therapy [online], 2016. Available: https://beckinstitute.org/get-informed/what-is-cognitive-therapy/ [Accessed 16 Jul 2019].
11 Green J, Thorogood N. *Qualitative methods for health research*. 3rd edn. London, 2014.
12 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:101.
13 Llewelyn S, Macdonald J, Aafjes-van Doorn K. Process–outcome studies. In: *APA handbook of clinical psychology: theory and research*. Washington: American Psychological Association, 2016: Vol 2. 451–63. http://content.apa.org/books/14773-020
14 O'Brien BC, Harris IB, Beckman TJ, *et al*. Standards for reporting qualitative research. *Academic Medicine* 2014;89:1251.
15 Cahill J, Barkham M, Hardy G, *et al*. A review and critical appraisal of measures of therapist-patient interactions in mental health settings. *Health Technol Assess* 2008;12
16 IAPT. Analysis document for improving access to psychological therapies (IAPT) referral rates by sex and age and sex and ethnicity [online]. London, 2017. Available: https://www.england.nhs.uk/publication/improving-access-to-psychological-therapies-services-analysis/
17 Montero-Marín J, Prado-Abril J, Botella C, *et al*. Expectations among patients and health professionals regarding web-based interventions for depression in primary care: a qualitative study. *J Med Internet Res* 2015;17:e67.
18 Rogers CR. The necessary and sufficient conditions of therapeutic personality change. *J Consult Psychol* 1957;21:103
19 Kawamichi H, Yoshihara K, Sasaki AT, *et al*. Perceiving active listening activates the reward system and improves the impression of relevant experiences. *Soc Neurosci* 2015;10:26
20 Schuller D, Schuller BW. The age of artificial emotional intelligence. *Computer* 2018;51:46
21 Knowles SE, Toms G, Sanders C, *et al*. Qualitative meta-synthesis of user experience of computerised therapy for depression and anxiety. *PLoS One* 2014;9:e84323.
22 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:e30.
23 Hatcher RL, Barends AW. Patients' view of the alliance in psychotherapy: exploratory factor analysis of three alliance measures. *J Consult Clin Psychol* 1996;64:1336
24 Naslund JA, Aschbrenner KA, Araya R, *et al*. Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. *Lancet Psychiatry* 2017;4:486–500.

Chapter 5: Practitioners' experience of the working alliance in a blended cognitive-behavioural therapy intervention for depression: qualitative study of barriers and facilitators (paper 2)

5.1 Summary of chapter 4

In the last chapter, I presented an adaptation of Bordin's theory [6,7] that considers the client working alliance demands in a b-CBT intervention [47]. The findings showed that Bordin's [6,7] goals, task, and bond were relevant in blended cognitive behavioural therapy (b-CBT), however a number of adaptations were made to the original conceptualisation to address the working alliance demands in b-CBT. The most prominent change related to the addition of another working alliance category that largely focused on the digital programme's contribution to the working alliance, called 'usability heuristics'[47], which refers to the 'active engagement, self-discovery and autonomous problem solving' [p.9], and which some clients described as a secure base. Specific working alliance demands in relation to b-CBT were reported in relation to goals, task, and bond. For example, clients reported a need to make the therapeutic task complementary across face-to-face and the digital programme, as well as needing their therapist to hold them accountable for tasks completed through the digital programme. The framework also distinguishes between activity-based tasks, and responsive support to the task. In respect to the role of the provider in fostering a working alliance, data revealed that almost all participants agreed that while the human therapist was central for an effective working alliance to be fostered, they also said they would prefer b-CBT over face-to-face CBT only, as they thought a blended approach was more conducive to developing a therapeutic alliance. Finally, the adapted framework provided guidance around which mode of delivery (i.e., face-to-face versus digital programme) can best address working alliance needs in a b-CBT context.

5.2 Introduction to chapter 5

In this chapter, I will present the second qualitative paper examining the working alliance in a b-CBT intervention for depression in the UK. This chapter will build on the previous chapter (paper 1), to understand the working alliance from the therapists' perspective [48]. Unlike paper 1, the findings from this paper will not be used to adapt Bordin's theory of the working alliance [6,7]. This is because conceptualisations of the working alliance (and variations thereof) have largely focused on client needs [13]. On the other hand, the therapist is largely responsible for setting the right conditions for the

working alliance to be established, developed, and maintained in therapy [6,7]. Consequently, this paper will explain therapist perceived barriers and facilitators to fostering the working alliance. Furthermore, this chapter will further build on the findings from paper 1, by not only exploring therapists' experiences of fostering Bordin's [6,7] tripartite working alliance (i.e., goals, task, and bond) with their clients, but will also explore their experience of additional demands reported in the client interviews (e.g., 'usability heuristics').

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1407974	**Title**	Ms
First Name(s)	Asmae		
Surname/Family Name	Doukani		
Thesis Title	A mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy intervention for depression in a multinational randomised controlled trial in Europe		
Primary Supervisor	Dr Ritsuko Kakuma		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BJPsych Open		
When was the work published?	25/07/2022		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

Type
Papers

Information
BJPsych Open , Volume 8 , Issue 4 , July 2022 , e142
DOI: https://doi.org/10.1192/bjo.2022.546[Opens in a new window]

Creative Commons

Copyright

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the concept of work for this paper, designed the qualitative interviews, and topic guides, with close consultations with PhD supervisors. I conducted participant individual interviews, while focus group discussions were conducted by Dr Jennifer Walke, with my assistance, to collect data at pace. I led all aspects of data analysis. Dr Ritsuko Kakuma analysed a portion of the data independently, and Professor Caroline Free supervised the initial coding stage of the analysis. I led the interpretation of data, that was overseen by PhD supervisors and advisors. I produced the first draft of the manuscript for co-authors to review, and was responsible for addressing comments from co-authors, and from peer reviewers following the submission of the paper. Supervisors and advisors provided guidance and feedback across all phases of research described. All authors provided feedback on successive drafts and approved the final version, ahead of submission.

SECTION E

Student Signature	[redacted]
Date	19/05/2023

Supervisor Signature	[redacted]
Date	26 May 2023

BJPsych Open (2022)
8, e142, 1–9. doi: 10.1192/bjo.2022.546

Practitioners' experience of the working alliance in a blended cognitive–behavioural therapy intervention for depression: qualitative study of barriers and facilitators

Asmae Doukani, Caroline Free, Ricardo Araya, Daniel Michelson, Arlinda Cerga-Pashoja and Ritsuko Kakuma

Background
Digital technologies have been widely acknowledged as a potentially useful resource for increasing mental healthcare access. The working alliance is a key influence on outcomes in conventional psychotherapy, but little is known about therapists' experiences of forming an effective working alliance in blended interventions that involve in-person psychotherapy and a digital programme.

Aims
To investigate psychological well-being practitioners' (PWPs') experiences of the working alliance in a trial of blended cognitive– behavioural therapy (b-CBT) for depression. Trial registration ISRCTN12388725.

Method
Semi-structured qualitative interviews were conducted with 13 PWPs who delivered b-CBT in a two-arm, non-inferiority randomised controlled trial investigating the effectiveness of b-CBT compared with face-to-face CBT. Thematic analysis was used to analyse the data.

Results
Participants reported four facilitating factors when building and maintaining a working alliance in b-CBT: having more time to deliver treatment, access to a wider toolkit, capacity to tailor components of b-CBT and receiving appropriate training and support. Participants also identified four barriers to building and maintaining a working alliance: time and resource constraints, usability challenges, limited flexibility to tailor the digital programme to patients' needs and lack of confidence in delivering b-CBT.

Conclusions
Our study is the first specifically to investigate practitioners' perceived facilitators and barriers to forming a working alliance in b-CBT for depression. Findings suggest that PWPs' experiences of the working alliance can be improved by: accounting for the time required to deliver b-CBT in service workflows to reduce time pressures; increasing opportunities to tailor the digital programme through offering transdiagnostic tools and adaptable features; and providing appropriate b-CBT training and technical support.

Keywords
Working alliance; mental health practitioner; blended cognitive–behavioural therapy; qualitative research; e-mental health.

Digital technologies have been widely acknowledged as a potentially useful resource for increasing access to mental healthcare, offering the promise of affordable, evidence-based interventions at scale, as well as opportunities to augment and extend treatments in new and innovative ways.[1–6] Digital interventions such as internet-based cognitive–behavioural therapy (i-CBT) have become increasingly popular in the past decade. i-CBT can be implemented with different levels of human support, ranging from no/minimal support, referred to as unguided i-CBT, to regular in-person sessions, referred to as blended CBT (b-CBT). Although there is some evidence to suggest that b-CBT is effective in treating depression compared with no treatment,[7] very little is understood about therapists' experiences of developing and maintaining a central concept of engagement in psychotherapy, called the working alliance.[8,9]

Working alliance

Edward Bordin[10,11] conceptualised a tripartite theory of the working alliance, consisting of three common factors that apply to most, if not all psychotherapeutic approaches: goals, the task and the bond. Goals or goal setting involves the collaborative effort between the therapist and patient to identify what the patient wants to achieve through therapy. Goals are generally established at the start of therapy and subsequently frame the activities (i.e. the task) selected in treatment. Goals are also reviewed and fine-tuned throughout therapy to ensure that they remain relevant to the patient. The task refers to an agreed therapist–patient exchange and activities that specify how the patient's goals can be achieved. The patient–therapist collaboration involves the active involvement of the patient in the selection of the task to ensure that it is relevant to their goals, with the therapist considered a major source of task selection owing to their clinical expertise and insights. Finally, the bond refers to a partnership that stems from shared activities and compatibility between therapist and patient. Bordin[10,11] describes shared activity as a sense of 'common commitment and shared understanding of the activities carried out in therapy', while compatibility is described in terms of liking, trusting and respecting one another.

The working alliance is important because it has been found to predict treatment outcomes for a range of psychological interventions, including conventional face-to-face CBT for depression.[12–14] Although some efforts have been directed towards understanding the working alliance from the patient's perspective both

quantitively[15-17] and qualitatively,[18] to our knowledge none have specifically explored therapists' perspectives of the working alliance in i-CBT or b-CBT. In a previous study[18] we examined the patient's experience of the working alliance and found that, while Bordin's[10,11] bond, goals and task largely remained relevant in a b-CBT setting, a fourth dimension called 'usability heuristics' underscored the impact of the digital programme on the working alliance. Usability heuristics was defined as the use of digital technologies to promote active engagement with the digital programme, through higher levels of accessibility, immediacy, ease of use, aesthetic appeal and opportunities for self-directed treatment. These findings indicate that the patient's working alliance demands are directed not only towards the therapist, who according to the research is largely responsible for maintaining the bond, goals and task, but also towards the digital programme.

A study by Titzler and colleagues[19] that explored therapists' general experiences of implementing b-CBT reported that a lack of autonomy in how patients used the intervention, a 'one size fits all' approach and persistent technical problems hindered the patient–therapist alliance.[19] These findings indicate that programme-related factors may influence how the working alliance is perceived.

Rationale and aim

There appears to be some evidence to suggest that patients' experience of the working alliance may be different in b-CBT, and that programme-related aspects of implementing and delivering b-CBT (e.g. a lack of autonomy and poor usability) can have a negative impact on therapists' perceptions of the patient–therapist alliance.[18,19] These findings warrant an in-depth examination of therapists' perceptions of managing the working alliance in a b-CBT context. Such insights can be used to optimise the working alliance and the implementation of b-CBT. Based on the reasoning oulined, our study aims to qualitatively examine therapists' experience of the working alliance in a b-CBT intervention for depression, on the E-COMPARED trial.

Method

Design of trial

This study was nested in the E-COMPARED project, a two-arm, non-inferiority randomised controlled trial investigating the effectiveness of b-CBT compared with treatment as usual (TAU) across nine European countries.[22] The study was conducted in the UK site and it enrolled patients aged 18 years or older who met the DSM-IV diagnostic criteria for major depressive disorder.

In summary, inclusion and exclusion criteria[22] applied on the E-COMPARED trial were as follows.[22]

Inclusion criteria: aged 18 years or older; meeting diagnostic criteria for major depressive disorder; score of 5 or higher on the Patient Health Questionnaire-9 (PHQ-9).

Exclusion criteria: high risk of suicide; psychiatric comorbidities (bipolar affective disorder, obsessive–compulsive disorder, psychotic illness and substance dependence); currently receiving psychological treatment; unable to speak or write English; no access to fast internet connection; does not have an android smartphone or is not willing to carry one provided by the research team.

Further information on the E-COMPARED trial can be found in the trial protocol.22

Participants

Eligible participants were low-intensity psychological well-being practitioners (PWPs) recruited from six Improving Access to Psychological Therapies (IAPT) services across the UK. IAPT services aim to improve access to, and delivery of, evidence-based psychological interventions within the National Health Service. IAPT services provide evidence-based treatments for adults with a range of anxiety and depressive disorders, and with comorbid presentations. The PWP workforce typically provide low-intensity, short-term, evidence-based treatments using cognitive–behavioural principles and in accordance with the National Institute for Health and Care Excellence (NICE) guidelines.[20] A 'low-intensity' PWP generally uses self-help material and engages in 6 h or less of contact with patients, with each session being around 30 min or less.[21] PWPs who delivered at least one face-to-face session on the b-CBT arm of the E-COMPARED trial were emailed a study information sheet before they were followed up and booked in for an individual interview or a focus group discussion (FGD) at the service in which they worked. The study aimed to maximise diversity in the sample, based on gender, age, years of experience, service location and number of participants seen in the b-CBT arm. Data collection took place between July 2016 and June 2017.

Ethics approval and informed consent

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants/patients were approved by the Health Research Authority's Ethics Committee on 17 April 2015 (REC reference: 15/LO/0511) and the London School of Hygiene and Tropical Medicine Research Ethics Committee on 9 June 2015 (Ethics Ref: 9409). Therapists provided written informed consent prior to participation in the individual interviews and the focus group interviews.

The b-CBT intervention

Treatment conditions on the E-COMPARED trial consisted of b-CBT and TAU for depression. The b-CBT was delivered by PWPs in the clinic and supported by i-CBT modules that were ideally completed outside of the clinic. The i-CBT Moodbuster[22] intervention includes four mandatory modules (psychological education, behavioural activation, cognitive restructuring and relapse prevention) and two optional modules (physical exercise and problem-solving). Moodbuster is supplemented with a mobile app, which allows patients to rate and visualise their mood and receive reminders of their scheduled behavioural activation activities. It was also used by the research team to collect ecological momentary data at the start and end of treatment. Trial participants in the b-CBT group were offered a target number of 11 alternate sessions, six face-to-face in the clinic and five via Moodbuster and the mobile app (hereafter, Moodbuster and the app are referred to collectively as the digital programme). PWPs were required to access a therapist portal on the Moodbuster platform to monitor patient progress on the modules, and mood and depression symptom ratings. PWPs were also able to book appointments and send direct messages to the patients between clinic sessions via a therapist portal.

Data collection tools

Qualitative data were collected using a mixture of individual interviews and FGDs, which were conducted according to semi-structured topic guides.[23] Areas of inquiry were loosely guided by Bordin's[10,11] theory of the working alliance. The topic guides for both individual interviews and FGDs aimed to understand PWPs' experiences of building a working alliance, covering a broad range of questions pertaining to the implementation/delivery of b-CBT

and the working alliance. Individual interviews (topic guide 1) aimed to gain in-depth insights of the working alliance in b-CBT and FGDs (topic guide 2) explored shared experiences of forming a working alliance in b-CBT[23] (the topic guides are shown in the supplementary material available at https://doi.org/10.1192/bjo.2022.546). The FGDs also enabled efficient data collection during a time-sensitive period of the trial. For pragmatic reasons two PWPs (P03 and P04) were involved in both the individual qualitative interviews and the FGDs. Steps were taken to ensure that the weighting of their perspectives did not skew the data, by identifying them as a single source during the data analysis and reporting of the findings. All individual interviews and FGDs were audio-recorded using an Olympus digital voice recorder WS-852 and were transcribed verbatim.

Analysis

Qualitative data from individual interviews and FGDs were combined and analysed using NVivo 12[24] on a personal computer. Thematic analysis was adopted owing to its theoretical flexibility and potential for in-depth description.[25] We took a primarily deductive approach to generate codes and themes, reflecting the study's overarching aims and drawing on Bordin's[10,11] aforementioned theory of working alliance and a previous study by our group[18] which used a qualitative design to formulate a conceptual framework of the working alliance in b-CBT for depression (Fig. 1). Data were also analysed inductively, by staying open to factors that positively or negatively affected the PWPs' experience of the working alliance. Thematic analysis involved reading the transcripts to enable familiarisation with the data. Data were then coded line by line and later reviewed to identify patterns to generate themes. Based on the emerging data, each theme was then categorised as either a facilitator or barrier to forming a working alliance. Themes were then reviewed to ensure that they were relevant to the working alliance.[25] Once a final list of themes and categories was developed, theme names were refined and each theme was described.[25] The qualitative analysis was conducted by author A.D. in full. Different phases of data analysis were partially reviewed and/or analysed by two co-authors to check that data were accurately coded, to maintain objectivity and avoid bias. This was done by checking the codes against the data to ensure that supporting quotations accurately depicted the loose deductive frameworks outlined in Fig. 1. Having several people involved in the coding process also helped bring different perspectives and interpretations to the analysis.[26] After A.D. coded two individual interview transcripts, C.F. reviewed all codes and supporting quotations. Following the completion of the initial coding phase by A.D., R.K. analysed a portion of the data consisting of one individual interview and one FGD. R.K.'s findings were compared with A.D.'s in a meeting to discuss similarities and discrepancies. Later stages of analysis involving the further development of themes were overseen by R. K. and in consultation with other co-authors. Themes were also discussed and refined over four meetings/consultations with co-authors, who were mental health and primary care service experts and who were very familiar with the concept of the working alliance.

Results

Participant characteristics

Out of the 29 PWPs approached about the study, 13 provided consent and participated in FGDs (n = 9), individual interviews (n = 2) and a combination of both (n = 2). Participants' mean age was 26.6 years (s.d. = 2.55) and they had worked as PWPs for a mean of 35.1 months (s.d. = 14.19) (see Table 1 for full participant characteristics).

Thematic analysis

Eight themes were identified and grouped as facilitators and barriers in building a working alliance. The facilitators were: (F1) expansion of time; (F2) wider toolkit; (F3) tailoring of b-CBT; and (F4) PWP training and support. An additional four themes were identified as barriers: (B1) time-intensive; (B2) usability problems; (B3) inflexible digital programme; and (B4) low confidence and practice. The analysis also identified four higher-order, cross-cutting categories that drew links between facilitators and barriers: experience of time (which encompasses F1 and B1), functionality of the digital programme (F2 and B2), flexibility to tailor b-CBT (F3 and B3) and confidence in delivering b-CBT (F4 and B4). See Fig. 2 for a diagrammatic representation of the facilitators, barriers and higher-order categories.

Time in b-CBT

Most PWPs fed back that b-CBT provided opportunities to extend patients' time in treatment but was time intensive, highlighting facilitators and barriers in building and maintaining all elements of the working alliance (bond, goals and task).

F1 Expansion of time

On one hand, PWPs reported that integrating the digital programme to in-person therapy extended the time of the patients' treatment course (i.e. hours that patients were engaged with the treatment), thereby also increasing patients' dosage of the task. They described the computerised modules as time-saving, removing the pressure of completing tasks during face-to-face sessions, which provided additional time for PWPs to talk to their patients and better reflect on treatment processes, in aid of further developing the patient–therapist bond.

> 'I think it's quite a subtle change in [the] therapeutic relationship when you're doing blended therapy to face-to-face, I think because ultimately that space is a lot more effective […], it's not quite so structured but you have to get through x, y and z in this time, you've got a bit more time to reflect on things, and it's [it gives you] a bit more agency …' (P03)

B1 Time intensive

On the other hand, PWPs also reported that implementing b-CBT was time intensive, as additional time was required to familiarise themselves with the content of the programme and prepare for each session by reviewing the patients' progress online. They also fed back that adapting the treatment to patients' needs was more time-consuming in a blended format. The time required to deliver the b-CBT intervention did not fit in with the service flow, thus putting additional strain on the PWPs' ability to learn and apply the task as intended:

> 'I think it was a steep learning curve for us to try to remember and to get our heads around the programme and feel confident and competent enough with it that if a patient came to us saying "Oh, I was looking at this section or that section – I don't understand what it is. Can you explain things?" Like that we'd have to kind of know what they were talking about not quickly looking it up.' (P04)

> 'It did [have an impact on my case-load] because with the c-CBT [computerised-CBT] reviews, the online reviews, they weren't counted as part of our target [….] So I suppose the online review was very much a case of trying sometimes to squeeze it in around the rest of your workload.' (P015)

> '… if you think of the IAPT framework, our service like we get about 1200 referrals a month […], face-to-face we're seeing people for about 6 to 8 weeks and then they're being moved

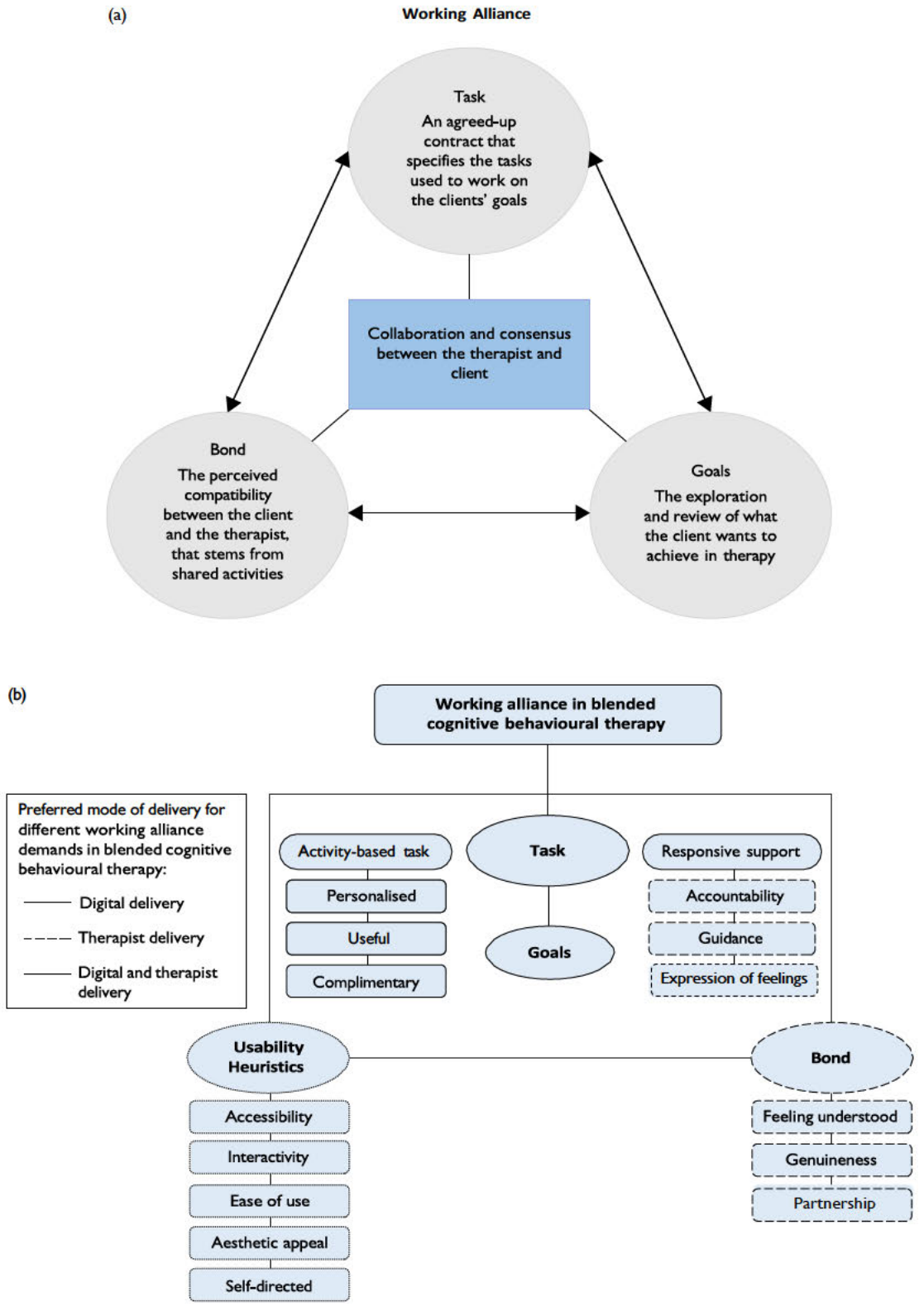


Fig. 1 The working alliance frameworks used to guide the topic guide. (a) Diagrammatic overview of Bordin's working alliance theory.[19,20] (b) Conceptual framework of the working alliance in a blended cognitive behavioural therapy for depression[18] (reproduced with permission of Asmae Doukani).

on or stepped up, whereas this would then delay it, you know, to 12 weeks. So it's just going to create a massive bottleneck where people are going to have to wait a lot longer to be seen, which could cause some problems there just because we're dealing with such a huge volume of referrals.' (P012)

Functionality of the digital programme

Some PWPs experienced the functionality of the digital programme as positive, enhancing their therapeutic toolkit in aid of addressing the task and goals, whereas others reported poor functionality that

Table 1 Participant characteristics

Characteristic[a]	
Age, years (s.d.), range	26.6 (2.55), 23–31
Female gender, n (%)	8 (61.5)
Experience, years (s.d.), range[b]	35.1 (14.19), 12–53 months
Patients on b-CBT, n (s.d.), range	2.7 (1.73), 1–6 patients
Qualifications (n = 10)	
Bachelor's degree, n (%)	4 (40)
Master's degree, n (%)	4 (40)
Professional diploma, n (%)	2 (20)
Interviews, n[c]	
Individual (topic guide 1)	4
FGD1 (topic guide 2)	5
FGD2 (topic guide 2)	2
FGD3 (topic guide 2)	3
Individual (topic guide 2)	1
Site	
Site A	9 (69.23)
Site B	4 (30.77)

b-CBT, blended cognitive–behavioural therapy; FGD, focus group discussion.
a. Data for age, gender, years of experience and qualification were based on 10 participants, as 3 participants from FGD1 (n = 1) and FGD3 (n = 2) did not provide demographic data.
b. Years of experience in role as a psychological well-being practitioner (PWP).
c. One individual interview was conducted using topic guide 2, as the participant could not attend a focus group.

limited the patients' engagement with the digital programme, which is essential for accessing the task (including tasks that are key to the goal-setting process) agreed on between the PWP and the patient.

F2 Wider toolkit

PWPs reported that the digital programme provided them with a wider toolkit to build a working alliance (e.g. ability to message the patient between sessions, track the patient's mood throughout treatment) and help the patient engage with the goals and task. Features of i-CBT provided new mechanisms of supportive accountability, allowing PWPs to monitor adherence to the task via a therapist portal. Other PWPs said that they were able to extend their presence outside of the clinic by using the messaging feature of the programme between sessions. PWPs also reported that the addition of i-CBT enabled a more systematic and comprehensive coverage of the task than would have otherwise been possible, given that patients were required to complete all core modules on the programme. PWPs also stated that the blended format provided the patients with additional opportunities to consolidate what was learned through the agreed task and goals, across different modes of delivery:

> 'I think it gives patients something to sort of focus on in between the sessions. I think it kind of reinforces those techniques so I really like the reminders on the phone, sort of looking at kind of diaries and things in more of an interactive way …' (P015)

> 'I guess I would say […] I found having the session once a fortnight good for the patients, it was great for them, I think they had a bit of extra time to consolidate learning so you could really see that improvement over 2 weeks. Whereas our standard sessions are weekly so sometimes they haven't had quite as much time to practise the techniques that were covered in session.' (P012)

B2 Usability problems

Although most participants said that the programme was generally user-friendly, concerns were expressed in relation to aspects of the digital programme's functionality. Some PWPs noted that technical issues or poor programme usability, particularly those that could not be readily fixed (e.g. malfunctioning mood-rating alerts on the mobile app that sounded multiple times a day and could not be turned off), may have had a negative impact on the working alliance. However, more straightforward technical issues (e.g. patients forgetting their ID) caused less concern for PWPs. Persistent usability problems therefore appeared to threaten 'usability heuristics'– that is, the patients' ability to use the digital programme to enable engagement, self-discovery and autonomous problem-solving in

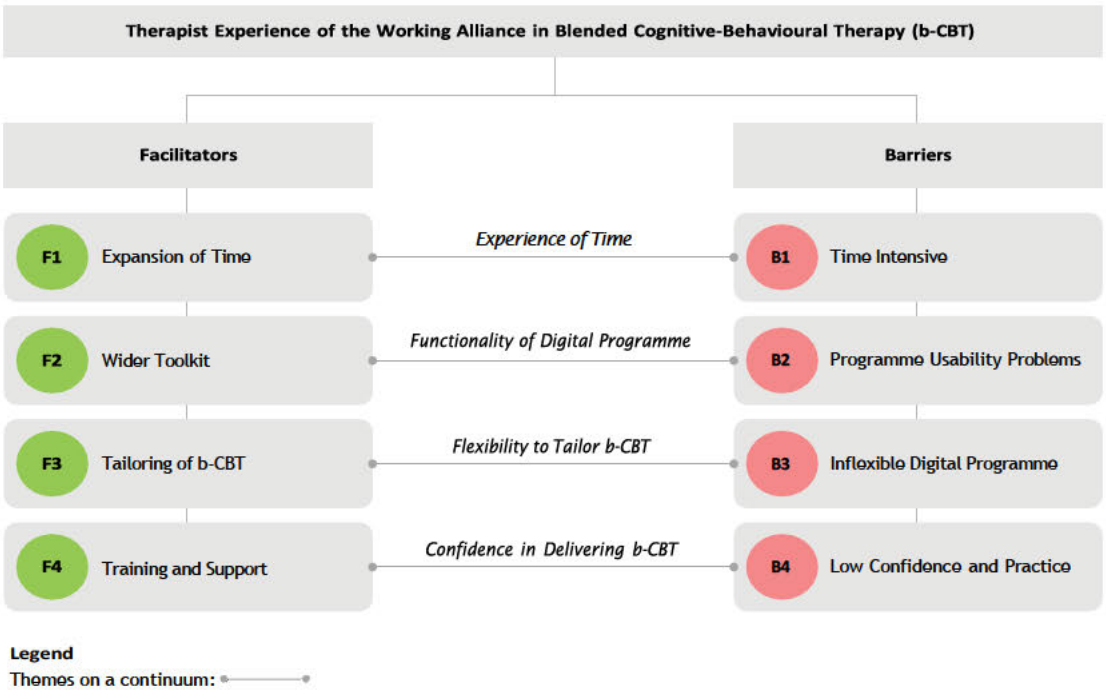


Fig. 2 Therapist-reported facilitators and barriers in building a working alliance in a blended cognitive behavioural therapy intervention. F, facilitator; B, barrier.

blended b-CBT – thereby creating barriers to addressing the working alliance needs in relation to accessibility, ease of use and self-directed use. Persistent usability problems that affect the patient's access to the tasks also hindered the PWPs' ability to deliver the task and goals as intended or to maintain a bond in respect to keeping the patient motivated and engaged in treatment:

> 'One person had practical problems with the phone in that it wasn't going off as often as it should, and then he wasn't sure when he should and shouldn't be doing it, and I did flag it with [researcher's name], but it's still, it's like confusing and he kept asking me these questions about it, and like having to forward it on to [researcher's name], and it was like I got stuck in the middle of it, and actually I don't know anything about them. Yeah, which wasn't ideal at the time.' (P03)

> 'So yeah, really user-friendly. The content was good. The only problems I suppose, but I guess it's just teething problems, [in relation to] how new the programme is, […] I remember they were saying when they were doing things like behavioural activation and using the planner, you couldn't set up recurring events for example in the diary or at least the person that I was working with couldn't. So they were finding it quite frustrating they were having to save they'd walked the dog at the same time every day when they were trying to plan it in, they were finding it frustrating having to put it in over and over again and they said they wished they could have done a bit of a, just a recurring entry instead. So just more things like that with the tools, they found some of them sent little reminders at the wrong time or yeah, little teething issues like that.' (P012)

> 'I think it always helps to have a smooth process, absolutely [….] I think if there were kind of glitches and things initially I would imagine, I don't know but I would imagine that it would be quite difficult to keep some people kind of motivated and on track with that if they were, […] I imagine maybe something like that for some people might be quite frustrating or maybe something to stop them from continuing or wanting to continue with it.' (P01)

Flexibility to tailor b-CBT

Most PWPs reported a range of experiences in relation to their ability to tailor b-CBT to the patient's needs, in which they described various aspects of the task and goal activities as tailorable or inflexible.

F3 Tailoring of b-CBT

Some PWPs highlighted that their role within b-CBT enabled them to tailor the task, by overseeing, setting, framing and tailoring the patient's therapy across face-to-face sessions and i-CBT to better address the patient's goals. PWPs also suggested that they were at times able to adapt elements of activities pertaining to the task and bond in i-CBT (e.g. advising on the selection of modules). Face-to-face sessions in the clinic enabled the PWP to provide support and address emerging needs that could not necessarily be covered through the digital programme, enabling the PWP to offer the patient a wider selection of tasks to effectively help the patient achieve their goals:

> 'I didn't go through all the modules with some people. So say for example the physical exercise one [optional module], if we didn't feel that was relevant we just spent another session really going over something like behavioural activation a little bit more. So for some patients we spent a lot more time focusing on a particular module and really making sure that was being understood, rather than just going through every module for the sake of it.' (P012)

B3 Inflexible digital programme

PWPs conveyed that the digital component allowed limited scope for tailoring the task and addressing patients' goals. For example, some PWPs noted that to unlock the final module, 'relapse prevention', the patient was required to complete the other three mandatory modules, which may not all have been relevant to them. This meant that patients who might have experienced rapid symptom resolution were still required to complete four core modules. PWPs also said that there was little opportunity to work transdiagnostically, since the content covered in the digital programme only addressed symptoms of depression, providing fewer opportunities to draw on tasks that addressed underlying causes that emerged during treatment. Although some PWPs addressed patients' unmet needs in relation to their treatment goals in the clinic, others did not want to stray too far from the treatment protocol owing to concerns that tasks covered in face-to-face appointments could not be integrated with the task from the digital programme. Collectively this had a negative impact on the working alliance, as the PWP was unable to apply the most appropriate task to address the patient's goals:

> 'I'd want to like not make it so […] strict so that, like I was talking about earlier with relapse prevention, like not having to complete all the modules to do that.' (P04)

> 'I think there was an element that was a little bit restrictive, I think because obviously sometimes if there's a mixed depression/anxiety and let's say, anxiety's forming a barrier, then things like relaxation exercises you obviously can't do that because it's not in the platform. I guess also knowing how MoodBuster goes through it, it goes through it from a very kind of classically "just depressed" state …' (P03).

> '[With] MoodBuster it comes back to that idea that we're kind of stuck sometimes with the things that are on there, so we'll go off-script, if you like, then I'm not actually utilising the programme. So there's been times when I've done relaxation or whatever in a session, which is part of a typical protocol for depression, but if it's come up, then we'd do it if it ever seems clinically relevant, and there's no way to incorporate that with MoodBuster for that session, because they didn't use it and I didn't give them any homework around it. And then again, that means that you can't then finish one of the modules in the time that we have, so it gets like a knock-on impact.' (P04)

Confidence in delivering b-CBT

Finally, PWPs also reported that their level of confidence in delivering b-CBT affected their ability to effectively build and maintain all components of a working alliance.

F4 Training and support

Some PWPs said that receiving training, having access to training resources and receiving technological support (e.g. related to patient log-in or technical issues) on how to use the i-CBT programme helped them feel more confident in delivering the task using the digital programme:

> 'I think the training was really good and I was able to kind of spend time looking at the programme and looking at what was involved. […] So, I think it was, I was well prepared for the session.' (P15)

> 'Well, a couple of times just with questions about things, more about things that had come up in sessions or questions I'd been asked […] so whenever I've needed to contact them [the research team] or ask anything I've always got a really quick response, really supportive.' (P14)

> 'I had quite a gap between having the training and then having a patient on the programme so I think the training was definitely helpful but I had to do a bit of a refresher beforehand.' (P04)

B4 Low confidence and practice

Most PWPs reported feeling apprehensive owing to lack of confidence in delivering b-CBT and were unclear about their precise role within the blended format of delivery. PWPs said that their lack of expertise and experience in delivering the intervention made them feel anxious and hindered their confidence when introducing and delivering the task. A few PWPs also mentioned that they felt less control over their management of the patient's treat- ment because they were unclear about how well their patients understood or benefitted from the tasks on the i-CBT programme, limiting the PWPs' ability to apply their judgement with respect to the selection of task to address a patient's needs and overarching goals and impeding their ability to effectively build a bond:

> 'I found it a bit more difficult, because my confidence was a lot lower using this approach. So I was probably more in my head like, what am I supposed to be doing in this session, rather than actually being able to develop an alliance with the person in front of me. I don't think I had much of a therapeutic alliance with the specific person. Consequently, their engagement was really, really low.' (P07)

> 'Yeah, so … I think I still felt connected with them, […] I guess I felt like I had a little bit less control over exactly what they were doing because they were doing it on the modules … Possibly a good thing but then you also think ultimately, I guess you have that really kind of slightly arrogant view that you have to be the one to do this [deliver CBT], that only I can do this properly!' (P03)

Discussion

General findings

Participants reported four facilitating factors in building a working alliance in b-CBT: expansion of time in treatment, having access to a wider toolkit, being able to tailor b-CBT, and receiving an appropriate level of training and support. Participants also reported four barriers to developing a working alliance: perceiving b-CBT as time and resource intensive, experiencing usability problems, not having the flexibility to tailor fixed elements of the digital programme to patients' needs, and feeling a lack of confidence in delivering the b-CBT intervention.

The higher-order categories outlined in Fig. 2 highlight a spectrum of PWPs' experiences of facilitators and barriers in building a working alliance. Facilitators such as 'expansion of time' and 'access to a wider toolkit' appear to enhance the PWPs' ability to engage the patient with treatment activities beyond what would have been possible in only face-to-face therapy. Conversely, 'flexibility to tailor the intervention' and 'training and support' appear to lay the foundations that enable the working alliance to be effectively developed. Barriers such as 'low confidence and practice' and 'time intensive' were perceived as short-term problems that could be resolved over time as PWPs became adept in delivering the intervention. On the other hand, not being able to effectively tailor fixed programme features such as content and tools appeared to pose a long-term threat to the working alliance. 'Programme usability problems' may present both short-term and long-term threats to the working alliance, depending on whether usability or technical issues can be resolved.

Evaluation in relation to other studies

Bordin's[10,11] task and goals appear to be the most affected by therapists' perceptions of the working alliance in a b-CBT context. This is expected considering that the therapeutic activities pertaining to the goals and task are predominantly accessed through the digital programme. Inflexible digital programme features and technical problems that affect patients' engagement with the agreed goals and task appear to diminish PWPs' role in collaboratively working on the agreed goals and task, and their role as a 'major source of selection' of the task.[10,11] On the other hand, digital programme features were perceived to extend treatment beyond the clinic and offer a wider selection of tasks to address patients' goals. Having in-person sessions appeared to be essential in reviewing and addressing unmet needs with respect to goals and task.[10,11] Bordin's[10,11] bond was also perceived to be affected by the b-CBT context, in which the i-CBT programme appeared to expand the time available for the PWP to work on the bond in clinic-based sessions. However, low confidence in delivering the intervention across PWP–patient shared activities appeared to undermine their capacity to forge an effective bond. Our findings also align with our previously described[18] framework of patients' working alliance demands in which a new component called usability heuristics outlines how functionality features (e.g. 'access and immediacy of the task' and 'ease of use') of the digital programme, and the capacity to offer personalised and complementary activities across in-person sessions and i-CBT, were critical in meeting patients' goal, task and bond needs, as well as in patients' ability to engage in supervised self-directed treatment.[18]

Our findings are supported by several qualitative studies that broadly explored therapists' experience of delivering internet-based psychotherapies. Our findings in relation to the impact of 'experiences of time' and 'flexibility in tailoring b-CBT' on the working alliance were consistent with findings from a systematic review of health professionals' perspectives on implementing internet-based therapies. The review found that guided and blended internet-based interventions were perceived to extend the time needed to develop a patient–therapist alliance, facilitate the building of rapport and allow the active monitoring and follow-up of patients.[27] The importance of the digital programme's functionality and customisability was also highlighted in a qualitative study of therapists' perspectives on barriers and facilitators in implementing b-CBT for depression conduced by a team at the German site of the E-COMPARED study.[19] Findings revealed that persistent technical problems that could not be resolved caused 'anger, frustration, and demotivation in both patients and therapists', while 'limited customisability and autonomy of decisions concerning blended therapy' had a negative impact on the patient–therapist alliance.[19]

PWP concerns regarding case-load management that stemmed from additional commitments attributed to b-CBT were also consistent with other health professionals' perspectives of implementing guided internet-based therapy, in which they emphasised the need for targeted training and organisational support to manage changed workflows and help therapists incorporate online therapies into their practice.[27]

The findings of our study appear to be relevant to broader implementation domains within the consolidated framework for implementation research (CFIR),[28] such as: adaptability of the core components of the digital programme; and the implementation climate, which affects the time available for treating each patient; and the level of compatibility between the intervention and the workflow of the service. These implementation domains could therefore be specifically considered in relation to strengthening the working alliance in b-CBT.[28]

The barriers outlined in our study suggest that key competencies relating to the building of a working alliance during the delivery of CBT for people with depression and anxiety in IAPT services may be compromised. Table 2 highlights how the barriers outlined may have a negative impact on competencies relating to PWPs' ability to: structure sessions and maintain appropriate pacing; manage obstacles

Table 2 Working alliance-related competencies for delivering cognitive–behavioural therapy (CBT) for depression and anxiety that may be negatively affected by the working alliance barriers identified in the current study

Perceived working alliance barriers	Therapist competencies[29] that may be at risk
Time intensive	Capacity to structure sessions and maintain appropriate pacing
Programme usability problems	Capacity to manage obstacles to cognitive–behavioural therapy (CBT)
Inflexible digital programme	Capacity to use clinical judgement when implementing treatment models
	Capacity to adapt interventions in response to patient feedback
	Sharing responsibility for session structure and content
Low confidence and practice	Ability to structure sessions
	Sharing responsibility for session structure and content
	Capacity to select and apply most appropriate behavioural therapy or CBT method
	Ability to engage a patient
	Ability to foster and maintain a good therapeutic alliance

to CBT therapy; use clinical judgement when implementing treatment models; adapt interventions in response to patient feedback; select and apply the most appropriate CBT method; and engage patients to foster and maintain a good therapeutic alliance.[29] Future research is required to directly evaluate these factors.

Strengths, limitations and future research

Although other studies have touched on the working alliance when exploring therapists' general experiences of implementing i-CBT, our study is the first to conduct a focused investigation of PWPs' experiences of the working alliance in a b-CBT intervention for depression, that delineates how the implementation of b-CBT can be used to strengthen the working alliance. A key methodological strength of our study involved adopting a guiding framework to understand the working alliance in b-CBT. Bordin's[10,11] conceptualisation of the working alliance and a more recent framework of the working alliance in b-CBT for depression[18] was used to ensure that barriers and facilitators were theoretically driven. Adopting two qualitative interview approaches (individual interviews and FGDs) enabled both in-depth analysis and opportunities to confirm shared insights in a group setting.[23]

Several limitations should be noted. Our sample (n = 13) was small owing to the limited number of PWPs meeting the inclusion criteria, the high number of PWPs leaving services before they were due to be interviewed (n = 7) and time constraints concerning data collection during the trial. The PWPs saw three patients on average, indicating little experience in delivering b-CBT prior to the interviews. Moreover, 40% of the PWPs had a bachelor's degree level of experience, and one PWP only had 12 months of experience, highlighting that some PWPs were at the low end of the experience spectrum. It is therefore possible that barriers pertaining to low confidence may have been resolved over time and with practice. Nevertheless, understanding short-term barriers could ensure that PWPs are effectively supported to use the full breadth of the digital programme's features. Two PWPs who took part in individual interviews were also later involved in FGDs, which may have affected the data generated in the FGDs. The emergence of COVID-19 might have resulted in PWPs becoming more familiar with and confident in using online therapeutic platforms, compared with when data collection took place (2015–2017). Only one type of digital programme and blended sequence was used in the study, which may have limited responses elicited on the working alliance. Taken together, these limitations may reduce the generalisability of our findings.

Despite these limitations, our findings appear to be sufficiently supported by studies using different digital programmes, delivery formats and mental healthcare professionals, thus lending greater confidence to our findings.[18,19,27,30,31] Future research should build on our study, to develop an implementation checklist that can be used to support services in optimising PWPs' experience in forming a working alliance.

Implications

The importance of the working alliance in psychotherapy appears to also extend to treatments that incorporate digital technologies.[32] 'Common elements of therapy', which encompass the working alliance, has been identified as a key research priority for digital technologies in mental healthcare.[9] With an increase in the use of digital technologies in mental healthcare, our findings may help PWPs and services navigate a hybrid format of delivery, to effectively harness and preserve a central mechanism of change in psychotherapy.

Our findings suggest that the working alliance in b-CBT can be enhanced in three ways. First, interventions and service workflows should align in terms of duration and frequency of sessions. Additional PWP duties in b-CBT (e.g. becoming familiar with the content of the programme, therapist portal activities such as sending messages to the patient or reviewing progress) should be considered when estimating the duration of the intervention, and the PWPs' overall case-loads should be taken into account to ensure that they are able to deliver the task effectively and leverage the full breadth of tools available on the programme to form a good working alliance. Second, the digital programme should offer trans- diagnostic tools and enable flexible and adaptable features (e.g. being able to choose the sequence and number of modules the patient completes) to enable the PWP to effectively tailor the interven- tion to their patient's needs. Third, PWPs should be provided with appropriate support in relation to the digital programme. As the use of digital tools in mental healthcare increases, so does the burden on the PWP, who will be required to learn how to operate multiple digital tools, manage patients' activities online and resolve technical problems. Wisniewski & Torous[33] have proposed a new role within care teams called 'digital navigators' to reduce the time pressure on PWPs. This is particularly important considering that numerous studies have reported high rates of stress and burnout among PWPs,[34,35] which can lead to PWPs' avoidance of the patient–therapist alliance.[36] The digital navigator's role would involve setting up the programme, troubleshooting technological problems, reviewing patient data and producing data summaries, to provide PWPs with additional sights and time to effectively form a working alliance.[33]

Asmae Doukani Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; Caroline Free, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; Ricardo Araya, Health Service and Population Research Department, King's College London, UK; Daniel Michelson School of Psychology, University of Sussex, Brighton, UK; Arlinda Cerga-Pashoja, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; Ritsuko Kakuma, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

Correspondence: Asmae Doukani. Email: asmae.doukani@lshtm.ac.uk

First received 26 Feb 2022, final revision 27 Jun 2022, accepted 28 Jun 2022

Acknowledgements

The authors thank the E-COMPARED trial for supporting this study and Jennifer Walke for facilitating the focus group discussions.

Supplementary material

Supplementary material is available online at http://doi.org/10.1192/bjo.2022.546.

Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author, A.D.

Author contributions

A.D. developed the concept of the work, with significant contributions from C.F. and R.A. A.D. designed the qualitative interviews with significant contributions from C.F., R.A. and A.C.-P. Individual interviews using topic guide 1 were collected by A.D. and focus group discussions using topic guide 2 were conducted by Jennifer Walke, with the assistance of A.D. A.D. led all aspects of data analysis; R.K. analysed a portion of the data independently, and C.F. supervised the initial coding stage of the analysis. The interpretation of data was conducted by A.D., overseen by R.K. and significantly contributed to by R.A., D.M. and C.F. A.D. prepared all iterations of the manuscript, with significant contributions from D.M., R.A., C.F., A.C.-P. and R.K.

Funding

This study was supported by the E-COMPARED trial, which was funded by the European Commission's Seventh Framework Programme (Health), grant agreement number 603098.

Declaration of interest

None.

References

1 Torous J, Jän Myrick K, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. *JMIR Ment Heal* 2020; 7(3): e18848.

2 Rodriguez-Villa E, Naslund J, Keshavan M, Patel V, Torous J. Making mental health more accessible in light of COVID-19: scalable digital health with digital navigators in low and middle-income countries. *Asian J Psychiatr* 2020; 54: 102433.

3 The King's Fund. *Mental Health Under Pressure (Briefing)*. The King's Fund, 2015.

4 Ben-Zeev D, Atkins DC. Bringing digital mental health to where it is needed most. *Nat Hum Behav* 2017; 1: 849–51.

5 Fairburn CG, Patel V. The impact of digital technology on psychological treatments and their dissemination. *Behav Res Ther* 2017; 88: 19–25.

6 Bockting CLH, Williams AD, Carswell K, Grech AE. The potential of low-intensity and online interventions for depression in low- and middle-income countries. *Glob Ment Health* 2016; 3: e25.

7 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(9): e306.

8 Torous J, Michalak EE, O'Brien HL. Digital health and engagement-looking behind the measures and methods. *JAMA Netw open* 2020; 3(7): e2010918.

9 Hollis C, Sampson S, Simons L, Bethan Davies E, Churchill R, Betton V, et al. Identifying research priorities for digital technology in mental health care: results of the James Lind Alliance Priority Setting Partnership. *Lancet Health Policy* 2018; 5: 845–54.

10 Bordin ES. The generalizability of the psychoanalytic concept of the working alliance. *Psychother Theory Res Pract* 1979; 16: 252–60.

11 Bordin ES. Theory and research on the therapeutic working alliance: new directions. In *The working alliance: Theory, Research, and Practice* (eds AO Horvath, S Greenberg Leslie): 13–37. John Wiley & Sons, 1994.

12 Lambert MJ. Psychotherapy outcome research: implications for integrative and eclectic therapists. In *Handbook of Psychotherapy Integration* (eds JC Norcross, MR Goldfried): 94–129. Basic Books, 1992.

13 Norcross JC, Wampold BE. Evidence-based therapy relationships: research conclusions and clinical practices. *Psychotherapy* 2011; 48: 98–102.

14 Cameron SK, Rodgers J, Dagnan D. The relationship between therapeutic alliance and clinical outcomes in cognitive behaviour therapy for adults with depression: a meta-analytic review. *Clin Psychol Psychother* 2018; 25: 446–56.

15 Vernmark K, Hesser H, Topooco N, Berger T, Riper H, Luuk L, et al. the working alliance as a predictor of change in depression during blended cognitive behaviour therapy. *Cogn Behav Ther* 2019; 48: 285–99.

16 Kooistra L, Ruwaard J, Wiersma J, van Oppen P, Riper H. Working alliance in blended versus face-to-face cognitive behavioral treatment for patients with depression in specialized mental health care. *J Clin Med* 2020; 9(2): 347.

17 Askjer S, Mathiasen K. The working alliance in blended versus face-to-face cognitive therapy for depression: a secondary analysis of a randomized controlled trial. *Internet Interv* 2021; 25:100404.

18 Doukani A, Free C, Michelson D, Araya R, Montero-Marin J, Smith S, et al. Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study. *BMJ Open* 2020; 10(9): e036299.

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: 150–64.

20 National Health Service. *Psychological Wellbeing Practitioner*. NHS, 2021 (https://www.healthcareers.nhs.uk/explore-roles/psychological-therapies/roles/psychological-wellbeing-practitioner [cited 7 Jan 2022]).

21 Shafran R, Myles-Hooton P, Bennett S, Öst LG. The concept and definition of low intensity cognitive behaviour therapy. *Behav Res Ther* 2021; 138: 103803.

22 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): 387.

23 Green J, Thorogood N. *Qualitative Methods for Health Research* (3rd edn). Sage, 2014.

24 QSR International Pty Ltd. *NVivo*. QSR International, 2020 (https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home).

25 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006; 3: 77–101.

26 O'Connor C, Joffe H. Intercoder reliability in qualitative research: debates and practical guidelines. *Int J Qual Meth* 2020; 19: 1–13.

27 Fiona D, Shepherd HL, Beatty L, Clark B, Butow P, Shaw J. Implementing web-based therapy in routine mental health care: systematic review of health professionals' perspectives. *J Med Internet Res* 2020; 22(7): e17362.

28 Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci* 2009; 4: 50.

29 Roth AD, Pilling S. Using an evidence-based methodology to identify the competences required to deliver effective cognitive and behavioural therapy for depression and anxiety disorders. *Behav Cogn Psychother* 2008; 36: 129–47.

30 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.

31 Hadjistavropoulos HD, Pugh NE, Hesser H, Andersson G. Therapeutic alliance in internet-delivered cognitive behaviour therapy for depression or generalized anxiety. *Clin Psychol Psychother* 2017; 24: 451–61.

32 Norcross JC, Lambert MJ. Psychotherapy relationships that work II. *Psychother Theory Res Pract Train* 2010; 48: 4–8.

33 Wisniewski H, Torous J. Digital navigators to implement smartphone and digital tools in care. *Acta Psychiatr Scand* 2020; 141: 350–5.

34 Owen J, Crouch-Read L, Smith M, Fisher P. Stress and burnout in Improving Access to Psychological Therapies (IAPT) trainees: a systematic review. *Cogn Behav Ther* 2021; 14: E20.

35 Westwood S, Morison L, Allt J, Holmes N. Predictors of emotional exhaustion, disengagement and burnout among improving access to psychological therapies (IAPT) practitioners. *J Ment Health* 2017; 26: 172–9.

36 Steel C, MacDonald J, Schröder T, Mellor-Clark J. Exhausted but not cynical: burnout in therapists working within improving access to psychological therapy services. *J Ment Health* 2015; 24: 33–7.

Chapter 6: Comparison of the working alliance in blended cognitive behavioural therapy and treatment as usual for depression in Europe: Secondary data analysis from the E-COMPARED randomized controlled trial (Paper 3)

6.1 Summary of chapter 5

In the previous chapter, I presented a host of factors that either facilitated or hindered the therapists' ability to foster a working alliance in b-CBT [48]. These factors were captured across four cross-cutting themes, relating to the therapists' experience of time in b-CBT, the functionality of the digital programme, their ability to tailor b-CBT, and their confidence in delivering b-CBT. Higher levels of each theme presented facilitators (i.e., extension of time, access to a wider toolkit, capacity to tailor components of b-CBT, and receiving appropriate training and support), while lower levels presented barriers (i.e., time / resource constraints, usability challenges, limited flexibility to tailor the digital programme to client needs, and a lack of confidence in delivering b-CBT).

6.2 Introduction to chapter 6

Paper 3 is the first of two quantitative papers evaluating the working alliance in a b-CBT intervention, that builds on the qualitative papers that provided a contextual and detailed account of the working alliance demands experienced by clients and therapists in a b-CBT context in the UK.

In this chapter, I present the third research paper that employed a secondary analysis of working alliance data collected across nine participating European country-sites of the E-COMPARED trial [23], to evaluate client ratings of the working alliance at 3-months post-randomisation follow-up assessments.

This paper reports the effects of treatment condition (i.e., b-CBT versus face-to-face CBT in treatment as usual for depression) on client working alliance scores. This study will also examine if client working alliance scores are associated with depression scores at 3-month assessments, in the b-CBT arm. Considering that the questionnaire used (i.e., working alliance inventory-short-revised-client) [16] was only designed to capture the alliance between the client and the therapist, and not the digital component in blended therapy, I undertook a preliminary and partial test of the framework adapted in Paper 1, that found that the digital programme impacted the working alliance through a set of unique demands that are specific to a b-CBT intervention (i.e., accessibility, interactivity, ease of use, aesthetic appeal, and

self-directed treatment), referred to as usability heuristics [47]. This paper will test one of the five categories called *ease of use* [47], using the system usability scale [148,205], that tested programme usability on the E-COMPARED trial. As such, this study will explore the influence of 'ease of use' on the client-outcome association [23].

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1407974	**Title**	Ms
First Name(s)	Asmae		
Surname/Family Name	Doukani		
Thesis Title	A mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy intervention for depression in a multinational randomised controlled trial in Europe		
Primary Supervisor	Dr Ritsuko Kakuma		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Medical Internet Journal
Please list the paper's authors in the intended authorship order:	Asmae Doukani, Matteo Quartagno, Francesco Sera, Caroline Free, Ritsuko Kakuma, Heleen Riper, Annet Kleiboer, Arlinda Cerga-Pashoja, Digna J.F. van Schaik,

]	Cristina Botella, Thomas Berger Karine Chevreul, Maria Matynia, Tobias Krieger, Jean-Baptiste Hazo, Stasja Draisma, Ingrid Titzler, Naira Topooco, Kim Mathiasen, Kristofer Vernmark, Antoine Urech, Gerhard Andersson, Anna Rogala, Rosa María Baños, Ricardo Araya,
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the concept of design for this paper. I led the acquisition of secondary data from the E-COMPARED study, which was supported by Professor Ricardo Araya (E-COMPARED Principle Investigator in the UK site), Professor Heleen Riper (E-COMPARED Chief Investigator), and Dr Annet Kleiboer (E-COMPARED trial Manager). I developed the analysis plan, conducted all statistical analyses and led data interpretation, which was reviewed and commented on by Dr Matteo Quartagno and Dr Francesco Sera. I produced the first draft of the manuscript for co-authors to review, and was responsible for addressing comments from co-authors. PhD supervisors and advisors provided guidance and feedback across all phases of the tasks described. All authors provided feedback on successive drafts and approved the final version ahead of submission.

SECTION E

Student Signature	[redacted]
Date	19/05/2023

Supervisor Signature	[redacted]
Date	26 May 2023

Original Paper

Authors' information

Asmae Doukani, M.Sc.
Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom.
(Asmae.doukani@lshtm.ac.uk)

Matteo Quartagno, PhD
MRC Clinical Trials Unit, Institute of Clinical Trials and Methodology, UCL, United Kingdom.
(m.quartagno@ucl.ac.uk)

Francesco Sera, PhD
Department of Statistics, Computer Science and Applications "G. Parenti", University of Florence, Florence, Italy.
(francesco.sera@unifi.it)

Caroline Free, PhD
Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine Keppel Street, London, United Kingdom.
(Caroline.Free@lshtm.ac.uk)

Ritsuko Kakuma, PhD
Faculty of Epidemiology and Population Health London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom.
(Ritsuko.Kakuma@lshtm.ac.uk)

Heleen Riper, PhD
Dept. of Psychiatry, Amsterdam University Medical Centre (VUmc), Amsterdam, the Netherlands.
(h.riper@vu.nl)

Annet Kleiboer, PhD
Department Clinical, Neuro, and Developmental Psychology, Vrije Universiteit Amsterdam, and Amsterdam Public Health Institute, Amsterdam, the Netherlands.
(a.m.kleiboer@vu.nl)

Arlinda Cerga-Pashoja, PhD

Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom.
(Arlinda.Cerga-Pashoja@lshtm.ac.uk)

Digna J.F. van Schaik, MD PhD
Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Psychiatry, Boelelaan 1117, Amsterdam, The Netherlands. GGZ inGeest Mental Health Care, Amsterdam the Netherlands
(a.vanschaik@ggzingeest.nl)

Cristina Botella, PhD
Department of Basic Psychology, Clinical and Psychobiology, Universitat Jaume I, Castellón de la Plana, Spain.
CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto Carlos III, Madrid, Spain.
(botella@uji.es)

Thomas Berger, PhD
Department of Clinical Psychology and Psychotherapy, University of Bern, Switzerland.
(thomas.berger@psy.unibe.ch)

Karine Chevreul, MD PhD
URC Eco Ile-de-France (AP-HP), Hotel Dieu, 1, Place du Parvis Notre Dame, 75004 Paris, France.
Eceve, Unit 1123, Inserm, University of Paris, Health Economics Research Unit, Assistance Publique-Hôpitaux de Paris, 75004 Paris, France.
(karine.chevreul@urc-eco.fr)

Maria Matynia, PhD
Faculty of Psychology, SWPS University of Social Sciences and Humanities, Warsaw, Poland.
(mszczepaniak@swps.edu.pl)

Tobias Krieger, PhD
Department of Clinical Psychology and Psychotherapy, University of Bern, Switzerland.
(tobias.krieger@psy.unibe.ch)

Jean-Baptiste Hazo, PhD
URC Eco Ile-de-France (AP-HP), Hotel Dieu, 1, Place du Parvis Notre Dame, 75004 Paris, France.
Eceve, Unit 1123, Inserm, University of Paris, Health Economics Research Unit, Assistance Publique-Hôpitaux de Paris, 75004 Paris, France.

(jean-baptiste.hazo@sante.gouv.fr)

Stasja Draisma, PhD
Department on Aging, Netherlands Institute of Mental Health and Addiction (Trimbos Institute), PO Box 725, 3500, AS Utrecht, the Netherlands
(SDraisma@trimbos.nl)

Ingrid Titzler, M.Sc.
Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.
(ingrid.titzler@fau.de)

Naira Topooco, PhD
Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden.
Department of Psychology, Uppsala University, Uppsala, Sweden
(naira.topooco@liu.se)

Kim Mathiasen, PhD
Department of Clinical Medicine, Faculty of Health Sciences, University of Southern Denmark, Denmark.
Centre for Tele-psychiatry, Mental Health Services of Southern Denmark, Denmark.
(kmathiasen@health.sdu.dk)

Kristofer Vernmark, PhD
Department of Behavioural Sciences and Learning, Linköping University, Linköping, Sweden
(kristofer.vernmark@liu.se)

Antoine Urech, PhD
Interdisciplinary Sleep-Wake-Epilepsy-Center and Swiss Sleep House Bern, Inselspital, Bern University Hospital, University of Bern & Department of Clinical Psychology and Psychotherapy, University of Bern, Switzerland.
(antoine.urech@insel.ch)

Anna Rogala, PhD
Faculty of Psychology, SWPS University of Social Sciences and Humanities, Warsaw, Poland.
(arogala1@swps.edu.pl)

Gerhard Andersson, PhD
Department of Behavioral Sciences and Learning, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden.
Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden.
(gerhard.andersson@liu.se)

Matthias Berking, MD PhD
Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Naegelsbachstrasse 25, 91052 Erlangen, Germany.
(matthias.berking@fau.de)

Rosa María Baños, PhD
Department of Personality, Evaluation and Psychological Treatments, Universidad de Valencia, Valencia, Spain.
CIBER Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto Carlos III, Madrid, Spain.
(rosa.banos@uv.es)

Ricardo Araya, PhD
Health Service and Population Research Department, King's College London, De Crespigny Park, London, SE5 8AF, United Kingdom.
(ricardo.araya@kcl.ac.uk)

Corresponding author
Asmae Doukani, MS.c.
Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom.
Email: Asmae.Doukani@lshtm.ac.uk
Telephone: +44(0)207 927 246

Type of paper
Original research

6.4 Abstract

Background: Increasing interest has centred on the psychotherapeutic working alliance as a means of understanding clinical change in digital mental health interventions in recent years. However, little is understood about how and to what extent a digital mental health programme can have an impact on the working alliance and clinical outcomes in a blended (therapist plus digital program) cognitive behavioural therapy (b-CBT) intervention for depression.

Objective: To test the difference in working alliance scores between b-CBT and face-to-face CBT in treatment-as-usual (TAU); examine association between working alliance and depression severity scores in both arms; and test for an interaction between system usability and working alliance, on the association between the working alliance and depression scores in b-CBT at 3-month post-randomisation.

Methods: A secondary analysis of a subset of a non-inferiority trial comparing different formats of b-CBT with TAU for adults with depression across nine European countries was conducted. Data were collected in primary care and specialised services across nine European countries between April 2015 and December 2017. Eligible participants were aged 18 years or older and diagnosed with major depressive disorder. Data were used from participants randomly allocated to b-CBT or TAU. b-CBT consisted of 6-20 sessions of b-CBT (involving face-to-face sessions with a therapist and an internet-based program). TAU consisted of usual care for depression. The main outcomes were scores on working alliance (measured by Working Alliance Inventory-Revised-Client (WAI-SR-C)); depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)), at 3-months. Other variables included system usability scores (System Usability Scale-Client (SUS-C)) at 3-months and demographic information collected at baseline. Data from baseline and 3-month assessments were analysed using linear regression models that adjusted for a set of baseline variables.

Results: All cases from the b-CBT arm (n=476), and only cases from five out of the nine country-sites that compared b-CBT (n=200) with face-to-face CBT in TAU (n=200) were used. Across all samples, participants were mostly female, middle-aged, and with a university degree or higher, with mean PHQ-9 scores reflecting depression of moderate severity. b-CBT was associated with higher composite WAI-SR-C scores compared to TAU (unstandardised coefficients beta [95% CI]: 2.63 [1.13 to 4.86]). Higher WAI-SR-C composite scores were associated with a significant decrease in PHQ-9 scores in b-CBT (e.g., composite scores: -0.12 [-0.17 to -0.06]). Finally, there was a significant interaction of SUS-C and WAI-SR-C, on an inverse association between higher WAI-SR-C scores and lower PHQ-9 scores in b-CBT (*b*= -0.030 [95% CI: -0.05 to -0.01], *P*=0.005]).

Conclusion and relevance: To our knowledge, this is the first study to show that b-CBT may enhance the client working alliance when compared to routine care for depression. The working alliance in b-CBT was also associated with clinical improvements, that appear to be enhanced by good programme usability. Our findings add further weight to the view that the addition of iCBT to face-to-face CBT, can positively augment experiences of the working alliance.

Trial registration: France: ClinicalTrials.gov NCT02542891. Registered on 4 September 2015; Germany: German Clinical Trials Register DRKS00006866. Registered on 2 December 2014; The Netherlands: Netherlands Trials Register NTR4962. Registered on 5 January 2015; Poland: ClinicalTrials.Gov NCT02389660. Registered on 18 February 2015; Spain: ClinicalTrials.gov NCT02361684. Registered on 8 January 2015; Sweden: ClinicalTrials.gov NCT02449447. Registered on 20 May 2015; Switzerland: ClinicalTrials.gov NCT02410616. Registered on 2 April 2015; United Kingdom: ISRCTN registry, ISRCTN12388725. Registered on 20 March 2015. Denmark: ClinicalTrials.gov NCT02796573. Registered 1st June 2016.

Keywords

Working alliance, therapeutic alliance, blended psychotherapy cognitive behavioural therapy, programme usability, usability heuristics, clinical trial, depression; mental health, digital interventions in mental health; psychotherapy and Europe.

6.5 Introduction

6.5.1 Background

Depression is one of the most significant contributors to the global burden of disease, affecting an estimated 264 million people globally [2,206]. Depression accounts for 7.2% of the overall burden of disease in Europe, costing an estimated €113,405 billion per year. However, 50% of people with major depression will go untreated [24]. High costs and suboptimal access to mental health care are among many reasons to foster digital mental health interventions (DMHIs), which promise greater quality of care and lower costs of delivery [22,207].

Evidence concerning the effectiveness of DMHIs has increased substantially over the past decade. Growing evidence indicates that internet-delivered cognitive behavioural therapy (iCBT) might be just as effective as face-to-face CBT for a range of mental health conditions, not least depression [31,117,125,208–212]. iCBT is delivered with varying degrees of support ranging from a stand-alone self-administered programme to a blended treatment with the active involvement of a therapist through regular face-to-face meetings [22]. Blended psychotherapies provide higher levels of therapist support compared to guided approaches that provide minimal or some guidance from a mental health practitioner [22]. Blended delivery has gained interest, with emerging evidence suggesting that such interventions can lead to improved adherence and treatment outcomes [44].

As interest in DMHIs has increased, considerable attention has centred around the concept of the client-therapist alliance of which there are many variations (i.e., therapeutic, working, helping, and so on) [37–40]. While different therapeutic approaches have historically failed to agree on a definition of the alliance, Bordin [6,7,131] proposed a pan-theoretical tripartite conceptualisation called the working alliance, that is characterised by three key dimensions including the emotional 'bond' between the client and the therapist, the agreement on the therapeutic 'goals', and the 'tasks' needed to advance the client's goals toward clinical improvement. This concept is particularly important because it has consistently predicted positive treatment outcomes for a range of psychological approaches, including CBT for depression [8,9,129].

The client-therapist alliance was identified as a key research priority for research policy and funding in digital technologies in mental health care, in a large consensus study involving people with lived experience of mental health problems/service-use, their carers, and mental health practitioners [38]. The integration of digital technologies in psychotherapy has led to changes in the way the alliance is conceptualised and captured [8], with variability depending on the type of DMHI (e.g., digital programme [132], avatar [134], or mobile application [133]).

6.5.2 Prior work

The literature on the client-therapist alliance has largely focused on addressing two key questions. First, do 'alliance' scores predict changes in clinical outcomes [36–40,213]. Second, and to a lesser extent, does the alliance vary between psychological therapies? Systematic reviews that have addressed these questions specifically in relation to interventions that are guided, adopt CBT [38], and/or target the treatment of depression [39], found that the working alliance can be established in guided DMHIs at a comparable level to face-to-face therapy [38], however the literature on the outcome-alliance relationship is mixed [38–40].

To this end, only three studies have examined the working alliance in b-CBT. The first study was an uncontrolled study in Sweden, which offered 4 face-to-face, and 10 iCBT sessions to a total of 73 participants in primary care services, which was part of the E-COMPARED study [41]. The Second study was conducted in the Netherlands, recruited 102 participants from specialist care-services. Participants were either randomized to b-CBT (n=47) that consisted of a 20-week intervention (10 face-to-face, and 10 online sessions) or a control condition (n=45) that consisted of 15-20 face-to-face CBT sessions (n=45) [42]. The third and most recent study was conducted in Denmark [43]. The study recruited a total of 76 participants that were either randomised to b-CBT (n=38) consisting of 6 face-to-face sessions that were alternated with 6-8 online modules of an internet-based program, or a control condition (n=38) consisting of 12 face-to-face CBT sessions [43]. Studies that included a control group did not find a significant difference in client working alliance scores between b-CBT and face-to-face CBT for depression [42,43]. Moreover, none of the studies found a significant association between client-rated working alliance and depression scores post-treatment [41–43]. However, the study conducted in Denmark showed that when client and therapist scores were pooled, higher working alliance ratings across both conditions was significantly associated with better treatment outcomes [43]. These findings may indicate the study was not powered enough to detect an association for client ratings in each treatment condition.

While research has mainly focused on measuring the alliance between the client and a human therapist, emerging qualitative research suggests that DMHIs may offer additional relational alliance benefits [34–36]. An example comes from a qualitative study that examined the working alliance demands in a b-CBT intervention for people with mild-to-moderate depression in the UK, on the E-COMPARED trial [23]. Qualitative data appeared to indicate that a potential fourth dimension called 'usability heuristics', uniquely promoted the working alliance in b-CBT. Usability heuristics defines the digital program's role in promoting active engagement, self-discovery, and autonomous problem-solving, with higher levels expected to enhance the quality of the working alliance. Features that promote 'usability heuristics' include digital technologies that: increase access and immediacy to the therapeutic task

(availability), appropriately respond to the client's input (interactivity), are easy to use, have aesthetic appeal and promote self-directed therapy [47]. Findings regarding usability heuristics and respective sub-categories were also found in another qualitative study that tested this framework in a Spanish sample of participants who either experienced self-guided or low-intensity supported iCBT [214]. It is therefore possible that experiences of digital programme features may influence the way that the working alliance is experienced in blended formats of CBT [47].

6.5.3 Aim and objectives

To our knowledge, we report the largest investigation of the working alliance in b-CBT for depression, using pooled data from nine country-sites involved in a pragmatic non-inferiority randomised controlled trial investigating the effectiveness of b-CBT for depression, when compared to treatment as usual (TAU) [23]. Further to this, our study will also explore if system usability, a newly conceptualised feature of the working alliance in b-CBT interacts with the working alliance and treatment outcome association [47]. Our primary objectives are to: test the difference in working alliance scores between b-CBT versus face-to-face CBT in TAU (objective 1), and determine if working alliance scores are associated with depression scores in b-CBT (objective 2). Our secondary objective is to test for an interaction between system usability and working alliance, on the association between the working alliance and depression scores in b-CBT (objective 3).

6.6 Methods

6.6.1 Study design and settings

We conducted a non-prespecified secondary analysis of a sub-set of data collected on the E-COMPARED study, a large European two-arm, non-inferiority randomised controlled trial investigating the effectiveness of b-CBT compared to TAU across nine European countries [23,45]. Data were collected between April 2015 and December 2017. Clients seeking treatment for depression were recruited, assessed, and treated across routine primary care in Germany, Poland, Spain, Sweden, and the United Kingdom (UK), and specialised mental health services in France, The Netherlands, Switzerland, and Denmark [215]. Following the start of recruitment, an additional satellite site was added in Denmark to boost recruitment [45]. The E-COMPARED trial was funded by the European Commission, FP7-Health-2013-Innovation-1 programme (grant agreement number: 603098) [23].

6.6.2 Participants

Recruitment procedures differed in each country, however all sites screened new clients seeking help for depression and that scored 5 or higher on the Patient Health Questionnaire-9 (PHQ-9) [23,106]. The study was explained to potential participants either face-to-face or over a telephone call. Clients who agreed to take part in the study were invited to an initial appointment to assess eligibility. The inclusion and exclusion criteria applied in all sites included [23], being aged ≥18 years and meeting diagnostic criteria for Major Depressive Disorder as confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.) version 5.0 [51]. The exclusion criteria included; high risk of suicide, psychiatric comorbidity (i.e., substance dependence, bipolar affective disorder, psychotic illness, or obsessive compulsive disorder) assessed during the M.I.N.I. interview; receiving psychological treatment for depression in primary or specialised mental health care at the point of recruitment; inability to comprehend the spoken and written language of the country-site; lacking access to a computer and/or to a fast internet connection (i.e., broadband or comparable), and; not having a smartphone or being unwilling to carry a smartphone if one was provided by the research team.

After baseline assessments, participants were randomised to one of two treatment arms, b-CBT and TAU using block randomisation, stratified by country [23]. All participants provided written informed consent before taking part in the trial. The trial was conducted in accordance with the Declaration of Helsinki and approved by all local ethics committees. Ethical approval to conduct a secondary analysis was obtained from London School of Hygiene and Tropical Medicine Research Ethics Committee on 7th October 2019 (Ethics Ref: 17852). For further information on the trial, including local ethical approvals and the randomisation process can be found in the see trial protocol by Kleiboer and colleagues [23].

6.6.3 Interventions: b-CBT and treatment as usual

6.6.3.1 b-CBT

b-CBT for depression consisted of integrating a digital programme (iCBT plus mobile application) to face-to-face CBT in one treatment protocol [216]. iCBT programs included four mandatory core modules of CBT (i.e., psychoeducation, behavioural activation, cognitive restructuring, and relapse prevention) plus optional modules (e.g., physical exercise and problem solving), that were typically completed at home, while face-to-face CBT was delivered in the clinic [23]. Clients worked through treatment modules, completed exercises, and monitored their symptoms using the digital program, while face-to-face sessions were used by the therapist to set-up modules, monitor client progress, and address client-specific needs. The sequencing and time spent on each module were flexibly applied,

providing the four mandatory modules were completed. It was not possible to blind therapists to treatment allocation; however, assessors were blinded [23,45].

Based on registered data, 194 therapists delivered trial interventions. In Germany, therapists only delivered b-CBT in the treatment arm, whereas therapists from the remaining eight country-sites delivered interventions across both treatment arms [23]. The risk of contamination was not perceived as a concern, as CBT was also offered in TAU and the focus of the trial was to investigate the blending of an internet-based CBT program with face-to-face CBT, when compared to routine care. Data on therapist ratings of the working alliance will be published in a separate paper to enable comprehensive reporting and discussion of the findings.

6.6.3.2 TAU

TAU included all possible interventions offered in usual care for depression, within the services recruited from, that consisted of a wide range of psychological and pharmacological interventions (See Table 6.1 for a breakdown of interventions offered by all country-sites) [23,41,217]. Information on the treatment and dosage received in TAU were not collected on the E-COMPARED trial. Due to the heterogeneity of interventions offered in the TAU group, a subset of data that only included country-sites that compared b-CBT with face-to-face CBT in the TAU arm (i.e., Denmark, France, Poland, Switzerland, and the UK) were used to investigate the effects of treatment conditions on working alliance scores. Using this subset of the population enabled the working alliance in b-CBT to be directly compared with a defined treatment comparator [218–220]. It should also be noted that b-CBT was not offered in the TAU arm by any of the country-sites. Data from the TAU arm was not used to explore the alliance-outcome association, as the heterogenic composition of TAU is likely to limit the reliability of the estimates generated.

Table 6.1. Overview of recruitment on the trial, b-CBT format and dosage, and treatments offered in TAU by country-site [23,45]

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
Country	Treatment setting	Recruitment procedure	Platform	Duration (weeks)	Online/ face-to face	[a]Sequencing	
France	Specialised mental health care	New or regular patients recruited by CBT therapists from 11 experts centres throughout France.	Moodbuster	16	8/8	Alternate	Face-to-face CBT
Germany	Primary care	Recruitment in the waiting room of GP clinics or during GP consultations.	Moodbuster	11-13	10/6	Alternate	[b]GP care (e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT)
Netherlands	Specialised mental health care	Recruited through mood disorder departments of three outpatient clinics in Amsterdam and Leiden.	Moodbuster	20	10/10	Alternate	[b]Face-to-face psychotherapy (mainly CBT, interpersonal psychotherapy, problem-solving therapy, antidepressant medication, or a combination of these).
Poland	Primary care	Recruited through primary care centres by CBT therapists (licenced and in training) in five major cities in Poland	Moodbuster	6-10	6/7	Alternate	Face-to-face CBT

Table 6.1. Overview of recruitment on the trial, b-CBT format and dosage, and treatments offered in TAU by country-site [23,45]

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
		(Warsaw, Sopot, Poznan, Katowice, and Wroclaw).					
Spain	Primary care	Recruitment through routine primary care from the Spanish National Health System in several cites (Valencia, Castellón, and Zamora).	Smiling is fun	10	8/3	1-4-1-4-2	[b]Prescribed medication by the GP and/or received face-to-face CBT, interpersonal psychotherapy or supportive therapy once a month
Sweden	Primary care	Recruitment through collaborating primary care clinics in three Swedish counties (Stockholm, Linköping, Västerås). Posters and leaflets were distributed in the waiting areas and/or were administered to GPs in clinics, who in turn referred potentially eligible participants.	Iterapi	10	6/4	Alternate	[b]Usual care paths in Sweden; including general practitioner care, e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT
Switzerland	Specialised mental health care	Recruitment through two outpatient clinics (Bern and Zurich) and individual therapists.	Deprexis	18	9/9	Alternate	Face-to-face CBT
United Kingdom	Primary care	Recruited through a primary mental health programme that delivers	Moodbuster	11	5/6	Alternate	Face-to-face CBT

Table 6.1. Overview of recruitment on the trial, b-CBT format and dosage, and treatments offered in TAU by country-site [23,45]

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
		psychological therapies to people with depression and anxiety disorders, in Northern and Southern England.					
Denmark	Specialised mental health care	Recruited through Centre for Telepsychiatry in specialised mental health care at the Mental Health Services of the Region of Southern Denmark, where patients are referred to the study by clinicians. Initially patients are self-referred to the Centre for Telepsychiatry.	NoDep	12	6-8/6	Alternate	Face-to-face CBT

Abbreviations: b-CBT, blended cognitive behavioural therapy; CBT, cognitive behavioural therapy; GP, general practitioner; NHS, National Health Service; TAU, treatment as usual.

[a]Sequencing of face-to-face and online can include more than one session per week for either component.

[b]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites.

6.6.4 Measures

6.6.4.1 Diagnostic

A diagnosis of Major Depression according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) was established at baseline using the M.I.N.I. [51], a structured diagnostic interview which has been translated into 65 languages and is used for both clinical and research practice. The interview compares well with the Structured Clinical Interview for DSM-IV disorders [221] and the Composite International Diagnostic Interview [51,221]. The M.I.N.I. interview was also used to assess comorbid disorders that were part of the exclusion criteria: substance dependence, bipolar affective disorder, psychotic illness, and obsessive-compulsive disorder. The M.I.N.I. was administered via telephone or face-to-face at baseline and 12-month follow-up assessments. Telephone administration of diagnostic interviews have shown good validity and reliability [222,223].

6.6.4.2 Outcomes measures

The study outcomes were the working alliance and depression severity, that were measured using the Working Alliance Inventory-Short Revised–Client (WAI-SR-C) [16], and the Patient Health Questionanire-9 [106], respectively. The WAI-SR-C scale is based on Bordin's [6,7] theory of working alliance containing three-item subscales assessing Bordin's [6], bond, task, and goals. The 12 items are rated on a scale of, 1=seldom to 5= always, with total scores ranging between 12-60. Higher scores on the scale indicate better working alliance. WAI-SR-C has demonstrated good reliability for all three factors, bond, task, and goals subscales (Cronbach's alpha = 0.92, 0.92, and 0.89, respectively) [19]. The scale has been correlated with other therapeutic alliance scales such as the California Therapeutic Alliance Rating System [8,156] and the Helping Alliance Questionnaire-II [8,157]. WAI-SR-C was only administered at 3-month post-randomisation assessments. Data for WAI-SR-C were not collected in the TAU arm of the Swedish country-site.

The PHQ-9 [106] was used to assess depression as the trial's primary clinical outcome. The PHQ-9 is a nine-item scale that can be used to screen and diagnose people for depressive disorders. The nine items are each scored on a 4-point scale between, 0=not at all to 3=nearly every day. Total scores range between 0–27, with higher scores indicating greater symptom severity. Depression severity can be grouped into the following: mild=0-5, moderate=6-10, moderately severe=11-15, and severe depression=16 and higher. The PHQ-9 has been shown to have good psychometric properties [106], and has demonstrated its utility as a valid diagnostic tool [224]. The PHQ-9 was administered at baseline, 3, 6 and 12-month assessments, however this study will only utilise baseline and 3-month assessments data as the study is interested in investigating depression scores that largely correspond with post-treatment.

6.6.4.3 Other variables

System Usability Scale-Client (SUS-C) [148,205] was used to assess the usability of the digital programs. The scale is a 10-item self-reported questionnaire. Items are measured on a 5-point scale ranging from 1=strongly disagree to 5=strongly agree. Total SUS-C scores range between 10–50 to produce a global score. Higher scores indicate better system usability. The total sum score has been found to be a valid and interpretable measure to assess the usability of internet-based interventions by professionals in mental health care settings [177]. The SUS has shown high internal reliability (e.g., coefficient Omega= 0.91), good concurrent validity and sensitivity [148,177]. The SUS-C was administered at 3-month follow-up assessments.

Demographic information on participants' gender, age, educational attainment, marital status, and country-site were collected at baseline assessments. Baseline variables that were used as covariates in the regression models included age, gender (i.e., male, female and other), marital status (i.e., single, divorced, widowed, living together, and married), and educational level (i.e., low, middle, and high, corresponding to secondary school education or equivalent [low], college or equivalent [middle], and university degree or higher [high], respectively) [23]. Baseline data were either completed, online, face-to-face, via telephone, or a combination of these approaches [23]. The 3-month follow-up assessments were largely completed online, with the exception of the PHQ-9 that was also collected via telephone to maximise data collection of the trial's primary outcome [23]. Data that was directly collected by researchers (i.e., either in person or telephone) was double entered to increase accuracy of the data entry-process. The number of sessions completed was not collected in TAU, or systematically collected in b-CBT.

6.6.5 Statistical analysis

The study used an intention to treat (ITT) population for the data analysis, including everyone that was randomised on the study, that may or may not have completed treatment [184]. While the ITT approach is standard for RCTs, some methodologists advise that a per-protocol population would be more suitable for pragmatic non-inferiority trials, due to concerns that a 'flawed trial' is likely to incorrectly demonstrate non-inferiority (e.g., a trial that loses the ability to distinguish any true differences between treatment groups that are present) [184]. However, contrary to the primary analysis in the E-COMPARED trial [23], we did not perform any non-inferiority tests in our analyses. We have therefore decided to use a pure ITT population, in order to maintain the original treatment group composition achieved after the random allocation of trial participants, therefore minimising confounding between the treatment groups and providing unbiased estimates of the treatment effects on the working alliance [184].

Data from the E-COMPARED trial was downloaded from a data repository. All analyses employed an intention-to-treat population, however due to the heterogeneity in the TAU arm, analyses investigating the treatment effects on the working alliance will only use a subset of the data that compared b-CBT with face-to-face CBT in TAU. Moreover, the association between the working alliance and depression will only be explored in the b-CBT arm of the trial. All models adjusted for baseline PHQ-9 scores, age, gender, marital status, educational attainment, and country-site. Analyses were performed on SPSS (version 26 or above) [225], STATA (version 16 or above) [226], and PROCESS Macro plug-in for SPSS (version 3.5 or above) [227]. Reported *P* values are 2-tailed with significance levels at $P \leq .05$.

Prior to accessing the dataset, a power analysis was calculated to estimate the sample size required to detect a significant effect of treatment condition on client working alliance scores. This calculation can be found in eMethods 1 in Appendix 17. As this analysis was explorative and cannot establish statistical generalisability [189,190], the findings of the power calculation will not be reported in the main text. Moreover, retrospective power calculations are not recommended for secondary data analyses since the sample size cannot be increased to address Type I and II errors [228].

6.6.5.1 Treatment assignment as a predictor for WAI-SR-C scores

In order to test if treatment assignment predicted WAI-SR-C (objective 1), a fixed effects linear regression model [229] was fitted separately for WAI-SR-C composite and subscale scores (i.e., goals, task and bond). This analysis only included a subset of data from countries (n=5) that compared b-CBT with face-to-face CBT (i.e., Denmark, France, Poland, Switzerland, and the UK). Four models were fitted altogether.

6.6.5.2 Association between post-treatment PHQ-9 scores and WAI-SR-C scores

To determine if WAI-SR-C scores were associated with PHQ-9 scores at 3-month assessments (objective 2), a fixed effects linear regression model was fitted to investigate the alliance-outcome association in the b-CBT arm, using data from all nine trial country-sites. The model was fitted separately for WAI-SR-C composite and subscale scores. Eight models were fitted altogether.

6.6.5.3 Testing the interaction between WAI-SR-C and SUS-C on the relationship between WAI-SR-C and PHQ-9

To test if an interaction between SUS-C and WAI-SR-C, in a model examining the association between WAI-SR-C and PHQ-9 at 3-month assessments, a multiple regression model was fitted separately for WAI-SR-C composite and subscale scores, to estimate the size of the interaction, in the b-CBT arm, using data from all trial country-sites (n=9). Four models were fitted altogether.

6.6.6 Missing data

Multiple imputation was used to handle high levels of missing data, under the missing at random (MAR) assumption. In particular, out of a possible 943 cases, 36.6% (n=345) of data were missing for the PHQ-9, 20.7% (n=195) for WAI-SR-C, and 27.7% (n=133/476) for SUS-C, at 3-month assessments. We imputed datasets using the chained equation approach [178]. Tabulations of missing data across treatment condition and country-sites are presented in eMethods 2, Appendix 18. Chi-square results showing differences in missing and complete data between E-COMPARED country-sites are presented in eMethods 3 in Appendix 17. In the imputation model we included all variables that were part of the analyses, including observations from the PHQ-9 at baseline and demographic variables. To account for the interaction term in the regression model, data were imputed using the just another variable (JAV) approach [179]. Multiple imputation was performed separately for b-CBT and TAU, to allow for condition specific variables to be considered. For example, the SUS-C variable was only entered in the b-CBT arm, as participants allocated to TAU did not use a digital program.

6.6.7 Post-hoc analysis

Post-hoc sensitivity analyses were conducted to examine if the multiple imputation approach that was used to handle missing data, results in different conclusions when compared to a complete case analysis under the MAR assumption. Consistent findings between the primary analysis and sensitivity analysis can strengthen the reliability of the findings [180–183], at least in situations where both the primary and sensitivity analyses are expected to be valid under similar assumptions (e.g. multiple imputation and complete case analysis under MAR in the outcome variable only). The sensitivity analysis will replicate the main analysis using unimputed data.

A sub-group analysis was conducted to explore the magnitude of treatment effects on the working alliance when using a subset of the sample, that compared b-CBT, with face-to-face CBT offered in the TAU arm in Denmark, France, Poland, Switzerland, and the UK. The sub-analysis will replicate the main analysis using only five country-sites in relation to: (a) exploring the working alliance and treatment outcome association, and (b) testing the interaction between working alliance on system usability on the relationship between the working alliance and depression scores. This will enable a comparison between the primary analysis that included all 9 country-sites in the b-CBT arm, with the 5 country-sites that compared b-CBT with face-to-face CBT in TAU [218–220].

6.7 Results

6.7.1 Clinical and demographic characteristics

Table 6.2 summarises the baseline characteristics of client participants on the E-COMPARED trial. There were 943 participants consented and randomised to the trial (b-CBT=476 and TAU=467). The trial profile is included in eFigure 1 in Appendix 17. This study will use all cases from the b-CBT arm (n=476), and cases from five country-sites that compared b-CBT with face-to-face CBT in TAU (n=200), with different analyses drawing on different samples (please see Section 6.6.5 for further clarifications). The subset of data appears to have similar participant characteristics to the full sample (see Table 6.2), in which participants were mostly female, middle-aged, and with a university degree or higher and with mean PHQ-9 scores reflecting depression of moderate severity. Post-treatment PHQ-9 scores at 3-months will be reported in the main trial paper which is being prepared. In the full b-CBT group sample, mean WAI-SR-C scores at 3-month assessments was 47.09 (SD=7.65), and Mean SUS was 40.89 (SD=6.63) in b-CBT. In the sub-sample that only included sites that compared b-CBT with face-to-face CBT, mean WAI-SR-C was 46.83 (SD=7.73) in b-CBT, and 44.22 (SD=7.57) in face-to-face CBT in TAU. See Appendix 17 for the mean and SD of WAI-SR-C and SUS-C scores across treatment groups, for the full trial and sub-group samples. eResults Table 7 in Appendix 17 includes the mean and standard deviations (SD) of WAI-SR-C and SUS-C scores by country-site for the full trial sample and sub-group sample.

Table 6.2. Baseline characteristics of participants for the full (n=9 country-sites) and subgroup samples (n=5 country-sites). Figures are numbers (percentages) of participants unless otherwise indicated

	Full trial sample			Sub-group sample		
Characteristic at baseline	b-CBT (n=476)	TAU [d] (n=467)	Total (n=943)	b-CBT (n=200)	TAU (n=200)	Total (n= 400)
Mean (SD) min-max, age in years	39.03 (13.10) 18-74	38.73 (13.07) 18-78	38.97 (13.08) 18-78	39.48 (12.99)	38.82 (12.99)	39.15 (12.99)
Gender (Female), n (%)	318 (67)	326 (70)	644 (68)	135 (68)	135 (68)	270 (68)
Marital status						
Single	159 (33)	155 (33)	314 (33)	73 (37)	75 (38)	148 (37)
Divorced	60 (13)	43 (9)	103 (11)	28 (14)	20 (10)	48 (12)
Widowed	3 (1)	6 (1)	9 (1)	0	2 (1.0)	2 (0.5)
Living together	95 (20)	111 (24)	206 (22)	39 (20)	41 (21)	80 (20)
Married	159 (33)	152 (33)	311 (33)	60 (30)	62 (31)	122 (31)
Level of education[a]						
Secondary School, equivalent	72 (15)	74 (16)	146 (16)	32 (16)	34 (17)	66 (17)
College, equivalent	179 (38)	170 (36)	349 (37)	81 (41)	65 (33)	146 (37)
University degree or higher	225 (47)	222 (48)	447 (47)	87 (44)	101 (51)	188 (47)
Country-site (n=943)[b]						
Germany	86 (18)	87 (19)	173 (18)	n/a	n/a	n/a
Sweden	73 (15)	68 (15)	141 (15)	n/a	n/a	n/a
Netherlands	53 (11)	49 (11)	102 (11)	n/a	n/a	n/a

Table 6.2. Baseline characteristics of participants for the full (n=9 country-sites) and subgroup samples (n=5 country-sites). Figures are numbers (percentages) of participants unless otherwise indicated

	Full trial sample			Sub-group sample		
Characteristic at baseline	b-CBT (n=476)	TAU [d] (n=467)	Total (n=943)	b-CBT (n=200)	TAU (n=200)	Total (n= 400)
UK	49 (10)	52 (11)	101 (11)	49 (10)	52 (11)	101 (11)
Spain	64 (13)	63 (14)	127 (14)	n/a	n/a	n/a
France	51 (11)	54 (12)	105 (11)	51 (11)	54 (12)	105 (11)
Switzerland	26 (6)	24 (5)	50 (5)	26 (6)	24 (5)	50 (5)
Poland	42 (9)	42 (9)	84 (9)	42 (9)	42 (9)	84 (9)
Denmark	32 (7)	28 (6.0)	60 (6)	32 (7)	28 (6.0)	60 (6.)
Mean (SD) and min-max of baseline PHQ-9 scores[c]	15.35(4.89) 4-27	15.38 (4.65) 5-26	15.36 (4.77) 4- 27	15.38 (4.95)	15.33 (4.68)	15.38 (4.95)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; PHQ-9, patient health questionnaire-9; SD, standard deviation; TAU, treatment as usual.

[a]Data collected was in respect to what would be considered low, middle, and high level of education in each setting. Data was missing for n=1/ 943 (0.2%) in the b-CBT arm.

[b]Self-reported country of birth can be found in eTable 1 eMethods 2

[c] PHQ-9 severity cut-off points are: 5-9 indicate mild depression, 1-14 for moderate depression, 15-19 moderately severe depression, and ≥ 20 for severe depression [106].

[d]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites. Data for the full TAU sample is summarised to enable comparison between full and subset trial samples.

Table 6.3. Mean (SD) WAI-SR-C composite and subscale scores and SUS-C scores collected at 3-month assessments for the full trial sample (n=9 country-sites) and subgroup sample (n=5 country-sites) in b-CBT and TAU

	Full trial sample			Subgroup sample		
Scales	b-CBT (n=476)	TAU (n=467)	Total (n=943)	b-CBT (n=200)	TAU[a] (n=200)	Total (n=400)
WAI-SR-C						
Composite	47.09 (7.65)	41.55 (9.66)	44.56 (9.05)	46.83 (7.73)	44.22 (7.57)	45.52 (7.75)
Goals	16.14 (2.93)	13.81 (3.72)	15.09 (3.51)	15.83 (2.98)	14.49 (3.02)	15.16 (3.07)
Task	14.39 (3.05)	12.52 (3.86)	13.54 (3.56)	14.76 (2.87)	14.18 (2.98)	14.47 (2.94)
Bond	16.56 (2.97)	15.21 (3.51)	15.94 (3.29)	16.24 (3.03)	15.55. (2.82)	15.89 (2.95)
SUS-C	42 (9)	n/a	40.89 (6.63)	40.34 (6.84)	n/a	40.34 (6.84)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; PHQ-9, patient health questionnaire-9; SUS-C, system usability scale-client; TAU, treatment as usual; WAI-SR-C, working alliance inventory-short revised-client.

[a]In the subgroup sample, TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites. Data for the full TAU sample is summarised to enable comparison between full and subset trial samples.

6.7.2 Treatment assignment as a predictor for WAI-SR-C scores

Treatment assignment significantly predicted WAI-SR-C composite, goals, task and bond scores (n=5 country-sites). Being allocated to b-CBT was related to higher WAI-SR-C composite and all subscale scores at 3-month follow-up assessments, when compared to participants receiving face-to-face CBT in TAU. See Table 6.4 for model summaries.

Table 6.4. Adjusted linear regression models of treatment assignment as a predictor for WAI-SR-C. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-C (outcome)	*B* (95% CI)	*P V*alue
Composite	2.63 (1.13 to 4.12)	.001
Goals	1.36 (0.79 to 1.94)	<.001
Task	0.63 (0.07 to 1.18)	.028
Bond	0.64 (0.07 to 1.21)	.029

Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short-revised client.

6.7.3 Association between post-treatment PHQ-9 scores and WAI-SR-C scores

In b-CBT (n=9 country-sites), WAI-SR-C composite, goals, and task subscales scores were significantly associated with post-treatment PHQ-9 scores, in which lower PHQ-9 scores were associated with higher WAI-SR-C composite, goals and task scores. However, WAI-SR-C bond scores were not significantly associated with PHQ-9 scores (See Table 6.5 for model summaries).

Table 6.5 Adjusted linear models of association between post-treatment PHQ-9 and WAI-SR-C scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-C (outcome)[a]	*B* (95% CI)	*P* value
Composite	-0.12 (-0.17 to -0.06)	<.001
Goals	-0.26 (-0.41 to -0.11)	.001
Task	-0.38 (-0.52 to -0.24)	<.001
Bond	-0.13 (-0.27 to 0.02)	.095

Abbreviations*:* 95% CI, 95% confidence intervals; *B*, unstandardized beta; b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client.

[a]Separate models were generated for WAI-SR-C composite and subscale scores (i.e., goals, task, and bond).

6.7.4 Testing the interaction between WAI-SR-C and SUS-C on the relationship between WAI-SR-C and PHQ-9

In b-CBT (n=9 country-sites), there was a significant interaction between WAI-SR-C and SUS-C on the association between WAI-SR-C composite scores and PHQ-9 scores at 3-months (*b*=-0.01 [95% CI: -0.01 to -0.00], *P*=0.03), as were models with the goals (*b*=-0.021 [95% CI: -0.04 to -0.00], *P* =0.03) and task (*b*=-0.02 [95% CI:-0.05 to -0.01], *P* =0.003) subscales, but not for the bond subscale (*b*=-0.01, [CI 95:-0.03 to 0.01], *P*=0.30). See *Figure 6.1* for multiple line graphs of the interactions described.

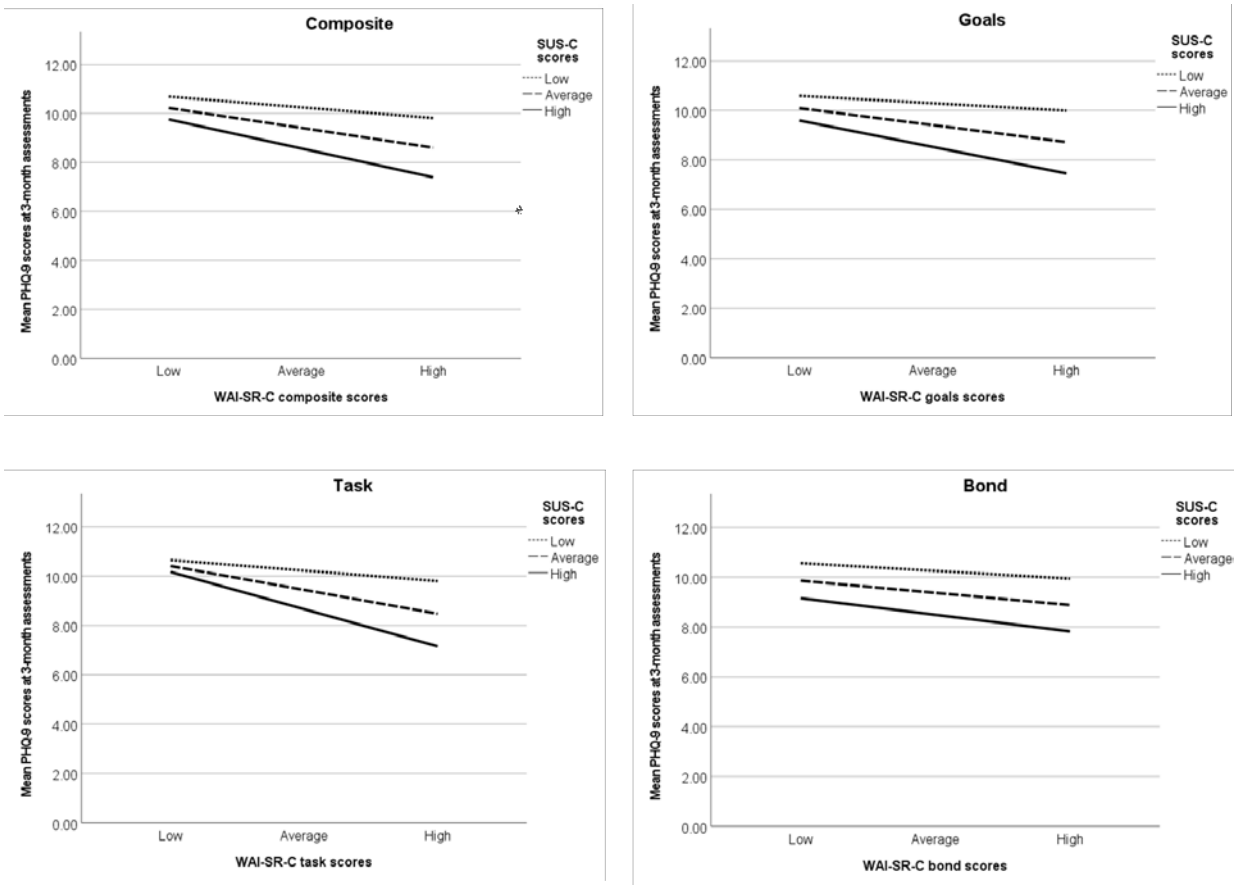


Figure 6.1. Multiple line graphs of the interaction between SUS-C and WAI-SR-C on the association between WAI-SR-C composite and subscale scores (goals, task, bond) and PHQ-9 scores at 3-month assessments in b-CBT

Legend: PHQ-9, patient health questionnaire-9; SUS-C, system usability scale-client; WAI-SR-C, working alliance inventory-short revised-client.

6.7.5 Sensitivity and subgroup results

The results from the sensitivity and sub-analyses aligned with the main results in respect to the alliance-outcome association, which were significant. A detailed breakdown of the findings is summarised below. Descriptive data for model summaries can be found in Appendix 17.

6.7.5.1 Sensitivity analysis

Post-hoc sensitivity analyses were conducted to examine if the multiple imputation approach that was used to handle missing data, results in different conclusions when compared to a complete case analysis.

Treatment assignment did not significantly predict WAI-SR-C (n=5 country-sites) for composite scores (*b* = -0.67 [95% CI: -1.69 to 3.03], *P*=.58), goals (*b* = -0.57 [95% CI: -0.30 to 1.44], *P*=.20), task (*b* = -0.06 [95% CI, 0.76 to 0.91], *P*=.89) and bond (*b* = -0.02 [95% CI: -0.90 to 0.86], *P*=.96) subscale scores.

In the b-CBT arm (n=9 country-sites), the association between PHQ-9 and WAI-SR-C composite scores was significant (*b* = -0.12 [95% CI: -0.18 to -0.05], *P*=. 001). Models with goals (*b* = -0.27 [95% CI: -0.45 to -0.09], *P*=.004), task (*b* = -0.39 [95% CI: -0.55 to -0.22], *P*=.001), and bond (*b* = -0.22 [95% CI: 95: -0.40 to -0.34], *P*=.02) were also significant. These models indicate that as WAI-SR-C increased, PHQ-9 scores at 3-month assessments decreased.

In the b-CBT arm (n=9 country-sites) the association between WAI-SR-C composite scores and PHQ-9 scores did not appear to be moderated by SUS (*b* = -0.06 [95% CI: -0.06 to 0.00], *P* = 0.18). Moreover, no significant interactions were observed for the goals (*b* = -0.02, [95% CI: -0.05 to 0.01], *P* = .18), task (*b* = -0.02 [95% CI: -0.05 to 0.05], *P* = .10) and the bond (*b* = -0.01 [95% CI: -0.04 to 0.01], *P* = 0.27) subscale scores.

Subgroup analysis

A sub-group analysis was conducted to explore the magnitude of treatment effects on the working alliance when using a subset of the sample, that compared b-CBT, with face-to-face CBT offered in the TAU arm in Denmark, France, Poland, Switzerland, and the UK.

In the b-CBT arm (n=5 country-sites), the association between PHQ-9 and working alliance composite scores was significant (*b* = -0.16 [95% CI: -0.25 to -0.07], *P*=. 001). Models with the goals (*b* = -0.33, [95% CI: -0.57 to -0.10], *P*=.006), task, (*b* = -0.45 [95% CI: -0.69 to -0.21], *P*=.001), and bond (*b* = -0.22 [95% CI: -0.40 to -0.34], *P*=.006) subscale scores were also significant.

In the b-CBT arm (n=5 country-sites), the association between WAI-SR-C composite scores and PHQ-9 scores does not seem to be moderated by SUS (*b* = -0.06 [95% CI: -0.06 to 0.00], *P* = .18]. Moreover, no significant interactions were observed for the goals (*b* = -0.019 [95% CI: -0.05 to 0.01], *P* = .18),

task (b = -0.02 [95% CI: -0.05 to 0.05], P = 0.10) and bond (b = -0.01 [95% CI: -0.04 to 0.01], P = 0.27) subscale scores.

6.8 Discussion

6.8.1 Principle Results

This study investigated the client-rated working alliance in a b-CBT intervention for depression and when compared to TAU [23]. Overall, our study found that treatment allocation (i.e., b-CBT versus face-to-face CBT in TAU) was a significant predictor of working alliance scores, in which working alliance scores (i.e., composite scores and the goals, task, and bond subscales scores) were higher in b-CBT compared to TAU. The working alliance was significantly associated with treatment outcomes in b-CBT. As depression scores decreased, working alliance scores increased for composite scores, goals, and task subscale scores but not for bond subscale scores. Finally, there was a significant interaction between average, and above average system usability and higher working alliance (i.e., composite, goals, task, but not the bond subscales) scores when examining the relationship between posttreatment working alliance and depression scores.

6.8.2 Limitations

Several study limitations should be noted. First, working alliance data was collected at a single point at 3-month assessments that corresponds with post-treatment. While this is common in clinical trials [37,229], the measurement of the alliance is recommended early, within the first five sessions, and at different points across treatment [13,230–232]. However, the number of face-to-face sessions varied between the nine country-sites (e.g., 5 to 10 sessions), which would have posed significant challenges for the systematic data collection required in a clinical trial [184]. Second, the study engages in multiple comparison, which may increase the risk of type 1 error, that a positive result may be due to chance. However, given the exploratory nature of this analysis and that different outcomes are likely to be highly correlated, a multiple adjustment comparison was not deemed necessary [233]. Third, the results of the analysis are valid under the MAR assumption, which we believe to be plausible because the effect of country-site appears to affect missingness of the main outcome variables. This is supported by chi-squared test that indicate significantly higher rates of missing data for the PHQ-9 and WAI-SR-C across some country-sites compared to others. Nevertheless, it should be noted that this paper cannot rule out that data is missing not at random. It is therefore important to acknowledge that any missing data is a source of bias, and the method adopted to address missing data will rely on assumptions that cannot be tested. The quantitative results from my thesis should be interpreted with caution, and future research

may conduct a sensitivity analysis to differentiate between MAR and missing not at random or replicate and verify our findings [179]. Future research can explore this further using a sensitivity analysis in a separate paper. Fifth, the heterogeneity of interventions offered in the full TAU group limited the study from conclusively tying causation to a specific comparator intervention. As a result, this study used a subset of trial country-sites that only offered face-to-face CBT in TAU. The sixth limitation relates to variations in the way the b-CBT arm was delivered across the trial's country-sites in relation to the number of sessions offered across each site, and the type of iCBT interventions delivered. The b-CBT arm was focused on investigating the non-inferiority of blended CBT, given that there is a sufficient level of evidence concerning other treatment components such as the CBT approach, and different delivery formats, including in-person delivery and internet-based platforms [33,234]. Although the number of treatment sessions varied between settings, to our knowledge there is no evidence to suggest that the number of sessions of CBT impacts the client-therapist alliance as the alliance is typically developed early in treatment and within the first five sessions [13,230–232]. Moreover, another study exploring usage of different components of b-CBT and treatment engagement, when compared to intended use on the E-COMPARED study concluded that personalised blended care was more suitable compared to attempting to achieve a standardised optimal blend [235]. Variations in the number of treatment sessions may therefore enable a pragmatic understanding of the working alliance in real world clinical settings [219]. However, as data concerning the treatment type and dosage was not collected, it is not clear, if and how many, face-to-face CBT sessions were received by clients in TAU. Attending fewer sessions than needed to develop an effective working alliance may have limited opportunities for clients and therapists to effectively develop a good working alliance, which may in turn negatively impact treatment outcomes in TAU.

6.8.3 Comparison with prior work

To our knowledge our study is the first to report that working alliance, composite, and all subscale scores, were higher in b-CBT compared to face-to-face CBT in TAU. These findings indicate that a blended approach may offer additional alliance building benefits, when compared to face-to-face CBT. A possible explanation for our findings is that the digital elements of the intervention may enable better definition and coverage of the goals and the task than what might be possible in face-to-face sessions alone [48]. A study exploring program usage across four country-sites of the E-COMPARED study found that clients received an average of 10 messages from their therapist online [235]. Features of the digital programme that enabled the client to receive contact from their therapist away from the clinic may therefore play a role in increasing the availability of the therapist and enhance opportunities to further strengthen the working alliance.

Further support for our findings come from a qualitative study that examined the working alliance in b-CBT, in the UK country-site of the E-COMPARED trial, that found participants preferred blended CBT compared to face-to-face CBT alone [47]. The 'immediacy' of access to the therapeutic task was reported to enhance their engagement with the intervention and provide a higher sense of control and independence. The digital programme was also described as a 'secure-base' that allowed participants to progressively explore self-directed treatment [47]. Similarly, a qualitative study from the German country-site of the E-COMPARED study found that b-CBT was perceived to strengthened client self-management and autonomy in relation to place and location [137].

Our study appears to be the first to find a significant association between lower depression scores and higher working alliance composite scores, goals, task, but not the bond subscale scores in the b-CBT group. In alignment with our findings, a narrative review of the working alliance in online therapy found most guided iCBT studies showed significant associations between treatment outcomes and the task and goals subscale scores, but not for the bond subscale [40]. A possible explanation could be that the bond is experienced differently in b-CBT compared to traditional formats of CBT, however further research is needed to investigate this [40]. Edward Bordin's [6,7], conceptualisation of the working alliance suggests that while his pan-theoretical theory allows for the basic measurement of the goals, task and bond to produce beneficial therapeutic change, the ideal alliance profile is likely to be different across therapeutic approaches and interventions [6,7,9].

Our finding that average and high system usability may strengthen working alliance, especially the task, may suggest that digital programs have the potential to influence the working alliance. This is not surprising given that CBT activities (e.g., content, exercises) were primarily completed on the iCBT programme and may indicate its relevance in the building of the working alliance, in supporting the task within a capacity that is potentially parallel to the bond. These findings partially test and support a conceptual framework of the working alliance that incorporates features that are derived from the digital program within a blended setting, called 'digital heuristics' (i.e., the promotion of active engagement and autonomous problem solving) in which 'ease of use' and 'interactivity' were identified as key features for optimizing 'active engagement' with the task on the iCBT program [47]. These qualitative findings were mirrored in another study that tested this framework, in which digital heuristics emerged as a fourth dimension when examining the working alliance in self-guided and low-intensity supported iCBT for depression [214]. High and low iCBT programme functionality was also identified by therapists as either a facilitator or a barrier (respectively) in the implementation and building of the working alliance in b-CBT, in the German and UK country-sites of the E-COMPARED study, respectively [47,137,236,237]. Although, our findings remain preliminary and do not show a causal effect. Exploring the role of the digital programme on the working alliance may be a fruitful direction for future research.

The sample in this study was largely well educated, a trend that has also been found in other iCBT trials in Europe [238,239]. To my knowledge, there is no evidence to suggest that educational level impacts the working alliance in supported iCBT [8,118], however, higher levels of education have been widely associated with better engagement to iCBT programs [194,195,200,201]. For example, a study that explored user engagement to an iCBT program found that people with a higher level of education had significantly higher compliance (54.2%), compared to non-compliance (36.5%) to the iCBT program [235]. While compliance is not a measure of the working alliance, these concepts are interlinked [135], warranting future research to explore if educational attainment impacts the working alliance in a b-CBT intervention for depression. To address this potential effect, all models controlled for educational level to reduce bias [202].

Collectively our findings suggest that blending face-to-face CBT with an iCBT programme may enhance the working alliance and treatment outcomes for depression when compared to face-to-face CBT. These findings hold important implications for clinical practice, especially following the COVID-19 pandemic that resulted in major shifts from in-person care to blended healthcare provision [26]. The findings of this study suggest that a blended approach may enhance rather than worsen mental health care. Our study's findings regarding the interaction between system usability and the working alliance, on treatment outcomes is a preliminary step to quantitively understand the role of the digital program, in how the working alliance is experienced in b-CBT. While further research is required to explore digital taxonomies that contribute towards fostering the working alliance in b-CBT, our findings build on previous qualitative research [35,36,47,48] to explore a conceptualization of the working alliance that goes beyond the client and the therapist, to consider the role of the digital program. The impact of the digital programme on the working alliance may support the case of employing digital navigators who can help clients use the intervention and troubleshoot technology and programme usability issues, and remove the added burden of managing programme related problems, that would otherwise fall on the therapist [137,237,240].

We propose four directions for future research. First, further research is required to build a comprehensive understanding of what, how and when digital features (e.g., usage, interface, interactivity, and accessibility) influence the working alliance [47]. Second, psychometric scales measuring the working alliance in b-CBT should be adapted or developed to conceptually reflect a construct that also incorporates the client-programme working alliance [217]. Third, the working alliance should be investigated early in the intervention and across multiple stages of treatment [232]. Fourth, future research should investigate if our results can be replicated across different DMHIs and treatment dosages.

6.8.4 Conclusions

To our knowledge, this is the first study to show that b-CBT may enhance the working alliance when compared to face-to-face CBT in routine care. The working alliance in b-CBT was also associated with clinical improvements, that may be enhanced by good program usability. Our findings appear to add further weight to the view that the addition of iCBT to face-to-face CBT, can positively augment experiences of the working alliance.

Acknowledgements

Ms Doukani had full access to all of the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Concept of design: Doukani with significant contributions from Matteo, Sera, Araya and Free.

Drafting of the manuscript: Doukani

Critical revision of the manuscript for important intellectual content: Doukani with significant contributions from Araya, Quartagno, Sera, Free, Kakuma, Riper, Kleiboer, Cerga-Pashoja, van Schaik, Botella, Berger, Chevreul, Matynia, Krieger, Hazo, Draisma, Titzler, Topooco, Mathiasen, Vernmark, Urech, Rogala Andersson, Berking and Baños.

Data collection, acquisition, analysis, or interpretation of data: Data were collected by all nine E-COMPARED country-sites represented by co-authors**.** Data acquisition, analysis, interpretation, was led by Doukani with significant contributions from Quartagno, Araya, Riper, Sera, Kleiboer, Kakuma, Free, Cerga-Pashoja, and Draisma.

Statistical analysis: Doukani

Administrative, technical, or material support: Riper, Draisma, Kleiboer, Berking and Cerga-Pashoja.

Supervision/ of study: Doukani, Araya, Quartagno, Sera, Kakuma and Free,

Conflict of interest disclosures

None declared.

Abbreviations

B: unstandardized beta

b-CBT: blended cognitive behavioural therapy intervention

CBT: cognitive behavioural therapy

DMHIs: digital mental health interventions

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV

E-COMPARED: European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual

ITT: intention to treat

JAV: just another variable

MAR: missing at random

M.I.N.I.: MINI International Neuropsychiatric Interview

PHQ-9: patient health questionnaire-9

SUS-C: system usability scale-client

TAU: treatment-as-usual

WAI-SR-C: working inventory-short revised-client

Chapter 7: Comparison of the therapist-rated working alliance in a blended cognitive behavioural therapy intervention for depression: A secondary data analysis from a multi-site randomised controlled trial in Europe (paper 4)

7.1 Summary of chapter 6

In the last chapter, I presented a secondary analysis of pooled data of 945 client participants from nine trial country-sites of the E-COMPARED trial, which revealed that working alliance ratings were significantly higher in blended cognitive behavioural therapy (b-CBT) compared to face-to-face cognitive behavioural therapy (CBT) in treatment as usual (TAU). I also found that working alliance scores were associated with lower post-treatment depression scores in b-CBT. Finally, a significant interaction of client system usability and working alliance scores was found, on the association between higher working alliance scores and lower depression scores in b-CBT [105].

7.2 Introduction to chapter 7

In this chapter I present the findings of a secondary analysis of working alliance data collected on the E-COMPARED trial [23] that follows the same research questions as paper 3, but focuses on therapist ratings of the working alliance, using the working alliance inventory-short-revised-therapist [145] at 3-month follow-up assessments post-randomisation. Therapist ratings of the working alliance were not available for Denmark (a satellite recruitment site) and so therapist ratings of the working alliance were only used for 8 country-sites. Thus, the objectives of this paper are as follows:

- To test the difference in therapist working alliance scores, between b-CBT versus face-to-face CBT in TAU for depression.
- To determine if therapist working alliance scores are associated with client depression scores at 3-month assessments in b-CBT.
- To test for an interaction between therapist system usability and working alliance, on the association between the therapist working alliance and client depression scores at 3-month assessments in b-CBT.

This paper will build on paper 3 by comparing models predicting client depression scores using client and therapist working alliance ratings in one analysis. The aim of this analysis is to determine if therapist ratings of the working alliance predict variance in addition to client depression scores at 3-month

follow-up assessments, when adjusting for client ratings of the working alliance, which has historically been shown to have a stronger association with treatment outcomes [8].

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1407974	**Title**	Ms
First Name(s)	Asmae		
Surname/Family Name	Doukani		
Thesis Title	A mixed methods evaluation of the working alliance in a blended cognitive behavioural therapy intervention for depression in a multinational randomised controlled trial in Europe		
Primary Supervisor	Dr Ritsuko Kakuma		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BJPsych

Please list the paper's authors in the intended authorship order:	Asmae Doukani, Matteo Quartagno, Francesco Sera, Ricardo Araya, Ritsuko Kakuma and Caroline Free. At least two people from each of the nine E-COMPARED study country sites will be invited to co-author the paper, as per E-COMPARED study publication committee guidance.
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the concept of design for this paper. I led the acquisition of secondary data from the E-COMPARED study, which was supported by Professor Ricardo Araya (E-COMPARED Principle Investigator in the UK site), Professor Heleen Riper (E-COMPARED Chief Investigator), and Dr Annet Kleiboer (E-COMPARED trial Manager), and Dr Ritsuko Kakuma. I developed the analysis plan, conducted all statistical analyses and led data interpretation, which was reviewed and commented on by Dr Matteo Quartagno and Dr Francesco Sera. I produced the first draft of the manuscript for co-authors to review, and was responsible for addressing comments from co-authors. PhD supervisors and advisors provided guidance and feedback across all phases of the tasks described. All authors provided feedback on successive drafts.

SECTION E

Student Signature	[redacted]
Date	19/05/2023

Supervisor Signature	[redacted]
Date	26 May 2023

Comparison of the therapist-rated working alliance in a blended cognitive behavioural therapy intervention for depression: A secondary data analysis from a multi-site randomised controlled trial in Europe

7.4 Abstract

Background

The working alliance is a consistent predictor for treatment outcomes in face-to-face psychological interventions. However, relatively little is known about the therapist working alliance in blended cognitive behavioural therapy (b-CBT), that involves clients receiving CBT through therapist sessions and a digital programme.

Aims

To test the difference in therapist working alliance scores between b-CBT and face-to-face cognitive behavioural therapy (CBT) in treatment as usual (TAU); determine if therapist working alliance scores are associated with post-intervention depression scores and when controlling for client working alliance scores; and to test for an interaction between system usability and therapist-rated working alliance, on the association between the therapist working alliance and client post-treatment depression scores in b-CBT.

Method

A secondary analysis using a subset of data from a clinical trial was conducted. Altogether 194 therapists completed working alliance ratings in relation to 616 client participants (i.e., 67.5% female, mean age of 39 (standard deviation=13)) from a clinical trial comparing different formats of b-CBT versus TAU for adults with depression. The main outcomes were therapist working alliance, measured by Working Alliance Inventory-Short-Revised-Therapist (WAI-SR-T) and client depression severity measured by the Patient Health Questionnaire-9 (PHQ-9) at 3-month assessments. Other variables included system usability scores (measured by System Usability Scale-therapist (SUS-T)) and client-rated working alliance (Working Alliance Inventory Short-Revised Client (WAI-SR-C)) collected at 3-month post randomisation assessments, and demographic information collected at baseline. Data were analysed using linear regression models, adjusted for a set of baseline variables.

Results

All cases from the b-CBT arm (n=444), while one analysis used cases from 4 out of the 9 country-sites that compared b-CBT (n=167) and face-to-face CBT in TAU (n=172). Therapist working alliance did

not statistically differ between b-CBT and face-to-face CBT in TAU (unstandardised coefficients beta [95% CI]: -0.60 [-1.68 to 0.47]). Higher therapist working alliance scores were associated with lower PHQ-9 scores at 3-month assessments, even after controlling for client WA scores, in b-CBT (e.g., composite scores: -0.15 [-0.23 to -0.08]) and when controlling for WAI-SR-C (e.g., composite scores: -0.11 [-0.20 to -0.03]). There was a significant interaction of SUS-T and WAI-SR-T bond subscale scores, on the association between higher WAI-SR-T bond scores and lower PHQ-9 scores in b-CBT (-0.067, [-0.12 to 0.01]), but not for composite and other subscale scores.

Conclusion

The findings of this study suggest that higher ratings of therapist working alliance may lead to better depression outcomes in b-CBT when accounting for client working alliance ratings, and that may be enhanced by good system usability. Collectively these findings suggest that a b-CBT format for treating depression might be more conducive to strengthening the therapist-client working alliance.

Trial registration

France: ClinicalTrials.gov NCT02542891. Registered on 4 September 2015; Germany: German Clinical Trials Register DRKS00006866. Registered on 2 December 2014; The Netherlands: Netherlands Trials Register NTR4962. Registered on 5 January 2015; Poland: ClinicalTrials.Gov NCT02389660. Registered on 18 February 2015; Spain: ClinicalTrials.gov NCT02361684. Registered on 8 January 2015; Sweden: ClinicalTrials.gov NCT02449447. Registered on 30 March 2015; Switzerland: ClinicalTrials.gov NCT02410616. Registered on 2 April 2015; United Kingdom: ISRCTN registry, ISRCTN12388725. Registered on 20 March 2015. Denmark: ClinicalTrials.gov NCT02796573. Registered 1st June 2016.

Keywords

Psychotherapist, working alliance, depression, blended therapy, cognitive behavioural therapy, system usability, randomised controlled trial, and Europe.

7.5 Introduction

Depression is a significant contributor to the global burden of disease, affecting an estimated 264 million people globally [2,206]. However, between 35-50% of people living in Europe do not have access to mental health care [241]. The use of digital technologies has been put forward as a promising solution for improving the access and quality of mental health care [242].

There is a growing body of evidence on the feasibility and effectiveness of digital mental health interventions (DMHIs). DMHIs are commonly based on cognitive-behavioural therapy (CBT) principles and are either unguided (digital programme with no external support), guided (digital programme with human support) or blended (digital programme with in-person psychotherapy that commonly offers the highest level of therapist support) [22]. While DMHIs promise scalable and cost-effective implementation of evidence-based interventions, many questions remain concerning real-world engagement with the digital programme [243–245]. The literature on engagement has largely centred on the client-provider relationship, commonly referred to as the working alliance. This concept encompasses three key dimensions, including the emotional 'bond' between the client and therapist, and the agreement between them on the treatment 'goals' and 'tasks' [6,7]. The working alliance has emerged as a consistent predictor for positive psychotherapeutic outcomes across a range of psychological interventions [13] including conventional in-person CBT for depression [129] and for internet-based psychotherapy that includes internet-based CBT (iCBT) [10].

Few studies have examined the therapist-rated alliance in blended internet-based CBT interventions. To our knowledge, only three studies have investigated the therapist working alliance in blended CBT (b-CBT) for depression [41–43]. Two of these studies compared therapist working alliance scores between b-CBT and face-to-face CBT, in specialised [42] and primary care services [43], but did not find a significant difference. Only one out of the three studies found a significant alliance-outcome association, in which higher therapist working alliance scores were associated with lower depression score change during treatment [41].

Emerging qualitative evidence appears to suggest that digital elements of treatment can augment or influence the working alliance [34–36]. In particular, a qualitative study that examined clients' experience of the working alliance in b-CBT established a fourth working alliance dimension in addition to bond, goals, and task, called usability heuristics [47]. This refers to the use of digital technologies to promote active engagement with intervention content that encompasses, accessibility, immediacy, ease of use, aesthetic appeal, and client (self) directed treatment. However, no studies have attempted to examine these concepts quantitively.

This study builds on the existing literature on the therapist working alliance outlined above [23,41,43,47]. First, this study will employ a large and varied sample of participants from a multinational randomised controlled trial (RCT) [41] that applied different blended formats and digital programmes, to increase the generalisability of the findings. Furthermore, our study will also explore if a digital programme feature (i.e., programme usability) influences the association between the working alliance and treatment outcomes.

7.5.1 Aim and objectives

This study aimed to investigate the working alliance in blended-CBT, when compared to treatment as usual (TAU), for depression. We addressed this aim by conducting a secondary analysis of a pragmatic non-inferiority randomised controlled trial (RCT) called E-COMPARED, that investigated the effectiveness and cost-effectiveness of b-CBT for mild to moderate depression, when compared to treatment as usual [23]. The specific objectives were to:

1. Test the difference in therapist-rated working alliance scores at 3-month post-randomisation assessments, between b-CBT and face-to-face CBT in TAU.
2. Determine if working alliance scores were associated with client depression scores at 3-month assessments in b-CBT.
3. Determine if working alliance scores were associated with depression scores at 3-month assessments, when controlling for 3-month client-rated working alliance, in b-CBT.
4. Test for an interaction between therapist-rated system usability and therapist-rated working alliance, on the association between the therapist-rated working alliance and post-treatment client depression scores at 3 month assessments, in b-CBT.

7.6 Methods

7.6.1 Design

This study utilised a non-prespecified secondary analysis of data collected on the E-COMPARED study, that was funded by the European Commission, FP7-Health-2013-Innovarion-1 programme (grant agreement number: 603098) [23]. E-COMPARED is a two-arm, non-inferiority pragmatic RCT investigating the effectiveness of b-CBT compared to treatment as usual (TAU) across eight European countries [23]. Client participants were recruited, assessed and treated across routine primary care services in Germany, Poland, Spain, Sweden and the United Kingdom, and specialised mental health care in France, The Netherlands and Switzerland [23]. An additional satellite recruitment site was added in specialised mental health services in Denmark, in aid of optimising recruitment [45], however this site did not collect therapist working alliance data and was therefore excluded from the analysis. Data

were collected between April 2015 and December 2017 [23]. The recruitment procedure and treatments offered per country are reported in Table 7.1 [23]. Additional information about the design of E-COMPARED, can be found in the trial protocol by Kleiboer and colleagues [23].

7.6.2 Therapists

Therapists recruited to the study delivered the intervention across both treatment conditions (b-CBT and TAU), with the exception of German therapists, who only provided treatment in the b-CBT arm. CBT was an active intervention in both b-CBT and TAU, therefore treatment contamination was not anticipated to be a problem [23]. Therapists involved in the trial were required to complete questionnaires on the working alliance and programme usability. Although, demographic data collection was not stipulated on the E-COMPARED study [23]. 194 therapists completed questionnaires on perceived working alliance, and programme system usability. Of these therapists 82 delivered treatment (both b-CBT and TAU) in specialised services, and 102 provided treatment in primary care services. While therapist characteristics were not collected in the trial, therapists within the services recruited from were CBT therapists that were either licenced or were in training.

7.6.3 Client participants

Recruitment procedures for enrolled cases differed across the eight country-sites. People accessing services with presentations of depression and that scored 5 or higher on the PHQ-9 screening questionnaire [106] were introduced to the study [23]. Clients interested in taking part were screened for eligibility, using the same core inclusion and exclusion criteria [23].

Table 7.1. Overview of recruitment of client participants, b-CBT format and dosage and treatments offered in TAU by country-site [23]

	Recruitment		**b-CBT format and dosage**				**TAU allocation**
Country	Treatment setting	Recruitment procedure	Platform	Duration (weeks)	Online/ face-to face	Sequencing[a]	
France	Specialised mental health care	New or regular patients recruited by CBT therapists from 11 experts centres throughout France.	Moodbuster	16	8/8	Alternate	Face-to-face CBT
Germany	Primary care	Recruitment in the waiting room of GP clinics or during GP consultations.	Moodbuster	11-13	10/6	Alternate	[b]GP care (e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT)

	Recruitment		b-CBT format and dosage				TAU allocation
Netherlands	Specialised mental health care	Recruited through mood disorder departments of three outpatient clinics in Amsterdam and Leiden.	Moodbuster	20	10/10	Alternate	[b]Face-to-face psychotherapy (mainly CBT, interpersonal psychotherapy, problem-solving therapy, antidepressant medication, or a combination of these).
Poland	Primary care	Recruited through primary care centres by CBT therapists (licenced and in training) in five major cities in Poland (Warsaw, Sopot, Poznan, Katowice, and Wroclaw).	Moodbuster	6-10	6/7	Alternate	Face-to-face CBT

	Recruitment		b-CBT format and dosage				TAU allocation
Spain	Primary care	Recruitment through routine primary care from the Spanish National Health System in several cites (Valencia, Castellón, and Zamora).	Smiling is fun	10	8/3	1-4-1-4-2	Prescribed medication by the GP and/or received face-to-face CBT, interpersonal psychotherapy or supportive therapy once a month

	Recruitment		b-CBT format and dosage				TAU allocation
Sweden	Primary care	Recruitment through collaborating primary care clinics in three Swedish counties (Stockholm, Linköping, Västerås). Posters and leaflets were distributed in the waiting areas and/or were administered to GPs in clinics, who in turn referred potentially eligible participants.	Iterapi	10	6/4	Alternate	[b]Usual care paths in Sweden; including general practitioner care, e.g. watchful waiting, medication prescription, referral to medical specialist or Face-to-face CBT.
Switzerland	Specialised mental health care	Recruitment through two outpatient clinics (Bern and Zurich) and individual therapists.	Deprexis	18	9/9	Alternate	Face-to-face CBT

	Recruitment		b-CBT format and dosage				TAU allocation
United Kingdom	Primary care	Recruited through a primary mental health programme that delivers psychological therapies to people with depression and anxiety disorders, in Northern and Southern England.	Moodbuster	11	5/6	Alternate	Face-to-face CBT

Abbreviations*:* b-CBT, blended cognitive behavioural therapy; CBT, cognitive behavioural therapy; GP, general practitioner; NHS, National Health Service; TAU, treatment as usual.

[a]Sequencing of face-to-face and online can include more than one session per week for either component.

[b]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites.

The inclusion criteria comprised of being aged 18 years or older, and meeting the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnostic criteria for Major Depressive Disorder as confirmed by the telephone-administered Mini International Neuropsychiatric Interview (M.I.N.I.) version 5.0. [51,246]. Potential participants were excluded from the study if they showed a high risk of suicide and reported specific psychiatric comorbidity (i.e., substance dependence, bipolar affective disorder, psychotic illness and obsessive compulsive disorder) as assessed by the M.I.N.I. interview. Other exclusions included receiving psychological treatment for depression in primary or specialised mental health care at the point of recruitment [23], not being able to comprehend the spoken and written language of the country, not having access to a computer with an adequate Internet connection (i.e., broadband or comparable), and not having access to a personal Android smartphone and not willing to use one if offered by the research team. Written consent was provided by all participants on the trial. Information on recruitment and randomisation can be found in the trial protocol by Kleiboer and colleagues [23]. Client rated working alliance data were reported in a separate paper.

7.6.4 Intervention: b-CBT and TAU

b-CBT

In the b-CBT arm, client participants attended clinic-based therapy sessions and completed an internet-based CBT (iCBT) programme which was largely expected to be completed outside of the clinic [23]. There were four mandatory core modules of CBT on the iCBT programme (i.e., psychoeducation, behavioural activation, cognitive restructuring, and relapse prevention) and two optional modules (e.g., most commonly physical exercise and problem solving) [23]. The iCBT programmes, blended formats, ratio and sequencing of online and face-to-face CBT and treatments offered by services in TAU across country-sites are outlined in Table 7.1 [23]. Therapists delivering interventions could not be blinded to the intervention arm, however assessors were blind.

TAU

TAU included all possible interventions offered in usual care for depression within the services recruited from, that consisted of a wide range of psychological and pharmacological interventions (See Table 7.1 for a breakdown of interventions offered in all E-COMPARED country-sites) [23,41,217]. Information on the treatment and dosage received in TAU were not collected on the E-COMPARED trial. Due to the heterogeneity of interventions offered in the TAU group, a subset of the data that only included country-sites that compared b-CBT with face-to-face CBT in the TAU arm (i.e., France, Poland, Switzerland, and the UK) were used to investigate the effects of treatment condition on working alliance scores. Using this subset of the population enabled the working alliance in b-CBT to be directly compared with a defined treatment comparator [218–220]. It should also be noted that b-CBT was not offered in the TAU arm of all country-sites. Data from the TAU arm was not used to explore the

alliance-outcome association, as the heterogenic composition of TAU is likely to limit the reliability of the estimates generated [219].

7.6.5 Measures

Therapist-rated working alliance was measured using the Working Alliance Inventory-Short Revised-Therapist (WAI-SR-T) a 10-item self-report questionnaire incorporating a 5-point scale (from 1=Seldom to 5=Always) [18]. Client-rated working alliance was measured using the Working Alliance Inventory–Short Revised-Client (WAI-SR-C) [145]. The 12 items are rated on a 5-point Likert scale (1=seldom to 5=always). Both scales are revisions of the original inventory that was developed and validated by Horvath and Greenberg [16]. The measures were developed to reflect Bordin's [6,7] conceptualisation of the working alliance, that consists of three dimensions (bond, task, and goals). Subscales for bond, task and goals were calculated across both measures. Higher scores indicated better working alliance. WAI-SR-C has demonstrated good internal consistency for bond, task, and goals subscales (Cronbach's alpha = 0.92, 0.92, and 0.89, respectively) [19,145]. Client depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) [106], that included nine symptom-based items, rated on a 4-point scale (0=not at all to 3= nearly every day). Higher scores indicated greater symptom severity. The PHQ-9 has demonstrated good psychometric properties [106], and utility as a diagnostic tool [224]. Therapists' experience of the digital program's usability in b-CBT was assessed using the System Usability Scale-Therapist (SUS-T) [148], a 10-item self-report questionnaire, measured on a 5-point scale (1=strongly disagree to 5=strongly agree). The SUS has been found to have high internal reliability (e.g. coefficient Omega= 0.91) and good concurrent validity and sensitivity [148,177]. WAI-SR-T, WAI-SR-C, and the SUS-T measures were administered at the 3-month follow-up assessment. PHQ-9 data were collected at multiple stages, however, data were only used for baseline and 3-month follow-up assessments. Client demographic data including gender (i.e., male, female, other), age, educational attainment (i.e., low, middle, and high, corresponding to secondary school education or equivalent, college or equivalent, and university degree or higher, respectively), marital status (i.e., single, divorced, widowed, living together, and married), country of birth, were collected at baseline assessments [23]. The number of sessions attended were not collected in TAU, or systematically collected in b-CBT.

7.6.6 Statistical analysis

Data from the E-COMPARED trial was downloaded from a data repository. The study used an intention to treat (ITT) population for the data analysis, a standard approach used in RCTs to maintain the original treatment arm composition achieved after random allocation including those who may or may not have completed treatment [184]. All analyses were performed on SPSS (version 26 or above) [225], STATA

(version 16 or above) [226], and PROCESS Macro plug-in for SPSS (version 3.5 or above) [227]. Linear regression models were used to address the study objectives. The analysis will report *P* values that are 2-tailed with significance levels at $P \leq .05$.

7.6.6.1 Treatment assignment as a predictor for WAI-SR-T scores

A generalised linear regression model was used to test if treatment assignment (i.e., b-CBT vs TAU) predicted WAI-SR-T scores at 3-month follow-up assessments. The analysis was conducted separately for WAI-SR-T subscale scores (i.e., goals, task, and bond). This analysis only included a subset of countries (n=4) that compared b-CBT with face-to-face CBT (i.e., France, Poland, Switzerland, and the UK). Overall, four models were fitted.

7.6.6.2 Association between post-treatment PHQ-9 scores and WAI-SR-T scores

A linear regression model (LRM) was fitted to determine if WAI-SR-T scores were associated with post-treatment PHQ-9 scores at 3-month assessments in the b-CBT arm, using data from all trial country-sites with available data (n=8). The model was conducted separately for WAI-SR-T composite and subscale scores (i.e., goals, task and bond). Four models were fitted altogether.

7.6.6.3 Association between post-treatment PHQ-9 scores and WAI-SR-T scores, when adjusting for WAI-SR-C

A nested LRM was performed to determine if an association between WAI-SR-T and PHQ-9 scores, explains additional variance in client PHQ-9 sores, above and beyond the effects of WAI-SR-C scores at 3-month assessments in the b-CBT arm, using data from all trial country-sites with available data (n=8). The model was conducted separately for WAI-SR-T composite and subscale scores (i.e., goals, task and bond). Four models were fitted altogether in the b-CBT arm.

7.6.6.4 Testing the interaction between WAI-SR-T and SUS-T on the relationship between WAI-SR-T and PHQ-9

An LRM was performed to test an interaction between WAI-SR-T and SUS-T, on the association between the WAI-SR-T and PHQ-9 scores at 3-month assessments in the b-CBT arm, using data from all trial country-sites with available data (n=8). The model was conducted separately for WAI-SR-T composite and subscale scores (goals, task, bond). Four models were fitted altogether.

All analyses adjusted for client age, gender, baseline PHQ-9 scores, marital status, educational attainment, and country-site.

7.6.7 Missing data

A high proportion of data were missing in the original dataset. Notably, the WAI-SR-T measure had 27.2% (129/444) missing ratings in b-CBT, and 52.6% (231/439) missing ratings in TAU. Multiple imputation was used to treat missing data under the missing at random (MAR) assumption, using a chained equation approach [178]. Tabulations of missing data across treatment condition and country-sites; and chi-square results of differences in missing and complete data across trial country-sites are presented in eMethods 1 of Appendix 18. All variables included in the statistical analyses were added to the imputation model, including demographic variables, PHQ-9 scores at baseline, and WAI-SR-C, SUS-T, and PHQ-9 scores at 3-month assessments. Multiple imputation was performed separately for b-CBT and TAU to enable condition specific variables to be accounted for (e.g., SUS-T was only administered in the b-CBT arm). Data that were entered into the analysis with an interaction term were imputed using the Just Another Variable (JAV) approach [179] to address the interaction term used in the regression model [179,187].

7.6.8 Post-hoc analyses

A post hoc sensitivity analysis was conducted to examine if there were any differences between the multiply imputed dataset that was used to address missing data, and the original complete case dataset. Under the MAR assumption, consistent results may increase the reliability of the findings, assuming that the missingness mechanism is not dependent on the outcome [186]. The sub-analysis will replicate the main analysis using unimputed data.

A sub-group analysis was conducted to explore the magnitude of treatment effects on the working alliance when using a subset of the sample, that compared b-CBT with face-to-face CBT offered in the TAU arm in France, Poland, Switzerland, and the UK. The sub-analysis will replicate the main analysis in the four country-sites and will be conducted for the analyses, (a) exploring the working alliance and treatment outcome association, and (b) testing the interaction between working alliance on system usability scores on the relationship between the working alliance and depression scores. This will enable a comparison between the primary analysis that included all 8 country-sites in the b-CBT arm, with the 4 country-sites that compared b-CBT with face-to-face CBT in TAU.

7.7 Results

7.7.1 Clinical and demographic characteristics

Table 7.2 summarises baseline characteristics for client participants. This study used all cases from the b-CBT arm (n=444) and from the four country-sites that compared b-CBT with face-to-face CBT in TAU (n=172), with different analyses drawing on different samples (please see Section 7.5.7 for further

clarifications). The original E-COMPARED trial profile is presented in eFigure 1, in eResults 1 of the *Appendix 18*. Among the 883 client participants, 444 were randomly allocated to b-CBT, while 439 were allocated to TAU across all 8 country-sites. Altogether, 194 therapists that were registered in the locked database were considered in the analysis. The subset of data appears to have similar client participant characteristics to the full sample (see *Table 7.2*), in which client participants were mostly female, middle-aged, and with a university degree or higher, with mean PHQ-9 reflecting depression of moderate severity. Post-treatment PHQ-9 scores at 3-months will be reported in the main trial paper which is being prepared. In the full b-CBT group sample, mean WAI-SR-C scores at 3-month assessments was 39.48 (standard deviation [SD]=13), and mean SUS was 41.31 (6.63) in b-CBT. In the subsample that only included sites that compared b-CBT with face-to-face CBT, mean WAI-SR-T was 41 (SD=5.30), in b-CBT, and 41.68 (SD=4.87) in face-to-face CBT in TAU. See *Table 7.3* for the mean and SD of WAI-SR-T and SUS-T across treatment groups, for the full population (n=8 country-sites) and sub-group population (n=4 country-sites). See *eResults 2* in *Appendix 17* for mean and SDs for WAI-SR-T and SUS-T scores by country-site for both full and sub samples.

Table 7.2. Baseline characteristics of client participants for the full trial sample (n=8 country sites) and a subgroup sample (n=4 country sites). Figures are numbers (percentages) of participants unless otherwise indicated

	Full trial sample			Sub-sample		
Characteristic at baseline	**b-CBT** (n=444)	**TAU**[a] (n=439)	**Total** (n=883)	**b-CBT** (n=168)	**TAU** (n=172)	**Total** (n=340)
Mean (SD) min-max, age in years	39.48 (13) 18-74	38.83 (13) 18-78	39.15 (13) 18-78	38 (23.75) 18-74	35 (21.75) 18-70	36.50 (22) 18-74
Gender (Female)	291 (65.5)	305 (69.5)	596 (67.5)	108 (64)	114 (66)	222 (65)
Marital status						
Single	147 (33)	146 (33)	293 (33)	61 (36)	66 (38)	127 (37)
Divorced	55 (12)	38 (9)	93 (11)	23 (14)	15 (9)	38 (11)
Widowed	3 (1)	6 (1)	9 (1)	0 (0)	2 (1)	2 (1)
Living together	86 (19)	106 (24)	192 (22)	30 (18)	36 (21)	66 (19)
Married	153 (35)	143 (33)	296 (34)	54 (32)	53 (31)	107 (32)
Level of education*						
Secondary School, equivalent	56 (13)	59 (14)	115 (13)	16 (10)	19 (11)	35 (10)
College, equivalent	166 (37)	159 (36)	325 (37)	68 (40)	54 (31)	122 (36)
University degree or higher	222 (50)	220 (50)	442 (50)	84 (50)	99 (58)	183 (54)

Table 7.2. Baseline characteristics of client participants for the full trial sample (n=8 country sites) and a subgroup sample (n=4 country sites). Figures are numbers (percentages) of participants unless otherwise indicated

	Full trial sample			Sub-sample		
Characteristic at baseline	**b-CBT** (n=444)	**TAU**[a] (n=439)	**Total** (n=883)	**b-CBT** (n=168)	**TAU** (n=172)	**Total** (n=340)
Country-site						
Germany	86 (19)	87 (20)	173 (19.6)	n/a	n/a	n/a
Sweden	73 (16)	68 (16)	141 (16.0)	n/a	n/a	n/a
Netherlands	53 (12)	49 (11)	102 (11.5)	n/a	n/a	n/a
UK	49 (11)	52 (12)	101 (11.4)	49 (29)	52 (30)	101 (29)
Spain	64 (14)	63 (14)	127 (14.4)	n/a	n/a	n/a
France	51 (12)	54 (12)	105 (11.9)	51 (30)	54 (31)	105 (31)
Switzerland	26 (6)	24 (6)	50 (5.7)	26 (15)	24 (14)	50 (15)
Poland	42 (10)	42 (9)	84 (9.5)	42 (25)	42 (24)	84 (25)
Mean (SD) and min-max of baseline PHQ-9 scores	15. 37(4.96) 4-27	15.33 (4.70) 5-26	15.35 (4.83) 4-27	16 (7) 5-27	15.50 (7) 5-26	16 (7) 5-27

Abbreviations: b-CBT, blended cognitive behaviour therapy; PHQ-9, patient health questionnaire-9; TAU, treatment as usual.

*data was missing for n=1(0.2%) in the control arm.

[a]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites. Data for the full TAU sample is summarised to enable comparison between full and subset trial samples.

Table 7.3. Mean (SD) of WAI-SR-T composite and subscale scores, and SUS-T and WAI-SR-C scores at 3-month assessments for the full trial sample (n=8 country-sites) and subgroup sample (n=4 country-sites) in b-CBT and TAU

	Full trial sample			Subsample		
	b-CBT (n=444)	TAU[a] (n=439)	Total (n=883)	b-CBT (n=168)	TAU (n=172)	Total (n=340)
WAI-SR-T						
Composite	39.69 (6.20)	41.09 (4.91)	40.33 (5.69)	49.99 (5.30)	41.68 (4.87)	41.34 (5.09)
Goals	11.16 (2.50)	11.86 (1.90)	11.48 (2.27)	11.63 (2.08)	11.98 (1.97)	11.81 (2.03)
Task	10.98 (2.43)	11.74 (2.02)	11.32 (2.22)	11.30 (1.97)	11.48 (2.04)	11.40 (2.01)
Bond	17.55 (2.22)	17.49 (2.14)	17.52 (2.18)	19.06 (2.13)	18.22 (2.18)	18.12 (2.15)
SUS-T	28.81 (4.50)	n/a	28.81 (4.50)	28.37 (2.69)	n/a	28.37 (2.69)
WAI-SR-C						
Composite	47.37 (7.77)	41.44 (9.88)	44.62 (9.26)	47.27 (8.07)	44.43 (7.79)	45.84 (8.04)
Goals	16.25 (2.96)	13.83 (3.81)	15.15 (3.58)	16.29 (3.13)	14.64 (3.13)	15.34 (3.18)
Task	14.15 (3.12)	12.44 (3.95)	13.52 (3.65)	14.93 (3.01)	14.27 (3.09)	14.59 (3.06)
Bond	15.17 (3.55)	15.17 (3.55)	15.95 (3.33)	16.29 (3.13)	15.53 (2.81)	15.90 (2.99)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; PHQ-9, patient health questionnaire-9; SUS-C, system usability scale-client; TAU, treatment as usual; WAI-SR-C, working alliance inventory-short revised-client; WAI-SR-T, working alliance inventory-short revised-therapist.

[a]TAU data for Germany, Sweden, The Netherlands, and Spain were excluded from the main analysis due to the heterogeneity in the treatments offered by the sites. Data for the full TAU sample is summarised to enable comparison between full and subset trial samples.

7.7.2 Treatment assignment as a predictor for WAI-SR-T scores

Treatment assignment did not significantly predict WAI-SR-T composite and subscale (i.e., goals, task and bond) scores. See Table 7.4 for model summaries.

Table 7.4 Adjusted linear regression models of treatment assignment as a predictor for WAI-SR-T scores. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-T (outcome)	*B* (95% CI)	*P V*alue
Composite	-0.60 (-1.68 to 0.47)	.271
Goals	-0.35 (-0.78 to 0.08)	.109
Task	-0.15 (-0.57 to 0.28)	.491
Bond	-0.10 (-0.56 to 0.35)	.660

Abbreviations: 95% CI, 95% confidence intervals*; B*, unstandardized beta; PHQ-9, patient health questionnaire-9; WAI-SR-T, working alliance inventory-short revised-therapist.

7.7.3 Association between post-treatment PHQ-9 scores and WAI-SR-T scores

In the b-CBT arm, models with WAI-SR-T composite, goals and task subscale scores were significantly associated with PHQ-9 scores at 3-month assessments, in which lower PHQ-9 scores were associated with higher WAI-SR-T composite and subscale (i.e., goals and task) scores. WAI-SR-T bond scores were not significantly associated with PHQ-9 scores (see Table 7.5 for model summaries).

Table 7.5. Adjusted linear regression models of association between PHQ-9 scores and WAI-SR-T scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR (outcome)	*B* (95% CI)	P value
Composite	-0.15 (-0.23 to -0.08)	<.001
Goals	-0.37 (-0.57 to -0.18)	<.001
Task	-0.46 (-0.66 to -0.26)	<.001
Bond	-0.14 (-0.36 to -0.08)	.206

Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; WAI-SR-T, working alliance inventory-short revised-therapist.

7.7.4 Association between post-treatment PHQ-9 and WAI-SR-T scores, adjusting for WAI-SR-C scores

In the b-CBT arm, the nested LRM indicates that adding WAI-SR-T in step 2, to WAI-SR in step 1, as an additional predictor for PHQ-9 scores at 3-month assessments, explains an additional 1% of the variance in PHQ-9 scores, for composite, goals, task, but not bond scores. Table 7.6 summarises the findings from the four models in the b-CBT arm.

Table 7.6 Nested linear regression models of associations between PHQ-9 scores and WAI-SR-C scores in step 1 and WAI-SR-T scores in step 2 in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

Variables		Composite		Goals		Task		Bond	
		B (CI 95)	*P* Value	*B* (CI 95)	P Value	*B* (CI 95)	*P* Value	*B* (CI 95)	*P* Value
Step 1									
	Constant	5.90 (2.36 to 9.44)	.001	4.52 (1.18 to 7.88)	.008	5.78 (2.78 to 8.78)	<.001	2.72 (-0.80 to 6.23)	.130
	WAI-SR-C	-0.11 (-0.17 to -0.06)	<.001	-0.25 (-0.40 to -0.10)	.001	-0.38 (-0.53 to -0.24)	<.001	-0.13 (-0.28 to 0.03)	.103
Step 2									
	Constant	8.64 (4.57 to 12.71)	<.001	6.23 (2.72 to 9.74)	.001	7.31 (4.12 to 10.51)	<.001	4.59 (-0.35 to 9.15)	.068
	WAI-SR-C	-0.09 (-0.15 to -0.03)	.006	-017 (-0.33 to -0.01)	.034	-0.29 (-0.45 to -0.14)	<.001	-0.12 (-0.27 to 0.04)	.140
	WAI-SR-T	-0.11 (-0.20 to -0.03)	.009	-0.30 (-0.51 to -0.10)	.004	-0.29 (-0.51 to -0.07)	.009	-0.12 (-0.34 to 0.10)	.289

Composite: $R^2 = .29$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.009); Goals 2: $R^2 = .27$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.004); Task 3: $R^2 = .29$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.009); Bond: $R^2 = .26$ for step 1: $\Delta R^2 = .00$ for step 2 (ps. =.289).

Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client; WAI-SR-T, working alliance inventory-short revised-therapist.

7.7.5 Testing the interaction between WAI-SR-T and SUS-T on the relationship between WAI-SR-T and PHQ-9 scores

The interaction between WAI-SR-T and SUS-T on the association between WAI-SR-T composite scores, and client PHQ-9 scores at 3-month assessments was not significantly associated with WAI-SR-T composite scores (*b*=-0.02, *t*(424)=-1.59 [95% CI: -0.03 to 0.00], *p*=0.11,) and the goals (*b*=-0.03, *t*(424)=-1.18 [95% CI: -0.07 to 0.02], *p*=0.24) and task (*b*=-0.02, *t*(424)=-0.86 [95% CI: -0.07 to 0.03], *p*=0.39,) subscale score models. A significant interaction was found for the WAI-SR-T bond subscale scores (*b*=-0.07, *t*(424)=-2.39 [95% CI: -0.12 to 0.01], *p*=0.018,). Figure 7.1 shows a trend for an inverse association between composite bond WAI-SR-T and PHQ-9 scores among therapists who rated SUS-T higher.

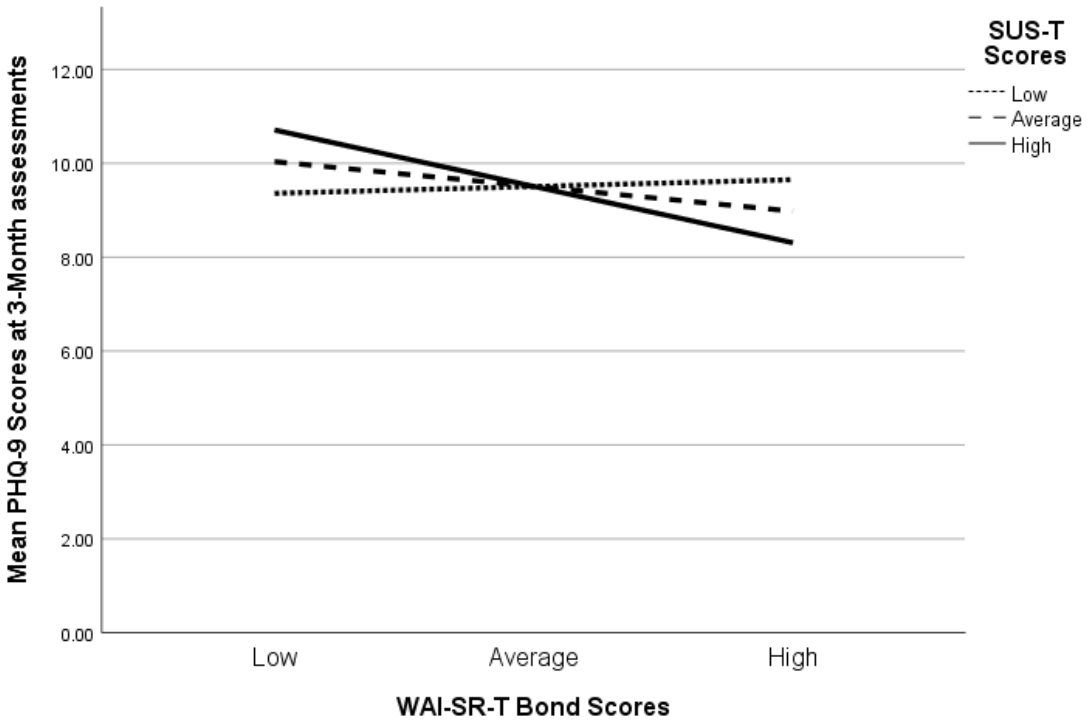


Figure 7.1. Multiple line graph of the interaction between SUS-T and WAI-SR-T bond scores on the association between WAI-SR-T bond and client PHQ-9 scores at 3-month assessments in b-CBT

Legend: PHQ-9, patient health quesionnaire-9; SUS-T, system usability scale-therapist; WAI-SR-T, working alliance inventory-short revised-therapist.

7.7.6 Post-hoc analyses

The findings of the sensitivity analysis largely aligned with the main findings. Considering that the sub-analysis used a limited sample size (country-sites=4), the findings in relation to the alliance-outcomes association, when controlling for WAI-SR-C, and when including an interaction term between SUS-T and client PHQ-9 scores at 3-month assessments, did not reach significance. A detailed breakdown of the findings are summarised below. Model summaries and descriptive data can be found in Appendix 18.

Sensitivity analyses

Post-hoc sensitivity analyses were conducted to examine if the multiple imputation approach that was used to handle missing data under MAR, resulted in different conclusions when compared to a complete case analysis.

Treatment assignment did not significantly predict WAI-SR-T (n=4 country-sites), composite scores (b = -0.48 [95% CI:-1.85 to 0.89], p=.50), and for the goals (b = -0.20 [95% CI: -0.73 to 0.34,], p=.47), task (b = -0.08 [95% CI: -0.61 to 0.45], p=.76) and bond (b = -0.22 [95% CI: -0.66 to 0.44], p=.70) subscale scores.

In the b-CBT arm (n=8 country-sites) the association between the WAI-SR-T composite scores was significant (b =-0.14 [95% CI: -0.22 to -0.06], p=.001). Models with the goals (b =-0.35 [95% CI: -0.55 to -0.14], p=.001), task (b =-0.42 [95% CI: -0.63 to -0.21], p=.001) subscales scores were also significant, while the model with bond subscale scores was not (b =-0.12 [95% CI: -0.35 to-0.11], p=.31).

In the b-CBT arm (n=8 country-sites) the association between WAI-SR-T and PHQ-9 scores at 3-month assessments, when controlling for WAI-SR-C were not significant for models including composite scores (R^2 change =0.01, F(1, 251)=, 2.34, p=.13), and the task, (R^2 change =0.01, $F(1,258)$=3.51, p=.062) and bond (R^2 change = 0.00, F(1, 254)=0.34, p=.56) subscale score. However, the model that included goals scores was significant (R^2 change = 0.01, F(1,258)=4.70, p=.03). These findings suggest that therapist ratings of goals provides a more predictive model of client PHQ-9 scores, than the model with the WAI-SR-C goals scores.

In the b-CBT group (n=8 country-sites), the interaction between WAI-SR-T and SUS-T on the association between WAI-SR-T composite scores and client PHQ-9 at 3-months was not significant for WAI-SR-T composite scores (b=-0.02, t(308)=-1.84 [95% CI: -0.04 to 0.00], p=0.06), and the goals (b=-0.04, t(308)=-1.54 [95% CI: -0.08 to 0.01], p=0.239) and task (b=-0.03, t(308)=-1.18 [95% CI: -

0.08 to 0.02], p=0.24) subscale scores. A significant interaction was however found for the WAI-SR-T bond subscale scores (b=-0.062, t(308)=-2.09 [95% CI: -0.12 to 0.00], p=0.038), that shows an inverse association between higher WAI-SR-T bond subscale scores and lower PHQ-9 scores among therapists with higher SUS-T scores.

Sub-analyses

In the b-CBT arm (n=4 country-sites) PHQ-9 scores at 3-month assessments were significantly associated with the WAI-SR-T task subscale (b =-0.41 [95% CI: -0.81 to -0.00], p=.048), but not for composite scores (b =-0.13 [95% CI: -0.29 to 0.02], p=.09), and the goals (b =-0.31 [95% CI:-0.70 to 0.08], p=.12), and bond (b =-0.16 [95% CI: -0.58 to 0.25], p=.43) subscale scores.

In the b-CBT arm (n=4 country-sites) the association between WAI-SR-T and PHQ-9 scores at 3-month assessments, when controlling for WAI-SR-C were not significant for models for composite scores (R^2 change = 0.00, F(1, 155)=0.62, p=.43); and the goals (R^2 change = 0.00, F(1,155)=0.79, p=.38); task (R^2 change =0.00, F(1,155)=0.83, p=.36); and bond (R^2 change = 0.00, F(1, 155)=0.21 p=.65) subscale scores.

In the b-CBT arm (n=4 country-sites) the interaction between WAI-SR-T and SUS-T on the association between WAI-SR-T composite scores and client PHQ-9 at 3-months was not significant for WAI-SR-T composite scores (b=-0.03, t(153)=-0.84 [95% CI: -0.04 to 0.10], p=0.40), and the goals (b=-0.05, t(213)=-1.04 [95% CI: -0.07 to 0.23), p=0.13), task (b=-0.15, t(153)=-1.73 [95% CI: -0.02 to 0.32], p=0.09) and bond (b=-0.071, t(153)= 0.77 [95% CI: -0.025 to 0.11], p=0.45) subscale scores.

7.8 Discussion

7.8.1 Overview

The findings of our study showed that therapist ratings of the working alliance between b-CBT and face-to-face CBT in TAU did not significantly differ. However, working alliance scores were significantly associated with client depression scores at 3-months assessments in the b-CBT arm. These findings showed that as the therapist working alliance scores increased, client depression scores decreased in b-CBT. Therapist working alliance scores were found to significantly improved the model's ability to predict client post-treatment depression scores in b-CBT. Moreover, an interaction term between therapist working alliance bond subscale scores and therapist system usability scores on the association between bond and client depression scores, showed that higher therapist system usability strengthened the association between higher therapist bond scores and lower client depression scores post-treatment.

7.8.2 Evaluating findings in response to other studies

Our study did not find a statistical difference between working alliance in b-CBT, compared to treatment as usual. These findings were in accord with some available evidence in which therapist working alliance ratings did not differ significantly between blended and face-to-face CBT for depression [42,43].

On the other hand, this study found a significant association between therapist rated working alliance and client treatment outcomes in the b-CBT arm. Therapist working alliance was also found to account for additional variance in client depression scores at 3-months, when adjusting for client ratings of the working alliance. This may suggest that therapist ratings of the working alliance may contribute uniquely and additionally to client ratings of the working alliance in predicting client depression scores. This is contrary to reports that client ratings of the working alliance is a more reliable predictor of treatment outcomes [8,247,248]. Our findings align with a study conducted on the Switzerland country site of the E-COMPARED trial, that found that therapist working alliance scores were predictive of subsequent changes in depression scores during treatment [41]. However, other studies investigating the working alliance in b-CBT did not find a significant association between the working alliance and treatment outcomes [42,43,249]. Qualitative studies exploring the therapists' experience of the working alliance in b-CBT highlighted a range of facilitators that were reported to enhance the working alliance, including perceptions that time was expanded in treatment to allow greater opportunities for in-person interactions [48]. Other perceived facilitators included having a wider-toolkit that can be drawn from, and opportunities to tailor b-CBT during in-person sessions as a means of enhancing the therapeutic task. Moreover, the literature on the therapists' experience of delivering supported/blended internet-based CBT, suggested that the digital programme increased engagement in face-to-face sessions, extended therapy beyond the clinic, prevented therapeutic rifts between sessions. It was also found to facilitate the building of rapport, enable the active monitoring of clients, and extend the time needed to develop a therapeutic relationship [138,237]. The facilitators attributed to the digital programme in b-CBT across other studies, may explain why the working alliance was significantly associated with treatment outcomes in b-CBT.

Our study appears to be the first to find that therapist ratings of system usability influenced the strength of association between therapist working alliance scores and client depression scores. These findings are supported by a qualitative framework of the working alliance in b-CBT that was developed in the UK site of the E-COMPARED trial, in which a subtheme called 'ease of use' was identified as an important factor for empowering the working alliance in a blended format of CBT [47]. Another study that tested this framework in a Spanish sample that received self-guided or low intensity supported

iCBT, also found that the digital programme and 'ease of use' played an important role in forging the working alliance [214]. Moreover, an RCT on the effects of the user interface on treatment engagement in a self-guided digital problem-solving programme, found that participants who were allocated to an optimised user-interface (i.e., based on user experience design principles with automated features) showed significantly greater engagement to the intervention, as measured by intervention use and the total and mean number of generated solutions across the therapeutic task, when compared to those allocated to the basic user-interface (e.g., that included less automation) [250]. Taken together, these findings point to the importance of the digital program's functionality, although further research is required to investigate this quantitively.

7.8.3 Limitations

Several study limitations should be noted. First, the E-COMPARED study collected working alliance data at a single point, at the end of the intervention for both treatment arms, which largely coincided with the 3-month follow-up assessments. While post-treatment measurement of the working alliance is widely used in clinical trials [37,229], the prevailing view is that the alliance should be measured during early stages of therapy, typically within the first five sessions, as well as at different intervals across treatment. However, the varied number of face-to-face sessions between the nine country-sites (e.g., 5 to 10 sessions), would have posed significant challenges for the systematic data collection required in a trial [13,230–232]. Second, the heterogeneity of interventions offered in the TAU arm prevent the study from conclusively tying causation to a particular intervention. As a result, a subset of the population comparing b-CBT with face-to-face CBT was conducted, thus the full sample could not be used. Third, the study engages in multiple comparisons, which may increase the risk of type 1 error [233]. Nevertheless, considering the exploratory nature of this analysis, and that different outcomes are likely to be highly correlated, a multiple adjustment comparison was not deemed necessary [233]. Fourth, a substantial amount of data was missing for WAI-SR-T and the PHQ-9 scales. Although it is recommended for multiple imputation to be conducted with less than 50% missing data, multiply imputing data is still more reliable than other approaches under the MAR assumption [186]. The results of the analysis are valid under the MAR assumption, which we believe to be plausible because the effect of country-site appears to affect missingness of the main outcome variables. This is supported by chi-squared tests that indicate significantly higher rates of missing data for the PHQ-9 and WAI-SR-T across some country-sites compared to others. Multiple imputation is associated with greater power, estimate precision, low bias, or no harm [251]. However, the validity of the approach depends on the MAR assumption being correct [179]. The MAR assumption can only be based on 'reasonable evidence' and cannot be tested or differentiated from the missing not at random assumption [183]. For this reason, it is important to acknowledge that any missing data is a source of bias, and the method adopted to address missing data in my thesis will rely on assumptions that cannot be tested. The

quantitative results from my thesis should be interpreted with caution, and future research should conduct a sensitivity analysis to differentiate between MAR and missing not at random (MNAR) or replicate this study to verify the findings [179].

Despite these limitations, the data from this study were generated in a multinational pragmatic RCT, that involved eight country-sites, recruited therapist participants from both primary and specialised mental health services, and applied b-CBT using five different iCBT programmes, treatment dosages and blended formats, thereby increasing the generalisability of our findings.

7.8.4 Implications of the findings

The findings of our study suggest that therapists can establish a working alliance that may positively influence treatment outcomes in a b-CBT intervention for depression. While the literature has mainly focused on client ratings of the working alliance to predict treatment outcomes [13], our study indicates that measuring the therapist working alliance can explain additional variance in client depression scores post-treatment, above and beyond client working alliance ratings. Therapists' working alliance should therefore be considered when measuring the working alliance in b-CBT interventions for depression.

The usability of the digital programme may influence the association between the working alliance and treatment outcomes. Taking our findings together with the qualitative literature on the important role of the digital programme [36,47,48,214,252], highlight the importance of building intuitive digital tools and the provision of appropriate therapist training on how to use the digital programme. Digital navigators maybe used to assist therapists in processing data or addressing technical issues to enable a smoother delivery of the b-CBT intervention [240]. The user-interface should not only be developed to consider clients' experiences of using the digital programme, but also consider therapists' needs, to ensure that they are comfortable in building and optimising the working alliance in a b-CBT setting.

7.8.5 Future research

A lack of confidence in delivering b-CBT may have resulted in similar working alliance scores between b-CBT and face-to-face CBT in TAU. While this is only speculative, future research should build on research conducted prior to the COVID-19 pandemic when the use of DMHI were less common [48]. This will enable an updated understanding of the working alliance in b-CBT considering widespread exposure to digital tools within mental health care following the COVID-19 pandemic [25,253]. Future research should also attempt to understand if other programme related factors reported to enhance working alliance in b-CBT (i.e., accessibility, interactivity, aesthetic appeal, self-directed use) can directly impact the working alliance and treatment outcomes, to provide better insights on how the

working alliance can be optimised. Finally attempts should be made to replicate this study with different iCBT programmes, approaches to blending treatment, and mental health practitioners, to explore if the findings of this study apply to other interventions, treatment dosages and mental healthcare providers.

7.8.6 Conclusion

Our findings indicate that while therapists ratings of the working alliance did not differ in TAU compared to b-CBT, their working alliance ratings were associated with symptom reduction in b-CBT. Our study was the first to find that higher therapist system usability scores influenced an inverse association between higher therapist rated bond subscale scores and lower client depression scores post-treatment. Collectively our findings suggest that the therapist working alliance may influence treatment outcomes, and that the ease of use of digital technologies may augment the strength of the alliance-outcomes association in b-CBT, although further research is required to establish a cause and effect.

Author contribution

The concept of design was developed by Doukani, with significant contributions by Araya, Free and Ritsuko. Asmae drafted the manuscript and led on all revisions of the manuscript, with significant contributions from Quartagno, Sera, Michelson, Kakuma, Free and Araya. Data were collected by the E-COMPARED consortium. Data acquisition was led by Doukani, and contributions from Araya, Kakuma, Cerga-Pashoja. Administrative support and approval relating to the acquisition was provided by Riper, Kleiboer, and Draisma. The statistical analysis plan was developed by Doukani, with significant contributions from Quartagno and Sera. All statistical analyses were conducted by Doukani. Data interpretation was led by Doukani, and significantly contributed to by Quartagno and Sera.

Conflict of interest disclosures

None declared.

7.9 Summary of chapter 7 and introduction to chapter 8

In the previous chapter, I presented the findings of a secondary analysis, in which I found that therapist ratings of the working alliance were similar between blended cognitive behavioural therapy (b-CBT), and face-to-face CBT in treatment as usual. However, higher therapist working alliance ratings were significantly associated with improvements in depression scores in the b-CBT group, even when controlling for client-ratings of the working alliance. Moreover, there was a significant interaction between therapist rated system usability and the working alliance bond subscale scores, in which higher therapist system usability scores were associated with higher working alliance bond scores and lower client depression scores in b-CBT. However, significant interactions were not found for other subscale scores.

The discussion chapter that will follow, will look across all findings to draw links between papers 1 to 4, provide crosscutting conclusions using a mixed methods approach to evaluate the working alliance in a b-CBT intervention for depression.

Chapter 8: Discussion

8.1 Introduction to chapter 8

Chapter 8 will provide an analysis of the results, which will delve into the meaning, importance, and relevance of the findings of my thesis using a mixed methods interpretation. This chapter will begin by providing a recap of the aims, objectives (*Section 8.2*), and a brief summary of the findings (S*ection 8.3*). Three conclusions will be drawn based on all findings using a mixed methods interpretation (*Section 8.4*). This will be followed by examining the implications of the findings (*Section 8.5*). The chapter will then discuss the overarching strengths, limitations, and methodological considerations of my thesis (*Section 8.6*). This chapter will end by providing future research and clinical recommendations (*Section 8.7)* and some general conclusions from the findings of my thesis *(Section 8.8*).

8.2 Recap of aims, objectives and findings

The working alliance is an important mechanism of change in psychological therapies. However, the emergence of digital mental health interventions (DMHIs) in mental health care, such as internet-based programmes has raised new questions about the nature of the working alliance, that is little understood in a context of blended cognitive behavioural therapy (b-CBT) [26,29,102]. My thesis aimed to evaluate the working alliance from clients' and therapists' perspectives in a b-CBT intervention, and when compared to usual care, for adults with depression in the E-COMPARED trial [23] in Europe, using a mixed methods approach. My thesis has eight objectives, that are addressed across four papers, listed below:

Paper 1

Objective 1: Qualitatively examine clients' working alliance demands in b-CBT to adapt Bordin's [6,7] working alliance theory for a b-CBT intervention for depression, in primary care services in the UK.

Paper 2

Objective 2: Qualitatively examine PWPs' experience of the working alliance in a b-CBT intervention for depression, in primary care services in the UK.

Paper 3

Objective 3: Test the difference in client working alliance scores between b-CBT versus face-to-face CBT in treatment as usual (TAU) for depression at 3-month (post-randomisation) assessments using a subset of the pooled E-COMPARED trial data.

Objective 4: Determine if client working alliance scores are associated with depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

Objective 5: Test for an interaction between client system usability and working alliance scores, on the association between the client working alliance and depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

Paper 4

Objective 6: Test the difference in therapist working alliance scores, between b-CBT versus face-to-face CBT in TAU for depression at 3-month assessments using a subset of pooled E-COMPARED trial data.

Objective 7: Determine if therapist working alliance scores are associated with client depression scores at 3-month assessments and when controlling for client working alliance scores, in b-CBT using pooled E-COMPARED trial data.

Objective 8: Test for an interaction between therapist system usability and working alliance scores, on the association between the therapist working alliance and client depression scores at 3-month assessments in b-CBT using pooled E-COMPARED trial data.

8.3 Summary of findings

Client qualitative interviews revealed a new working alliance dimension called 'digital heuristics', which promotes active engagement, self-discovery, and autonomous problem-solving (Objective 1) [47]. Therapists' qualitative interviews outlined barriers and facilitators to fostering the working alliance with clients in relation to experiences of time in b-CBT, the functionality of the digital programme, ability to tailor b-CBT, and confidence in delivering b-CBT (Objective 2) [48]. Quantitative client ratings of the working alliance were significantly higher in b-CBT compared to face-to-face CBT in TAU for clients, but not for therapists (Objectives 3 and 6). Higher client and therapist working alliance scores were associated with improvements in depression scores in b-CBT (Objectives 4 and 7) and were influenced by programme usability scores (Objectives 5 and 8) in b-CBT. See Appendix 19 for dissemination activities associated with the findings of my thesis.

8.4 Mixed methods interpretation of findings

Looking across all of my PhD findings, three important conclusions emerged about the working alliance in b-CBT. First, blended delivery of CBT appears to enhance the working alliance compared to face-to-face CBT (Conclusion i). Second, the working alliance needs in b-CBT are also directed to the digital programme through a newly emerging factor, called *Usability Heuristics* (Conclusion ii). Third, the therapists' ability to effectively foster a working alliance in b-CBT may depend on the support received at an individual and organisational level (Conclusion iii). The following sections expand on each of these conclusions.

Conclusion i: Blended delivery of CBT may enhance the working alliance compared to face-to-face CBT

This conclusion is supported by findings from both the quantitative and qualitative components of my thesis. The quantitative analysis that tested the effect of treatment condition (b-CBT versus face-to-face CBT in TAU) on client ratings of the working alliance (i.e., paper 3), found that higher working alliance scores were significantly associated with the b-CBT arm compared to TAU**.** Client ratings of the working alliance were also associated with depression scores in the b-CBT arm at 3-month follow-up assessments. It should also be noted that despite the fact that therapists' ratings of the working alliance did not significantly differ between treatment conditions, a significant association between higher working alliance and lower depression scores at 3-months assessments was found in the b-CBT arm.

Qualitative findings highlight that b-CBT can provide additional working alliance benefits. For example, client participants in the UK unanimously expressed their preference for a blended format of CBT compared to having only face-to-face sessions [47]. Moreover, the findings from therapist qualitative interviews revealed a host of factors that facilitated the working alliance in b-CBT, including experiencing time saving benefits that enabled therapists to build a stronger bond with the client [48]. Other facilitators included having access to a wider toolkit through the digital programme, while being able to tailor the therapeutic task, through both the digital programme but largely through face-to-face sessions [48]. Although these findings are limited to select therapists in the UK, similar reports have been documented in the qualitative literature, in which therapist perceived blended and guided internet-based interventions to enable the building of rapport, facilitate the active monitoring of clients and extend the time needed to develop a client–therapist alliance [138,254]. Taken together, these findings appear to suggest that the blended CBT format may strengthen the working alliance.

To my knowledge, my PhD is the first study to find a difference in client working alliance ratings between b-CBT and face-to-face CBT in TAU. The few available studies that evaluated the working alliance in b-CBT did not find an effect for treatment condition (b-CBT versus face-to-face CBT) or a

significant association between client working alliance scores and treatment outcomes [41,43,46]. However, one study did find a significant association between therapist-rated working alliance, and depression scores post-treatment [41]. Due to the few available studies evaluating the working alliance in b-CBT, and the heterogeneity in study designs and interventions offered (e.g., measuring the alliance at different time points [41], using different, measures of depression [46], digital programmes [41,43] and treatment dosages [41,43,46]), it is not possible to determine the reason for the lack of congruence between the findings of my thesis and the available literature. One speculation is that these studies used comparatively smaller sample sizes (i.e., ranging between 38 and 73 in the b-CBT arm) that might have prevented the analysis from detecting an effect [41,43,46]). Nevertheless, future research should aim to profile features of research studies and/or interventions that lead to significant alliance-outcome associations.

Conclusion ii: Working alliance needs are directed to the digital programme through ***usability heuristics***

This conclusion is supported by both qualitative, and quantitative findings of my thesis. Qualitative interviews with clients revealed that working alliance needs were also directed towards the digital programme, through a new working alliance dimension called *usability heuristics*. This refers to the 'active engagement, self-discovery, and autonomous problem-solving, in b-CBT' [47:p.9]. Usability heuristics appears to take on a supportive role within therapy that is parallel to Bordin's [6,7] bond. For example, having a digital programme that is accessible, interactive, easy to use, aesthetically pleasing, and promotes autonomous self-directed use may facilitate the clients' completion of the therapeutic tasks and goals, away from the clinic when their therapist might not be available to provide support [47]. These findings were also reflected in therapist qualitative interviews in which aspects of the digital programme were reported to either positively or negatively impact the working alliance (e.g., accessing a wider toolkit to work on the goals and task and having more time to build a bond, versus experiences of poor programme functionality, respectively) [48]. *Figure 8.1* provides a visual presentation of Bordin's [6,7] bond, task, and goals, produced by Henson and colleagues [15: p.270], that has been adapted to demonstrate the role of usability heuristics [47].

Figure 8.1. Working alliance in a blended cognitive behavioural therapy intervention for depression. The figure has been adapted to include usability heuristics depicted by the blue handrail. This figure is an adaptation of Henson et al. [15: p.270] patient-app model

The working alliance for the b-CBT framework developed in paper 1 [47] was recently tested in qualitative interviews that explored the working alliance in a clinical trial that offered self-guided and low-intensity internet-based CBT interventions for depression in community health services in Spain [214]. The findings revealed that the main categories (i.e., goals, task, bond, and usability heuristics) and all respective sub-categories were endorsed across participants allocated to self-guided and minimally guided internet-based CBT (iCBT) [214]. See Figure 8.2 for a comparison of the original framework by Doukani and colleagues [47: p.9], and the framework based on the Spanish sample developed by Barceló-Soler and colleagues [215: p.7]. Several qualitative studies from unguided digital mental health programmes have also emphasized the importance of considering the contribution of the digital programme in the alliance building process. For example, these studies have found that unique or non-traditional alliance features may stem from the digital programme, including experiences of higher levels of flexibility, control, independence over treatment [34,254], availability, interactivity [35,36], responsiveness, personalisation, and client initiative [35]. Moreover, therapists' perspective of guided and blended online interventions highlight the importance of being able to personalise the intervention, and that a poorly functioning digital programme in a b-CBT intervention may hinder the working alliance [137], and burden practice more broadly [237].

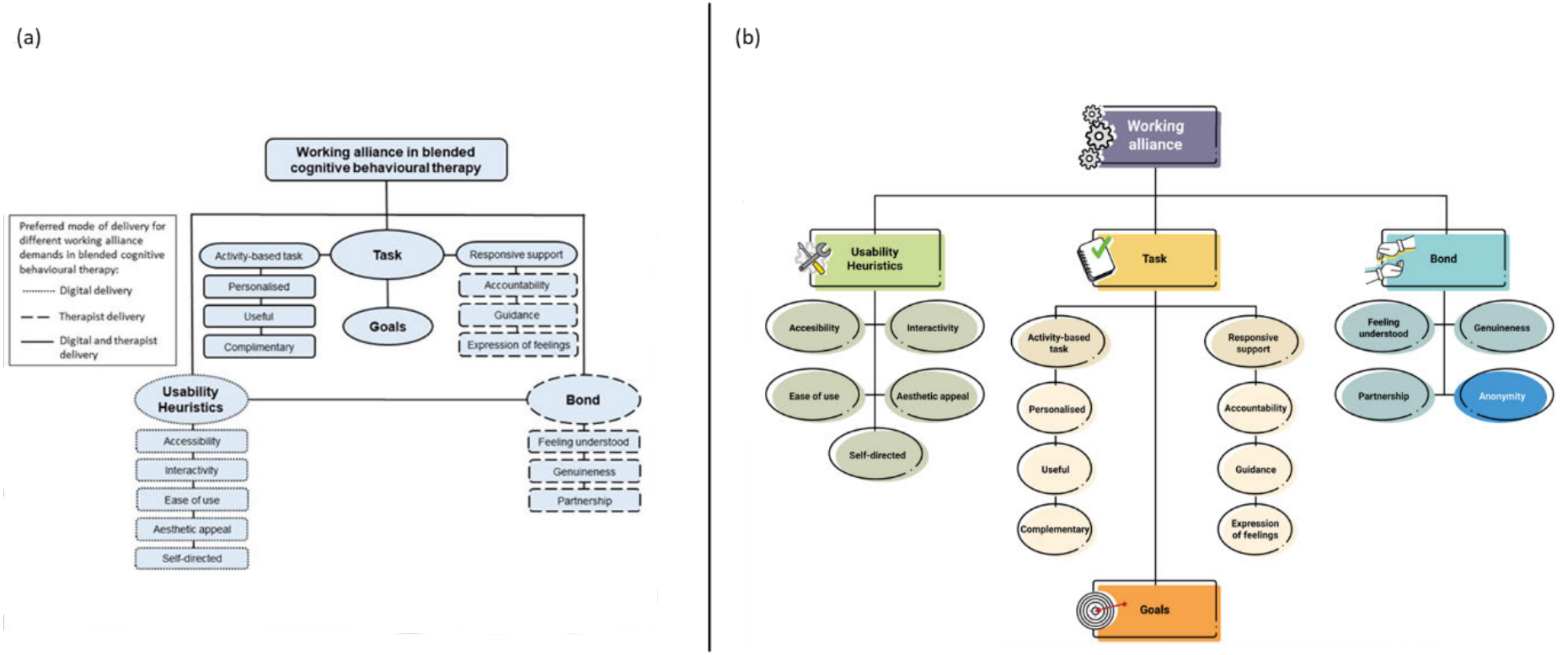


Figure 8.2. Client working alliance needs in, (a) blended cognitive behavioural therapy intervention for depression in the UK [47: p.9], and (b) low-intensity online CBT intervention in primary care in Spain adapted from Doukani et al. [215: p.7]

A notable finding from my thesis is that only the goals and task subscales, but not bond, were significantly associated with better treatment outcomes for both client and therapist ratings in b-CBT. These results are consistent with a narrative review of the working alliance in guided iCBT, that also found that treatment outcomes were largely significantly associated with task and goals but not the bond subscale [40]. While this is only speculative, these findings may suggest that the bond is less relevant, in a task focused intervention such as CBT in which the therapeutic task was completed through the digital programme [8,127]. It is likely that support with the goals and the task may have largely been dependent on 'usability heuristics' as a model of support.

One component of 'usability heuristics' was partially and preliminarily tested in the quantitative components of my thesis. The system usability scale [148] that measured programme usability on the E-COMPARED trial [23], was used as a proxy measure of the ease of use, which is a sub-category of usability heuristics [47]. Interaction terms were generated between system usability and the working alliance (i.e., composite and all subscale scores) to investigate the association between the working alliance and client depression scores, at 3-month assessments. The interaction term between system usability and client rated goals and task working alliance scores was found to be significant and appeared to lead to stronger effects between higher working alliance, and lower client depression scores.

Although further research is required to validate usability heuristics (and categories there in), as an additional alliance building dimension in b-CBT, these findings add further weight that the digital programme should be considered when conceptualising and assessing the quality of the working alliance in a blended format of CBT for depression.

Conclusion iii: The therapists' ability to foster a working alliance in b-CBT depends on individual and organisational support

This conclusion is also supported by findings from the qualitative and quantitative components of my thesis. Qualitative interviews with therapists in the UK highlighted a number of barriers to fostering a working alliance, that included feeling a lack of confidence around delivering the b-CBT intervention, concerns that the intervention did not align with service structure and workflows, and experiencing sub-optimal digital programme flexibility and functionality [48]. In alignment with these findings, a study that explored clients' experiences of a transdiagnostic blended intervention for emotional regulation, found that perceiving a therapist to have limited knowledge of the intervention negatively impacted the clients' perception of the therapeutic relationship [254]. A qualitative study on therapists' perspectives of b-CBT for depression conducted on the E-COMPARED study, found that programme usability problems led to frustration in clients and therapists, while a 'lack of customisability and decision making concerning the b-CBT intervention negatively impacted therapists' perception of the therapeutic alliance

[137]. Moreover, a study on the therapeutic relationship and service-user satisfaction found that having a high work load hindered clients' impression of the therapeutic relationship [252].

Interestingly, when exploring the influence of therapists' ratings of system usability on the alliance-outcome association in my thesis (in paper 4), only the interaction term between system usability and bond scores were significant. It should be noted that therapists' ratings of bond were only significantly associated with client depression scores, after entering an interaction term with therapist system usability scores. These findings suggest that better therapist experiences of the digital programme, led to an association between higher bond scores, and lower client depression scores at 3-month assessments. While these findings are preliminary, they are consistent with findings from the therapist qualitative interviews, in which a lack of confidence in delivering the b-CBT intervention, and concerns around the functionality of the digital programme were perceived to hinder therapists' perceptions of the working alliance [48], and thus my thesis contributes towards addressing this important future direction for research. Nevertheless, these findings are from a cross-sectional sample, and require the use of an RCT design and appropriate structural modelling to establish a moderating effect of system usability between the working alliance and treatment outcomes [255].

Finally, the composition of the sample used in the b-CBT arm of the E-COMPARED study were largely female (67%), middle-aged (mean age 39 years, SD=13), with a higher level of education (47%), and that presented with moderate depression. These findings appear to align with samples observed in iCBT trials for depression in Europe, that consisted of 58% to 78% of women [238,239,256], had a mean age of 35 to 42 years [238,239,256], and a high educational attainment that accounted for 48% and 67% of trial samples [238,239]. It should be noted that at a global level, being female [257], and older age [258,259] are characteristics that pose risks for experiencing depression. Moderate depression was also the most common presentation at baseline within iCBT trials (Mean=12, SD=4.3) [33], guided iCBT for depression in routine care (Mean=15.14; SD=5.30) [238], and blended CBT, in which moderate depression accounted for 73.9% of the sample [256]. Based on this data, the E-COMPARED trial sample appears to be descriptively representative of clinical samples in iCBT trials that were largely based in Europe [33,238,239,256,258,259]. While participant characteristics have not been investigated in relation to the working alliance and blended CBT interventions, there is some evidence that older age [118,194–197], being female [118,194,195,198,199], and having a higher level of education [194,195,200,201], may increase engagement to iCBT, while being male [198], and having higher symptoms severity [118,195,199,201] may lead to poorer engagement. These findings warranted the need to control for participant characteristics in my thesis, to partial out the effects described [202].

8.5 Implications of findings

The findings of my thesis offer new contributions to the digital mental health field, in which the qualitative components (papers 1 and 2) are the first to specifically examine qualitative experiences of the working alliance in a b-CBT context, for both clients and therapists [47,48]. Moreover, the quantitative study on client working alliance ratings (paper 3) was the first to find a significant effect for treatment group (b-CBT versus face-to-face CBT in TAU), and to test the influence of system usability on the association between the working alliance and treatment outcomes in a b-CBT intervention for depression. International, inter-disciplinary, multi-stakeholder consensus studies have identified the alliance as an important consideration for future research in DMHIs [26,102], and thus my thesis aims to contribute towards addressing this important direction for research.

Specifically, my thesis may contribute to the advancement of the digital mental health field in four key directions. First, my findings suggest that using a blended approach to delivering CBT can lead to better experiences of the working alliance that may lead to enhancements in care and outcomes. While further research is required to replicate the findings from my thesis, these findings may indicate that the use of the digital programme could potentially be leveraged to enhance the working alliance by not only ensuring that the goals, task, and bond are effectively established, but to also empower 'digital heuristics', to provide clients with an increased sense of control and autonomy over their treatment in a supervised setting.

Second, the findings of my thesis also highlight the need to consider the digital programme when assessing the working alliance in a b-CBT intervention. To date, many studies (including the E-COMPARED study [23]) have employed traditional measures of the working alliance between the client and the therapist, that do not consider the impact of the digital programme [38,39], which risks only partially capturing the working alliance, thus leading to important blind spots that can impede engagement with treatment, and as a result hinder clinical outcomes.

Third, my findings in addition to current and future literature can also be used to anticipate and address potential barriers in relation to fostering the working alliance, through education, training, practice and implementation, to provide guidance concerning the ideal conditions for the working alliance to be empowered. In support of this recommendation, a consensus study on the challenges and potential solutions for digital mental health, emphasised the importance of organisational change in facilitating effective implementation and delivery of DMHIs [26]. Moreover, several calls have been made to provide digital competency and e-mental health training to ensure that practical aspects of e-mental health delivery do not obstruct opportunities for the alliance to be fostered [25,26,240,260].

Fourth, reflecting beyond blended CBT interventions, the findings of my thesis may have important implications for blended treatments in other types of health care settings. While the topic of the alliance is generally allied with psychological care, the importance of this concept has also been recognised in different health disciplines, including (although not limited to) general practice [261,262], nursing [263], cancer care [264,265], and physical rehabilitation [266–269]. The alliance is a cross-cutting concept, as building a meaningful engagement to treatment bears relevance to all health disciplines [8]. Equally, poor engagement presents a momentous barrier to realising the full benefits of emerging digital tools, that have the potential to expand the health workforce and bridge health care inequalities worldwide [260]. The work of understanding the alliance is especially pertinent following the COVID-19 pandemic, in which digital technologies were used to support communication and information dissemination, and provide different levels of health services, among other domains of support [26]. In Europe, calls have been made to further build on the progress made in digital health during the pandemic [142], in which deploying blended models of mental health care are proposed to increase the reach of treatment to both clinical and sub-clinical populations, in aid of building mentally resilient populations [143]. In England, a policy report on digital health and social care outlines plans to scale up digital self-help therapies, as well as widen access to digitally enabled therapies in Improving Access to Psychological Therapies (IAPT) [144]. The policy shifts towards blended self-care models further emphasises the importance of developing a better understanding of how such interventions can optimize active ingredients, and dimensions of engagement, such as the working alliance. Thus, the findings of my thesis may provide insights around the client and therapist working alliance needs, the quality of the working alliance experienced, and aspects of the digital intervention that may impact the working alliance, as a starting point, to help inform future research concerning the alliance in other health care settings adopting blended care.

8.6 Strengths, limitations and methodological considerations

There are several strengths, limitations, and methodological considerations associated with my thesis as a whole (please note that study specific limitations are outlined in Chapters 4 to 7).

8.6.1 Strengths

My thesis engaged patient and public involvement (PPI) to help shape the design of my research, ensuring that the objectives of my thesis align with service-user needs, thereby increasing the relevance to those accessing blended intervention for depression in healthcare settings [164]. Another strength associated with my thesis is the use of a mixed methods design, which allowed me to verify aspects of knowledge, as well as explore the unknowns around the working alliance within a novel blended format

of CBT [166]. Finally, data from my thesis was drawn from a pragmatic RCT, that, to my knowledge, is the largest sample used to investigate the working alliance in a b-CBT intervention for depression when compared to TAU. The RCT design minimises bias, confounding factors, and enables direct comparison with routine care for depression, to establish differences in the working alliance quality and that increases generalisability.

8.6.2 Limitations and methodological considerations

Several limitations and methodological challenges should be noted. First, the working alliance on the E-COMPARED trial [23] was measured during the first follow-up assessment at 3-months, which corresponds to the end of treatment for 78% of the sample. While taking measurement at the end of treatment is a widely used method in clinical trials [13,229] and when evaluating the alliance in DMHIs [38–40], the dominant view is that measurement should be taken at the start of therapy, typically within the first five sessions [13,230–232]. This is because early measurement is generally considered to be a more robust time point to estimate the association between treatment outcomes, and dropout rates, compared to mid and late phases of treatment [230,231]. Future research should therefore measure the working alliance early in therapy to understand if results differ or remain consistent when taking measurement during later phases of therapy.

The second limitation relates to the lack of representativeness of the qualitative findings, as data were only collected from one country-site, whereas quantitative secondary data were collected across 8-9 country-sites, that applied different digital platforms (n=5), formats of blending sequences (n=9), and recruited patients from different types of services (e.g., primary, and specialised services). The links that have been made between the qualitative and quantitative data should therefore be interpreted with caution. Nevertheless, it is noteworthy that the findings of the qualitative paper appear to align with the qualitative literature on the alliance [34–36,138] and that provide accounts of the alliance in b-CBT from other country-sites on the E-COMPARED study [270,271]. Moreover, while the data used to adapt Bordin's [6,7] working alliance was only drawn from the UK, the findings of this study were entirely endorsed by clients allocated to minimally guided or unsupported iCBT in a Spanish sample [214]. This suggests that the adapted framework from my thesis may be relevant to contexts outside of the UK.

Third, data across the TAU arm could not be used in its entirety because information about the treatments allocated to clients in TAU were not collected within the E-COMPARED trial [23]. The heterogeneity of interventions offered in TAU prevent the study from tying causation to a specific comparator group [272]. As a result, my thesis attempted to address this limitation by using a subset of country-sites that offered face-to-face CBT in the TAU arm, which showed comparable results to the

main findings. The small sample size may have resulted in non-significant results when comparing treatment conditions when using therapist ratings of the working alliance.

Fourth, another methodological consideration was that the measurement scales used in the E-COMPARED trial [23] for clients [145] and therapists [18]) were used to evaluate the working alliance in a dyadic partnership involving the patient and the therapist, and was not developed or validated to consider the influence of the digital programme. My thesis attempted to address this limitation by conducting qualitative interviews that unearthed client and therapist working alliance needs within a b-CBT context. The quantitative papers also attempted to investigate working alliance features identified in the conceptual framework (i.e., ease of use), by investigating the influence of system usability scores on the alliance-outcome association.

Fifth, data collection for my thesis was conducted between 2015 and 2017, before the COVID-19 pandemic. Virus containment measures prompted by the pandemic are widely reported to have accelerated uptake of digital technologies, which might in turn have created greater familiarity and confidence in using digital technologies to aid psychological care [25,26,260]. However, this is likely to largely be true for teleconferencing technologies and it is not clear if the adoption of digital tools in mental health services increased [26]. A 2023 consensus study, involving an international panel of experts on digital mental health innovations, concluded that adapting services to aid therapists to deliver hybrid approaches to mental health treatments was critical for fully harnessing the benefits of digital mental health interventions [26]. Moreover, the readiness of digital technologies such as IT and mobile infrastructure, usability of software, and timely access to patient data were found to present barriers in general practice following the pandemic [273]. The findings of this thesis therefore add further weight concerning the importance of adapting services to support the implementation of digital tools, to establish the necessary conditions for a high-quality working alliance to be fostered.

Sixth, an important limitation concerns the substantial amount of missing data for the working alliance and depression measures (which is up to 40% in a given treatment condition). Missing data in this study has led to a loss of information required for an ITT analysis, which may result in a loss of statistical power, precision, and biased estimates, that can culminate in misleading conclusions if not appropriately and carefully addressed [251,274]. Missing data from papers 3 and 4 were addressed using the multiple imputation approach. This approach fills in missing values by generating multiple imputations that use predictive distributions from observable data to generate plausible estimates [274,275]. Multiple imputation was used because missing data was deemed plausible under the MAR assumption, and because missing data did not exceed the 40% to 50% rule of thumb for producing reliable estimates (See Section 3.6.3 for further information on the use of multiple imputation approach for missing data)

[186,203]. It should also be noted that missing data under the missing at random assumption has been found to provide reliable estimates even when 90% of data are missing from continuous variables [186]. Multiple imputation is also widely considered to reduce bias under the MAR assumption, and when compared to complete-case analysis and single imputation methods [251,274], as the approach is able to increase power, reduce bias, and produce estimates with greater precision in aid of reducing false positive, or false negative conclusions [275]. While multiple imputation is associated with greater accuracy, or no harm, the validity of the approach depends on the MAR assumption being correct [179]. However, the MAR assumption can only be based on 'reasonable evidence', and cannot be tested or differentiated from missing not at random [203]. For this reason, it is important to acknowledge that any missing data is a source of bias, and the method adopted to address missing data in my thesis will rely on assumptions that cannot be tested. The quantitative results from my thesis should be interpreted with caution, and additional research that takes appropriate steps to reduce missing data, may be required to verify or replicate the findings from papers 3 and 4 [251].

8.7 Future research and clinical recommendations

A number of recommendations are proposed for future research and clinical practice.

8.7.1 Future research

8.7.1.1 Addressing methodological limitations of my thesis

Several recommendations can be made for future research. Efforts should build on my thesis by addressing the methodological limitations pertaining to the E-COMPARED trial [23], through: (a) measuring the working alliance during early phases of the b-CBT intervention; (b) including a mix of intention-to-treat and per-protocol populations, by collecting data on treatment completion and adherence across both treatment conditions; (c) recruiting a sample of participants that reflects the original sample of the study for qualitative interviews, to explore if the findings of my thesis can be replicated, and (d) compare b-CBT with face-to-face CBT across all sites within the trial

.

8.7.1.2 Building on the findings of my thesis

The working alliance framework adapted for a b-CBT intervention for depression, in paper 1 [47], should be further tested and adapted into a generic model that can be applied across all blended psychological interventions. This model will be synonymous with Bordin's [6,7] original conceptualisation which he presented as a generic model for in-person psychological therapies. A recent paper that tested my framework, validated all categories and subcategories, with clients in primary mental health services, who were allocated to unguided and minimally guided iCBT in a clinical trial in Spain [214]. These findings add strength to the framework's reliability and validity. However, future

research should therefore build on these efforts, by further testing the framework across different digital mediums (e.g., mobile applications, gamification, virtual reality), and clinical populations. Testing this framework in different contexts will also enable a granular understanding of intervention and population specific working alliance needs that can be used to adapt the generic model for specific psychological interventions. Working alliance measurement tools intended for blended psychological interventions, should be adapted to consider the role of the digital programme as well as the therapist. The adaptation of the measure may draw on the working alliance in b-CBT framework from my thesis [47].

8.7.1.3 Translational research

Building on the findings of my thesis, and the research recommendations outline above, I aim to translate the findings of my thesis to deliver impact in the digital mental health space across public healthcare services and industry. This will involve conducting research to further develop and expand the working alliance theory to enable intervention developers to understand the behavioural techniques and actions that are required to promote different working alliance dimensions and categories in a digital programme, within a blended context. Building on current working alliance conceptualisations [6,7,47], my framework will use Mohr and colleagues Behavioural Intervention Technology (BIT) model [276], to define specific behavioural change strategies (how), technological characteristics (what), and workflows (when) required to empower the working alliance in a psychological digital programme. While there are a range of models that use different approaches to affect behavioural change (e.g., motivational, fear-based, stage-based and so forth) [277], this model will be the first to harness a relational approach to establishing, developing and maintaining a working alliance that is argued to be critical for influencing positive clinical change in all psychological therapies, including interventions that include digital technologies.

8.7.2 Clinical Recommendations

The evaluation of the working alliance in b-CBT should adopt measurement scales that capture client working alliance needs in relation to the therapist and the digital programme to aid clinical practice. This will enable clinicians to comprehensively gauge the alliance that incorporates all components of treatment, in order to promote engagement and positive treatment outcomes in blended models of psychological therapies.

Mental health services should ensure that therapists are equipped with relevant education and training on how to effectively establish, develop, and maintain a working alliance in blended psychological interventions, which appears to differ from in-person therapy. Working alliance facilitators and barriers identified in my thesis [97], and in the wider literature in digital mental health, should be further

evaluated, synthesised, and disseminated within relevant professional training courses (e.g., Postgraduate Diploma in CBT) and across competency frameworks (e.g., IAPT core competency framework) [141].

Mental health services should assess organisational readiness for deploying blended psychological interventions, and take relevant steps to adapt service workforce, infrastructure, processes, and policies to ensure that therapists receive adequate time and support to effectively deliver a blended intervention, which in turn empowers an environment that facilitates the working alliance to be fostered. Efforts should be made to ensure that b-CBT can be effectively integrated into service-workflows, and that there are no constraints in time, in relation to completing additional duties associated with digital programmes (e.g., processing client information online, checking the client's progress on the digital programme) required for the effective implementation of b-CBT. In addition to this, a new workforce called digital navigators, proposed by Wisniewski and colleagues [240], should be adopted to buffer against therapists' toll of performing additional tasks associated with the digital programme and to help therapists navigate through digital technologies that are used within a blended approach. Digital navigators can help the client register on the digital programme, process and synthesis client outputs for the therapist, and address technical issues that arise during blended therapy [240]. Receiving this level of assistance can ensure therapists are not overburdened, thereby minimising associated barriers that negatively impact therapists' experiences of the working alliance. The utility of a new cadre of the mental health workforce should therefore be investigated. However, future research should therefore build on these efforts, by further testing the framework across different digital mediums (e.g., mobile applications, gamification, virtual reality), and clinical populations.

8.8 Conclusions

A mixed methods evaluation of the working alliance enabled a multi-layered understanding of the impact of blended delivery of CBT on the clients' and therapists' working alliance. My thesis addresses digital mental health priorities and future directions proposed by expert consensus studies, that emphasised a need to empower the alliance in DMHIs, amidst a landscape of growing digital mental health innovation and adoption [25,26,96].

My thesis advances the understanding of the working alliance by offering several new contributions to the literature. My findings suggest that the addition of a digital platform may optimise the working alliance when compared to face-to-face CBT, adding further support to calls for adopting blended models of mental healthcare. My thesis is the first to adapt the working alliance framework [6,7] to account for the blended context of CBT for depression, in which my thesis introduces a new working

alliance dimension that is specific to the digital programme called usability heuristics. Finally, my thesis highlights therapists' needs in relation to fostering a working alliance that includes, receiving support in delivering b-CBT at an individual level (e.g., blended therapy training) and service level (e.g., adjusting workflows and ensuring digital programme functionality).

My findings may hold important implications for clinical practice, service implementation, and how the working alliance is conceptualised in blended contexts. Future research and clinical recommendations should focus on adapting measurement scales for a b-CBT context, providing clinical training concerning blended delivery, and ensuring adaptations to service processes, to support therapists in their role.

The working alliance is critical for influencing positive treatment outcomes, through enabling clients to meaningfully engage in therapy. Developing a comprehensive understanding of the working alliance can help increase engagement in DMHIs, and fully leverage the benefits associated with digital interventions in blended care.

References

1. World Health Organization. Depression [Internet]. World Health Organization. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
2. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov;392(10159):1789–858.
3. Lam RW, Kennedy SH, McIntyre RS, Khullar A. Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment. Can J Psychiatry. 2014 Dec;59(12):649.
4. National Institute of Health, Excellence C. Depression in adults: treatment and management: NICE guideline short version [Internet]. London; 2018 May. Available from: https://www.nice.org.uk/guidance/gid-cgwave0725/documents/short-version-of-draft-guideline
5. BMJ Best Practice. Depression in adults: Symptoms, diagnosis and treatment [Internet]. 2019. Available from: https://bestpractice.bmj.com/topics/en-gb/55
6. Bordin ES. The generalizability of the psychoanalytic concept of the working alliance. Psychother Theory, Res Pract. 1979;16(3):252–60.
7. Bordin ES. Theory and research on the theraputic working alliance: New directions. In: Horvath AO, Greenberg Leslie S, editors. New York: John Wiley & Sons, INC; 1994. p. 13–37.
8. Norcross JC, Lambert MJ. Psychotherapy relationships that work II. Psychother Theory Res Pract Train. 2010;48(1):4–8.
9. Lambert MJ. Psychotherapy outcome research: implications for integrative and eclectic therapists. In: John C Norcross & Marvin R Goldfried, editor. Handbook of psychotherapy intergration. 1st ed. New York: Basic Books; 1992.
10. Flückiger C, Del AC, Wampold BE, Horvath AO. The Alliance in Adult Psychotherapy: A Meta-Analytic Synthesis. Psychotherapy. 2018 Dec;55(4):316–40.
11. Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in Individual Psychotherapy. Psychotherapy. 2011 Mar;48(1):9–16.
12. Horvath AO, Symonds BD. Relation Between Working Alliance and Outcome in Psychotherapy: A Meta-Analysis. J Couns Psychol. 1991 Apr;38(2):139–49.
13. Norcross JC, Wampold BE. Evidence-based therapy relationships: research conclusions and clinical practices. Psychotherapy (Chic). 2011;48(1):98–102.
14. Cavanagh K, Millings A. (Inter)personal computing: The role of the therapeutic relationship in E-mental health. J Contemp Psychother. 2013;43:197–206.

15. Henson P, Peck P, Torous J. Considering the Therapeutic Alliance in Digital Mental Health Interventions. Harv Rev Psychiatry [Internet]. 2019 Jul;27(4):268–73. Available from: https://journals.lww.com/hrpjournal/Fulltext/2019/07000/Considering_the_Therapeutic_Alliance_in_Digital.7.aspx
16. Horvath AO, Greenberg LS. Development and validation of the Working Alliance Inventory. J Couns Psychol. 1989;36:223–33.
17. Hatcher RL, Barends AW. Patients' view of the alliance of psychotherapy: exploratory factor analysis of three alliance measures. J Consult Clin Psychol [Internet]. 1996 Dec;64(6):1326–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8991319
18. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working Alliance Inventory-Short Revised (WAI-SR): psychometric properties in outpatients and inpatients. Clin Psychol Psychother [Internet]. 2010 May;17(3):231–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cpp.658
19. Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, et al. A review and critical appraisal of measures of therapist-patient interactions in mental health settings. Health Technol Assess (Rockv). 2008;12(24).
20. Horvath AO, Luborsky L. The role of the therapeutic alliance in psychotherapy. J Consult Clin Psychol. 1993;61(4):561–73.
21. World Health Organisation. Classification of Digital Health Interventions [Internet]. Geneva; 2018. Available from: http://who.int/reproductivehealth/topics/mhealth/en/.
22. Fairburn CG, Patel V. The impact of digital technology on psychological treatments and their dissemination. Behav Res Ther [Internet]. 2017 Jan;88:19–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28110672
23. 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 [Internet]. 2016 Aug;17(1):387. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27488181
24. WHO Euro. Depression in Europe: Facts and figures [Internet]. World Health Organization; 2019. Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/news/news/2012/10/depression-in-europe/depression-in-europe-facts-and-figures
25. 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.' Vol. 20, Internet Interventions. Elsevier B.V.; 2020.
26. Smith KA, Blease C, Faurholt-Jepsen M, Firth J, Daele T Van, Moreno C, et al. Digital mental

health: challenges and next steps. BMJ Ment Heal [Internet]. 2023 Feb;26(1):e300670. Available from: https://mentalhealth.bmj.com/content/26/1/e300670

27. National Institute for Health, (NICE) CE. Depression the treatment and management of depression in adults [Internet]. Laicester: UK: British Psychological Society; 2010. Available from: https://www.ncbi.nlm.nih.gov/books/NBK63740/
28. Fairburn CG, Patel V. The Global Dissemination of Psychological Treatments: A Road Map for Research and Practice. Am J Psychiatry [Internet]. 2014 May;171(5):495–8. Available from: http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.2013.13111546
29. Torous J, Hsin H. Empowering the digital therapeutic relationship: virtual clinics for digital health interventions. npj Digit Med [Internet]. 2018 Dec;1(1):16. Available from: http://www.nature.com/articles/s41746-018-0028-2
30. Torous J, Michalak EE, O'Brien HL. Digital Health and Engagement-Looking Behind the Measures and Methods. JAMA Netw open. 2020 Jul;3(7):e2010918.
31. Karyotaki E, Ebert DD, Donkin L, Riper H, Twisk J, Burger S, et al. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Vol. 63, Clinical Psychology Review. Elsevier Inc.; 2018. p. 80–92.
32. Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA. Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults With Depression: A Network Meta-analysis. JAMA Psychiatry [Internet]. 2019 Jul;76(7):700–7. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2730724
33. Karyotaki E, Efthimiou O, Miguel C, genannt Bermpohl FM, Furukawa TA, Cuijpers P, et al. Internet-Based Cognitive Behavioral Therapy for Depression: A Systematic Review and Individual Patient Data Network Meta-analysis. JAMA Psychiatry [Internet]. 2021 Apr;78(4):361–71. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2774861
34. Barazzone N, Cavanagh K, Richards DA. Computerized cognitive behavioural therapy and the therapeutic alliance: A qualitative enquiry. Br J Clin Psychol [Internet]. 2012 Nov;51(4):396–417. Available from: http://doi.wiley.com/10.1111/j.2044-8260.2012.02035.x
35. Clarke J, Proudfoot J, Whitton A, Birch M-R, Boyd M, Parker G, et al. Therapeutic Alliance With a Fully Automated Mobile Phone and Web-Based Intervention: Secondary Analysis of a Randomized Controlled Trial. JMIR Ment Heal [Internet]. 2016 Feb;3(1):e10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26917096
36. Tremain H, McEnery C, Fletcher K, Murray G. The Therapeutic Alliance in Digital Mental Health Interventions for Serious Mental Illnesses: Narrative Review. JMIR Ment Heal [Internet]. 2020 Aug;7(8):e17204. Available from:

/pmc/articles/PMC7442952/?report=abstract

37. Sucala M, Schnur JB, Constantino MJ, Miller SJ, Brackman EH, Montgomery GH. The therapeutic relationship in E-therapy for mental health: A systematic review. J Med Internet Res. 2012;14.

38. Pihlaja S, Stenberg J-H, Joutsenniemi K, Mehik H, Ritola V, Joffe G. Therapeutic alliance in guided internet therapy programs for depression and anxiety disorders – A systematic review. Internet Interv [Internet]. 2018 Mar;11:1–10. Available from: https://www.sciencedirect.com/science/article/pii/S2214782917300994

39. Wehmann E, Köhnen M, Härter M, Liebherz S. Therapeutic alliance in technology-based interventions for the treatment of depression: Systematic review [Internet]. Vol. 22, Journal of Medical Internet Research. JMIR Publications; 2020. p. e17195. Available from: http://www.jmir.org/2020/6/e17195/

40. Berger T. The therapeutic alliance in internet interventions: A narrative review and suggestions for future research. Psychother Res [Internet]. 2016 Jan;1–14. Available from: http://www.tandfonline.com/doi/full/10.1080/10503307.2015.1119908

41. Vernmark K, Hesser H, Topooco N, Berger T, Riper H, Luuk L, et al. Working alliance as a predictor of change in depression during blended cognitive behaviour therapy. Cogn Behav Ther [Internet]. 2019 Jul;48(4):285–99. Available from: https://www.tandfonline.com/doi/full/10.1080/16506073.2018.1533577

42. Kooistra, Ruwaard, Wiersma, van Oppen, Riper. Working Alliance in Blended Versus Face-to-Face Cognitive Behavioral Treatment for Patients with Depression in Specialized Mental Health Care. J Clin Med [Internet]. 2020 Jan;9(2):347. Available from: https://www.mdpi.com/2077-0383/9/2/347

43. Askjer S, Mathiasen K. The working alliance in blended versus face-to-face cognitive therapy for depression: A secondary analysis of a randomized controlled trial. Internet Interv [Internet]. 2021 Sep;25. Available from: https://pubmed.ncbi.nlm.nih.gov/34401364/

44. 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 [Internet]. Vol. 19, Journal of Medical Internet Research. Journal of Medical Internet Research; 2017. Available from: https://pubmed.ncbi.nlm.nih.gov/28916506/

45. Mathiasen K, Andersen TE, Riper H, Kleiboer AAM, Roessler KK. Blended CBT versus face-to-face CBT: a randomised non-inferiority trial. BMC Psychiatry [Internet]. 2016;16(1):432. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27919234

46. 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

[Internet]. 2014 Oct;14(1):1–11. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-014-0290-z

47. Doukani A, Free C, Michelson D, Araya R, Montero-Marin J, Smith S, et al. Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study. BMJ Open [Internet]. 2020 Sep;10(9):e036299. Available from: http://bmjopen.bmj.com/
48. Doukani A, Free C, Araya R, Michelson D, Cerga-Pashoja A, Kakuma Background R. Practitioners' experience of the working alliance in a blended cognitive–behavioural therapy intervention for depression: qualitative study of barriers and facilitators. BJPsych Open [Internet]. 2022 Jul;8(4):e142. Available from: https://www.cambridge.org/core/journals/bjpsych-open/article/practitioners-experience-of-the-working-alliance-in-a-blended-cognitivebehavioural-therapy-intervention-for-depression-qualitative-study-of-barriers-and-facilitators/8B6CDB300B27AA67F8F37877F38DD1CA
49. Kessler RC. The Costs of Depression. Psychiatr Clin North Am [Internet]. 2012 Mar;35(1):1. Available from: /pmc/articles/PMC3292769/
50. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Publishing; 2000.
51. Lecrubier Y, Sheehan D V, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry. 1997;12(5):224–31.
52. Shadrina M, Bondarenko EA, Slominsky PA. Genetics Factors in Major Depression Disease. Front Psychiatry [Internet]. 2018 Jul;9(JUL):334. Available from: /pmc/articles/PMC6065213/
53. National Research Council, of Medicine I. The Etiology of Depression. In: England MJ, editor. Depression in Parents, Parenting, and Children: Opportunities to Improve Identification, Treatment, and Prevention. Washington, DC: National Academies Press (US); 2009. p. 73–118.
54. Remes O, Francisco J, Templeton P. Biological, Psychological, and Social Determinants of Depression: A Review of Recent Literature. Brain Sci [Internet]. 2021 Dec;11(12). Available from: /pmc/articles/PMC8699555/
55. Wang J, Wu X, Lai W, Long E, Zhang X, Li W, et al. Prevalence of depression and depressive symptoms among outpatients: A systematic review and meta-analysis. Vol. 7, BMJ Open. BMJ Publishing Group; 2017.
56. Brådvik L. Suicide Risk and Mental Disorders. Int J Environ Res Public Health. 2018 Sep;15(9).
57. World Health Organisation. Depression and Other Common Mental Disorders Global Health Estimates [Internet]. Geneva; 2017. Available from:

http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf
58. Arias-de la Torre J, Vilagut G, Ronaldson A, Serrano-Blanco A, Martín V, Peters M, et al. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. Lancet Public Heal [Internet]. 2021 Oct;6(10):e729–e738. Available from: http://www.thelancet.com/article/S2468266721000475/fulltext
59. Vos T, Allen C, Arora M, Barber RM, Brown A, Carter A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct;388(10053):1545–602.
60. Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021 Nov;398(10312):1700–12.
61. Papakostas GI, Petersen T, Mahal Y, Mischoulon D, Nierenberg AA, Fava M. Quality of life assessments in major depressive disorder: a review of the literature. Gen Hosp Psychiatry [Internet]. 2004 Jan;26(1):13–7. Available from: https://www.sciencedirect.com/science/article/pii/S0163834303001142?via%3Dihub
62. Hammar Å, Årdal G. Cognitive functioning in major depression – a summary. Front Hum Neurosci [Internet]. 2009 Sep;3:26. Available from: http://journal.frontiersin.org/article/10.3389/neuro.09.026.2009/abstract
63. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, et al. Scaling-up treatment of depression and anxiety: a global return on investment analysis. The Lancet Psychiatry [Internet]. 2016 May;3(5):415–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2215036616300244
64. Department of Health. No health without mental health: a cross-government mental health outcomes strategy for people of all ages [Internet]. 2011. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/215808/dh_123993.pdf
65. World Health Organization. Mental health in the workplace [Internet]. World Health Organization . 2022. Available from: https://www.who.int/teams/mental-health-and-substance-use/promotion-prevention/mental-health-in-the-workplace
66. World Health Organization. Mental health [Internet]. World Health Organization. 2022. Available from: https://www.who.int/health-topics/mental-health#tab=tab_1
67. World Health Organization. 2011 mental health atlas [Internet]. Geneva; 2011. Available from: http://www.who.int/about/licensing/copyrig
68. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. 2004.
69. Van Beljouw I, Verhaak P, Prins M, Cuijpers P, Penninx B, Bensing J. Reasons and

determinants for not receiving treatment for common mental disorders. Psychiatr Serv [Internet]. 2010 Mar;61(3):250–7. Available from: https://ps.psychiatryonline.org/doi/10.1176/ps.2010.61.3.250

70. Winkler P, Krupchanka D, Roberts T, Kondratova L, Machů V, Höschl C, et al. A blind spot on the global mental health map: a scoping review of 25 years' development of mental health care for people with severe mental illnesses in central and eastern Europe [Internet]. Vol. 4, The Lancet Psychiatry. Elsevier Ltd; 2017. p. 634–42. Available from: http://www.thelancet.com/article/S2215036617301359/fulltext
71. Rössler W. The stigma of mental disorders: A millennia-long history of social exclusion and prejudices. EMBO Rep [Internet]. 2016 Sep;17(9):1250. Available from: /pmc/articles/PMC5007563/
72. British Medical Association. Measuring progress: Commitments to support and expand the mental health workforce in England [Internet]. London; 2020 Apr. Available from: https://www.bma.org.uk/media/2405/bma-measuring-progress-of-commitments-for-mental-health-workforce-jan-2020.pdf
73. Barbato A, Vallarino M, Rapisarda F, Lora A, Caldas De Almeida M. EU compass for action on mental health and well-being access to mental health MENTAL HEALTH CARE IN EUROPE-Consensus Paper [Internet]. Access to mental health care in Europe: Consensus paper . Brussels ; 2016. Available from: https://ec.europa.eu/health/sites/default/files/mental_health/docs/ev_20161006_co04_en.pdf
74. National Institute for Health, Excellence C. Depression: How common is it? [Internet]. 2022. Available from: https://cks.nice.org.uk/topics/depression/background-information/prevalence/
75. Moncrieff J. The antidepressant debate. Br J Psychiatry [Internet]. 2002;180(3):193–4. Available from: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/antidepressant-debate/74DCE8BB5098B73547486622E9CAECAA
76. Goldsmith L, Moncrieff J. The psychoactive effects of antidepressants and their association with suicidality. Curr Drug Saf [Internet]. 2011 Nov;6(2):115–21. Available from: https://pubmed.ncbi.nlm.nih.gov/21375477/
77. Antonuccio DO, Danton WG, DeNelsky GY, Greenberg RP, Gordon JS. Raising questions about antidepressants. Psychother Psychosom [Internet]. 1999 Jan;68(1):3–14. Available from: https://pubmed.ncbi.nlm.nih.gov/9873236/
78. Kirsch I, Moore TJ, Scoboria A, Nicholls SS. The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat. 2002 Jul;5(1).
79. Fenn K, Byrne M. The key principles of cognitive behavioural therapy. InnovAiT Educ Inspir Gen Pract [Internet]. 2013 Sep;6(9):579–85. Available from:

http://journals.sagepub.com/doi/10.1177/1755738012471029

80. David D, Cristea I, Hofmann SG. Why Cognitive Behavioral Therapy Is the Current Gold Standard of Psychotherapy. Front Psychiatry. 2018 Jan;9(JAN).

81. American Psychological Association. APA Clinical practice guideline for the treatment of depression across three age cohorts [Internet]. 2019. Available from: https://www.apa.org/depression-guideline

82. Beck Institute. What is Cognitive Behavior Therapy [Internet]. 2022. Available from: https://beckinstitute.org/get-informed/what-is-cognitive-therapy/

83. Wright JH. Cognitive Behavior Therapy: Basic Principles and Recent Advances. Focus (Madison) [Internet]. 2006 Apr;4(2):173–8. Available from: https://focus.psychiatryonline.org/doi/abs/10.1176/foc.4.2.173

84. American Psychological Association. APA Dictionary of Psychology [Internet]. 2023. Available from: https://dictionary.apa.org/

85. Wiles N, Thomas L, Abel A, Barnes M, Carroll F, Ridgway N, et al. Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: the CoBalT randomised controlled trial. Health Technol Assess. 2014;18(31):1–167.

86. Furukawa TA, Weitz ES, Tanaka S, Hollon SD, Hofmann SG, Andersson G, et al. Initial severity of depression and efficacy of cognitive-behavioural therapy: individual-participant data meta-analysis of pill-placebo-controlled trials. Br J Psychiatry [Internet]. 2017 Mar;210(3):190–6. Available from: https://pubmed.ncbi.nlm.nih.gov/28104735/

87. Gartlehner G, Wagner G, Matyas N, Titscher V, Greimel J, Lux L, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. BMJ Open [Internet]. 2017 Jun;7(6). Available from: /pmc/articles/PMC5623437/

88. Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. Lancet [Internet]. 2015 Jul;386(9988):63–73. Available from: http://www.thelancet.com/article/S0140673614622224/fulltext

89. Guidi J, Tomba E, Fava GA. The Sequential Integration of Pharmacotherapy and Psychotherapy in the Treatment of Major Depressive Disorder: A Meta-Analysis of the Sequential Model and a Critical Review of the Literature. Am J Psychiatry [Internet]. 2016 Feb;173(2):128–37. Available from: https://pubmed.ncbi.nlm.nih.gov/26481173/

90. Bockting CLH, Klein NS, Elgersma HJ, van Rijsbergen GD, Slofstra C, Ormel J, et al. Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive

relapse or recurrence (DRD study): a three-group, multicentre, randomised control. The lancet Psychiatry. 2018 May;5(5):401–10.

91. Cuijpers P, Koole SL, Van Dijke A, Roca M, Li J, Reynolds CF. Psychotherapy for subclinical depression: meta-analysis. Br J Psychiatry [Internet]. 2014 Oct;205(4):268–74. Available from: https://pubmed.ncbi.nlm.nih.gov/25274315/
92. Kolovos S, Kleiboer A, Cuijpers P. Effect of psychotherapy for depression on quality of life: meta-analysis. Br J Psychiatry [Internet]. 2016 Dec;209(6):460–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27539296/
93. López-López JA, Davies SR, Caldwell DM, Churchill R, Peters TJ, Tallon D, et al. The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. Psychol Med [Internet]. 2019 Sep;49(12):1937. Available from: /pmc/articles/PMC6712954/
94. Muñoz RF. Using evidence-based internet interventions to reduce health disparities worldwide. J Med Internet Res [Internet]. 2010 Dec;12(5):e60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21169162
95. Poppleton A, Gire N. mHealth: bridging the mental health gap in central and eastern Europe [Internet]. Vol. 4, The Lancet Psychiatry. Elsevier Ltd; 2017. p. 743–4. Available from: http://statystyka.policja.pl/st/
96. Torous J, Bucci S, Bell IH, Kessing L V, Faurholt-Jepsen M, Whelan P, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World Psychiatry [Internet]. 2021 Oct;20(3):318. Available from: /pmc/articles/PMC8429349/
97. Doukani A. Social Inclusion and mHealth. In: Liamputtong P, editor. Handbook of Social Inclusion [Internet]. Springer, Cham; 2022. p. 1–24. Available from: https://link.springer.com/referenceworkentry/10.1007/978-3-030-48277-0_109-4
98. Farvolden P, Denisoff E, Selby P, Bagby RM, Rudy L. Usage and longitudinal effectiveness of a Web-based self-help cognitive behavioral therapy program for panic disorder. J Med Internet Res [Internet]. 2005 Jan;7(1):e7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1550639&tool=pmcentrez&rendertype=abstract
99. Christensen H, Griffiths K, Groves C, Korten A. Free range users and one hit wonders: community users of an Internet-based cognitive behaviour therapy program. Aust N Z J Psychiatry [Internet]. 2006 Jan;40(1):59–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16403040
100. Gilbody S, Littlewood E, Hewitt C, Brierley G, Tharmanathan P, Araya R, et al. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT

trial): large scale pragmatic randomised controlled trial. BMJ [Internet]. 2015 Jan;351:h5627. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4641883&tool=pmcentrez&rendertype=abstract

101. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med. 2007 Mar;37(3):319–28.
102. Hollis C, Sampson S, Simons L, Bethan Davies E, Churchill R, Betton V, et al. Identifying research priorities for digital technology in mental health care: results of the James Lind Alliance Priority Setting Partnership. Lancet Heal Policy [Internet]. 2018; Available from: www.thelancet.com/psychiatry
103. Andersson G, Titov N. Advantages and limitations of Internet-based interventions for common mental disorders. World Psychiatry. 2014;13(1):4–11.
104. Barak A, Klein B, Proudfoot JG. Defining Internet-Supported Therapeutic Interventions. Ann Behav Med [Internet]. 2009 Aug;38(1):4–17. Available from: https://academic.oup.com/abm/article/38/1/4/4569461
105. 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. Pol Clin NCT02389660 Regist Clin NCT02449447 Regist. 2016;17(30).
106. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606–13.
107. Etzelmueller A, Vis C, Karyotaki E, Baumeister H, Titov N, Berking M, et al. Effects of internet-based cognitive behavioral therapy in routine care for adults in treatment for depression and anxiety: Systematic review and meta-analysis. J Med Internet Res [Internet]. 2020 Aug;22(8). Available from: https://pubmed.ncbi.nlm.nih.gov/32865497/
108. Luo C, Sanger N, Singhal N, Pattrick K, Shams I, Shahid H, et al. A comparison of electronically-delivered and face to face cognitive behavioural therapies in depressive disorders: A systematic review and meta-analysis. EClinicalMedicine [Internet]. 2020 Jul;24. Available from: http://www.thelancet.com/article/S2589537020301863/fulltext
109. Holst A, Björkelund C, Metsini A, Madsen JH, Hange D, Petersson ELL, et al. Cost-effectiveness analysis of internet-mediated cognitive behavioural therapy for depression in the primary care setting: results based on a controlled trial. BMJ Open [Internet]. 2018 Jun;8(6):e019716. Available from: https://bmjopen.bmj.com/content/8/6/e019716
110. Kraepelien M, Mattsson S, Hedman-Lagerlöf E, Petersson IF, Forsell Y, Lindefors N, et al.

Cost-effectiveness of internet-based cognitive–behavioural therapy and physical exercise for depression. BJPsych Open [Internet]. 2018 Jul;4(4):265. Available from: /pmc/articles/PMC6060490/

111. Piera-Jiménez J, Etzelmueller A, Kolovos S, Folkvord F, Lupiáñez-Villanueva F. Guided Internet-Based Cognitive Behavioral Therapy for Depression: Implementation Cost-Effectiveness Study. J Med Internet Res 2021;23(5)e27410 https//www.jmir.org/2021/5/e27410 [Internet]. 2021 May;23(5):e27410. Available from: https://www.jmir.org/2021/5/e27410
112. Donker T, Blankers M, Hedman E, Ljotsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med [Internet]. 2015 Dec;45(16):3357–76. Available from: https://pubmed.ncbi.nlm.nih.gov/26235445/
113. 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 [Internet]. 2020 Oct;4(10). Available from: https://pubmed.ncbi.nlm.nih.gov/33001835/
114. Shafran R, Myles-Hooton P, Bennett S, Öst LG. The concept and definition of low intensity cognitive behaviour therapy. Behav Res Ther. 2021 Mar;138:103803.
115. Aerts JEM, Van Dam A, Aerts JEM, Van Dam A. Blended e-Health in Cognitive Behavioural Therapy: Usage Intensity, Attitude and Therapeutic Alliance in Clinical Practice. Available from: http://creativecommons.org/licenses/by/4.0/
116. Schneider J, Sarrami Foroushani P, Grime P, Thornicroft G. Acceptability of online self-help to people with depression: users' views of MoodGYM versus informational websites. J Med Internet Res [Internet]. 2014 Jan;16(3):e90. Available from: http://www.jmir.org/2014/3/e90/
117. Ruwaard J, Lange A, Schrieken B, Emmelkamp P. Efficacy and effectiveness of online cognitive behavioral treatment: a decade of interapy research. Stud Health Technol Inform [Internet]. 2011 Jan;167:9–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21685634
118. Christensen H, Griffiths KM, Farrer L. Adherence in Internet Interventions for Anxiety and Depression: Systematic Review. J Med Internet Res [Internet]. 2009 Apr;11(2):e1194. Available from: https://www.jmir.org/2009/2/e13
119. Christensen H, Griffiths KM, Korten AE, Brittliffe K, Groves C. A comparison of changes in anxiety and depression symptoms of spontaneous users and trial participants of a cognitive behavior therapy website. J Med Internet Res [Internet]. 2004 Dec;6(4):e124. Available from: https://www.jmir.org/2004/4/e46
120. Fleming T, Bavin L, Lucassen M, Stasiak K, Hopkins S, Merry S. Beyond the Trial: Systematic Review of Real-World Uptake and Engagement With Digital Self-Help

Interventions for Depression, Low Mood, or Anxiety. J Med Internet Res [Internet]. 2018 Jun;20(6). Available from: https://pubmed.ncbi.nlm.nih.gov/29875089/

121. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JEWC. Persuasive System Design Does Matter: A Systematic Review of Adherence to Web-Based Interventions. J Med Internet Res 2012;14(6)e152 https//www.jmir.org/2012/6/e152 [Internet]. 2012 Nov;14(6):e2104. Available from: https://www.jmir.org/2012/6/e152
122. van Ballegooijen W, Cuijpers P, van Straten A, Karyotaki E, Andersson G, Smit JH, et al. Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. PLoS One [Internet]. 2014 Jan;9(7):e100674. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0100674
123. Hadjistavropoulos HD, Pugh NE, Hesser H, Andersson G. Therapeutic Alliance in Internet-Delivered Cognitive Behaviour Therapy for Depression or Generalized Anxiety. Clin Psychol Psychother [Internet]. 2017 Mar;24(2):451–61. Available from: http://doi.wiley.com/10.1002/cpp.2014
124. Mohr DC, Schueller SM, Montague E, Burns MN, Rashidi P. The behavioral intervention technology model: an integrated conceptual and technological framework for eHealth and mHealth interventions. J Med Internet Res [Internet]. 2014 Jun;16(6):e146. Available from: http://www.jmir.org/2014/6/e146/
125. Cuijpers P, Donker T, Johansson R, Mohr DC, van Straten A, Andersson G. Self-guided psychological treatment for depressive symptoms: a meta-analysis. Hempel S, editor. PLoS One. 2011 Jan;6(6):e21274.
126. Sieverink F, Kelders SM, Gemert-Pijnen V. Clarifying the concept of adherence to ehealth technology: Systematic review on when usage becomes adherence [Internet]. Vol. 19, Journal of Medical Internet Research. Journal of Medical Internet Research; 2017. Available from: https://pubmed.ncbi.nlm.nih.gov/29212630/
127. Wampold BE. How important are the common factors in psychotherapy? An update. World Psychiatry [Internet]. 2015 Oct;14(3):270–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26407772
128. Gelso CJ, Carter JA. The Relationship in Counselling and Psychotherapy: Components, Consequences and Theoretical Antecedents. Couns Psychol. 1985;13(2):155–243.
129. Cameron SK, Rodgers J, Dagnan D. The relationship between the therapeutic alliance and clinical outcomes in cognitive behaviour therapy for adults with depression: A meta-analytic review. Clin Psychol Psychother [Internet]. 2018 May;25(3):446–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29484770
130. Stubbe DE. The Therapeutic Alliance: The Fundamental Element of Psychotherapy. Focus J Life Long Learn Psychiatry [Internet]. 2018 Oct;16(4):402. Available from:

/pmc/articles/PMC6493237/

131. Raue PJ, Goldfried MR. The Working alliance : theory, research, and practice. Horvath AO, Greenberg LS, editors. New York: Wiley; 1994. pp 131–152.

132. Gómez Penedo JM, Berger T, Grosse Holtforth M, Krieger T, Schröder J, Hohagen F, et al. The Working Alliance Inventory for guided Internet interventions (WAI-I). J Clin Psychol [Internet]. 2020 Jun;76(6):973–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31240727

133. Henson P, Wisniewski H, Hollis C, Keshavan M, Torous J. Digital mental health apps and the therapeutic alliance: initial review. BJPsych Open [Internet]. 2019 Jan;5(1):e15. Available from: https://www.cambridge.org/core/product/identifier/S2056472418000868/type/journal_article

134. Heim E, Rötger A, Lorenz N, Maercker A. Working alliance with an avatar: How far can we go with internet interventions? Internet Interv [Internet]. 2018 Mar;11:41–6. Available from: https://pubmed.ncbi.nlm.nih.gov/30135758/

135. Cavanagh K, Millings a. Increasing engagement with computerised cognitive behavioural therapies. ICST Trans Ambient Syst [Internet]. 2013;13(2):e3. Available from: http://eudl.eu/doi/10.4108/trans.amsys.01-06.2013.e3

136. Timmermans S, Berg M. The practice of medical technology. Sociol Health Illn [Internet]. 2003;25:97–114. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14498932

137. 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 Jun;12:150–64.

138. Fiona, Shepherd HL, Beatty L, Clark B, Butow P, Shaw J. Implementing Web-Based Therapy in Routine Mental Health Care: Systematic Review of Health Professionals' Perspectives. J Med Internet Res 2020;22(7)e17362 https//www.jmir.org/2020/7/e17362 [Internet]. 2020 Jul;22(7):e17362. Available from: https://www.jmir.org/2020/7/e17362

139. Lavi-Rotenberg A, Kivity Y, Igra L, Atzil-Slonim D, Hasson-Ohayon I. A dyadic session-by-session assessment of therapeutic alliance and short-term outcome among clients with schizophrenia in comparison with clients with emotional disorders. Psychol Psychother Theory, Res Pract [Internet]. 2023 Dec;96(4):1029–43. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/papt.12494

140. Goldsmith LP, Lewis SW, Dunn G, Bentall RP. Psychological treatments for early psychosis can be beneficial or harmful, depending on the therapeutic alliance: an instrumental variable analysis. Psychol Med [Internet]. 2015 May;45(11):2365–73. Available from: https://pubmed.ncbi.nlm.nih.gov/25805118/

141. Roth AD, Pilling S. Using an Evidence-Based Methodology to Identify the Competences

Required to Deliver Effective Cognitive and Behavioural Therapy for Depression and Anxiety Disorders. Behav Cogn Psychother [Internet]. 2008 Mar;36(2):129–47. Available from: https://www.cambridge.org/core/journals/behavioural-and-cognitive-psychotherapy/article/abs/using-an-evidencebased-methodology-to-identify-the-competences-required-to-deliver-effective-cognitive-and-behavioural-therapy-for-depression-and-anxiety-disorders

142. Williams GA, Fahy N, Aissat D, Lenormand M-C, Stüwe L, Zablit-Schmidt I, et al. COVID-19 and the use of digital health tools: Opportunities amid crisis that could transform health care delivery. Eurohealth (Lond). 2022;28(1).
143. Mental Health Reform. Developing Policy on Digital Mental Health after the pandemic A priority for Sharing the Vision and in the wider Sláintecare context [Internet]. Dublin; 2021. Available from: https://www.mentalhealthreform.ie/wp-content/uploads/2021/10/Digital-MH-COF-1.pdf
144. Department of Health & Social Care. Policy Paper: A plan for digital health and social care [Internet]. 2022. Available from: https://www.gov.uk/government/publications/a-plan-for-digital-health-and-social-care/a-plan-for-digital-health-and-social-care
145. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. Psychother Res. 2006 Jan;16(1):12–25.
146. Creswell JW, Plano-Clark VL. Choosing a mixed methods design. In: Designing and conducting mixed methods research. Thousand Oaks, CA: Sage; 2007.
147. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol [Internet]. 2006 Jan;3(2):77–101. Available from: http://www.tandfonline.com/doi/abs/10.1191/1478088706qp063oa
148. Bangor A, Kortum PT, Miller JT. An Empirical Evaluation of the System Usability Scale. Int J Hum Comput Interact. 2008 Jul;24(6):574–94.
149. Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci [Internet]. 2011;13(2):217–24. Available from: /pmc/articles/PMC3181997/?report=abstract
150. Roland M, Torgerson DJ. Understanding controlled trials: What are pragmatic trials? BMJ [Internet]. 1998 Jan;316(7127):285. Available from: https://www.bmj.com/content/316/7127/285
151. Schumi J, Wittes JT. Through the looking glass: Understanding non-inferiority. Trials [Internet]. 2011 May;12(1):1–12. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-12-106
152. Hahn S. Understanding noninferiority trials. Korean J Pediatr [Internet]. 2012;55(11):403. Available from: /pmc/articles/PMC3510268/
153. Wang B, Wang H, Tu XM, Feng C. Comparisons of Superiority, Non-inferiority, and

Equivalence Trials. Shanghai Arch Psychiatry [Internet]. 2017 Dec;29(6):385. Available from: /pmc/articles/PMC5925592/

154. The National Collaborating Centre for Mental Health. The Improving Access to Psychological Therapies Manual [Internet]. London; 2021 Aug. Available from: https://www.england.nhs.uk/publication/the-improving-access-to-psychological-therapies-manual/

155. Mental Health Matters. Stepped Care [Internet]. Mental Health Matters. 2023. Available from: https://www.mhm.org.uk/pages/faqs/category/stepped-care

156. Fenton LR, Cecero JJ, Nich C, Frankforter TL, Carroll KM. Perspective is everything: the predictive validity of six working alliance instruments. J Psychother Pract Res. 2001;10:262–8.

157. Luborsky L, Barber JP, Siqueland L, Johnson S, Najavits LM, Frank A. The revised Helping Alliance Questionnaire (HAq-II): psychometric properties. J Psychother Pract Res. 1996;5:260–71.

158. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ [Internet]. 2019 Apr;365. Available from: https://www.bmj.com/content/365/bmj.l1476

159. Duncan B, Miller S, Sparks J, Claud D a., Reynolds LR, Brown J, et al. The Session Rating Scale: Preliminary psychometric properties of a "working" alliance measure. J Br Ther [Internet]. 2003;3(1):3–12. Available from: https://www.myoutcomes.com/documents/The_Session_Rating_Scale_Psychometric_Properties_of_a_Working_Alliance_Scale.pdf

160. Agnew-Davies R, Stiles WB, Hardy GE, Barkham M, Shapiro DA. Alliance structure assessed by the Agnew Relationship Measure (ARM). Br J Clin Psychol. 1998;37:155–72.

161. Hayes H, Buckland S, Tarpey M. Briefing notes for researchers: Public Involvement in NHS, public health and social care research [Internet]. 2012. 1–52 p. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Briefing+notes+for+researchers:+public+involvement+in+NHS,+public+health+and+social+care+research#2

162. Krueger RA. Focus groups : a practical guide for applied research. Second. London: Sage; 1994.

163. Staniszewska S, Brett J, Simera I, Seers K, Mockford C, Goodlad S, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ [Internet]. 2017 Aug;358:j3453. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28768629

164. Ocloo J, Matthews R. From tokenism to empowerment: Progressing patient and public involvement in healthcare improvement [Internet]. Vol. 25, BMJ Quality and Safety. BMJ Publishing Group; 2016. p. 626–32. Available from: http://dx.doi.org/10.1136/

165. Shorten A, Smith J. Mixed methods research: expanding the evidence base. Evid Based Nurs [Internet]. 2017 Jul;20(3):74–5. Available from: https://ebn.bmj.com/content/20/3/74
166. Creswell JW. Research Design. Fouth Edit. Thousand Oaks, CA: SAGA; 2014.
167. Fetters MD, Curry LA, Creswell JW. Achieving Integration in Mixed Methods Designs—Principles and Practices. Health Serv Res [Internet]. 2013;48(6 Pt 2):2134. Available from: /pmc/articles/PMC4097839/
168. Kukull WA, Ganguli M. Generalizability: The trees, the forest, and the low-hanging fruit. Neurology [Internet]. 2012 Jun;78(23):1886. Available from: /pmc/articles/PMC3369519/
169. Green J, Thorogood N. Qualitative methods for health research. Third edit. London; 2014.
170. Glaser BG, Strauss AL. The discovery of grounded theory : strategies for qualitative research. Aldine Pub. Co; 1967.
171. Sanders C, Rogers A, Bowen R, Bower P, Hirani S, Cartwright M, et al. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. BMC Health Serv Res [Internet]. 2012 Jul;12:220. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22834978
172. Knowles SE, Lovell K, Bower P, Gilbody S, Littlewood E, Lester H. Patient experience of computerised therapy for depression in primary care. BMJ Open [Internet]. 2015 Nov;5(11):e008581. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26621513
173. Furber C. Framework analysis: a method for analysing qualitative data. Afr J Midwifery Womens Health [Internet]. 2010 Apr;4(2):97–100. Available from: http://www.magonlinelibrary.com/doi/abs/10.12968/ajmw.2010.4.2.47612
174. Kitzinger J. The methodology of Focus Groups: the importance of interaction between research participants. Sociol Health Illn. 1994;16(1):103–21.
175. Bispo Júnior JP. Social desirability bias in qualitative health research. Rev Saude Publica [Internet]. 2022;56:101. Available from: /pmc/articles/PMC9749714/
176. Maramba I, Chatterjee A, Newman C. Methods of usability testing in the development of eHealth applications: A scoping review. Int J Med Inform. 2019 Jun;126:95–104.
177. Mol M, Van Schaik A, Dozeman E, Ruwaard J, Vis C, Ebert DD, et al. Dimensionality of the system usability scale among professionals using internet-based interventions for depression: A confirmatory factor analysis. BMC Psychiatry [Internet]. 2020 May;20(1):218. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-020-02627-8
178. Carpenter JR, Kenward MG. Multiple Imputation and its Application | Wiley [Internet]. Chichester: John Wiley & Sons; 2013. 364 p. Available from: https://www.wiley.com/en-gb/Multiple+Imputation+and+its+Application+-p-9780470740521
179. Von Hippel PT. How to Impute Interactions, Squares, and other Transformed Variables: http://dx.doi.org/101111/j1467-9531200901215.x [Internet]. 2009 Aug;39(1):265–91.

Available from: https://journals.sagepub.com/doi/10.1111/j.1467-9531.2009.01215.x

180. Parpia S, Morris TP, Phillips MR, Wykoff CC, Steel DH, Thabane L, et al. Sensitivity analysis in clinical trials: three criteria for a valid sensitivity analysis. Eye 2022 3611 [Internet]. 2022 May;36(11):2073–4. Available from: https://www.nature.com/articles/s41433-022-02108-0

181. de Souza RJ, Eisen RB, Perera S, Bantoto B, Bawor M, Dennis BB, et al. Best (but oft-forgotten) practices: sensitivity analyses in randomized controlled trials. Am J Clin Nutr [Internet]. 2016 Jan;103(1):5–17. Available from: https://academic.oup.com/ajcn/article/103/1/5/4569309

182. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, et al. A tutorial on sensitivity analyses in clinical trials: The what, why, when and how [Internet]. Vol. 13, BMC Medical Research Methodology. BioMed Central; 2013. p. 92. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-13-92

183. Morris TP, Kahan BC, White IR. Choosing sensitivity analyses for randomised trials: principles. BMC Med Res Methodol. 2014 Jan;14(1):1–5.

184. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. Perspect Clin Res [Internet]. 2016;7(3):144. Available from: /pmc/articles/PMC4936074/?report=abstract

185. Shah PB. Intention-to-treat and per-protocol analysis. CMAJ [Internet]. 2011 Apr;183(6):696; author reply 696. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21464181

186. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol. 2019 Jun;110:63–73.

187. Seaman SR, Bartlett JW, White IR. Multiple imputation of missing covariates with non-linear effects and interactions: An evaluation of statistical methods. BMC Med Res Methodol [Internet]. 2012 Apr;12(1):1–13. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-46

188. Edgar K, Roberts I, Sharples L. Including random centre effects in design, analysis and presentation of multi-centre trials. Trials [Internet]. 2021 Dec;22(1):1–10. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05266-w

189. Feaster DJ, Mikulich-Gilbertson S, Brincks AM. Modeling site effects in the design and analysis of multisite trials. Am J Drug Alcohol Abus. 2011;37(5):383–91.

190. Bell A, Fairbrother M, Jones K. Fixed and random effects models: making an informed choice. Qual Quant [Internet]. 2019 Mar;53(2):1051–74. Available from: https://link.springer.com/article/10.1007/s11135-018-0802-x

191. Neuhaus JM, Kalbfleisch JD. Between- and Within-Cluster Covariate Effects in the Analysis of Clustered Data. Biometrics. 1998 Jun;54(2):638.

192. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by

statistical analysis. Gastroenterol Hepatol from bed to bench [Internet]. 2012;5(2):79–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24834204

193. Field AP. Discovering statistics using IBM SPSS statistics : and sex and drugs and rock “n” roll. Fourth Edi. London: SAGA Publications Ltd; 2013.

194. Wangberg SC, Bergmo TS, Johnsen JAK. Adherence in Internet-based interventions. Patient Prefer Adherence [Internet]. 2008 Mar;2:57. Available from: /pmc/articles/PMC2770402/

195. Melville KM, Casy LM, Kavanagh DJ. Dropout from Internet-based treatment for psychological disorders. Br J Clin Psychol. 2010;4(49):455–71.

196. Buller DB, Woodall WG, Zimmerman DE, Slater MD, Heimendinger J, Waters E, et al. Randomized trial on the 5 a day, the Rio Grande Way Website, a web-based program to improve fruit and vegetable consumption in rural communities. J Health Commun [Internet]. 2008 Apr;13(3):230–49. Available from: https://pubmed.ncbi.nlm.nih.gov/18569356/

197. Anderson REE, Spence SH, Donovan CL, March S, Prosser S, Kenardy J. Working alliance in online cognitive behavior therapy for anxiety disorders in youth: comparison with clinic delivery and its role in predicting outcome. J Med Internet Res [Internet]. 2012 Jan;14(3):e88. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3414866&tool=pmcentrez&rendertype=abstract

198. El Alaoui S, Ljótsson B, Hedman E, Svanborg C, Kaldo V, Lindefors N. Predicting Outcome in Internet-Based Cognitive Behaviour Therapy for Major Depression: A Large Cohort Study of Adult Patients in Routine Psychiatric Care. Russo E, editor. PLoS One [Internet]. 2016 Sep;11(9):e0161191. Available from: https://dx.plos.org/10.1371/journal.pone.0161191

199. Spek V, Nyklíček I, Cuijpers P, Pop V. Predictors of outcome of group and internet-based cognitive behavior therapy. J Affect Disord [Internet]. 2008 Jan;105(1–3):137–45. Available from: https://pubmed.ncbi.nlm.nih.gov/17543392/

200. Alfonsson S, Johansson K, Uddling J, Hursti T. Differences in motivation and adherence to a prescribed assignment after face-to-face and online psychoeducation: an experimental study. BMC Psychol [Internet]. 2017 Jan;5(1). Available from: /pmc/articles/PMC5270286/

201. Ebert DD, Gollwitzer M, Riper H, Cuijpers P, Baumeister H, Berking M. For whom does it work? moderators of outcome on the effect of a transdiagnostic internet-based maintenance treatment after inpatient psychotherapy: randomized controlled trial. J Med Internet Res [Internet]. 2013;15(10). Available from: https://pubmed.ncbi.nlm.nih.gov/24113764/

202. Andersen LW, Holmberg MJ, Andersen LW. Adjustment for Baseline Characteristics in Randomized Clinical Trials. JAMA [Internet]. 2022 Dec;328(21):2155–6. Available from: https://jamanetwork.com/journals/jama/fullarticle/2798955

203. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be

used for handling missing data in randomised clinical trials - A practical guide with flowcharts. BMC Med Res Methodol [Internet]. 2017 Dec;17(1):1–10. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0442-1

204. Zhang Z. Too much covariates in a multivariable model may cause the problem of overfitting. J Thorac Dis [Internet]. 2014;6(9):E196. Available from: /pmc/articles/PMC4178069/

205. Brooke J. Usability Evaluation In Industry. Usability. Jordan PW, Thomas B, Weerdmeester BA, McClelland IL, editors. London: CRC Press; 1996.

206. WHO. Fact Sheet: Suicide [Internet]. WHO. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide

207. Torous J, Jän Myrick K, Rauseo-Ricupero N, Firth J. Digital Mental Health and COVID-19: Using Technology Today to Accelerate the Curve on Access and Quality Tomorrow. JMIR Ment Heal [Internet]. 2020 Mar;7(3):e18848. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32213476

208. Kaltenthaler E, Parry G, Beverley C. Computerized Cognitive Behaviour Therapy: a Systematic Review. Behav Cogn Psychother. 2004;32:31–55.

209. Foroushani PS, Schneider J, Assareh N. Meta-review of the effectiveness of computerised CBT in treating depression. BMC Psychiatry [Internet]. 2011 Dec;11(1):131. Available from: http://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-11-131

210. Ivarsson D, Blom M, Hesser H, Carlbring P, Enderby P, Nordberg R, et al. Guided internet-delivered cognitive behavior therapy for post-traumatic stress disorder: A randomized controlled trial. Internet Interv [Internet]. 2014 Mar;1(1):33–40. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2214782914000074

211. Andrews G, Basu A, Cuijpers P, Craske MG, McEvoy P, English CL, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: An updated meta-analysis. Vol. 55, Journal of Anxiety Disorders. Elsevier Ltd; 2018. p. 70–8.

212. Josephine K, Josefine L, Philipp D, David E, Harald B. Internet- and mobile-based depression interventions for people with diagnosed depression: A systematic review and meta-analysis. Vol. 223, Journal of Affective Disorders. Elsevier B.V.; 2017. p. 28–40.

213. Hayati R, Bastani P, Kabir MJ, Kavosi Z, Sobhani G. Scoping literature review on the basic health benefit package and its determinant criteria. Available from: https://globalizationandhealth.biomedcentral.com/track/pdf/10.1186/s12992-018-0345-x

214. Barceló-Soler A, García-Campayo J, Araya R, Doukani A, Gili M, García-Palacios A, et al. Working alliance in low-intensity internet-based cognitive behavioral therapy for depression in primary care in Spain: A qualitative study. Front Psychol [Internet]. 2023 Mar;14:1283. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1024966/full

215. 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).

216. 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 [Internet]. 2014 Dec;14(1):1–10. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-014-0355-z

217. Herrero R, Vara MD, Miragall M, Botella C, García-Palacios A, Riper H, et al. Working alliance inventory for online interventions-short form (Wai-tech-sf): The role of the therapeutic alliance between patient and online program in therapeutic outcomes. Int J Environ Res Public Health [Internet]. 2020 Sep;17(17):1–16. Available from: https://pubmed.ncbi.nlm.nih.gov/32854381/

218. Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. BMJ [Internet]. 2015 Nov;351. Available from: https://www.bmj.com/content/351/bmj.h5651

219. Dawson L, Zarin DA, Emanuel EJ, Friedman LM, Chaudhari B, Goodman SN. Considering Usual Medical Care in Clinical Trial Design. PLOS Med [Internet]. 2009 Sep;6(9):e1000111. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000111

220. Farrokhyar F, Skorzewski P, Phillips MR, Garg SJ, Sarraf D, Thabane L, et al. When to believe a subgroup analysis: revisiting the 11 criteria. Eye 2022 3611 [Internet]. 2022 Jan;36(11):2075–7. Available from: https://www.nature.com/articles/s41433-022-01948-0

221. Sheehan D V, Lecrubier Y, Harnett Sheehan K, Janavs J, Weiller E, Keskiner A, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry [Internet]. 1997 Jan;12(5):232–41. Available from: https://www.sciencedirect.com/science/article/pii/S092493389783297X

222. Rohde P, Lewinsohn PM, Seeley JR. Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. Am J Psychiatry. 1997 Nov;154(11):1593–8.

223. Ruskin PE, Reed S, Kumar R, Kling MA, Siegel E, Rosen M, et al. Reliability and Acceptability of Psychiatric Diagnosis Via Telecommunication and Audiovisual Technology. 2014 Oct;

224. Wittkampf KA, Naeije L, Schene AH, Huyser J, van Weert HC. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. Gen Hosp Psychiatry. 2007;29(5):388–95.

225. IBM Corp. IBM SPSS Statistics (Version 26) [Computer software]. IBM Corp; 2019.

226. Stata Corp. Stata statistical software (Version 16). Stata Corp; 2019.
227. Hayes A. Introduction to Mediation, Moderation, and Conditional Process Analysis: Second Edition: A Regression-Based Approach [Internet]. Second. Hayes Andrew F, editor. New York : Guilford Press ; 2017. Available from: https://www.guilford.com/books/Introduction-to-Mediation-Moderation-and-Conditional-Process-Analysis/Andrew-Hayes/9781462534654/new-to-edition
228. Dziak JJ, Dierker LC, Abar B. The Interpretation of Statistical Power after the Data have been Gathered. Curr Psychol [Internet]. 2020 Jun;39(3):870. Available from: /pmc/articles/PMC7286546/
229. Kirkwood Betty R, Stern JAC. Essential Medical Statistics. Second Edi. Blackwell Publishing, editor. Oxford; 2010.
230. Piper WE, Azim HFA, Joyce AS, McCallum M. Transference Interpretations, Therapeutic Alliance, and Outcome in Short-term Individual Psychotherapy. Arch Gen Psychiatry [Internet]. 1991 Oct;48(10):946. Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.1991.01810340078010
231. Eames V, Roth a. Patient attachment orientation and the early working alliance-a study of patient and therapist reports of alliance quality and ruptures. Psychother Res. 2000;10(4):421–34.
232. Crits-Christoph P, Gibbons MBC, Hamilton J, Ring-Kurtz S, Gallop R. The dependability of alliance assessments: The alliance-outcome correlation is larger than you might think. J Consult Clin Psychol [Internet]. 2011 Jun;79(3):267–78. Available from: www.apa.org/pubs/journals/ccp
233. Rothman KJ. No Adjustments Are Needed for Multiple Comparisons : Epidemiology. Epidemiology [Internet]. 1900 Jan;1(1):43–6. Available from: https://journals.lww.com/epidem/Abstract/1990/01000/No_Adjustments_Are_Needed_for_Multiple_Comparisons.10.aspx
234. Kambeitz-Ilankovic L, Rzayeva U, Völkel L, Wenzel J, Weiske J, Jessen F, et al. A systematic review of digital and face-to-face cognitive behavioral therapy for depression [Internet]. Vol. 5, npj Digital Medicine. Nature Publishing Group; 2022. p. 1–8. Available from: https://www.nature.com/articles/s41746-022-00677-8
235. Kemmeren LL, van Schaik A, Smit JH, Ruwaard J, Rocha A, Henriques M, et al. Unraveling the Black Box: Exploring Usage Patterns of a Blended Treatment for Depression in a Multicenter Study. JMIR Ment Heal [Internet]. 2019 Jul;6(7):e12707. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31344670
236. Titzler I, Berking M, Schlicker S, Riper H, Ebert DD. Barriers and Facilitators for Referrals of Primary Care Patients to Blended Internet-Based Psychotherapy for Depression: Mixed

Methods Study of General Practitioners' Views. JMIR Ment Heal 2020;7(8)e18642 https//mental.jmir.org/2020/8/e18642. 2020 Aug;7(8):e18642.

237. Cerga-Pashoja A, Doukani A, Gega L, Walke J, Araya R. Added value or added burden? A qualitative investigation of blending internet self-help with face-to-face cognitive behaviour therapy for depression. Psychother Res. 2020;

238. Nordgreen T, Blom K, Andersson G, Carlbring P, Havik OE. Effectiveness of guided Internet-delivered treatment for major depression in routine mental healthcare - An open study. Internet Interv. 2019 Dec;18:100274.

239. Ebert DD, Heber E, Berking M, Riper H, Cuijpers P, Funk B, et al. Self-guided internet-based and mobile-based stress management for employees: results of a randomised controlled trial. Occup Environ Med [Internet]. 2016 May;73(5):315–23. Available from: https://oem.bmj.com/content/73/5/315

240. Wisniewski H, Torous J. Digital navigators to implement smartphone and digital tools in care. Acta Psychiatr Scand [Internet]. 2020 Apr;141(4):350–5. Available from: https://onlinelibrary.wiley.com/doi/10.1111/acps.13149

241. OECD/EU. Health at a Glance: Europe 2018: State of Health in the EU cycle [Internet]. Paris: OECD Publishing; 2018. 216 p. Available from: https://doi.org/10.1787/health_glance_eur-2018-en%0Ahttps://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2018_health_glance_eur-2018-en

242. The Lancet Psychiatry. Digital psychiatry: moving past potential. The Lancet Psychiatry [Internet]. 2021 Apr;8(4):259. Available from: http://www.thelancet.com/article/S2215036621000961/fulltext

243. Gullo S, Lo Coco G, Gelso C. Early and Later Predictors of Outcome in Brief Therapy: The Role of Real Relationship. J Clin Psychol [Internet]. 2012 Jun;68(6):614–9. Available from: http://doi.wiley.com/10.1002/jclp.21860

244. Huppert JD, Kivity Y, Barlow DH, Shear MK, Gorman JM, Woods SW. Therapist effects and the outcome-alliance correlation in cognitive behavioral therapy for panic disorder with agoraphobia. Behav Res Ther. 2014;52(1):26–34.

245. Marcus DK, Kashy DA, Wintersteen MB, Diamond GS. The therapeutic alliance in adolescent substance abuse treatment: A one-with-many analysis. J Couns Psychol. 2011 Jul;58(3):449–55.

246. 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. J Clin Psychiatry. 1998 Jan;59 Suppl 2:22–33;quiz 34–57.

247. Zilcha-Mano S, Solomonov N, Chui H, McCarthy KS, Barrett MS, Barber JP. Therapist-

reported alliance: Is it really a predictor of outcome? J Couns Psychol. 2015 Oct;62(4):568–78.

248. Falkenström F, Josefsson A, Berggren T, Holmqvist R. How much therapy is enough? Comparing dose-effect and good-enough models in two different settings. Psychotherapy. 2016 Mar;53(1):130–9.

249. Preschl B, Maercker A, Wagner B. The working alliance in a randomized controlled trial comparing online with face-to-face cognitive-behavioral therapy for depression. BMC Psychiatry [Internet]. 2011;11(1):189. Available from: http://www.biomedcentral.com/1471-244X/11/189

250. Hentati A, Forsell E, Ljótsson B, Kaldo V, Lindefors N, Kraepelien M. The effect of user interface on treatment engagement in a self-guided digital problem-solving intervention: A randomized controlled trial. Internet Interv. 2021 Dec;26:100448.

251. Cummings P. Missing Data and Multiple Imputation. JAMA Pediatr [Internet]. 2013 Jul;167(7):656–61. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/1686979

252. Sweeney A, Fahmy S, Nolan F, Morant N, Fox Z, Lloyd-Evans B, et al. The Relationship between Therapeutic Alliance and Service User Satisfaction in Mental Health Inpatient Wards and Crisis House Alternatives: A Cross-Sectional Study. McInnis MG, editor. PLoS One [Internet]. 2014 Jul;9(7):e100153. Available from: http://dx.plos.org/10.1371/journal.pone.0100153

253. Rodriguez-Villa E, Naslund J, Keshavan M, Patel V, Torous J. Making mental health more accessible in light of COVID-19: Scalable digital health with digital navigators in low and middle-income countries. Asian J Psychiatr [Internet]. 2020 Dec;54. Available from: https://pubmed.ncbi.nlm.nih.gov/33271713/

254. Bielinski LL, Bur OT, Wälchli G, Suter JM, Walsh N, Kley MA, et al. Two sides of the same coin? Patient and therapist experiences with a transdiagnostic blended intervention focusing on emotion regulation. Internet Interv [Internet]. 2022 Dec;30:100586. Available from: https://pubmed.ncbi.nlm.nih.gov/36386404/

255. Donaldson GW, Nakamura Y, Moinpour C. Mediators, moderators, and modulators of causal effects in clinical trials - Dynamically Modified Outcomes (DYNAMO) in health-related quality of life. Qual Life Res [Internet]. 2009 Mar;18(2):137–45. Available from: https://link.springer.com/article/10.1007/s11136-008-9439-x

256. 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 Mar;2(1):77–83.

257. World Health Organization. Depressive disorder (depression) [Internet]. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/depression#:~:text=Women

258. Teo RH, Cheng WH, Cheng LJ, Lau Y, Lau ST. Global prevalence of social isolation among community-dwelling older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr. 2023 Apr;107:104904.
259. Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: a multivariate examination. Acta Psychiatr Scand [Internet]. 2003 Feb;107(2):132–41. Available from: https://onlinelibrary.wiley.com/doi/full/10.1034/j.1600-0447.2003.02056.x
260. Torous J, Wykes T. Opportunities From the Coronavirus Disease 2019 Pandemic for Transforming Psychiatric Care With Telehealth. JAMA Psychiatry [Internet]. 2020 Dec;77(12):1205–6. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2765953
261. Boeckxstaens P, Meskens A, Van Der Poorten A, Verpoort AC, Sturgiss EA. Exploring the therapeutic alliance in Belgian family medicine and its association with doctor-patient characteristics: A cross-sectional survey study. BMJ Open. 2020 Feb;10(2).
262. Sturgiss EA, Rieger E, Haesler E, Ridd MJ, Douglas K, Galvin SL. Adaption and validation of the Working Alliance Inventory for General Practice: qualitative review and cross-sectional surveys. Fam Pract [Internet]. 2019 Aug;36(4):516–22. Available from: https://pubmed.ncbi.nlm.nih.gov/30476031/
263. Molina-mula J, Gallo-estrada J. Impact of Nurse-Patient Relationship on Quality of Care and Patient Autonomy in Decision-Making. Int J Environ Res Public Health [Internet]. 2020 Feb;17(3). Available from: /pmc/articles/PMC7036952/
264. Wilkinson WM, Rance J, Fitzsimmons D. Understanding the importance of therapeutic relationships in the development of self-management behaviours during cancer rehabilitation: a qualitative research protocol. BMJ Open [Internet]. 2017 Jan;7(1):e012625. Available from: https://bmjopen.bmj.com/content/7/1/e012625
265. Schnur JB, Montgomery GH. A systematic review of therapeutic alliance, group cohesion, empathy, and goal consensus/collaboration in psychotherapeutic interventions in cancer: Uncommon factors? Clin Psychol Rev. 2010 Mar;30(2):238–47.
266. Hall AM, Ferreira PH, Maher CG, Latimer J, Ferreira ML. The Influence of the Therapist-Patient Relationship on Treatment Outcome in Physical Rehabilitation: A Systematic Review. Phys Ther [Internet]. 2010 Aug;90(8):1099–110. Available from: https://academic.oup.com/ptj/article/90/8/1099/2737932
267. Ferreira PH, Ferreira ML, Maher CG, Refshauge KM, Latimer J, Adams RD. The Therapeutic Alliance Between Clinicians and Patients Predicts Outcome in Chronic Low Back Pain. Phys Ther [Internet]. 2013 Apr;93(4):470–8. Available from: https://academic.oup.com/ptj/article-lookup/doi/10.2522/ptj.20120137

268. Hush JM, Cameron K, Mackey M. Patient Satisfaction With Musculoskeletal Physical Therapy Care: A Systematic Review. Phys Ther [Internet]. 2011 Jan;91(1):25–36. Available from: https://academic.oup.com/ptj/article/91/1/25/2735069
269. Schönberger M, Humle F, Zeeman P, Teasdale TW. Working alliance and patient compliance in brain injury rehabilitation and their relation to psychosocial outcome. http://dx.doi.org/101080/09602010500176476 [Internet]. 2007 Jun;16(3):298–314. Available from: https://www.tandfonline.com/doi/abs/10.1080/09602010500176476
270. Bührmann L, Schuurmans J, Ruwaard J, Fleuren M, Etzelmüller A, Piera-Jiménez J, et al. Tailored implementation of internet-based cognitive behavioural therapy in the multinational context of the ImpleMentAll project: a study protocol for a stepped wedge cluster randomized trial. Trials [Internet]. 2020 Dec;21(1):893. Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04686-4
271. 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 Jun;8:1–9.
272. Ernst E, Canter PH. Limitations of "pragmatic" trials [Internet]. Vol. 81, Postgraduate Medical Journal. The Fellowship of Postgraduate Medicine; 2005. p. 203. Available from: https://pmj.bmj.com/content/81/954/203
273. Hammerton M, Benson T, Sibley A. Readiness for five digital technologies in general practice: perceptions of staff in one part of southern England. BMJ Open Qual [Internet]. 2022 Jun;11(2):e001865. Available from: https://bmjopenquality.bmj.com/content/11/2/e001865
274. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ [Internet]. 2009;338. Available from: http://www.bmj.com/content/338/bmj.b2393
275. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. JAMA [Internet]. 2015 Nov;314(18):1966. Available from: /pmc/articles/PMC4638176/
276. 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(1).
277. Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. Health Psychol Rev [Internet]. 2015 Aug;9(3):323. Available from: /pmc/articles/PMC4566873/
278. van Agt HM, Essink-Bot ML, Krabbe PF, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. Soc Sci Med. 1994;39(11):1537–44.
279. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. 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

[Internet]. 2013 Jun;13:217. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23768141

280. van Roijen LH, van Straten A, Al M, Rutten F, Donker M. Cost-utility of brief psychological treatment for depression and anxiety. Br J Psychiatry. 2006 Apr;188(4):323–9.

281. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making. 1990;10(3):212–4.

282. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ. 2004 May;13(5):405–15.

283. NICE. Depression: management of depression in primary and secondary care. Clinical Guideline 90. London; 2009.

284. 52nd WMA General Assembly. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving humans. Edinburgh; 2000.

285. ICH. ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. Vol. 47. 1996 Jan.

286. Kirkwood BR, Sterne JAC. Essential Medical Statistics. Second Edi. Blackwell Publishing, editor. Medical statistics. Oxford; 2003. 513 p.

Appendices

Appendix 1. UK E-COMPARED trial protocol

Research Protocol

Version 1.11

E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

A generic protocol was produced by colleagues and E- COMPARED consortium partners in Amsterdam:

Authors

Dr. Annet Kleiboer, Prof. Dr. Pim Cuijpers, Prof. Dr. Heleen Riper

This version (UK) was finalised by:

Arlinda Cerga-Pashoja
Research Fellow
LSHTM

Asmae Doukani
Research Assistant
LSHTM

Ricardo Araya
Professor in Global Mental Health
LSHTM

Address for correspondence
Arlinda Cerga-Pashoja, Department of Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

Tel +44 (0)20 7927 8146 Email: arlinda.cerga-pashoja@lshtm.ac.uk
mailto:d.lowery@nhs.net

Table of Terms

CBT	Cognitive Behaviour Therapy
CRF	Case Report Form
EMA	Ecological Momentary Assessment
EU	European Union
FP7	Seventh Framework Programme (FP7)
GCP	Good Clinical Practice
HAQ-II	Helping Alliance Questionnaire
HTTPS	Hypertext Transfer Protocol Secure
IAPT	Access to Psychological Therapies
ICT	Information Communication Technology
ICT4D	ICT for Depression
INESC TEC,	The Institute for Systems and Computer Engineering, Technology and Science
IP	Internet Protocols
ITT	Intention to Treat
MDD	Major Depressive Disorder
MINI	MINI International Neuropsychiatric Interview
NI	Non-Inferiority
PHQ-9	Patient Health Questionnaire-9
PWP	Psychological Wellbeing Practitioners
REC	Research Ethics Committee
TAU	Treatment as Usual
TRL	Trial Record Log
VUA	Vrije Universiteit Amsterdam

Table of Content

SUMMARY

Background

In 2010, 30 million people across Europe were affected by depression and their number is still growing. About a quarter of the UK population will experience some kind of mental health problem in the course of a year, with mixed anxiety and depression as the most common mental disorder (The Office for National Statistics, 2001). In the UK between 8-12% of the population experience depression in any year (The Office for National Statistics, 2001). Half of people in need of mental care for depression do not have access to care services, do not always receive evidence based treatments, or are confronted with long waiting lists or high care expenditure (McCrone et al., 2008). Internet-supported treatments have the potential to address the drawbacks of standard care and keep depression treatment of high quality and affordable.

The European funded project E-COMPARED (http://www.e-compared.eu) will conduct comparative effectiveness research in IAPT settings on the effectiveness of internet-based treatment for depression in comparison with standard care.

E-COMPARED is a collaborative consortium of clinical and technical partners with extensive experience in similar research projects who are based in: in Belgium, France, Germany, Ireland, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland and the United Kingdom

Design

A pragmatic, randomised, single-blind, non-inferiority, feasibility trial. The two arms of the trail are: internet and mobile supported cognitive behaviour therapy (CBT) in addition to treatment as usual (TAU) in the intervention arm, and TAU alone as the control arm.

Setting

The study will be conducted in community settings, and will recruit participants from Improving Access to Psychological Services (IAPT) in London.

Sample

Adult participants with a clinical diagnosis of Major Depression Disorder (MDD) confirmed by MINI International Neuropsychiatric Interview (Lecrubier et al., 1997) and a score more than 5 in the Patient Health Questionnaire-9 (PHQ-9) (Zuithoff et al., 2010) will be eligible for participation in the trial.

Intervention

Internet based blended depression treatment combines individual face-to-face cognitive behavioural therapy (CBT) with CBT delivered through an internet-based treatment platform with mobile phone components. Traditional CBT treatment consists of face-to-face sessions only. In Internet-based blended depression treatment the number of face-to-face sessions is decreased and alternated by online treatment modules. Participants allocated in the intervention arm will receive 11 weekly therapy session overall: 6 face to face and 5 internet based. The sessions will be weekly alternated. The intervention is detailed in section 4.3, pp 35 of this protocol.

Both the intervention and TAU will be provided by IAPT therapists who will receive training on how to deliver the treatment.

AIMS AND OBJECTIVES OF THE PROJECT

Hypothesis

The trial hypothesises that both the treatment and control arm interventions will lead to similar clinical improvements (non-inferiority between groups), but that the blended approach can be offered at significantly lower cost.

Primary Objective

To assess acceptability and feasibility of Blended Cognitive Behavioural Therapy (CBT) for adults with major depressive disorder (MDD) in IAPT services in the UK.

To compare the clinical and cost-effectiveness of Blended CBT with treatment as usual (TAU) for adults with for adults with major depressive disorder.

Secondary Objectives

To assess the acceptability and satisfaction of the blended approach by patients and therapists.
To assess the therapeutic alliance between patients and therapists in both arms.

BACKGROUND

What is Major Depressive Disorder (MDD)

Depression is a serious and, in some cases, life-threatening condition, affecting around 350 million people worldwide (World Health Organization, 2012). The World Health Organization describes depression as a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.

Depression is associated with high morbidity and mortality with an estimated 3000 suicides daily worldwide. It also has a greater burden than lung, colorectal, breast and prostate cancers combined (World Health Organization, 2012).

Depression carries a serious burden not just to suffering individuals but also to their families and society in general. Other burdens caused by depression, surpass the health systems and include the loss of quality of life for the affected and their families, a loss of productivity for businesses and an increased risk of unemployment for individuals. The majority of costs (€54 billion) are indirect such as lost work productivity due to sick leave and early retirement (Olesen et al., 2012). Two in 5 employees suffer from a mental health problem and 1 in 10 has taken time off work for depression. On average, 36 working days are lost per depressive episode.

Conventional Treatments for Depression

Depression in general can effectively be treated with antidepressants, psychotherapy or a combination thereof (Cuijpers et al., 2008; DeRubeis et al., 2005).

Several studies have shown by means of randomized controlled trials that especially cognitive behavioural therapies (CBT), behavioural activation treatments, interpersonal therapies and problem-solving therapies are clinically effective (Cuijpers et al., 2011; Ekers et al., 2008; Malouff et al., 2007) as well as cost-effective (Vos et al., 2005). Within this domain professionally guided self-help interventions have become an attractive evidence-based alternative. Studies also indicate that people often prefer psychotherapy to pharmacological treatment (Beattie et al., 2009). However, these psychotherapies are not always available, accessible or affordable (Kohn et al., 2004; Singleton et al., 2001). A number of studies have investigated how depression treatment in primary and specialised care settings can be improved in terms of facilitated accessibility in the community (Clark, 2011), effectiveness and organisation of care e.g., by means of ‘collaborative care’ or ‘disease management’ approaches and ‘stepped care’ initiatives (Woltmann et al., 2014). However, many European citizens do not have access to low intensity, low cost, evidence-based depression treatments (McCrone et al., 2008). The treatment of depression (with or without chronicity) may thus be improved both in terms of accessibility and clinical and cost- effectiveness (Lynch et al., 2010).

Barriers to treatment

Research indicates that when diagnosed quickly and treated adequately, the majority of people can and do recover from depression, lead productive lives and make valuable contributions to society as a whole. However, depression remains under-diagnosed (Druss et al., 2000) and half of people in Europe in need

of mental care for depression do not have access to care services, do not always receive evidence-based treatments and are confronted with long waiting lists or high care expenditures

Currently the supply of psychotherapists is not high enough to meet the demand of people requiring to access evidence-based interventions, which tend to be therapist led-face-to-face interventions. Another issues, is that professionals are not distributed favourably to reach large groups of people, such as those who live in rural areas or small towns. Waiting lists are long and/or care expenditures substantial, and currently half of the Europeans in need of mental care for depression do not have access to care services (Huber et al., 2008). These conditions also apply other countries in the EU, where notable differences in access rates, depression treatment types, associated costs and health insurance policies exist**.**

Internet based treatments for MDD

Internet-based CBT for depression, also referred to as ICBT have been developed and utilised mostly in the last 15 years (Andersson and Hedman, 2013). ICBT are delivered on the internet, and they appear to be a very promising alternative to current routine depression treatment strategies. Meta-analyses have demonstrated that ICBT can be both clinically and cost effective in controlled research settings (Richards and Richardson, 2012; Spek et al., 2007). ICBT have the potential to address some of the drawbacks of standard care, such as accessibility and affordability whilst maintaining high quality treatment for people with depression. However, the ample evidence on the effectiveness of ICBT interventions comes mainly from randomised controlled clinical trials in research settings and not from research in routine daily practices (Zalcberg, 2011). Thus, little is known about the clinical and cost-efficiency of depression treatment in routine primary and specialised services. Patient populations in routine practices are often more heterogeneous in terms of patient characteristics, preferences and comorbidity levels than the populations and services in controlled research samples (Delgadillo et al., 2014; Ruwaard et al., 2011; Zalcberg, 2011). Certain groups e.g., the elderly, ethnic and low social economic populations are underrepresented in mental care service populations while they have often higher unmet needs compared to more regular populations (Unlü et al., 2010). In sum, effective depression treatment in primary and specialised settings is of the utmost importance both from a health and economic perspective.

E-COMPARED and blended treatment for depression

E-COMPARED will carry out a comparative effectiveness research in routine specialized mental health care and primary care settings on the clinical and cost effectiveness of internet-based treatment for depression in comparison with standard care.

A number of studies have investigated how depression treatment in primary and specialised care settings can be improved in terms of increased accessibility in the community and more efficient use of limited resources (Andersson, 2009). The effectiveness and efficiency of the way resources are delivered can be enhanced, by using innovative technology. Blending face-to-face treatment with computer-based treatment components is a powerful strategy, which may increase the cost-effectiveness of treatment for depression, increase access and decrease waiting times. Waiting lists can be shortened as patients can start their treatment via the internet immediately upon diagnosis. The number of face-to-face sessions will be lowered, providing therapists with time to treat more patients. Likewise, patients with limited mobility or those who live in areas without access to mental care services can communicate with care professionals and receive treatment via the internet without having to travel. E-COMPARED may improve treatment effectiveness as the project will provide insight into individual patient progress and treatment effectiveness both in terms of clinical and cost-effectiveness.

EXPERIMENTAL DESIGN AND METHODS

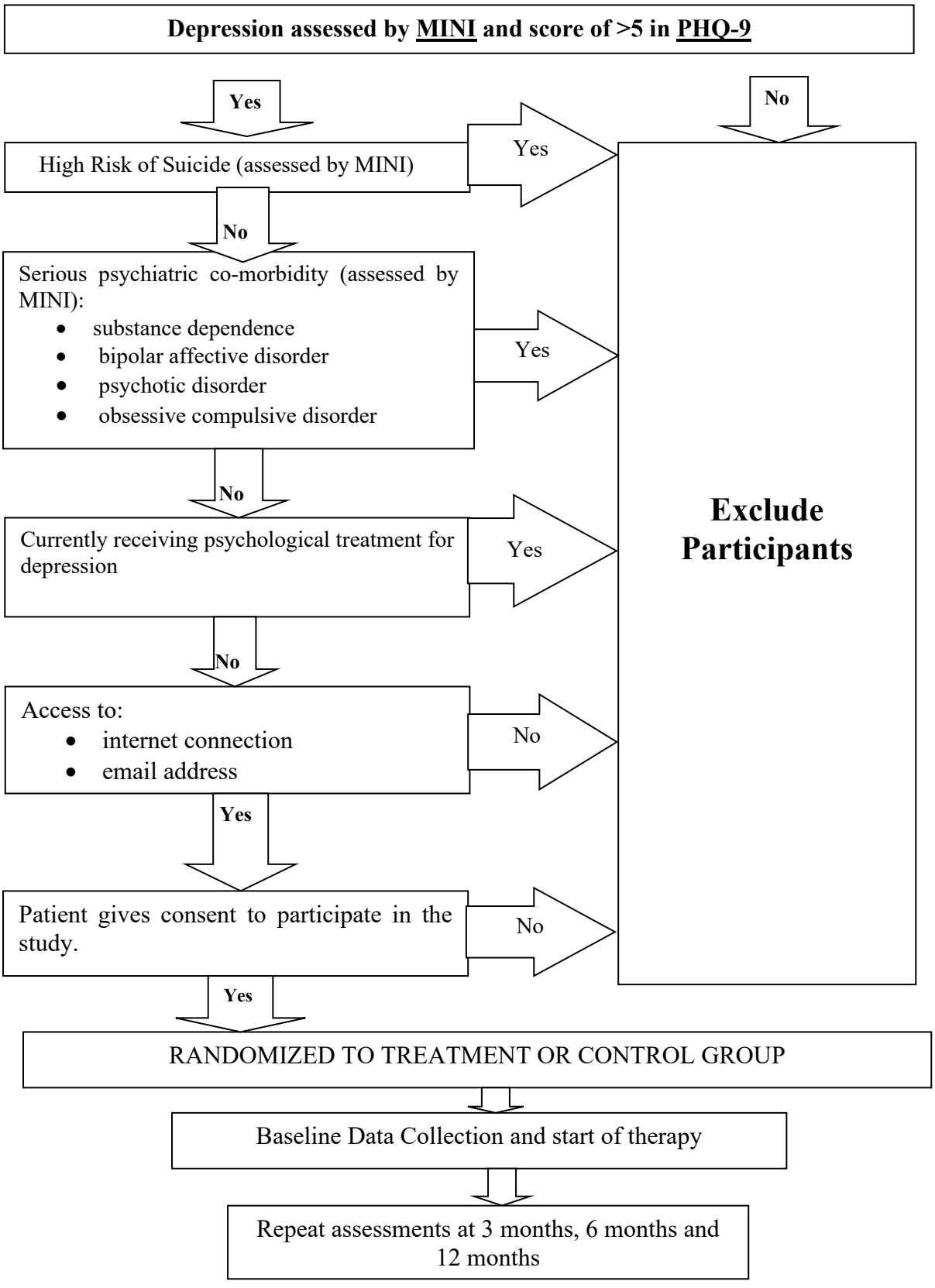
Study Design

We will undertake a pragmatic, randomised, controlled, single-blind, parallel-group, non-inferiority, feasibility trial. Individuals with a diagnosis of depression, who will be confirmed with M.I.N.I., will be recruited to the study. In order to be eligible, participants will need to score more than five points in the PHQ-9.

Community-dwelling adults (18 years old and over) will be recruited through Improving Access to Psychological Therapies (IAPT) services in London. IAPT is a national NHS programme that aims to increase the availability of primary care services across England for treatment of depression and anxiety disorders. IAPT is a free, confidential service available to adults registered with a GP in their local area. IAPT services employ a 'stepped care model' that means that the patient is generally offered a low intensity therapy in the first instance. If low intensity treatments are unsuccessful or inappropriate the patient is 'stepped up' to high intensity interventions. After consultations with specialists from high and low intensity IAPT services at Camden and Islington NHS Foundation Trust it was decided that the trial intervention may fit within both the low and high intensity approaches. Therefore, participants for E-Compared will be recruited from the low and high intensity-IAPT services. Risk assessment (will be performed to assess the suitability of participants for the intervention at baseline.

After confirming eligibility and obtaining patient consent to treatment, initial baseline assessments will be carried out. Participants will then be randomized into one of two arms: the intervention arm which

includes receipt of the blended intervention as well as TAU and the control arm that will receive TAU only.



Outcome Assessment

Assessments will be conducted according to **Error! Reference source not found.**. Participants will be visited in a mutually acceptable convenient location (e.g., IAPT clinic, LSTHM), by a trained research worker (RW) to obtain consent. After consent is obtained the RW will introduce the participants with the online questionnaires and ask them to complete those while the RW can observe and aid with any technical questions that may arise. The primary outcome measure (PHQ-9) and the MINI will be collected by the RW by telephone.

Both the treatment and control arms will be re-assessed for selected outcomes at 3 months, 6 months and 12 months. Therapists will be re-assessed at 3 months only.

Table 1 Assessment Schedule

Timeline	Control Group	Intervention Group	Therapist	Mode
Baseline	*Screens for eligibility* (MINI, PHQ-9, Screening) Obtains consent Demographics QIDS-SR 16 EQ-5D TIC-P CEQ RSQ ARM-5 Haq-II	*Screens for eligibility* (MINI, PHQ-9, Screening) Obtains consent Demographics QIDS-SR 16 EQ-5D TIC-P CEQ RSQ ARM-5 Haq-II	Obtains consent Demographics	RW[1]/telephone RW/face to face Online Online Online Online Online Online Online Online
	Independent researcher (IR) Randomisation and phone contact to inform therapist			
Week 1	Full diary every day			Mobile app

[1] Research Worker

Timeline	Control Group	Intervention Group	Therapist	Mode
Week 2-10	Full diary @ 1 random day per week + 1 mood rating every day			Mobile app
Week 11	Full diary every day			Mobile app
Week 12 (3 months)	PHQ-9 QIDS-SR 16 EQ-5D TIC-P CSQ WAI-SF RSQ ARM-5 Haq-II	PHQ-9 QIDS-SR 16 EQ-5D TIC-P CSQ WAI-SR RSQ ARM-5 Haq-II SUS b TAI-SF Qualitative Interviews (selected participants)	WAI-SF RSQ ARM-5 Haq-II SUS b Qualitative Interviews (selected therapists)	*RW*/telephone Online Online Online Online Online Online Online Online Online RW/face to face
Week 24 (6 months)	PHQ-9 QIDS-SR 16 EQ-5D TIC-P	PHQ-9 QIDS-SR 16 EQ-5D TIC-P		*RW*/telephone Online Online Online
Week 52 (12 months)	MINI PHQ-9 QIDS-SR 16 EQ-5D TIC-P	MINI PHQ-9 EQ-5D QIDS-SR 16 TIC-P		*RW*/telephone *RW*/telephone Online Online Online

Primary Outcome

The primary outcome measure will be the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). The PHQ-9 is a nine-item mood module that can be used to screen and to diagnose patients with depressive disorders. The 9 items are each scored on a 0–3 scale with the total score ranging from 0–27 and higher scores indicating more severe depression. The PHQ-9 has shown to have good psychometric properties (Kroenke et al., 2001) (Wittkampf et al., 2007).

Secondary outcomes

MINI - A diagnosis of depression will be assessed with the MINI International Neuropsychiatric Interview (M.I.N.I.) version 5.0. The M.I.N.I. is a structured diagnostic interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and on International Classification of Diseases (ICD-10) criteria. The M.I.N.I. has been translated into 65 languages and is used for both clinical and research practice. The interview compares well with Structural Clinical Interview for DSM-IV disorders (SCID) (Sheehan et al., 1998) and the Composite International Diagnostic Interview (CIDI) (Lecrubier et al., 1997; Sheehan et al., 1998). Telephone administration of diagnostic interview has been well validated (Rohde et al., 1997; Ruskin et al., 2014).

The M.I.N.I. 5.0, with exception of sections M (Anorexia Nervosa), N (Bulimia nervosa), and P (Antisocial personality disorder), will be assessed at baseline to assess lifetime and current depression, and current comorbid disorders that often co-occur with and predict the onset of depression (anxiety disorders and PTSD) and other comorbid disorders that are an exclusion criteria in this study (i.e. substance dependence, bipolar affective disorder, psychotic illness, and obsessive compulsive disorder). At 12 months follow-up, the depression, anxiety and PTSD sections will be assessed again.

QIDS-SR - The 16 item self-report version of the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-16-SR) US Translation (Rush et al., 2003) is used in addition to the PHQ-9 because it is a promising questionnaire for assessing depressive symptoms especially in specialized mental health care whereas the PHQ-9 is developed for use in primary care. The QIDS is a questionnaire that screens for depressive symptoms and assesses depression severity. The QIDS is available in both clinician-rated (IDS-C) and patient self-report (IDS-SR) forms. The QIDS consists of 16 items (each item scores 0-3) and includes symptom domains of MDD based on DSM-IV and Research Diagnostic Criteria (RDC). The QIDS has shown good psychometric properties.

Cost-effectiveness

Quality-adjusted-life-years (QALY's) will be assessed with the EQ-5D-5L (EuroQol). The EQ-5D-5L is a self-reported questionnaire that measures the health-related well-being for clinical and economic

appraisal. More precisely, EQ-5D-5L consists of five items: mobility, self-care, ordinary activities, discomfort, and mood state related to anxiety or depression. Each item consists of five categories ranging from no problems to a lot of problems [278]. EQ-5D-5L levels of severity have been translated to more than 100 different language versions.

TiC-P - *Health service uptake* and loss of *productivity due to illness*, which allow to estimate indirect economic costs, is measured with the Trimbos and iMTA Questionnaires on Costs Associated with Psychiatric Illness (TiC-P) [279,280]; The TiC-P is a self-reported questionnaire and consists of two parts that can be administrated separately. Part I will be used to assess the participants' healthcare utilization and medication use. Part II (short form health and labour questionnaire [SF-HLQ]) measures lost productivity resulting from absenteeism (being absent from work because of illness) and presenteeism (being present at work while ill which may lead to reduced efficiency) and consists of 11 items. Several demographic variables and history of treatment for mental health problems including medication is included in TiC-P.

Other assessments

WAI -The therapeutic alliance between therapists and patient will be assessed with the short version of the Working Alliance Inventory (WAI-SF). The WAI-SF is a 12-item self-reported questionnaire with responses on a 7-point Likert scale ranging from 1 (never) to 7 (always) (Hatcher and Gillaspy, 2006). The questionnaire covers three dimensions of working alliance: (1) therapeutic goals, (2) tasks, and (3) bond and the subscales have shown to have good internal consistencies. Both the patient and the 10-item therapist version of the questionnaire will be administered at 6 months follow-up. The alliance between the patient and technologies will be assessed with the WAI Online Therapy (Labpsitec, 2014) at 6 month follow-up.

CEQ - Patients' expectancy of treatment will be assessed with the Credibility and Expectancy Questionnaire (CEQ) of Devilly & Borkovec (2000) at baseline. Both factors (credibility andexpectancy) have shown to be stable across different populations, with high internal consistency within each factor. The scale consists of 6 questions, with answer options rated on a 10-point scale and on a 1-100% scale.

CSQ-8 - Patient's satisfaction with the treatment will be assessed with Client Satisfaction Questionnaire (CSQ-8) (Nguyen et al., 1983). This questionnaire has been translated in multiple languages and is used to measure global patient satisfaction. The questionnaire consists of 8 items that are measured on a 4 points scale with total scores ranging from 8 to 32 and has shown good psychometric properties.

SUS - Satisfaction with the platform will be evaluated with the system usability scale (SUS; Brooke 1996). This questionnaire will be completed by both clients and therapists. SUS is a simple 10 item scale giving a global view of subjective assessments of usability of a technology system. All items are measured on a 5-point scale ranging from strongly disagree until strongly agree. Total SUS scores have a range from 0-100. The questionnaire was reported to be highly reliable (α=0.91) and useful over a wide range of interface types (Bangor et al., 2008).

EMA - Ecological momentary assessments (EMA) will be measured during treatment in the intervention arm. EMA diaries will be completed through a mobile application and will include mood, rumination, sleep and accomplishment of activities (Table 2). EMA involves repeated sampling of participants' current behaviours and experiences, in natural environments. EMA aims to minimize recall bias and maximize ecological validity. EMA studies assess particular events in participants' lives at periodic intervals, by random time sampling, using technologies ranging from written diaries and telephones to electronic diaries and physiological sensors. In this study we will use mobile phones to assess EMA activities (Moskowitz and Young, 2006).

HAq-II – The Helping Alliance questionnaire (Luborsky et al., 1996) is a widely used questionnaire that measures the strength of the therapeutic alliance between the therapist and the patient. Internal consistency and test-retest reliability have been reported to be high (Luborsky et al., 1996).
ARM - The Agnew Relationship Measure (Agnew-Davies et al., 1998) a five item measure derived from the 28 Agnew Relationship Measure to assess the strength of the therapeutic relationship between the client and their therapist. Respondents rate their agreement with each item on a 7-point Likert scale (1= strongly disagree, 7= strongly agree). Based on the work of Bordin (1979) score alliance index is calculated as the mean of the item on three factor-based subscales: Bond, Partnership, and confidence. Evidence of the internal consistency and validity of the ARM has been reported elsewhere (Agnew-Davies et al., 1998).

RSQ - The relationship scales questionnaire (Griffin and Bartholomew, 1994) is a self-report measure based upon Bartholomew and Horowitz (1991) four category model. It consists of 30 statements drawn from the paragraph descriptions in Hazan and Shaver (1987) adult attachment categorical measure (ASS) and Collins and Read (1990) dimensional measure (adult attachment scales). Respondents rate how well they feel each statement fits their behaviour in a close relationship on a 5-point scale (1 = not al all like me, 5= very like me) and each can be assigned secure, fearful, preoccupied and dismissing scores. The RSQ is highly correlated with ASS and shows quite modest convergent validity with the authors own coded model (Griffin and Bartholomew, 1994).

Qualitative Interviews - The phenomenology of participants' and therapists' perspectives regarding the therapeutic relationship developed between them will be examined at the end of treatment with open-ended, in-depth interviews. Theoretical sampling will be used to ensure that an initial sample is drawn to represent a range of behaviours. It is anticipated that saturation will be reached after 15-20 interviews in each group. Selected participants will be approached with a separate information sheet (appendix 3 and 5) and will be asked to consent to participate in the interview as well as for the interview to be tape recorded (appendix 4 and 6).

The Intervention

The Internet platform includes a web-based interface providing patients access to CBT therapies. An existing internet-based treatment platform called ICT4Depression will be adapted to the trial requirements. ICT4Depression (ICT4D) is a platform developed and evaluated in the in a previous project of European Union's Seventh Framework Programme for Research and Technological Development . The internet based intervention will be supported by a platform called Moodbuster that comprises three elements: (1) a web-based interface providing the patients access to CBT therapies, (2) a web-based portal for therapists, where they can view patient progress and give feedback, (3) a mobile phone component which enables daily EMA monitoring of mood state, cognitions, activities, social interaction, and sleep of the patients (see Table 2).

- Patient portal
- Information
- Exercises
- Therapist portal
- Patient overview and progression
- Feedback
- Mobile application
- Monitoring mood, sleep and activities (EMA)
- Feedback and motivational messages

Patient's portal

The patient's portal home page is depicted in Figure 2. It contains: therapy modules under 'My Therapy'; mood evaluation under 'My mood'; communication with the therapist under 'Messages'; therapeutic exercises and a calendar to record physical activities. Progress on the current module is also displayed on the homepage (i.e. in Figure 2 the current module is 'problem solving' and progress is 78%).

Figure 8.3 Home page of patient's portal

An introduction to the therapy modules precedes the access to any of the components. The introduction section explains what blended treatment for depression is. It also gives an overview of treatment modules and environment including navigation on the website.

Therapy modules consist of 4 core, compulsory modules and 2 optional ones.

The compulsory modules are:

- 'Psycho-education' - which provides information about depression, goal setting and rewards. Exercises include:
- Life goals
- Treatment goals
- Rewards

'

'Behavioural activation' that focuses on: factors affecting mood; the difference between 'pleasant' and 'necessary' activities; balancing different activities and planning; increasing pleasant activities. Exercises for this module consist of:

- Pleasant activities table
- Registration of activities

- Necessary activities
- Planning
- Carrying out planning
- Increasing amount of pleasant activities

‘Cognitive restructuring’ explains the link between automatic thoughts, thinking errors and depression. This module teaches how to challenge automatic thoughts and replace them with new thoughts. Exercises focus on:

- Describing situation
- Registering automatic thoughts and their credibility
- Describing emotions and their strength
- Recognizing thinking Errors
- Challenging thoughts

‘Relapse prevention’ covers evaluation of treatment goals and learned skills. It also explains how to cope if/when symptoms reoccur. Exercises focus around:

- Goals
- Skills learned
- Action plan

An overview of all exercises used in the modules is presented in **Error! Reference source not found.**.

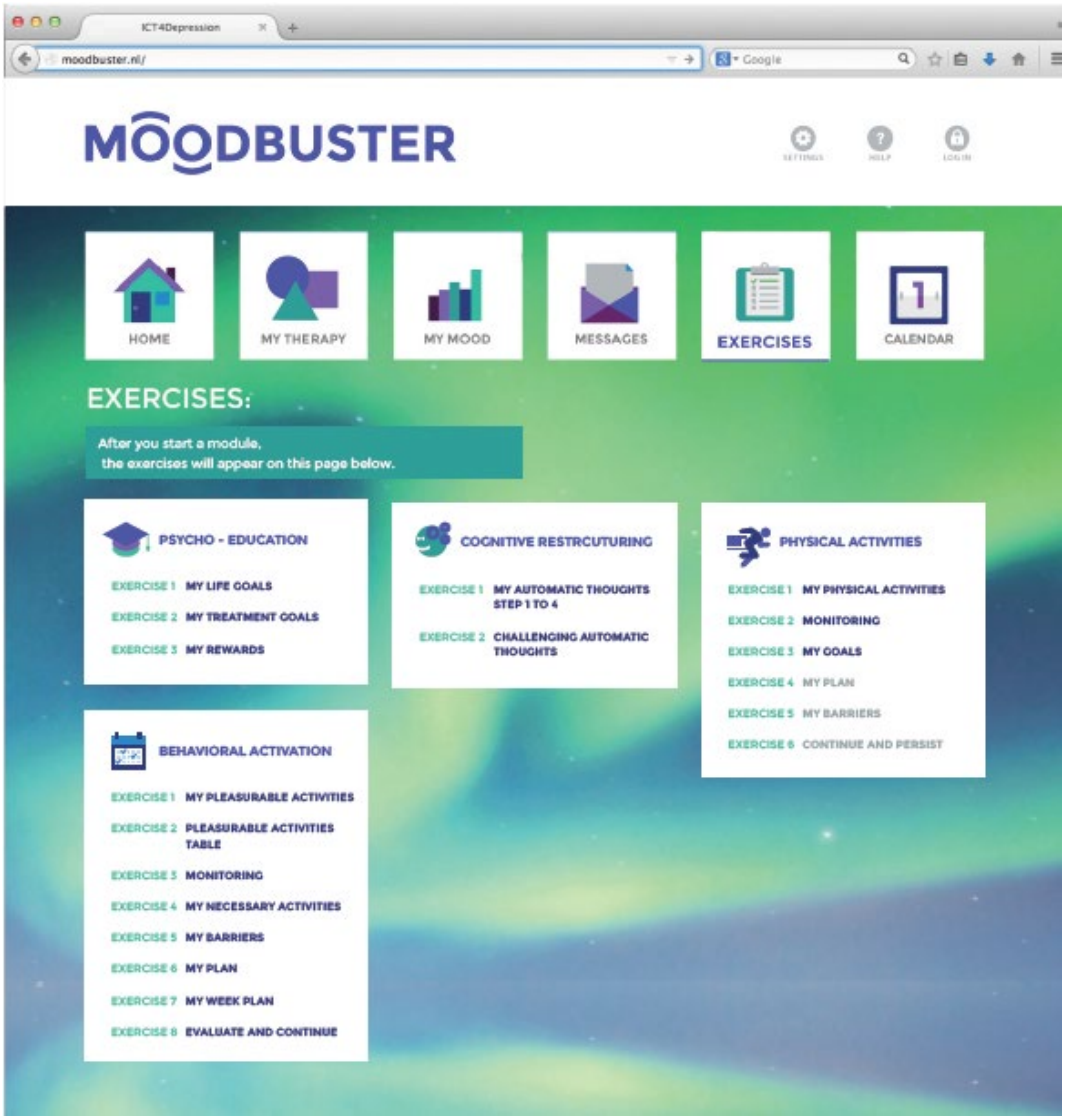


Figure 8.4 Overview of exercises

The optional modules in MoodBuster are:

'Physical exercise' where the relationship between physical activity and mood is discussed. The module explores different types of physical activities, explains ways how to cope with barriers, and suggests methods how to increase physical activity. Exercises include:

- Physical activities list
- Registration
- Goals
- Planning
- Barriers
- Adapting and persisting
- 'Problem solving' discusses important things in life; different type of problems as well as solving and coping with different types of such problems. Exercises are around:

- List of important things
- List of problems
- Categorise problems
- Cope with unsolvable problems
- Solve important problems; 6-step approach

Therapist Portal

The participating therapists will be given log-in details and access to individual accounts. Each therapist will then open accounts for their patients (intervention arm only) on the first day of therapy. The therapist and patient accounts will be linked and the therapist can check patient's progress online, communicate with patients, and vice versa, through an internal messaging system.

Mobile application

The mobile application will be used to capture EMA data. Participants will be sent questions directly to their mobiles at random times of day (restricted between 10am and 10pm). All questions will be on a Visual Analogue Scale (VAS) ranging from 1 to 10.

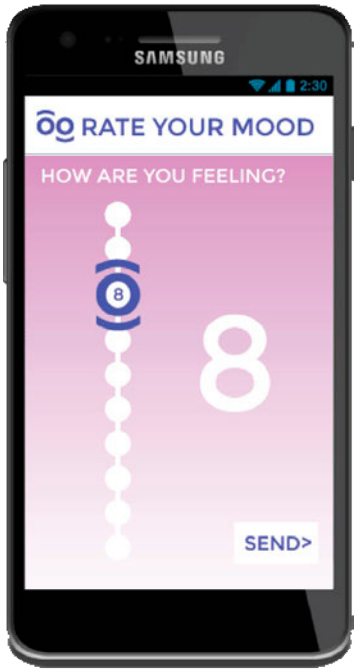


Figure 8.5 EMA for the mobile application

The lower end of the scale indicates more negative feelings/experiences and the higher end of the scale indicates the opposite details the frequency and schedule of mobile EMA. All EMA measures will be time and day stamped.

Full diary	Concept	Question	Scale
Morning Diary	Sleep	How well did you sleep last night?	VAS[2] 1-10
	Mood	How is your mood right now?	VAS 1-10
	Worrying	How much do you worry at the moment?	VAS 1-10
	Esteem	How do you feel about yourself right now?	VAS 1-10
Mood rating	Mood	How is your mood right now?	VAS 1-10
Evening Diary	Mood	How is your mood right now?	VAS 1-10
	Worrying	How much do you worry at the moment?	VAS 1-10
	Esteem	How do you feel about yourself right now	VAS 1-10
	Enjoy activities	How much did you enjoy activities today?	VAS 1-10
	Social contacts	How much were you involved in social interactions today?	VAS 1-10
	Activity level	To what extent did you accomplish pleasant activities today?	VAS 1-10
EMA assessment schedule: First 7 days of treatment and last 7 days of treatment : Full Diary Second week until the penultimate week of treatment: full EMA diary on 1 random day per week + 1 mood rating per day between 10am and 10pm			

Table 2 EMA schedule

Participants can access a graphical representation of their EMA recordings through the mobile application

[2] Visual Analogue Scale

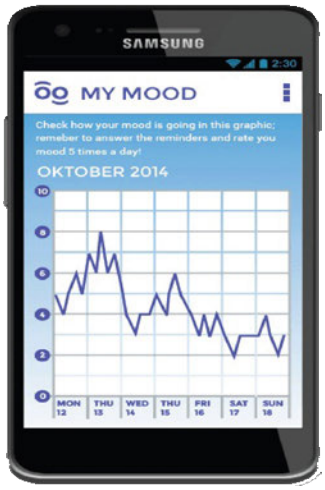


Figure 8.6 EMA recordings in a graphic form

Treatment fidelity

To ensure treatment fidelity it is required that: (1) a detailed treatment manual will be developed to guide therapists through the treatment, (2) therapists will register the number of sessions, the frequency of the sessions, the main strategies used in each session and the length of each contact (appendix 17), (3) training manual will be developed for therapists to guide patients in using MoodBuster. Therapist activities on the platform will be assessed through track and change functionalities in each country (logfiles). Therapists that will participate in the study will be allowed to deliver both treatment conditions. We are aware of the possibility of contamination between blended depression treatment and treatment as usual when therapists deliver both treatments, however, patients in the control arm would not be able to gain access to MoodBuster as logging in will need a registration which is authorised by the research team.

Treatment as usual includes CBT for depression (face to face), visits by health professionals, receipt of medication, self-help groups and any other treatment.

Randomisation

Participants will be randomly (see Figure1) allocated to receive treatment as usual (TAU) or internet supported therapy in addition to treatment as usual (blended therapy). Randomisation will be conducted centrally, in the University of Amsterdam (E-Compared consortium member), by an independent researcher who is not involved in the trial. Randomisation will take place at an individual level, stratified by country, after the eligibility assessment and obtaining consent from participants. The independent researcher will make the allocation scheme with a computerised random number generator. The allocation ratio will be 1:1. Block randomization with variable block sizes that vary between 6 and 12 allocations per block will be used. Subjects will be randomized into two groups: blended treatment for

depression or treatment as usual. The therapist will be notified about individual allocations by the Trial Manager who will be un-blinded to arm allocation. The therapist will in turn inform the client about which arm have they been allocated at the beginning of their first session.

Concealment and Blinding

In order to maintain blinding, randomisation will be performed independently of the research worker (RW) following baseline evaluation. An IAPT therapist who cannot be blinded to allocation will carry out the therapy. Baseline and subsequent evaluations will be undertaken by an independent RW. Therapists will be instructed not to disclose allocation to RW.

Participant Involvement

Individuals with a clinician's diagnosis of Major Depressive Disorder confirmed by MINI and a score of more than 5 on PHQ-9 would be eligible for the trial.

IAPT therapists who will participate in the trial will also be asked to complete some online questionnaires (appendix 6). For this reason they will be considered as trial participants and will be consented into the trial (appendix 6) in accordance with GCP guidelines.

Recruitment base

Participants will be recruited from Camden and Islington Psychological Therapies Services called iCope that provides evidence-based psychological therapies for adults in an inner London urban area (Camden and Islington). All eligible clients who will be accessing IAPT services will be invited into the study.

- Psychological interventions at IAPT services are delivered by trained therapists:
- Clinical Psychologists
- Trainee Clinical Psychologists
- Assistant Psychologists
- Psychological Wellbeing Practitioners (PWP)

Recruitment process

IAPT services recruited through the research team will be asked to inspect their waiting patient lists to identify potential participants with depression who fit our criteria and are suitable for the study. The IAPT therapists who assess patients referred to IAPT services will introduce the study to suitable patients at the end of their clinical assessment session and give them a Patient Information Sheet (Appendix 1). Interested patients will be asked by their therapist if they agree for a member of the research team to contact them by phone and if it ok for their telephone number to be passed to the research team. The therapist will inform the research team and pass details of potential participants who have agreed to be contacted. A researcher will contact by phone those people who express an interest

in participating in the study. During the phone call the researcher will explain the study, respond to any queries and screen for eligibility. Eligibility screening includes asking some screening questions (appendix 8) and by completing the PHQ-9 and the MINI. If the patient is eligible, the researcher will offer an opportunity to meet to explain the study further, administer additional eligibility measures, and seek formal consent for participation in the study. During this face-to-face meeting the researcher will go ahead with consent seeking procedures. These meetings will take place in the IAPT clinics or at the London School of Hygiene & Tropical Medicine, wherever is more convenient for the individual. Once consent is obtained participants will proceed to the baseline interview/assessment and then be randomised. The randomisation process has been described in section 0, pp252.

Inclusion criteria

- 18 years of age or older
- Scoring more than 5 points on PHQ-9.
- Meet DSM-IV diagnostic criteria for Major Depression Disorder as confirmed by the telephone administered MINI International Neuropsychiatric Interview version 5.0.
- Exclusion criteria
- Current high risk for suicide according to the MINI Interview section C.
- Serious psychiatric co-morbidity that requires alternative treatment including substance dependence, bipolar affective disorder, psychotic illness or obsessive compulsive disorder as established at the MINI interview.
- Currently receiving psychological treatment for depression in primary or specialised mental health care.
- Being unable to comprehend, speak, read or write English.
- Not having access to a fast internet connection (i.e. broadband or comparable).
- Not having or being unable to set up an email address that can be used to communicate with the therapist and research team.

Informed consent

All participants will provide written informed consent. The Informed Consent Form (*appendix 2*) will be signed and dated by both the patient and the research worker before they enter the trial. The research worker will explain the details of the trial and will encourage the potential participant to ask any questions that might help them make a decision on their potential involvement in the trial.

Informed consent will be collected from each participant before they undergo any interventions related to the study. One copy of the Informed Consent Form will be kept by the participant, one will be kept by the research worker, and a third will be retained in the participant's IAPT records.

Where a participant who appeared to be eligible and signed a consent form is subsequently found not to be eligible (e.g. the therapist concludes they fulfil one of the exclusion criteria) they will not be considered to have entered the study and both the therapist and patient will be informed of this.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form, which will need to be signed by the participant.

Statistical Methods

Sample size

Sample size calculation is based on the non-inferiority design and calculated for the primary clinical outcome symptoms of depression. Pooling data of the participating trial sites enables to generate more statistical power for study analyses. Each trial site will therefore include 150 patients which enables us to detect a difference in effect size of d=0.25 or larger between blended Internet-based treatment and TAU. If the difference is smaller than d=0.25 we will consider the treatments to be equally effective (Cuijpers et al., 2014).

Data entry

Double entry of data provided in paper form will be undertaken using automated consistency and logical checks. Data will be stored encrypted and password-protected on local drive with weekly backup. The central database will be maintained at London School of Hygiene and Tropical Medicine [LSHTM]. A log will be kept of data amendments.

Data protection

We will be fully compliant with the provisions of the Data Protection Act (UK Parliament, 1998) and Good Clinical Practice (GCP). All records will be kept in a locked filing cabinet at the UK study centre. Confidentiality of electronic records will be ensured by password protection. The databases will be designed so that participant names are not shown on screen. Participant names and contact addresses will be deleted from the database at the earliest opportunity (for example, if a participant withdraws from the trial). All personal information about the user will be encrypted in the database. Only the UK research team will have access to the code that connects the ID number to a person.

Data will be aggregated for reporting purposes. Only encrypted, anonymised, non-personal data will be shared among the collaborating sites and countries (strictly EU). Anonymised data of all countries will

be pooled for analyses. Unidentifiable final study data will be transferred to Netherlands in accordance with GCP practice and Data Protection Act.

Mobile and computer data (such as EMA) collected through MoodBuster will be of a non-personal nature. This data will be safely stored in Portugal with The Institute for Systems and Computer Engineering, Technology and Science of Porto (INESC TEC, Porto). INESC TEC is one of the E-Compared consortium members. Personal information such as names, dates of birth, addresses, phone numbers etc. will not be entered in the system. Mood Buster will be supported by ICT4D platform (see section 4.3 servers firewall, however INESC TEC computers are globally protected by a network firewall. For the moment, ICT4D database port is open for specific Internet Protocols (IPs) of the University of Amsterdam (Vrije Universiteit Amsterdam, VUA,) for the purpose of debugging the Reasoning Engine (a component of the ICT4D System developed by the VUA) however, once development phase is finished, this component will be installed in a server inside INESC TEC's network and external access to the database will be removed.

Database design ensures that no elements that can directly or indirectly identify the users are stored, therefore rendering data anonymous.

Data transmission relies on Hypertext Transfer Protocol Secure (HTTPS) for all communications with the server. Client applications such as the Moodbuster do not access directly to the ICT4D database. Instead, they rely on secure web services to fetch data from the database. Web services provide an extra layer of security, not only because they also operate over HTTPS, but also because they implement role based access control to patient's data. Currently, only the therapist, his supervisor and the patient himself can request patient data.

Applications use a standard login/password authentication method, which is then relayed to the secure web services layer. Further interactions are based on a token valid for that session.

Data preservation is attained by storage replication (mirroring) accompanied by an adequate backup plan.

Data analysis

Trial data will be pooled and multiple imputation will be used to deal with missing data. Intention-to-treat analyses (ITT) increase the risk of type I errors in non-inferiority (NI) trials and non-intention-to treat analyses are preferred over ITT analyses in NI designs. Therefore, the primary statistical analyses will be per protocol analyses meaning that only those patients that have completed the treatment will

be included in the analyses. ITT analyses will be used in sensitivity analyses to increase confidence in the results obtained by including all participants in the analyses independent of whether they have completed the treatment or not. Blended depression treatment is considered no less effective than care-as-usual when the two-sided 95% confidence interval (the range of plausible differences between the two treatments) lies entirely above the standard mean difference of 0.20 which is the non-inferiority margin and the smallest clinically acceptable difference.

Qualitative data will be simultaneously collected and analysed. The analysis will be aided by the use of the Nvivo computer software package. Line-by-line initial descriptive open coding will be carried out. Low-level categories will emerge from the data, which will be integrated into meaningful units to form higher-level categories, which will be grounded in the data. A coding paradigm will be applied to link categories with one another and create themes. The process of data collection and analysis will continue until theoretical saturation has been achieved.

Economic evaluation

Multiple imputation will be used to impute missing cost and effect data. Incremental cost-effectiveness ratios will be calculated by dividing the mean difference in costs between the blended treatment and TAU by the difference in effects. To account for the typically skewed distribution of costs, bias-corrected and accelerated bootstrapping (5000 replications) will be used to estimate the 95% confidence intervals around the mean cost differences and the uncertainty surrounding the ICERs. The bootstrapped ICERs will be graphically presented in cost-effectiveness planes [281]. Cost-effectiveness acceptability curves [282] will be estimated to show the probability of the intervention program to be cost-effective in comparison with usual care for a range of different ceiling ratios, thereby showing decision uncertainty.

Benefits and burdens for participants

The treatment protocols included in this proposal, are based on evidence-based face to face and Internet-supported (blended) therapy programs, based on cognitive behavioural therapy, that have been previously tested and whose efficacy have already been established, e.g. in a recommendation by the National Institute for Health and Clinical Excellence (NICE), UK [283]. Therefore, it can be expected that patients receiving this type of treatment in the context of E-COMPARED will also have therapeutic benefit. No patients will be withheld or delayed treatment by taking part in this trial. Moreover, by participating in E-COMPARED patients will be monitored carefully.

The assessment and intervention protocols designed in this project have been developed by expert clinical mental health professionals, with significant experience in research and applications of psychological assessment and treatments in the field of clinical psychology. Furthermore, the entire assessment and therapeutic process will be conducted and supervised by expert clinicians.

As for the intervention protocols used in this study, according to the existing knowledge in this field, there is nothing in the project that poses a risk to the participating patients. The treatment protocols in both conditions are based on cognitive-behaviour therapy (CBT), which is probably the most studied and evidence-based type of psychotherapy. CBT is first and foremost a learning- or taught-based therapy. Thus, the treatment is not invasive at a cognitive level, except as far as any learning or teaching is concerned. In addition, in both conditions General Practitioners, psychiatrists and other care professionals may prescribe antidepressants as is appropriate in routine practice and according to existing guidelines for the treatment of MDD.

E-COMPARED results will assist policy and decision makers in making informed decisions on the implementation of alternative (e-electronic) health care systems in the treatment of depression, which may lead to an increased uptake of e-Mental health approaches for depression treatment. E-COMPARED aims to improve clients' treatment accessibility among other benefits.

Participants of the E-COMPARED trial may become upset when discussing their feelings during the screening interviews and while completing self-report questionnaires online. These screening assessments will be supervised by fully trained research assistants to lessen patients' burden, and may even lead to the identification of patients whose depression has worsened and who are at risk of suicide. Researchers will have a procedure for taking action in such situations (appendix 7). The administrative burden of completing questionnaires will be minimised by providing these questionnaires online for participants to complete at a convenient time and pace.

Adverse Events and Risk Management

Attrition will be carefully monitored to determine its effects on the power of the study. If a participant withdraws from the intervention arm of the trial permission would be sought to continue monitoring outcomes.

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE does include a / an:

1. exacerbation of a pre-existing illness.
2. increase in frequency or intensity of a pre-existing episodic event or condition.
3. condition detected or diagnosed after intervention even though it may have been present prior to the start of the trial.
4. continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:
1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.
3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received exercise intervention or usual treatment that results in any of the following outcomes:
1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation for non-elective procedures
4. Sudden or rapidly progressive major disablement
5. An event that caused the participant to seek non-routine medical treatment.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality.
A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Reporting of adverse events
All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Principal Investigator and Trial Manager shall be responsible for all adverse event reporting.

During the trial we will conduct monitoring of adverse events. Participants will be asked to contact the trial site immediately in the event of any adverse event Adverse Events (AEs) will be brought to the attention of the study team by either:
Telephone call to the study team. Participants will be encouraged to call the study team if they experience any adverse effects during the study.
Notification by Therapist. Participant's therapist will be encouraged to contact the study team of any AEs they are made aware of.

On notification of an AE at the study centre, the Trial Manager will call the participant for further information. The Principal Investigator shall determine seriousness and causality in conjunction with therapist and any treating medical practitioners.

All adverse events will be recorded and closely monitored until resolution, stabilisation, or it has been demonstrated that the study treatment is not the cause.

Risk management
Suicidal risk will be minimised by assessment prior to randomisation and the use of the suicide manual (appendix 7).

Trial intervention related SAEs
A serious adverse event that is deemed directly related to or suspected to be related to the trial intervention shall be reported to the ethics committee. The reporting form for SAEs is shown in the appendix 6. The event shall be reported immediately of knowledge of its occurrence to the Trial Manager and Principal Investigator.

The Principal Investigator will:
Assess the event for seriousness, expectedness and relatedness to the trial treatment.
Take appropriate medical action, which may include halting the trial and inform the sponsor of such action.

If the event is deemed related to the trial treatment, shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
Within a further 8 days send any follow-up information and reports to the REC.
Make any amendments as required to the trial protocol and inform the REC as required.

Removal of participants from interventions, assessments or the trial

Participants may be withdrawn from the trial either at their own request or at the discretion of the therapist and/or investigator. The participants will be made aware that this will not affect their future care.

The research team will advise discontinuation of intervention or withdrawal from the trial if it poses a hazard to the safety of a participant, or if the participant poses a hazard to the safety of someone else.

Those who withdraw from the trial or follow-up will not be replaced. Participants should not be accepted as lost to follow-up unless 2 phone calls, letters or visits to the participant and carer have been fruitless.

Feasibility

The design allows for a total recruitment and follow up period of 18 months. We have obtained funds to recruit and employ one trial manager and one research assistant who are based at London School of Hygiene and Tropical Medicine for 24 months. Taking into account leave, sickness we expect 44 working weeks per year from the researcher. We believe it is possible to undertake an average of two participant contacts per day depending on location and complexity (in addition to other duties such as data entry).

Stopping Rule

The stopping rule will be as follows: once all participants have been randomised any recruitment interviews that have been arranged will be honoured. Participants yet to be contacted, as well as those subsequently expressing an interest in the trial, will be sent a letter thanking for their interest but explaining that recruitment for the trial is now closed.

End of Trial Notifications

Once the trial is completed a summary of the results will be sent to the participants and to their therapists.

Safety variables and endpoints

Safety variables will include suicide risk assessments and suicide manual. Safety endpoints will be significant adverse events (AEs) spontaneously reported during the study and discontinuations due to AEs.

Stopping rules and discontinuation

If there is a significant statistical difference ($p<0.05$) between the number of reported AE/SAE by the intervention and control groups the Principal Investigator (PI) will consider the discontinuation of the trial. See risk management procedures.

ETHICAL AND REGULATORY ASPECTS

Full ethical approval for the study will be sought from IRAS.

This research will be conducted in accordance with the Declaration of Helsinki [284], Good Clinical Practice (ICH-GCP) [285], Research Governance Framework for Health and Social Care (2005), the requirements of the law and relevant good practice guidelines relating to the conduct of research. Informed consent will be sought from all participants. The participants' therapists will have clinical responsibility for the participant throughout the trial. Study personnel will inform the therapists of any adverse events and any significant clinical problems that are brought to the investigators' attention.

All study records will be securely stored for 5 years after the completion of the study.
We will make every effort to maintain confidentiality of data supplied by participants. Participants will be free to withdraw from the study at any time and will be reassured that doing so will not affect their medical care.

Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and GCP and any other regulatory requirements that might be introduced. The researcher and the participant shall both sign and date the Informed Consent Form before the participant can participate in the trial.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes in the IAPT service and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The research worker shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The research worker will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

Records

Case report forms

Each participant will be assigned a unique Participant Identification Number for use on case report forms (CRFs), other trial documents and the electronic database. CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate Trial Recruitment Log (TRL) to record confidential participant information including, name, date of birth and Participant Identification Number. This permits identification of all participants enrolled in the trial, in case additional follow-up is required.CRFs shall be restricted to those personnel approved by the Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

Source documents

Source documents shall be filed at the investigator's site (LSHTM) and may include but are not limited to consent forms and questionnaires. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents shall be made available at all times for review by the Principal Investigator, and inspection by the sponsor [LSHTM] and relevant regulatory authorities, including the R&D departments.

QUALITY ASSURANCE & AUDIT

Research Staff Training

The researcher conducting the recruitment and outcome interviews will undergo training in administering the relevant questionnaires. In addition, the researchers will be up to date with their GCP training.

Monitoring and Audit

The Principal Investigator will conduct an internal audit at the study centre every six months to ensure: confidentiality and integrity of databases; effectiveness of database backup systems; confidentiality and integrity of paper records; reconciliation of enquiries with enquiry outcome; data entry procedures; numbers allocated to each treatment group; comparison of paper records and electronic records. Every two weeks, the Principal Investigator, together with the study team will review the progress of recruitment by recording number of letters sent, number of enquiries received, number of calls made, number of participants entered, number of participants randomised.

The study team will comply fully with any request for external audit by the Sponsors or funding body.

Indemnity arrangements

This project will be indemnified through London School of Hygiene & Tropical Medicine [LSHTM]. This covers participants in the event of negligent or non-negligent harm.

METHODS FOR DISSEMINATING AND IMPLEMENTING RESEARCH RESULTS

The trial will be published in peer-reviewed medical journals.

Abstracts will be submitted to identified relevant conferences to inform other researchers of the work. The support of the European Commission's Seventh Framework Programme for Health- '*Comparative Effectiveness Research (CER) in health systems and health services interventions'* will be credited in all publications that arise from this project in accordance with the acknowledgment and disclaimer agreed between EC and the E-COMPARED Consortium.

Table 3 Project Timetable

Year	EC	Month	General Administrative Tasks	Milestones	Technical management tasks	Target recruitment (cumulative)
	11	November		Trial Manager and Research Assistant employed, Protocol development	Translational work finalised	

Year	EC	Month	General Administrative Tasks	Milestones	Technical management tasks	Target recruitment (cumulative)
2014	12	December	Steering Group established	Site identification, Contact Clinicians, Attend clinical meetings	Piloting task finalised, Technical issues resolved	
2015	13	January		Ethics and R&D approvals	Therapist training	
	14	February				
	15	March		Recruitment begins		0
	16	April				25
	17	May				50
	18	June	Steering Group			75
	19	July				100
	20	August				125
	21	September		Recruitment ends		150
	22	October				
	23	November				
	24	December	Steering Group			
2016	25	January				
	26	February				
	27	March		Final follow-up begins		0
	28	April		Data entry		25
	29	May		Data entry		50
	30	June	Steering Group	Data entry		75
	31	July		Data entry		100
	32	August		Data entry		125
	33	September		Final follow-up ends		150

Year	EC	Month	General Administrative Tasks	Milestones	Technical management tasks	Target recruitment (cumulative)
	34	October		Data integration and analysis		
	35	November	Steering Group	Final reports/publications		
	36	December				

SIGNATURE PAGES (Signatories to Protocol)

Principal Investigator: Prof. Ricardo Araya

Signature: _____

Date: 11/02/2015

Trial Manager: Arlinda Cerga Pashoja

Signature: _____

Date: 11/02/2015

Research Assistant: Asmae Doukani

Signature: _____

Date: 11/02/2015

REFERENCES

52nd WMA General Assembly. (2000), World Medical Association Declaration of Helsinki: Ethical principles for medical research involving humans, Edinburgh, Scotland.

Agnew-Davies, R., Stiles, W.B., Hardy, G.E., Barkham, M. and Shapiro, D.A. (1998), "Alliance structure assessed by the Agnew Relationship Measure (ARM)", British Journal of Clinical Psychology, Vol. 37 No. 2, pp. 155–172.

Van Agt, H., Essink-Bot, M., Krabbe, P. and Bonsel, G. (1994), "Test-retest reliability of health state valuations collected with the EuroQol questionnaire", Social Science & Medicine, Elsevier, Vol. 39 No. 11, pp. 1537–1544.

Andersson, G. (2009), "Using the Internet to provide cognitive behaviour therapy.", Behaviour research and therapy, Vol. 47 No. 3, pp. 175–80.

Andersson, G. and Hedman, E. (2013), "Effectiveness of guided internet-based cognitive behavior therapy in regular clinical settings", Verhaltenstherapie, Vol. 23 No. August, pp. 140–148.

Bangor, A., Kortum, P.T. and Miller, J.T. (2008), "An Empirical Evaluation of the System Usability Scale", International Journal of Human-Computer Interaction, Taylor & Francis, Vol. 24 No. 6, pp. 574–594.

Bartholomew, K. and Horowitz, L.M. (1991), "Attachment styles among young adults: a test of a four-category model.", Journal of personality and social psychology, Vol. 61 No. 2, pp. 226–44.

Beattie, A., Shaw, A., Kaur, S. and Kessler, D. (2009), "Primary-care patients' expectations and experiences of online cognitive behavioural therapy for depression: a qualitative study.", Health expectations : an international journal of public participation in health care and health policy, Vol. 12 No. 1, pp. 45–59.

Black, W.C. (1990), "The CE plane: a graphic representation of cost-effectiveness.", Medical decision making : an international journal of the Society for Medical Decision Making, Vol. 10 No. 3, pp. 212–4.

Bordin, E.S. (1979), "The generalizability of the psychoanalytic concept of the working alliance.", Psychotherapy: Theory, Research & Practice, Vol. 16 No. 3, pp. 252–260.

Bouwmans, C., De Jong, K., Timman, R., Zijlstra-Vlasveld, M., Van der Feltz-Cornelis, C., Tan Swan, S. and Hakkaart-van Roijen, L. (2013), "Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P).", BMC health services research, Vol. 13, p. 217.

Brooke, J. (1996), Usability Evaluation In Industry, (Jordan, P., Thomas, B., Weerdmeester, B. and McClelland, I.,Eds.), CRC Press, London, Usability ., p. 252.

Clark, D.M. (2011), "Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience.", International review of psychiatry (Abingdon, England), Vol. 23 No. 4, pp. 318–27.

Collins, N.L. and Read, S.J. (1990), “Adult attachment, working models, and relationship quality in dating couples.”

Cuijpers, P., Donker, T., Johansson, R., Mohr, D.C., van Straten, A. and Andersson, G. (2011), “Self-guided psychological treatment for depressive symptoms: a meta-analysis.”, (Hempel, S.,Ed.)PloS one, Public Library of Science, Vol. 6 No. 6, p. e21274.

Cuijpers, P., van Straten, A., van Oppen, P. and Andersson, G. (2008), “Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies.”, The Journal of clinical psychiatry, Vol. 69 No. 11, pp. 1675–85; quiz 1839–41.

Cuijpers, P., Turner, E.H., Koole, S.L., van Dijke, A. and Smit, F. (2014), “What is the threshold for a clinically relevant effect? The case of major depressive disorders.”, Depression and anxiety, Vol. 31 No. 5, pp. 374–8.

Delgadillo, J., McMillan, D., Leach, C., Lucock, M., Gilbody, S. and Wood, N. (2014), “Benchmarking routine psychological services: a discussion of challenges and methods.”, Behavioural and cognitive psychotherapy, Vol. 42 No. 1, pp. 16–30.

DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., O’Reardon, J.P., et al. (2005), “Cognitive therapy vs medications in the treatment of moderate to severe depression.”, Archives of general psychiatry, Vol. 62 No. 4, pp. 409–16.

Devilly, G.J. and Borkovec, T.D. (2000), “Psychometric properties of the credibility/expectancy questionnaire”, Journal of Behavior Therapy and Experimental Psychiatry, Vol. 31 No. 2, pp. 73–86.

Druss, B.G., Hoff, R.A. and Rosenheck, R.A. (2000), “Underuse of antidepressants in major depression: prevalence and correlates in a national sample of young adults.”, The Journal of clinical psychiatry, Vol. 61 No. 3, pp. 234–7; quiz 238–9.

Ekers, D., Richards, D. and Gilbody, S. (2008), “A meta-analysis of randomized trials of behavioural treatment of depression.”, Psychological medicine, Vol. 38 No. 5, pp. 611–23.

Fenwick, E., O’Brien, B.J. and Briggs, A. (2004), “Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions.”, Health economics, Vol. 13 No. 5, pp. 405–15.

Griffin, D. and Bartholomew, K. (1994), “The metaphysics of measurement: the case of adult attachment”, in Bartholomew, K. and Perlman, D. (Eds.),Advances in personal relationships, attachment processes in adulthood, 5thed., pp. 17–52.

Hatcher, R.L. and Gillaspy, J.A. (2006), “Development and validation of a revised short version of the working alliance inventory”, Psychotherapy Research, Routledge, Vol. 16 No. 1, pp. 12–25.

Hazan, C. and Shaver, P. (1987), “Romantic love conceptualized as an attachment process.”, Journal of personality and social psychology, Vol. 52 No. 3, pp. 511–24.

Huber, M., Stanciole, A., Wahlbeck, K., Tamsma, N., Torres, F., Jelfs, E. and Bremner, J. (2008), Quality in and equality of access to healthcare services, Brussels.

ICH. (1996), ICH harmonized tripartite guideline: Guideline for Good Clinical Practice., Vol. 47, pp. 45–50.

Kohn, R., Saxena, S., Levav, I. and Saraceno, B. (2004), The treatment gap in mental health care, pp. 858–866.

Kroenke, K., Spitzer, R.L. and Williams, J.B. (2001), "The PHQ-9: validity of a brief depression severity measure.", Journal of general internal medicine, Vol. 16 No. 9, pp. 606–13.

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., Janavs, J., et al. (1997), "The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI", European Psychiatry, Vol. 12 No. 5, pp. 224–231.

Luborsky, L., Barber, J.P., Siqueland, L., Johnson, S., Najavits, L.M., Frank, A. and Daley, D. (1996), "The Revised Helping Alliance Questionnaire (HAq-II) : Psychometric Properties.", The Journal of psychotherapy practice and research, Vol. 5 No. 3, pp. 260–71.

Lynch, D., Laws, K.R. and McKenna, P.J. (2010), "Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials.", Psychological medicine, Vol. 40 No. 1, pp. 9–24.

Malouff, J.M., Thorsteinsson, E.B. and Schutte, N.S. (2007), "The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis.", Clinical psychology review, Vol. 27 No. 1, pp. 46–57.

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M. and Lawton-Smith, S. (2008), Paying the price: The cost of mental health care in England to 2026, London.

Moskowitz, D.S. and Young, S.N. (2006), "Ecological momentary assessment: what it is and why it is a method of the future in clinical psychopharmacology.", Journal of psychiatry & neuroscience : JPN, Vol. 31 No. 1, pp. 13–20.

Nguyen, T.D., Attkisson, C.C. and Stegner, B.L. (1983), "Assessment of patient satisfaction: development and refinement of a service evaluation questionnaire.", Evaluation and program planning, Vol. 6 No. 3-4, pp. 299–313.

NICE. (2009), Depression: management of depression in primary and secondary care. Clinical Guideline 90, London.

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U. and Jönsson, B. (2012), "The economic cost of brain disorders in Europe.", European journal of neurology : the official journal of the European Federation of Neurological Societies, Vol. 19 No. 1, pp. 155–62.

Richards, D. and Richardson, T. (2012), “Computer-based psychological treatments for depression: a systematic review and meta-analysis.”, Clinical psychology review, Vol. 32 No. 4, pp. 329–42.

Richardson, J.R.J., Peacock, S.J., Hawthorne, G., Iezzi, A., Elsworth, G. and Day, N.A. (2012), “Construction of the descriptive system for the Assessment of Quality of Life AQoL-6D utility instrument.”, Health and quality of life outcomes, Vol. 10 No. 1, p. 38.

Rohde, P., Lewinsohn, P.M. and Seeley, J.R. (1997), “Comparability of telephone and face-to-face interviews in assessing axis I and II disorders.”, The American journal of psychiatry, Vol. 154 No. 11, pp. 1593–8.

Van Roijen, L.H., van Straten, A., Al, M., Rutten, F. and Donker, M. (2006), “Cost-utility of brief psychological treatment for depression and anxiety.”, The British journal of psychiatry : the journal of mental science, Vol. 188 No. 4, pp. 323–9.

Ruskin, P.E., Reed, S., Kumar, R., Kling, M.A., Siegel, E., Rosen, M. and Hauser, P. (2014), “Reliability and Acceptability of Psychiatric Diagnosis Via Telecommunication and Audiovisual Technology”, American Psychiatric Publishing.

Ruwaard, J., Lange, A., Schrieken, B. and Emmelkamp, P. (2011), “Efficacy and effectiveness of online cognitive behavioral treatment: a decade of interapy research.”, Studies in health technology and informatics, Vol. 167, pp. 9–14.

Sheehan, D. V, Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., et al. (1998), “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.”, The Journal of clinical psychiatry, Vol. 59 Suppl 2, pp. 22–33;quiz 34–57.

Singleton, N., Bumpstead, R., O’Brien, M., Lee, A. and Meltzer, H. (2001), Psychiatric Morbidity Among Adults Living in Private Households, 2000, London.

Spek, V., Cuijpers, P., Nyklícek, I., Riper, H., Keyzer, J. and Pop, V. (2007), “Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis.”, Psychological medicine, Vol. 37 No. 3, pp. 319–28.

The Office for National Statistics. (2001), Psychiatric Morbidity Report.

UK Parliament. (1998), The Data Protection Act, London.

Unlü, B., Riper, H., van Straten, A. and Cuijpers, P. (2010), “Guided self-help on the Internet for Turkish migrants with depression: the design of a randomized controlled trial.”, Trials, Vol. 11 No. 1, p. 101.

Vos, T., Haby, M.M., Magnus, A., Mihalopoulos, C., Andrews, G. and Carter, R. (2005), “Assessing cost-effectiveness in mental health: helping policy-makers prioritize and plan health services.”, The Australian and New Zealand journal of psychiatry, Vol. 39 No. 8, pp. 701–12.

Wittkampf, K.A., Naeije, L., Schene, A.H., Huyser, J. and van Weert, H.C. (2007), “Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review.”, General hospital psychiatry, Vol. 29 No. 5, pp. 388–95.

Woltmann, E., Grogan-Kaylor, A., Perron, B., Georges, H., Kilbourne, A.M. and Bauer, M.S. (2014), “Comparative Effectiveness of Collaborative Chronic Care Models for Mental Healt Conditions Across Primary, Specialty, and Behavioral Health Care Settings: Systematic Review and Meta-Analysis”, American Psychiatric Publishing Arlington, VA.

World Health Organization. (2012), Disorders Management - Mental Health.

Zalcberg, J.R. (2011), “Comparative effectiveness research - a proposal for a new NHMRC funding stream”, The Medical Journal of Australia, Vol. 196 No. January, pp. 22–23.

Zuithoff, N.P.A., Vergouwe, Y., King, M., Nazareth, I., van Wezep, M.J., Moons, K.G.M. and Geerlings, M.I. (2010), “The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a crosssectional study.”, BMC family practice, Vol. 11, p. 98.

Appendix 2.Participant information sheet for trial–Client

Prof. Ricardo Araya
Department of Population Health
London School of Hygiene & Tropical
Medicine
Keppel Street
London WC1E 7HT

Phone: 020 7927 8141
Email: ricardo.araya@lshtm.ac.uk

Re. E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

We would like to invite you to take part in a research study called E-COMPARED. Before you decide, it is important for you to understand why we're asking you to take part in this study and what it will involve.

Please take time to read the following information carefully.

What is the purpose of the study?

Depression is a serious mental health condition, affecting around 350 million people worldwide. Depression can be treated effectively with antidepressants, psychotherapy or a combination of both. Studies indicate that people often prefer psychotherapy, such as cognitive behaviour therapy (CBT) to medical treatment. However, psychotherapy is not always available, accessible or affordable. Internet supported interventions attempt to bridge this gap and make psychotherapy more accessible to individuals.

Why have I been chosen?

You have been identified as a person who is waiting to receive therapy for depression, who might like to take part in the study. We hope to speak to about 150 people in a similar situation.

Do I have to take part?

No, it is entirely up to you whether you decide to take part or not. If you do decide to take part you will be given this information sheet to keep. If you would prefer not to take part, the way you access services will not be affected in any way.

What will happen if I don't want to carry on with the study?

Once you have agreed to participate, you will still be able to withdraw at any time you like and you do not have to give a reason.

What will happen to me if I take part?

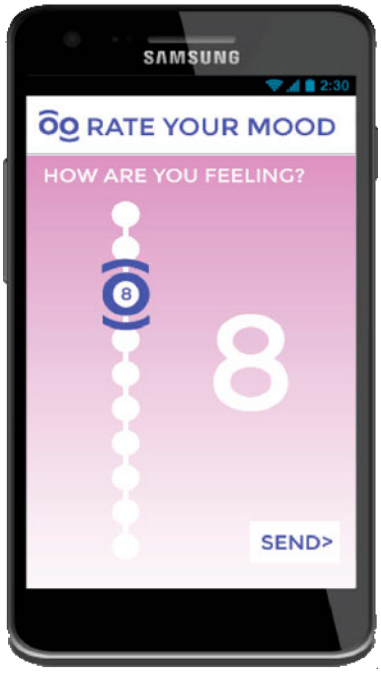
Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We will put people into groups: blended therapy or treatment-as-usual; the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). You would have an equal chance of being in either group and the research team **cannot** choose who will be put into which group.

- The treatment-as-usual group will carry on as normal with scheduled face to face therapy sessions.
- The blended therapy group will receive weekly, alternated, face to face therapy sessions and therapy on the internet (online). These sessions will last for **11 weeks**, with **one session happening every week**. One week you will have a face-to-face session with your therapist and the week after you will carry out therapy modules online. Internet therapy will be delivered through MoodBuster, which is a computer and mobile platform that connects you and your therapist online.

In order to find out if therapy has made any difference to the way you feel; you will be asked some questions designed to be used in studies like this. Questions will be asked:

- By telephone four times: at screening and after 3, 6 and 12 months.
- Online, four times: at the beginning of therapy, after 3, 6 and 12 months. We will not ask you any questions after 12 months.

It is important that we ask you these questions whichever group you are assigned to.



- Participants in the blended therapy group only will be given access to a mobile application that will send questions that aim to rate mood and other activities directly to their mobilephones at random times of the day (10am-10pm). During the first and the last week of the treatment participants will be sent 11 such questions everyday. For the rest of the period participants will be sent 1 question everyday, and in one random day of the week they will answer 11 such questions.

A few participants will be asked some questions about their experiences of the trial at the end of therapy (after 11 weeks). This interview will be audio-recorded. Participants would need to travel to the clinic to be interviewed. If you agree to participate in this interview you will be given a separate information sheet and asked to sign a new consent form.

If at any time during the study you cannot continue with the interviews or questionnaires, we can agree what will be best for you at that time. This could include taking a break, returning to the interview/questionnaire at a later date or withdrawing from the study.

What are the possible disadvantages and risks of taking part?

You may become upset when discussing your feelings during the screening interview and while completing questionnaires. The screening interview will be conducted by a researcher who is trained to support you accordingly if such situation arises. The administrative burden of completing questionnaires will be minimised by providing these questionnaires online for you to complete at a time and pace that is convenient for you.

This trial intervention does not pose any other risks to you. The treatment interventions in both groups are based on cognitive behavioural therapy (CBT), which is a teaching-based, non-invasive therapy.

What are the possible benefits of taking part?

Your participation in this study will help furthering our understanding of non-medical treatments for depression. Your support will help us improve the care people with depression receive. You may benefit from using the internet platform to learn more about depression and how to manage its symptoms at your own time and pace. Your travel expenses will be paid if a researcher arranges to see you outside your scheduled therapist's meetings. You will also receive two payments of £10 (£20 in total) for your time and effort for participating in the trial.

What if something goes wrong?

The London School of Hygiene & Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that the School is at fault. This does not affect your legal rights to seek compensation.

Will my comments/data be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the London School of Hygiene & Tropical Medicine. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you and your answers will be anonymous and a code will be used rather than your name. This information will be stored securely on a computer at the London School of Hygiene & Tropical Medicine and only members of the E-COMPARED research team will have access to this.

However, the research team may not be able to keep confidential any disclosure or endorsement of thoughts to harm yourself or others. Depending on how intense your thoughts are or how much you feel like hurting yourself or others, the researcher may work with you to contact your therapist to discuss these thoughts.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with Arlinda Cerga-Pashoja (Trial Manager) who will do their best to answer your questions (tel: **020 7927 8146**). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your therapist and the IAPT team.

What will happen to the results of the research study?

The trial will be published in a peer-reviewed medical journal. Abstracts will be submitted to relevant conferences to inform other researchers of the work. We'd be happy to provide participants with a copy of the published research, should they wish to have one.

Who is organising and funding the research?

This study is funded by the European Union Commission, Seventh Framework Programme and is hosted by the London School of Hygiene & Tropical Medicine. The EU grant agreement number is 603098.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES Committee London - Camden and Kings Cross and the London School of Hygiene & Tropical Medicine Ethics Committee.

Contact for Further Information

If you would like further information, please do not hesitate to contact:

Arlinda Cerga-Pashoja
Trial Manager
Tel: 020 7958 8146
arlinda.cerga-pashoja@lshtm.ac.uk

Asmae Doukani
Research Assistant
Tel: 020 7927 2463
asmae.doukani@lshtm.ac.uk

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

You can also visit our website: http://www.E-COMPARED.eu/

Appendix 3. Participant information sheet for trial - Therapist

Prof. Ricardo Araya
Department of Population Health
London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT

Phone: 020 7927 8141
Email: ricardo.araya@lshtm.ac.uk

Therapist Information Sheet

Re. E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

We would like to invite you to take part in a research study called E-COMPARED. Before you decide, it is important for you to understand why we're asking you to take part in this study and what it will involve.

Please take time to read the following information carefully

What is the purpose of the study?
Depression is a serious mental health condition, affecting around 350 million people worldwide. Depression can be treated effectively with antidepressants, psychotherapy or a combination of both. Studies indicate that people often prefer psychotherapy, such as cognitive behaviour therapy (CBT) to medical treatment. However, CBT is not always available, accessible or affordable. Internet supported interventions attempt to bridge this gap and make CBT more accessible to individuals.

This study is called E-COMPARED and it aims to evaluate internet supported Cognitive Behaviour Therapy as an intervention for the treatment of depression. The trial will consist of a blended treatment condition and a treatment-as-usual condition. Blended treatment entails a combination of internet/mobile-based, and face-to-face interventions.

Why have I been chosen?

You have been identified as an IAPT therapist, who might like to help deliver and take part in the study.

Do I have to take part?

No, it is entirely up to you whether you decide to take part or not. If you do decide to take part you will be given this information sheet to keep. Once you have agreed to participate, you will still be able to withdraw at any time you like and you do not have to give a reason.

What will happen to me if I take part?

If you agree, we would provide you with the necessary training to deliver the blended therapy, which will occur over 11 weeks. We anticipate that the training will not take longer than 4 hours in total. You would have an equal chance of providing therapy for clients who will be randomly allocated in treatment-as-usual and blended therapy groups as well as to patients who will not participate in the trial.

- The treatment-as-usual group and clients who will not participate in the trial will carry on as normal with scheduled face to face therapy sessions.
- The blended therapy group will receive weekly, alternated, face to face therapy sessions and therapy on the internet (online). These sessions will last for **11 weeks**, with **one session happening every week**. One week you will deliver a face-to-face session with your client and the week after you will carry out therapy modules online. Internet therapy will be delivered through MoodBuster, which is a computer and mobile platform that connects you and your client online.
- You may be selected to take part in a short interview about your experience of delivering a blended therapy. This will involve one session lasting between 30-50 minutes.

In order to find out what you think about the usability of the blended therapy system we will ask you **once** to complete a short online questionnaire. We will also require that you complete a short online questionnaire at the end of therapy for each of your clients that are participating in the trial. It is important that you complete this questionnaire whichever group your client is assigned to.

What are the possible disadvantages and risks of taking part?

Participating in this trial does not pose any risks to you. The training provided in order to deliver the blended therapy may take up some of your time. However, your managers have agreed that this will be accounted from your normal working hours and you do not need to put additional time towards training or the trial in general. The administrative burden of completing questionnaires will be minimised by providing these questionnaires online for you to complete at a time and pace that is convenient for you.

What are the possible benefits of taking part?

Your participation in this study will help furthering our understanding of non-medical treatments for depression. Your support will help us improve the care people with depression receive. The internet platform may help you utilize new therapeutic strategies, decrease the number of face to face consultations and increase work efficiency.

What if something goes wrong?

The London School of Hygiene & Tropical Medicine holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that the School is at fault. This does not affect your legal rights to seek compensation.

Will my comments/data be kept confidential?

All information collected about you will be kept strictly confidential. Any information about you and your answers will be anonymous and a code will be used rather than your name. This information will be stored securely on a computer at the London School of Hygiene & Tropical Medicine (LSHTM) and only members of the E-COMPARED research team will have access to this. Data collected during your Interview will be recorded using an encrypted (password access) audio recorder, which will only allow the research team to access this information. All recordings will be immediately transferred to a secure computer at LSHTM, which only the E-COMPARED research team will have access to. Any information about you and your responses will be assigned a code so that they stay anonymous. The audio recordings will be destroyed at the end of the study.

What will happen to the results of the research study?

The interviews will be transcribed by the research team and analysed using a computer package by a researcher. At the end of the research, I will write a report and the results, which may be published in peer reviewed journals and presented at conferences. The overall trial will be published in a peer-reviewed medical journal. Abstracts will be submitted to relevant conferences to inform other researchers of the work. The research team can provide participants with a copy of the published research, should they wish to have one.

Who is organising and funding the research?

This study is funded by the European Union Commission, Seventh Framework Programme and is hosted by the London School of Hygiene & Tropical Medicine. The EU grant agreement number is 603098.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES Committee London - Camden and Kings Cross and the London School of Hygiene & Tropical Medicine Ethics Committee.

Contact for Further Information

If you would like further information, please do not hesitate to contact:

Arlinda Cerga-Pashoja
Trial Manager
Tel: 020 7927 8146
arlinda.cerga-pashoja@lshtm.ac.uk

Asmae Doukani
Research Assistant
Tel: 020 7927 2463
asmae.doukani@lshtm.ac.uk

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT

You can also visit our website: http://www.E-COMPARED.eu/

Appendix 4. Participant consent form for trial – Client

E-COMPARED Study
Department of Population Health, London
School of Hygiene & Tropical Medicine,
Keppel Street London WC1E 7HT

Tel: +44 (0)20 7958 8146
Email: arlinda.cerga-pashoja@lshtm.ac.uk

Participant Identification Number ☐

PARTICIPANT CONSENT FORM

Title of Project: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

Principal Investigator: Prof Ricardo Araya, London School of Hygiene and Tropical Medicine

---

Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet, version 1.4, dated 10 April '15, for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my participation in the above study will not affect the standard of care I receive. ☐

4. I agree to my GP being informed of my participation in the above study. ☐

5. I agree to take part in the above study. ☐

6. I agree to be approached at a later date to take part in a tape-recorded interview about participation in this trial. ☐

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Research Worker	Date	Signature

☐ Participant's Copy ☐ Researcher's Copy ☐ IAPT Copy

Appendix 5. Participant consent form for trial – Therapist

E-COMPARED Study
Department of Population Health, London
School of Hygiene & Tropical Medicine,
Keppel Street London WC1E 7HT

Tel: +44 (0)20 7958 8146

Email: arlinda.cerga-pashoja@lshtm.ac.uk

Participant Identification Number ☐

THERAPIST CONSENT FORM

Title of Project: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

Principal Investigator: Prof Ricardo Araya, London School of Hygiene and Tropical Medicine

---

Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet, version 1.3, dated 10 April '15, for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I agree to take part in an interview that will be audio recorded. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

_____	_____	_____
Name of Research Worker	Date	Signature

☐ Participant's Copy ☐ Researcher's Copy

Appendix 6. Participant information sheet for qualitative interviews – Client

Prof. Ricardo Araya
Department of Population Health
London School of Hygiene & Tropical
Medicine
Keppel Street
London WC1E 7HT

Participant Information Sheet –Interview

Re. E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

We would like to invite you to an interview about your experience of participating in the E-COMPARED study.

Before you decide, it is important for you to understand why we're asking you to take part in this interview and what it will involve.

Please take time to read the following information carefully.

What is the purpose of this interview?

You recently consented to take part in a research project testing the usefulness of computer supported interventions as therapy for depression. Your participation is greatly appreciated and is helping us answer many questions about the treatment of depression.

However, we are keen to hear more about your experiences of taking part in this research. We would therefore like to meet with you one more time to discuss about your experiences and in particular about the relationship between you and the therapist.

Why have I been chosen?

You have been chosen because, you are currently participating on the E-COMPARED study. We are looking to interview people who have different experiences of using the blended intervention. In selecting you, we have carefully considered your background and have chosen you because we think you might have a different perspective from the other people we have asked.

Do I have to take part?

No, it is entirely up to you whether you decide to take part or not. If you do decide to take part you will be given this information sheet to keep. If you would prefer not to take part, the way you access services will not be affected in any way. Once you have agreed to participate, you will still be able to withdraw at any time you like and you do not have to give a reason.

What will happen to me if I take part?

If you choose to take part the research team will organise an interview at a location that is convenient for you. If you agree, the researcher (Asmae Doukani) will arrange to see you for one visit. You will discuss your experiences of taking part in the E-COMPARED intervention.

The interview will last between 30-50 minutes. The researcher will meet you at a place and time that is convenient to you. In order for the researcher to concentrate on what you are saying, your discussion will be recorded using an encrypted audio-recorder, which cannot be accessed by anyone outside of the research team. Your discussion will be transcribed (typed-out) to help us pick out your key points and the audio-recordings. The audio recordings will be deleted or destroyed at the end of the study.

If at any time during the interview you want to stop, you will be able to continue at another time. This could include taking a break, returning to the interview at a later date or withdrawing from the interview.
What are the possible disadvantages and risks of taking part?

The only disadvantage will be that this will take up more of your time. However, the interview should not take longer than 50 minutes.

What are the possible benefits of taking part?

Your participation in this interview will help further our understanding into therapeutic relationships between patients and their therapists when interventions are supported by computer based technology. Your support will help us improve the way we design and deliver computer based interventions, in particular for people with depression. This will also give you an opportunity to talk freely about your experience. Your help will be very much appreciated.

Will my comments/data be kept confidential?

All information collected will be kept strictly confidential. Interviews will be recorded using an encrypted (password access) audio recorder, which will only allow the research team to access this information. All recordings will be immediately transferred to a secure computer at London School of Hygiene & Tropical Medicine, which only members of the E-COMPARED research team will have

access to. Any information about you and your responses will be assigned a code so that they stay anonymous.

All information during the interview will be kept confidential, unless you disclose information that suggests that you are at risk of being harming yourself, which may have to be communicated to your care team. We will always inform and discuss this with you first.

What will happen to the results of the research study?

Your answers will be analysed, picking out your key points. Yours and other participants' key points will then be summarised into a final report, which will be published in a relevant peer-reviewed journal. No research participant will be identifiable from any publications. Abstracts will be submitted to relevant conferences to inform other researchers of the work. We'd be happy to provide you with a copy of the published research, should you wish to have one.

Who is organising and funding the research?

This study is funded by the European Union Commission, Seventh Framework Programme and is hosted by the London School of Hygiene & Tropical Medicine. The EU grant agreement number is 603098.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES Committee London - Camden and Kings Cross and the London School of Hygiene & Tropical Medicine Ethics Committee.

Contact for Further Information

If you would like further information, please do not hesitate to contact:

Asmae Doukani
Research Assistant
Tel: 020 7927 2463
asmae.doukani@lshtm.ac.uk
Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT
You can also visit our website: http://www.E-COMPARED.eu/

Appendix 7. Participant Information sheet for qualitative interviews – Therapist

Prof. Ricardo Araya
Department of Population Health
London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT

Phone: 020 7927 8141
Email: ricardo.araya@lshtm.ac.uk

Therapist Information Sheet

Re. E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

Dear Sir/Madam

We would like to invite you to take part in a research study called E-COMPARED. Before you decide, it is important for you to understand why we're asking you to take part in this study and what it will involve.

Please take time to read the following information carefully

What is the purpose of the study?
Depression is a serious mental health condition, affecting around 350 million people worldwide. Depression can be treated effectively with antidepressants, psychotherapy or a combination of both. Studies indicate that people often prefer psychotherapy, such as cognitive behaviour therapy (CBT) to medical treatment. However, CBT is not always available, accessible or affordable. Internet supported interventions attempt to bridge this gap and make CBT more accessible to individuals.

This study is called E-COMPARED and it aims to evaluate internet supported Cognitive Behaviour Therapy as an intervention for the treatment of depression. The trial will consist of a blended treatment condition and a treatment-as-usual condition. Blended treatment entails a combination of internet/mobile-based, and face-to-face interventions.

▪

Why have I been chosen?

You have been identified as an IAPT therapist, who might like to help deliver and take part in the study.

Do I have to take part?

No, it is entirely up to you whether you decide to take part or not. If you do decide to take part you will be given this information sheet to keep. Once you have agreed to participate, you will still be able to withdraw at any time you like and you do not have to give a reason.

What will happen to me if I take part?

If you agree, we would provide you with the necessary training to deliver the blended therapy, which will occur over 11 weeks. We anticipate that the training will not take longer than 4 hours in total. You would have an equal chance of providing therapy for clients who will be randomly allocated in treatment-as-usual and blended therapy groups as well as to patients who will not participate in the trial.

- The treatment-as-usual group and clients who will not participate in the trial will carry on as normal with scheduled face to face therapy sessions.
- The blended therapy group will receive weekly, alternated, face to face therapy sessions and therapy on the internet (online). These sessions will last for **11 weeks**, with **one session happening every week**. One week you will have a face-to-face session with your client and the week after you will carry out therapy modules online. Internet therapy will be delivered through MoodBuster, which is a computer and mobile platform that connects you and your client online.
- You may be selected to take part in a short interview about your experience of delivering a blended therapy. This will involve one session lasting between 30-50 minutes.

In order to find out what you think about the usability of the blended therapy system we will ask you **once** to complete a short online questionnaire. We will also require that you complete a short online questionnaire at the end of therapy for each of your clients that are participating in the trial. It is important that you complete this questionnaire whichever group your client is assigned to.

What are the possible disadvantages and risks of taking part?

Participating in this trial does not pose any risks to you. The training provided in order to deliver the blended therapy may take up some of your time. However, your managers have agreed that this will be accounted from your normal working hours and you do not need to put additional time towards training

or the trial in general. The administrative burden of completing questionnaires will be minimised by providing these questionnaires online for you to complete at a time and pace that is convenient for you.

What are the possible benefits of taking part?

Your participation in this study will help furthering our understanding of non-medical treatments for depression. Your support will help us improve the care people with depression receive. The internet platform may help you utilize new therapeutic strategies, decrease the number of face to face consultations and increase work efficiency.

Will my comments/data be kept confidential?

All information collected about you will be kept strictly confidential. Any information about you and your answers will be anonymous and a code will be used rather than your name. This information will be stored securely on a computer at the London School of Hygiene & Tropical Medicine (LSHTM) and only members of the E-COMPARED research team will have access to this. Your interview audio recordings

Data collected during your Interview will be recorded using an encrypted (password access) audio recorder, which will only allow the research team to access this information. All recordings will be immediately transferred to a secure computer at LSHTM, which only the E-COMPARED research team will have access to. Any information about you and your responses will be assigned a code so that they stay anonymous. The audio recordings will be destroyed at the end of the study.

What will happen to the results of the research study?

The interviews will be transcribed by the research team and analysed using a computer package by a researcher. At the end of the research, I will write a report and the results, which may be published in peer reviewed journals and presented at conferences. The overall trial will be published in a peer-reviewed medical journal. Abstracts will be submitted to relevant conferences to inform other researchers of the work. The research team can provide participants with a copy of the published research, should they wish to have one.

Who is organising and funding the research?

This study is funded by the European Union Commission, Seventh Framework Programme and is hosted by the London School of Hygiene & Tropical Medicine. The EU grant agreement number is 603098.

Contact for Further Information

If you would like further information, please do not hesitate to contact:

Arlinda Cerga-Pashoja
Trial Manager
Tel: 020 7927 8146
arlinda.cerga-pashoja@lshtm.ac.uk

Asmae Doukani
Research Assistant
Tel: 020 7927 2463
asmae.doukani@lshtm.ac.uk

Address: London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7H

You can also visit our website: http://www.E-COMPARED.eu/

Yours sincerely

Prof. Ricardo Araya
Professor of Global Mental Health

Appendix 8. Participants consent form for qualitative interviews – Client

E-COMPARED Study
Prof Ricardo Araya
Principle investigator
Department of Population Health, London
School of Hygiene & Tropical Medicine,
Keppel Street London WC1E 7HT
Tel: +44 (0)20 7927 8146
Email: Ricardo.araya@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Participant Identification Number ☐

PARTICIPANT CONSENT FORM

Title of Project: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

---

Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet dated 5 February '15 or the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my participation in the above study will not affect the standard of care I receive. ☐

4. I agree to the interview being recorded using audio equipment. ☐

5. I agree to take part in the above study.

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Research Worker	Date	Signature

☐ Participant's Copy ☐ Researcher's Copy ☐ Service's copy

Appendix 9. Participant consent form for qualitative interviews - Therapist

E-COMPARED Study
Department of Population Health, London
School of Hygiene & Tropical Medicine,
Keppel Street London WC1E 7HT

Tel: +44 (0)20 7958 8146
Email: arlinda.cerga-pashoja@lshtm.ac.uk

Participant Identification Number ☐

PARTICIPANT CONSENT FORM

Title of Project: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

Principal Investigator: Prof Ricardo Araya, London School of Hygiene and Tropical Medicine

Please initial box to indicate agreement

1. I confirm that I have read and understand the information sheet, version 1, dated 5 February '15, for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I agree to take part in an interview that will be audio recorded. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Research Worker	Date	Signature

☐ Participant's Copy ☐ Researcher's Copy

Appendix 10. Measures used in the secondary data analysis

Working Alliance Inventory – Short Revised–Client (WAI-SR-C)

Instructions: Below is a list of statements and questions about experiences people might have with their therapy or therapist. Some items refer directly to your therapist with an underlined space -- as you read the sentences, mentally insert the name of your therapist in place of _____ in the text. Think about your experience in therapy, and decide which category best describes your own experience.

1. As a result of these sessions I am clearer as to how I might be able to change.

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

2. What I am doing in therapy gives me new ways of looking at my problem.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

3. I believe my therapist likes me.

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

4. **My therapist and I collaborate on setting goals for my therapy**.

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

5. My therapist and I respect each other.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

6. My therapist and I are working towards mutually agreed upon goals.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

7. I feel that my therapist appreciates me.

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

8. My therapist and I agree on what is important for me to work on.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

9. I feel my therapist cares about me even when I do things that he/she does not approve of.

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

10. **I feel that the things I do in therapy will help me to accomplish the changes that I want**.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

11. My therapist and I have established a good understanding of the kind of changes that would be good for me.

○	○	○	○	○
Always	Very Often	Fairly Often	Sometimes	Seldom

12. **I believe the way we are working with my problem is correct.**

○	○	○	○	○
Seldom	Sometimes	Fairly Often	Very Often	Always

Working Alliance Inventory – Short Revised- Therapist (WAI-SR-T)

Instructions: Below is a list of statements about experiences people might have with their client. Some items refer directly to your client with an underlined space -- as you read the sentences, mentally insert the name of your client in place of ___ in the text.

IMPORTANT! Please take your time to consider each question carefully.

1. My client and I agree about the steps to be taken to improve his/her situation.

□ □ □ □ □

Seldom Sometimes Fairly Often Very Often Always

2. I am genuinely concerned for my client's welfare.

□ □ □ □ □

Always Very Often Fairly Often Sometimes Seldom

3. We are working towards mutually agreed upon goals.

□ □ □ □ □

Seldom Sometimes Fairly Often Very Often Always

4. My client and I both feel confident about the usefulness of our current activity in therapy.

□ □ □ □ □

Seldom Sometimes Fairly Often Very Often Always

5. I appreciate my client as a person.

□ □ □ □ □

Always Very Often Fairly Often Sometimes Seldom

6. We have established a good understanding of the kind of changes that would be good for my client.

□ □ □ □ □

Always Very Often Fairly Often Sometimes Seldom

7. My client and I respect each other.

□ □ □ □ □

Seldom Sometimes Fairly Often Very Often Always

8. My client and I have a common perception of his/her goals.

□ □ □ □ □

Always Very Often Fairly Often Sometimes Seldom

9. I respect my client even when he/she does things that I do not approve of.

□ □ □ □ □

Seldom Sometimes Fairly Often Very Often Always

10. We agree on what is important for my client to work on.

□ □ □ □ □

Always Very Often Fairly Often Sometimes Seldom

Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all (0)	Several Days (1)	More than half the days (2)	Nearly every day (3)
1. Little interest or pleasure in doing things.	☐	☐	☐	☐
2. Feeling down, depressed or hopeless.	☐	☐	☐	☐
3. Trouble falling asleep or sleeping too much.	☐	☐	☐	☐
4. Feeling tired or having little energy.	☐	☐	☐	☐
5. Poor appetite or over-eating.	☐	☐	☐	☐
6. Feeling bad about yourself, or that you are a failure or have let yourself or family down.	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching TV.	☐	☐	☐	☐
8. Moving or speaking so slowly that other people have noticed. Or the opposite – being fidgety, restless and moving around more than usual.	☐	☐	☐	☐
9. Thoughts that you would be better off dead or hurting yourself in some way.	☐	☐	☐	☐

Demographic form administered in the UK

DEMOGRAPHICS QUESTIONNAIRE

Date of Birth / /

Gender (Please tick): **Male** ☐ **Female** ☐

Years of Education

Occupation

What is your Ethnicity?

White British or other white ☐ Asian or Asian British (Other Asian background) ☐

Mixed or Multiple Ethnic Group ☐ Black/African/Caribbean/Black British ☐

Other ethnic group (please specify) ☐ _____

What is your present Marital Status?

☐ Married	☐ Separated
☐ Civil Partnership	☐ Single
☐ Divorced	☐ Co-habiting
☐ Widowed	☐ Other (please specify) _____

Your living arrangements

☐ Alone

☐ With family

☐ With partner

☐ Other living arrangements (please specify)_____

Treatment History

Are you currently receiving medication for low mood?

Yes ☐ **No** ☐

If yes:

Name of medication_____ Dosage_____

How long has it been taken for _____

Name of medication_____ Dosage_____

How long has it been taken for _____

(continue in the next page if more meds)

System usability scale for clients and therapists

Participant ID: _____ Date: ___/___/___

System Usability Scale

Instructions: For each of the following statements, mark one box that best describes your reactions to the website *today*.

		Strongly Disagree				Strongly Agree
1.	I think that I would like to use this system frequently.	☐	☐	☐	☐	☐
2.	I found this system unnecessarily complex.					
3.	I thought this system was easy to use.	☐	☐	☐	☐	☐
4.	I think that I would need assistance to be able to use this system.					
5.	I found the various functions in this system were well integrated.	☐	☐	☐	☐	☐
6.	I thought there was too much inconsistency in this system.					
7.	I would imagine that most people would learn to use this system very quickly.	☐	☐	☐	☐	☐
8.	I found this system very cumbersome/awkward to use.					
9.	I felt very confident using this system.	☐	☐	☐	☐	☐
10.	I needed to learn a lot of things before I could get going with this system.					

Please provide any comments about this website:

Appendix 11. Client qualitative interviews topic guide

Qualitative interviews topic guide – client

Warm up questions

[Use as many as you need to get flow of the discussion going]

Examples:

When did you start therapy on the study?

Who was your therapist?

Interview questions

1. Can you tell me about your experience of therapy?

2. **How did you feel about your therapy?**
    - What helped you to feel good about it?
    - What prevented you feeling good?
    - What were the best/worst things?
    - What surprised you? Why?

3. **Can you tell me what you did in therapy:**
    - During your face-to-face appointments?
    - When using moodbuster?
    - How were face-to-face and Moodbuster blended in your therapy?
    - Did the things you worked on in therapy help in any way?

4. **Was there anything about therapy that made you want to continue to engage in your treatment?**
    - How so?
    - What helped?
    - What didn't help?

5. **Can you tell me about how motivated you were during therapy:**
    - Face-to-face?
    - Moodbuster?
    - Was it easy?

- Was it difficult?

6. **How committed would you say you were to your treatment?**
    - What helped?
    - What prevented this?

7. **Can you tell me if or how well you were able to:**
    - Get on with or relate to your therapist?
    - What did you think your therapist thought of you?
    - What would have helped you interact better?
    - How well did you feel you were able to interact with the moodbuster platform?
    - What would have helped you interact better with the Moodbuster platform?

8. **Did you feel you got what you wanted through your therapy?**
    - Can you tell me how you think this happened?
        - Was your therapist aware of the things you wanted to achieve?
    - Were therapy goals set?
        - How so?
    - Did you feel that what you wanted from therapy was being addressed?
    - How did you feel after your last therapy session?

9. **At any point during your time in therapy, did you experience any difficulties, problems or setbacks?**
    - Can you give me some examples? [make a list]
    - Can you tell me what happened when situation X took place … [review all situations]
    - Why was this difficult?
    - Did it get resolved?
    - Tell me how things were resolved / I would be interested to know how X situation wasn't resolved
    - How did you try and get support for this?
        - Was the support received sufficient?
        - How could you have been better supported?

10. **How do you think your experience would have been without the face-to-face element of therapy?**

11. **How do you think your experience would have been without the Moodbuster element of therapy?**

12. **If you had to change one or more things about the intervention, what would it be?**

Ending Questions

----------Provide summary----------

1. **Based on everything we have spoken about, what would you say were the most important aspects that helped you stay engaged?**

2. **Is there anything you wanted to mention but haven't had the opportunity to discuss?**

3. **I have one last question, as a whole, how well would you say you were at using technology?**

Appendix 12. Therapist qualitative interviews for individual interviews (topic guide 1) and focus group discussions (topic guide 2)

Topic guide 1: Individual Interviews

"[Instructions: Special efforts should be taken to cover different perspectives using prompts in the topic guide or as necessary]"

Warm-up questions

Examples:

1. Could you remind me of how many patients you have seen in the blended therapy arm?
2. Could you tell me about your experience of blended therapy with your most recent patient?

Open Questions

1. **Can you tell me about your experience of delivering blended therapy?**

- Was there anything that surprised you about it?
    - In a good way?
    - In a bad way?
- How did your patients respond?
- How did this compare to delivering face-to-face therapy?
- How did you feel about using the blended intervention?
- After you used it for the first time, did you feel you wanted to try it again?
- Did you feel it was useful for your patients?
- Did you feel supported and encouraged by your managers to use it?

2. **Can you tell me about your initial expectation of delivering blended therapy?**
    - How did you think your patients were going to respond?
    - Did you think this was a good idea or something that you wanted to try?
    - Did you think it was too complex and a bit of a burden?
    - Did you feel confident you would be able to use it?

3. **At any point during your sessions, did you experience any difficulties, problems, or setbacks?**
    - Can you give me some examples? [make a list]

- Can you tell me what happened when 'X situation took place' … [review all situations]?
- Why was this difficult?
- Did it get resolved?
- Can you tell me how things were resolved? OR I would be interested to know why you *think x situation* wasn't resolved.

4. **Based on your experience, could you tell me what you think the advantages are of using a blended approach?**

5. **Based on your experience, could you tell me what you think the disadvantages are of using a blended approach?**

Specific Questions

1. **I would like to know about your experience of using the Moodbuster platform?**
   - What did you think about the platform?
   - Was this helpful for your practice?
   - Was this helpful for your patients?
   - Is there anything that could have been included that would have been helpful to you or your patients?
   - Was there anything challenging that you experience?
   - Did you feel confident from the start that you knew enough about how to use the platform?

2. **Did you experience any problems when using the platform?**
   - Could you tell me more about some of the problems you've experienced?
   - How did this affect therapy?
   - (if so) how did this make you feel ….?
   - How did you cope/ or deal with these problems?
   - Did this affect your attitude towards the platform?

3. **Can you tell me about how the patients goals were established?**
   - What helped?
   - Were the patient goals static throughout therapy or did they change?
   - What hindered your ability to …do this?

- Was there any differences in the way goals were set between blended and face-to-face therapy?

4. **Generally speaking, how well were you able to engage your patient to the modules of Moodbuster?**
    - How were the tasks selected?
    - What did you think about this approach?
    - How does this compare to engaging patients to face-to-face therapy?
    - Did you notice any benefits?
    - Did you check with patients if they are using Moodbuster?

5. **Can you tell me about your experience of building an alliance or relationship, with your patient?**
    - What helped?
    - What hindered your ability to… do this?
    - How does this compare to patients in face-to-face therapy?
    - Does the computerised component affect how you engaged with the patient?
    - How so?

6. **Would you say you felt committed to delivering blended therapy?**
    - What helped?
    - What prevented this?

Ending Questions

----------Provide summary----------

4. **If you had to change one or more things about the intervention, what would it be?**

5. **Do you think there is room for this type of blended intervention in IAPT?**

6. **Outside of the trial, would you consider using a blended approach with prospective patients?**

7. **I have one last question, on a whole, how good do you think you are at using technology?**

Thank and close

Topic guide 2: Focus group discussions

"[Instructions for interviewers: Special efforts should be taken to cover different perspectives using prompts in the topic guide or as necessary]"

Focus group discussions topic guide

1. **What was your experiences of blending e-interventions with therapy?**
    - What is your view on the blended therapy approach within psychological treatments?
    - Can you tell me if you have or had any reservations about using this approach?

2. **Can you tell us if or how you blended the treatment?**
    - Did you try different ways, what worked better?

3. **Did you feel prepared and supported to carry out the treatment?**
    - Did you feel supported by the service and research team?

4. **What do you think about Moodbuster?**
    - Was it user friendly?
    - Did it have the right content?
    - Did you encounter any problems with the platform?
    - What do you see as the advantages of Moodbuster to you or your patients?

5. **How does Moodbuster compared to other platforms that you've used?**
    - Do you think we've used Moodbuster to its full potential?
    - Do you think it could have been implemented more effectively?
    - if so, how?

6. **Generally speaking, how well were you able to engage your patient to the modules of Moodbuster?**
    - How were the tasks selected?
    - What did you think about this approach?
    - How does this compare to engaging patients to face-to-face therapy?
    - Did you notice any benefits to this approach?
    - Did you check with patients if they are using Moodbuster?

7. **How were the patients goals established?**
    - What helped?
    - What hindered your ability to do this?
    - Were the patient goals static throughout therapy or did they change?
    - Was there any difference in the way goals were set between blended and face-to-face therapy?

6. **Can you tell me about your experience of building a therapeutic (working / alliance) relationship, with your patient?**
    - What helped?
    - What hindered your ability to… do this?
    - How goes this compare to patients in face-to-face therapy?
    - Does the computerised component affect how you engaged with the patient?
    - How so?

8. **Would you say you felt committed to delivering blended therapy?**
    - Do you feel your attitudes to blended therapy have changed?

9. **Is there anything you wanted to mention that we didn't get a chance to talk about?**

Thank and close

Appendix 13. Ethical approvals for primary data collection: Health Research Authority and LSHTM

NHS
Health Research Authority
NRES Committee London - Camden & Kings Cross
Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne & Wear
NE32 3DT

Telephone: 0191 4283545

17 April 2015

Arlinda Cerga Pashoja
Research Fellow
Department of Population Health
London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT

Dear Ms Cerga Pashoja

Study title:	**E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial**
REC reference:	**15/LO/0511**
Protocol number:	**1.11**
IRAS project ID:	**172186**

Thank you for your letter of 16 April 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Hayley Henderson, nrescommittee.london-camdenandkingscross@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor's Insurance]		
GP/consultant information sheets or letters	1.2	10 April 2015
Interview schedules or topic guides for participants [Topic Guides]	1	14 April 2015
Letter from funder [EU-funder's doc]		
Participant consent form [Participant Consent Form]	1.4	05 February 2015
Participant consent form [Follow-up Consent]	1.4	05 February 2015
Participant consent form [Therapist Consent Form]	1	11 February 2015
Participant information sheet (PIS) [Follow-up PIS]	1	05 February 2015
Participant information sheet (PIS) [PIS Revised]	1.4	10 April 2015
Participant information sheet (PIS) [Therapist IS Revised]	1.3	10 April 2015
REC Application Form [REC_Form_16042015]		16 April 2015
Research protocol or project proposal [Protocol]	1.11	11 February 2015
Response to Request for Further Information		16 April 2015
Summary CV for Chief Investigator (CI) [RA CV]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports

- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0511	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp [redacted]

Ms Heidi Chandler
Vice Chair

Email:nrescommittee.london-camdenandkingscross@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Mrs Arlinda Cerga Pashoja

Ms Lynis Lewis, Camdan and Islington NHS Foundation Trust, North Central London Research Consortium (NoCLoR)

Prof Ricardo Araya, London School of Hygiene and Tropical Medicine

Amendment to recruit from Northumberland, Tyne and Wear NHS Foundation Trust

NHS
Health Research Authority
London - Camden & Kings Cross Research Ethics Committee
Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne & Wear
NE32 3DT

Tel: 0207 104 8087

08 March 2016

Arlinda Cerga Pashoja
Research Fellow/Trial Manager
Department of Population Health
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT

Dear Arlinda

Study title:	**E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial**
REC reference:	**15/LO/0511**
Protocol number:	**1.11**
Amendment number:	**SA1**
Amendment date:	**25 February 2016**
IRAS project ID:	**172186**

The above amendment was reviewed by the Sub-Committee in correspondence.

Summary of amendment

This amendment was submitted to add a sub-contracted trial therapist to provide therapy to all participants who enrol at the Northumberland, Tyne and Wear NHS Foundation Trust; the Principal Investigator at this site would also be able to provide therapy. General Practitioners would now also be able to refer participants to this study, and self-referrals would also now be accepted. A flyer for use at the site and a self-referral form were developed for use, and the protocol was updated to reflect the changes.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee commented that the invitation letter should have less jargon if this was being given to potential participants post-diagnosis. Examples would be to remove the term 'intervention' with 'study procedure' and replace the term 'evaluate' with the term 'compares'. If these amendments were undertaken, this could be submitted as a minor amendment to the Committee.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [E-Compared Study Flyer]	1	25 February 2016
Notice of Substantial Amendment (non-CTIMP)	SA1	25 February 2016
Other [E-Compared Mailshot Letter]	1	25 February 2016
Research protocol or project proposal [Highlighted Changes]	1.12	25 February 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/LO/0511:	**Please quote this number on all correspondence**

Yours sincerely
pp

[redacted]

Mrs Rosie Glazebrook
Chair

E-mail: nrescommittee.london-camdenandkingscross@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Lynis Lewis, Camdan and Islington NHS Foundation Trust, North Central London Research Consortium (NoCLoR)*

LSHTM Research Ethics Committee

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Prof Ricardo Araya
Professor of Global Mental Health
Department of Population Health (DPH)
Epidemiology and Population Health (EPH)
LSHTM

9 June 2015

Dear Ricardo

Study Title: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

LSHTM Ethics Ref: 9409

Thank you for responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Covering Letter	LSHTM ethics	15/05/2015	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

LSHTM Amendment to collect data from another site

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Prof Ricardo Araya
Professor of Global Mental Health
Department of Population Health (DPH)
LSHTM

19 April 2016

Dear Prof Ricardo

Study Title: E-COMPARED - Internet Supported CBT for Depression: A randomised, pragmatic, feasibility trial

LSHTM Ethics Ref: '9409 - 1'

Thank you for your application for the above amendment to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	Fav opinion, 17.04.15	17/04/2015	1
Other	E-COMPARED_STUDY_FLYER_v1_25Feb2016_1	25/02/2016	1.2
Other	e-COMPARED Mailshot letter_v1_25Feb2016_2	25/02/2016	1.2
Other	Protocol V1.12	25/02/2016	1.12

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 14. Ethical approval to conduct a secondary data analysis: LSHTM

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Asmae Doukani

LSHTM

7 October 2019

Dear Ms Asmae Doukani,

Study Title: An evaluation of the working alliance in a blended-cognitive behavioural therapy intervention for people with depression

LSHTM Ethics Ref: 17852

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Local Approval	Fav opinion, 17.04.15	17/04/2015	V1.0
Consent form	Consent-partV1.5	13/07/2015	1.5
Covering Letter	Patient Information Sheet 1.4	30/07/2015	1.4
Local Approval	LSHTM Ethics approval	09/10/2015	v1.0
Covering Letter	Your DAF and DATA downloading	01/11/2017	1.0
Covering Letter	Data Application Form Approval Email	03/11/2017	1.0
Protocol / Proposal	Asmae Doukani PhD upgrading report	30/11/2017	V.1.1
Investigator CV	Research CV _Asmae Doukani August 2019	22/08/2019	V1.0
Covering Letter	Ethics Covering Letter	23/08/2019	1.0
Covering Letter	Ethics Covering Letter 23 09 2019	23/09/2019	1.1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 15. Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2) Short Form

The form was completed in relation to patient and public involvement included in PhD paper titled: *Towards a conceptual framework of the working alliance in a blended low-intensity cognitive behavioural therapy intervention for depression in primary mental health care: a qualitative study*

Table 1. GRIPP2 short form

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	Pages 2-3 (published article) Pages 96-97 (PhD thesis)
2: Methods	Provide a clear description of the methods used for PPI in the study	Pages 2-3 (published article) Pages 96-97 (PhD thesis)
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	Pages 2-3 (published article) Pages 96-97 (PhD thesis)
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	Pages 2-3 (published article) Pages 96-97 (PhD thesis)
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	Pages 2-3 (published article) Pages 96-97 (PhD thesis)

Abbreviations: PPI, Patient and public involvement.

Appendix 16. Supplementary file for Chapter 6

Table of contents

eTable 14. Adjusted linear models of association between post-treatment PHQ-9 and WAI-SR-C scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

eMethods 1. Power calculations for the effects of treatment condition on the working alliance

Data from eight European countries originally involved in the E-COMPARED trial will be combined for analysis. The recruitment target for each site is n=150 (total of 1200). However, it has been estimated that the overall recruitment rate is likely to be closer to n=1000 for the original eight sites. Accounting for 20% loss to follow-ups, the power calculation will use a conservative sample size estimate of n=800.

Descriptive statistics (mean and standard deviation) of WAI-SR-C for guided computerised CBT for depression could not be attained from existing literature. For this reason, power was calculated using the first wave of data collected from the UK site of the E-Compared trial:

- b-CBT arm (n=15), Mean=46, SD=10
- Face-to-face CBT (n= 11), Mean=36, SD= 6.9.

A sample size of 400 participants in each arm, with a significance level set at 0.05, will allow [286]:

- 81% power to detect at least a 2 point increase in WAI-SR-C scores between treatment groups (The calculation is based on the conservative assumption that the standard deviation for both arms is 10).
- 99% power to test the standardised coefficient measuring the association between WAI-SR-C scores and PHQ-9 scores.

It should also be noted that both sample size and power calculations rely on the assumption that the mean values for WAI-SR-C and the PHQ-9 are correct and applicable to data outside of the UK.

eMethods 2. Country of birth

eTable 1. Self-reported country of birth across nine trial country-sites

Country-site (n=943)	Country of Birth
Germany (n=173)	Germany, n=16, Bosnia and Herzegovina (n=1), Bulgaria (n=1), China, (n=1), Italy (n=1), Kazakhstan (n=1), Romania (1), Russia (n=2), Serbia (n=1), Indonesia (n=1), Ukraine (n=1), and USA (n=1)
Sweden (141)	Sweden n=133 and Missing data n=8.
Netherlands (102)	Netherlands (n=83), (Chile (n=1), Colombia (n=1), Iraq (n=1), Iran (n=1), Macedonia (n=1), Mexico (n=1), Morocco (n=6), Suriname (n=3) and Turkey (n=4).
United Kingdom (101)	UK (n=95), China (n=2), Colombia (n=1), Romania (n=1), Sri Lanka (n=1), and Ukraine (n=1)
Spain (127)	Spain, (n=127), Paraguay (n=1) and Argentina (n=1)
French (105)	French (n=86), Algeria (n=3), Belgium (n=1), Côte d'Ivoire (n=2), Madagascar (n=1), Morocco (n=4), Portugal (n=1), Martinique (n=2), Mauritius (1), Serbia (n=1), Syria (n=1), and Tunisia (n=2)
Switzerland (50)	Switzerland (n=44), Albania (n=2), Austria (n=1), Kosovo (n=1), Turkey (n=1) and missing data (n=1).
Poland (84)	Poland n=84.
Denmark (60)	Denmark n=60.

eMethods 3. Missing and complete data count and chi-square analyses

eTable 2. Missing and complete data for WAI-SR-C and PHQ-9 scores at 3-months assessment across treatment conditions (n=943)

	WAI-SR-C (N=943)		PHQ-9 (N=943)	
	Missing	Complete	Missing	Complete
b-CBT	141	335	107	369
TAU	204	263	88	379

Abbreviations: b-CBT, blended-cognitive behavioural therapy; TAU, treatment as usual; PHQ-9, Patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client.

eTable 3. Tabulation of missing and complete data for PHQ-9 scores at 3-month assessments across country-sites on the E-COMPARED trial (n=943)

Country-site	**Missing**	**Complete**	**Total**
Germany	9	164	173
Sweden	16	125	141
Netherlands	19	83	102
UK	25	76	101
Spain	35	92	127
France	26	79	105
Switzerland	6	44	50
Poland	38	46	84
Denmark	21	39	60
Total	195	748	943

Abbreviations: PHQ-9, patient health questionnaire-9

eTable 4. Tabulation of missing and complete data for WAI-SR-C at 3-month follow-ups across country-sites on the E-COMPARED trial (n=943)

Country-site	Missing	Complete	Total
Germany	43	130	173
Sweden	85	56	141
Netherlands	23	79	102
UK	47	54	101
Spain	39	88	127
France	34	71	105
Switzerland	6	44	50
Poland	43	41	84
Denmark	25	35	60
Total	345	598	943

Abbreviations: WAI-SR-C, working alliance inventory-short revised-client

eTable 5. Comparison of missingness of data (missing versus complete cases) for WAI-SR-C across country-sites derived from different models

Models	X^2 (df, N=) X^2 value, *P* level
Germany vs Netherlands	X^2 (1, N=943)=9.71, *P* = .002
Germany vs UK	X^2 (1, N=943)=4.83, *P* = .028
Germany vs Spain	X^2 (1, N=943)=2.19, *P* = .139
Germany vs France	X^2 (1, N=943)=0.90, *P* = .343
Germany vs Switzerland	X^2 (1, N=943)=13.76, *P* = .000
Germany vs Poland	X^2 (1, N=943)=8.49, *P* = .004
Germany vs Denmark	X^2 (1, N=943)=0.71, *P* = 398

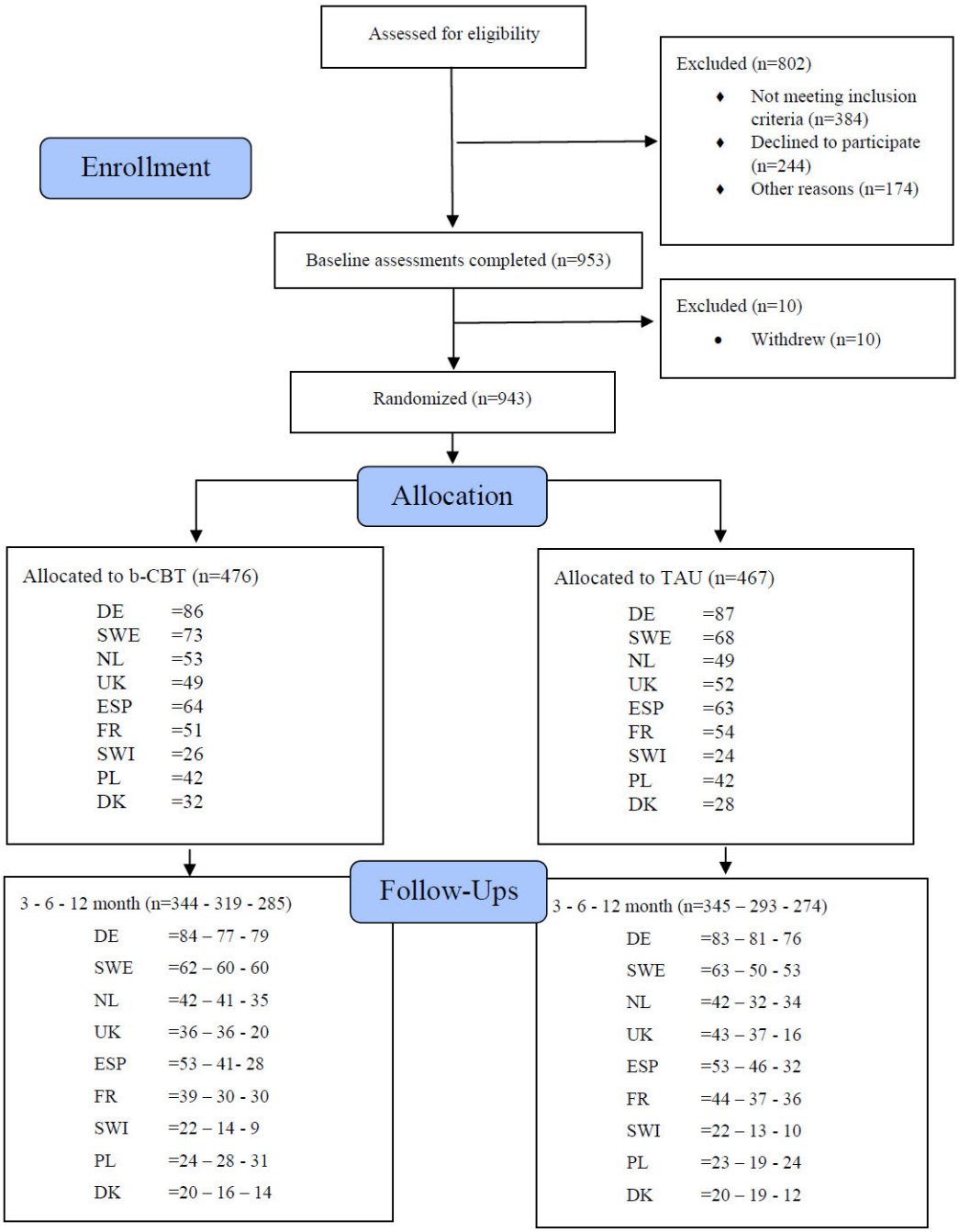
Abbreviations: WAI-SR-C, working alliance inventory-short revised-client

eTable 6. Comparison of missingness of data (missing versus complete cases) for PHQ-9 across country-sites, derived from different models

Models	**X^2 (df, N=) X^2 value, P level**
Germany vs Sweden	X^2 (1, N=943)=8.80, *P* = .003
Germany vs Netherlands	X^2 (1, N=943)=0.29, *P* = .588
Germany vs UK	X^2 (1, N=943)=1.14, *P* = .285
Germany vs Spain	X^2 (1, N=943)=4.24, *P* = .040
Germany vs France	X^2 (1, N=943)=1.20, *P* = .273
Germany vs Switzerland	X^2 (1, N=943)=2.43, *P* = .119
Germany vs Poland	X^2 (1, N=943)=33.91, *P* =.000
Germany vs Denmark	X^2 (1, N=943)=8.01, *P* = .005

Abbreviations: PHQ-9, patient health questionnaire-9

eResults 1: Trial profile diagram, means, and standard deviation of working alliance and system usability scores



Abbreviations: b-CBT, blended- Cognitive Behavioural Therapy; TAU, Treatment as Usual; DE, Germany; SWE, Sweden; NL, Netherlands; UK, United Kingdom; ESP, Spain; NL, Netherlands; UK, United Kingdom; ESP, Spain; FR, France; SWI, Switzerland; PL, Poland; DK, Denmark

eFigure 1. E-COMPARED trial profile

eTable 7. Mean (SD) imputed WAI-SR-C scores across country-sites and treatment group

Country	b-CBT	TAU	Total
Germany	48.83 (7.96)	36.81 (10.55)	42.78 (11.11)
Sweden	46.66 (5.74)	n/a	46.66 (5.74)
Netherlands	46.44 (7.01)	42.67 (9.34)	44.63 (8.39)
UK	46.58 (7.49)	41.91 (8.07)	44.17 (8.10)
Spain	46.57 (9.15)	38.73 (11.37)	42.68 (12)
France	46.59 (8.60)	45.11 (6.72)	45.83 (7.69)
Switzerland	46.44 (10.17)	45.94 (9.58)	46.30 (9.79)
Poland	49.41 (6.31)	45.63 (7.08)	47.62 (6.90)
Denmark	44.50 (5.12)	42.90 (5.98)	43.75 (5.55)

Abbreviations: b-CBT, blended cognitive behaviour therapy; TAU, treatment as usual; SD, standard deviation; WAI-SR-C, working alliance inventory-short revised-client.

eTable 8 Mean (SD) imputed SUS-C scores across country-sites in b-CBT)

Country	b-CBT arm
Germany	43.74 (4.99)
Sweden	41.37 (7.41)
Netherlands	37.11 (6.04)
UK	41.61 (6.18)
Spain	41.34 (5.74)
France	37.56 (7.57)
Switzerland	43.02 (5.72)
Poland	41.70 (5.59)
Demark	38.89 (5.45)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; SD, standard deviation; SUS, system usability-client.

eResults 2: Results of sensitivity analysis using complete case analysis

The means and standard deviations (SDs) for WAI-SR-C (composite and all subscales scores) across condition are summarised in *eTable 10*. WAI-SR-C and total SUS-C scores, across trial country-sites are summarised in *eTables 11* and *eTable12*, respectively.

eTable 9. Mean (SD) of unimputed WAI-SR-C composite and subscale scores (goals, task, and bond) across treatment group (n=5)

WAI-SR-T scores	**b-CBT (n=200)**	**TAU (n=200)**	**Total (n=400)**
Composite	46.70 (9.82)	45.79 (9.30)	46.24 (9.56)
Goals	15.72 (3.64)	15.09 (3.67)	15.41 (3.66)
Task	14.98 (3.53)	14.84 (3.43)	14.91 (3.47)
Bond	15.95 (3.65)	15.89 (3.50)	15.92 (3.57)

Abbreviations: WAI-SR-C, working alliance inventory-short revised-client; b-CBT, blended cognitive behaviour therapy; TAU, treatment as usual.

eTable 10. Mean (SD) unimputed WAI-SR-C scores across country-sites and treatment group

Country	**b-CBT (n=335)**	**TAU (n=263)**	**Total**
Germany	49.13 (8.67)	34.76 (12.40)	41.72 (12.68)
Sweden	46.54 (6.53)		46.54 (6.53)
Netherlands	46.30 (8.06)	42.82 (10.47)	44.58 (9.43)
UK	46.23 (10.31)	42.39 (11.02)	44.24 (10.76)
Spain	46.32 (11.04)	37.55 (13.44)	41.93 (13.00)
France	46.28 (10.25)	46.71 (7.86)	46.49 (9.09)
Switzerland	46.45 (11.08)	46.27 (8.15)	43.20 (10.40)
Poland	51.90 (8.19)	50.20 (8.15)	51.07 (8.12)
Demark	42.44	43.65 (7.59)	43.03 (6.74)

Abbreviations: b-CBT, blended cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-C, working alliance inventory short-revised-client.

eTable 11. Mean (SD) unimputed system usability scale-client (SUS-C) scores across country-sites (n=335)

Country	b-CBT
Germany	43.99 (5.08)
Sweden	41.28 (8.03)
Netherlands	37.15 (6.64)
UK	42.22 (7.78)
Spain	41.32 (6.12)
France	37.34 (8.60)
Switzerland	43.36 (6.06)
Poland	42.16 (8.88)

Abbreviations: b-CBT, blended cognitive behaviour therapy; SUS-C, system usability scale-client.

Sensitivity Analysis: Impact of multiple imputation on the results

A sensitivity analysis that mirrors the main analysis was conducted using a complete case population, to understand the impact of multiple imputation on the results. The full findings of the sensitivity analysis are summarized below.

Treatment assignment as a predictor for WAI-SR-C scores

Treatment assignment did not significantly predict WAI-SR-C composite, goals, task and bond scores. See *eTable 13* for model summaries.

Association between Post-treatment PHQ-9 Scores and WAI-SR-C Scores

In the b-CBT arm, WAI-SR-C composite, goals, task, and bond subscales scores were significantly associated with post-treatment PHQ-9 scores, in which lower PHQ-9 scores were associated with higher WAI-SR-C composite, goals, task and bond scores. See *eTable 14* for model summaries.

Testing the interaction between WAI-SR-C and SUS-C on the relationship between WAI-SR-C and PHQ-9

The association between the WAI-SR-C task subscale and PHQ-9 scores was moderated by SUS scores (b = 0.34, [95% CI: -0.06 to -0.01]; P = .006]. *eFigure 2* shows a trend for an inverse association between higher composite WAI-SR-C and lower PHQ-9 scores among those with higher SUS-C scores. No significant interactions were observed in other WAI-SR-C subscales scores.

eTable 12. Adjusted linear regression models of treatment assignment as a predictor for WAI-SR-C scores. Composite and subscale (goals, task, bond) scores are independent models

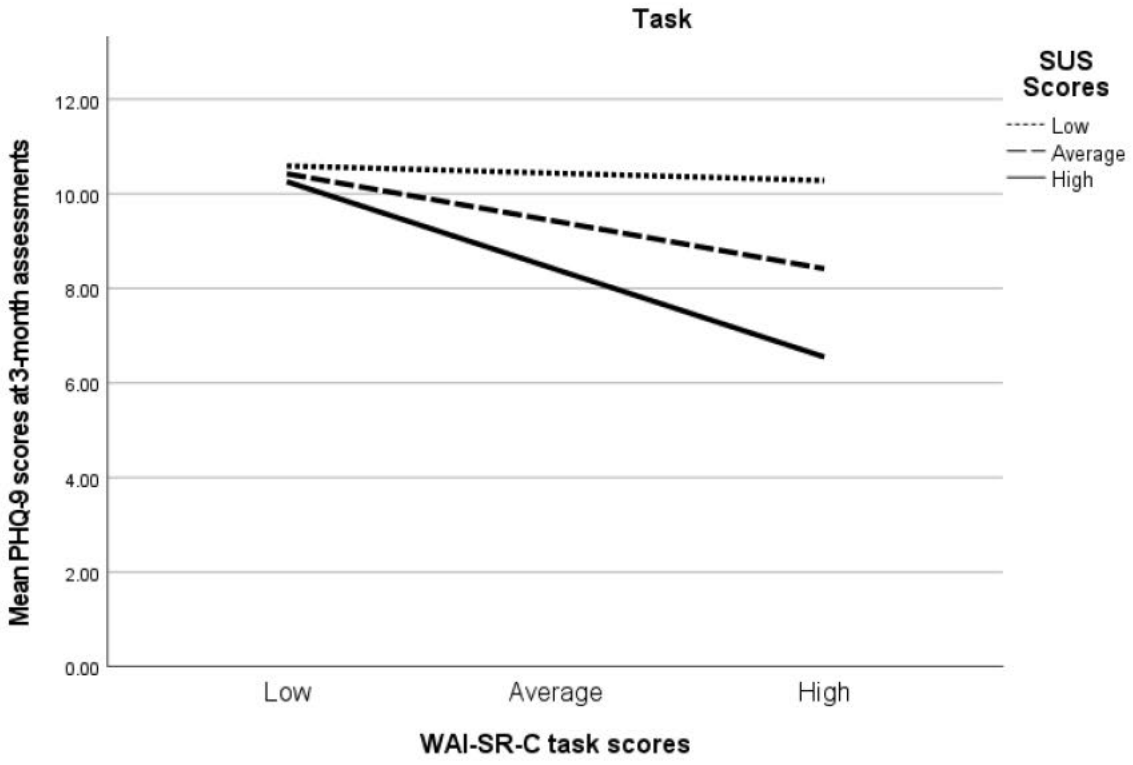
WAI-SR (outcome)	*B* (95% CI)	*P V*alue
Composite	-0.67 (-1.69 to 3.03)	.58
Goals	-0.57 (-0.30 to 1.44)	.20
Task	-0.06 (-0.76 to 0.91)	.89
Bond	-0.02 (-0.90 to 0.86)	.96

Abbreviations: *B*, unstandardized beta; 95% CI, 95% confidence intervals; PHQ-9, patient health questionnaire-9, WAI-SR-C, working alliance inventory-short revised-client.

eTable 13. Adjusted linear models of association between post-treatment PHQ-9 and WAI-SR-C scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR (outcome)	*B* (95% CI)	*P* value
Composite	-0.12 (-0.18 to -0.05)	<.001
Goals	-0.27 (-0.45 to -0.09)	.004
Task	-0.39 (-0.55 to -0.22)	<.001
Bond	-0.22 (-0.40 to -0.34)	.020

Abbreviations: 95% CI, 95% confidence intervals; *B,* unstandardized beta; b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client.



eFigure 2. Multiple line graph of the interaction between SUS-C on WAI-SR-C task scores on the association between WAI-SR-C task scores and PHQ-9 scores at 3-month assessments in b-CBT.

Legend: b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; SUS-C, system usability scale-client; WAI-SR-C, working alliance inventory-short revised-client.

eResults 3: Results of sub-analysis using data from sites that only offered face-to-face cognitive behavioral therapy (CBT) in treatment as usual (TAU) (i.e., France, Denmark, Poland, Switzerland & UK).

A sub-analysis was conducted with only 5 out of the 9 country-sites that offered b-CBT versus face-to-face CBT in TAU.

Association between post-treatment PHQ-9 scores and WAI-SR-C scores

In b-CBT, WAI-SR-C composite scores and all subscale scores (i.e., goals, task and bond) were significantly associated with post-treatment PHQ-9 scores, in which lower PHQ-9 scores were associated with higher WAI-SR-C composite, goals and task scores. It should be noted that there were missing correlations between PHQ-9 scores at 3-months, and marital status (single versus widow) that was entered as a covariate. See *eTable 15* for model summaries.

Testing the interaction between WAI-SR-C and SUS-C on the relationship between WAI-SR-C and PHQ-9

The association between WAI-SR-C composite scores and PHQ-9 scores does not seem to be moderated by SUS (*b* = -0.06 [95% CI: -0.06 to 0.00], *P* = 0.18). Moreover, no significant interactions were observed for the goals (*b* = -0.02 [95% CI: -0.05 to 0.01], *P* = 0.18), task (*b* = -0.022 [95% CI: -0.05 to 0.05], *P* = 0.10) and bond (*b* = -0.01 [CI 95: -0.04 to 0.01], *P* = 0.27) subscales.

eTable 14. Adjusted linear models of association between post-treatment PHQ-9 and WAI-SR-C scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-C (outcome)	*B* (95% CI)	*P* value
Composite	-0.16 (-0.25 to -0.07)	.001
Goals	-0.33 (-0.57 to -0.10)	.006
Task	-0.45 (-0.69 to -0.21)	<.001
Bond	-0.32 (-0.55 to -0.09)	.006

Abbreviations: b-CBT, blended-cognitive behavioural therapy; *B,* unstandardized beta; 95% CI, 95% confidence intervals; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client.

Appendix 17. Supplementary file for Chapter 7

Table of contents

eMethods 1. Missing and complete data count and chi-square analyses for WAI-SR-T and client PHQ-9 scores

eTable 1. Tabulation of missing and complete data for working alliance inventory-short revised-therapist WAI-SR-T and patient health questionnaire (PHQ-9) scores at 3-months assessment across treatment conditions

	WAI-SR-T		**PHQ-9**	
	Missing	Complete	Missing	Complete
b-CBT	85	355	79	350
TAU	203	236	95	379

Abbreviations: b-CBT, blended cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; TAU, treatment as usual; WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 2. Tabulation of missing and complete data for WAI-SR-T at 3-month follow-ups across country-sites on the E-COMPARED trial (n=883)

Country-site	**Missing**	**Complete**	**Total**
Germany	27	146	173
Sweden	75	66	141
Netherlands	16	86	102
UK	25	76	101
Spain	96	31	127
France	35	70	105
Switzerland	3	47	50
Poland	15	69	84
Total	292	591	883

Abbreviations: WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 3. Tabulation of missing and complete data for PHQ-9 data at 3-month assessments across country-sites on the E-COMPARED trial (n=883)

Country-site	Missing	Complete	Total
Germany	9	164	173
Sweden	16	125	141
Netherlands	19	83	102
UK	25	76	101
Spain	35	92	127
France	26	79	105
Switzerland	6	44	50
Poland	38	46	84
Total	174	709	883

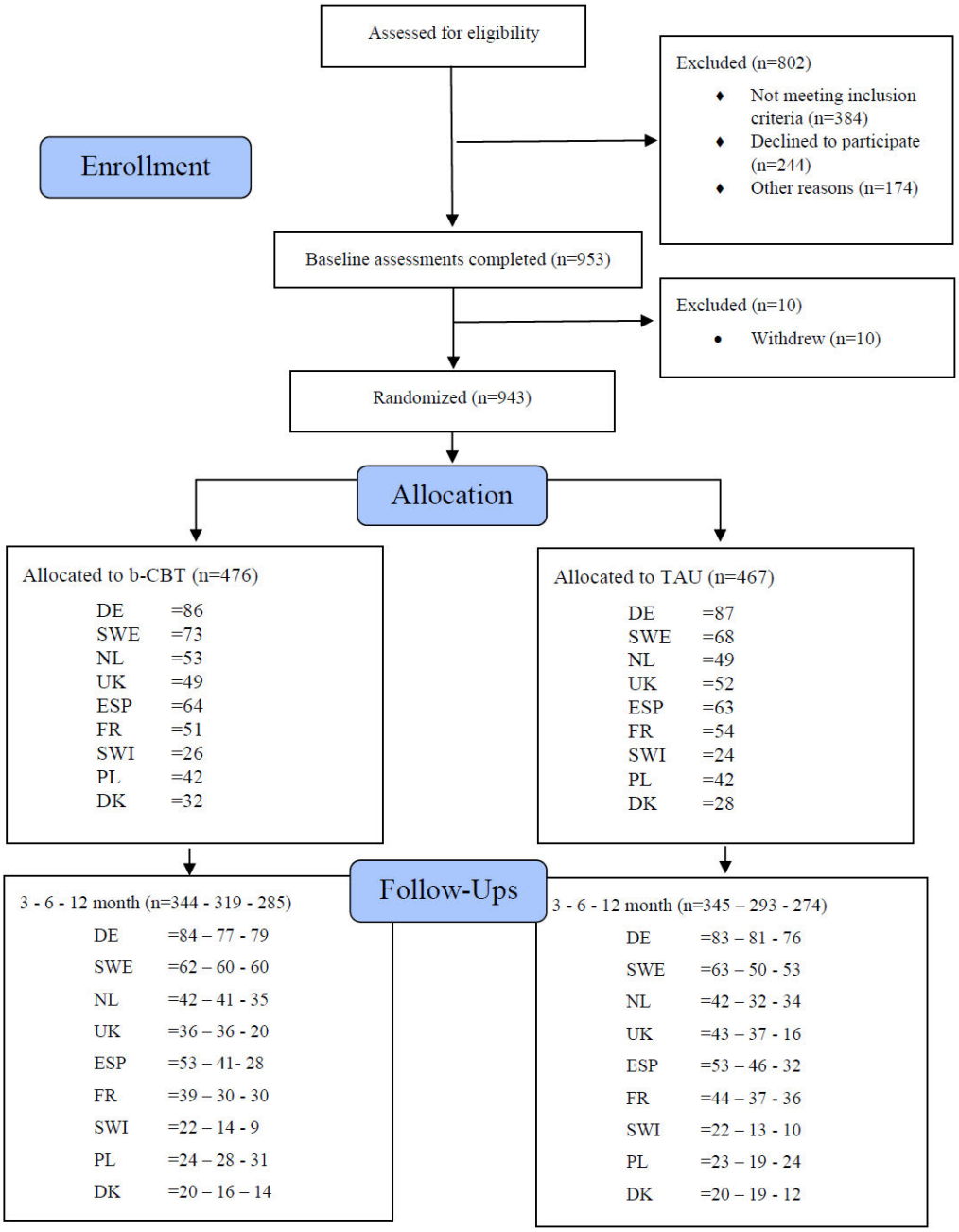
Abbreviations: PHQ-9, patient health questionnaire-9.

eTable 4. Chi-square comparison of missingness of data (missing versus complete cases) for WAI-SR-T across country-sites, derived from different models

Models	X^2 (df, N=) X^2 value, P level
Germany vs Sweden	$X^2(1, N=883)=30.70$, $P = .000$
Germany vs Netherlands	$X^2(1, N=883)=15.74$, $P =.000$
Germany vs UK	$X^2(1, N=883)=3.56$, $P = .059$
Germany vs Spain	$X^2(1, N=883)=121.17$, $P = .000$
Germany vs France	$X^2(1, N=883)=0.00$, $P = .951$
Germany vs Switzerland	$X^2(1, N=883)=17.55$, $P = .000$
Germany vs Poland	$X^2(1, N=883)=9.71$, $P = .002$

Abbreviations: WAI-SR-T, working alliance inventory-short revised-therapist.

eResults 1: Trial profile diagram, means, standard deviations for working alliance (therapist and client) and system usability for the main analysis



Abbreviations: b-CBT, blended- Cognitive Behavioural Therapy; TAU, Treatment as Usual; DE, Germany; SWE, Sweden; NL, Netherlands; UK, United Kingdom; ESP, Spain; NL, Netherlands; UK, United Kingdom; ESP, Spain; FR, France; SWI, Switzerland; PL, Poland; DK, Denmark

eFigure 1. E-COMPARED trial profile

eTable 5. Mean (SD) WAI-SR-T composite and subscale scores (goals, task, and bond) across treatment groups

WAI-SR-T scores	b-CBT (n=444)	TAU (n=439)	Total (n=883)
Composite	40.99 (5.30)	41.68 (4.87)	41.34 (5.09)
Goals	11.63 (2.08)	11.98 (1.97)	11.81 (2.03)
Task	11.30 (1.97)	11.48 (2.04)	11.39 (2.01)
Bond	18.05 (2.13)	18.22 (2.18)	18.14 (2.15)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-T; working alliance inventory-short-revised-therapist

eTable 6. Mean (SD) WAI-SR-T scores across country-sites and treatment group

Country	b-CBT (n=444)	TAU (n=439)	Total (n=883)
Germany	37.27 (7.36)	42.59 (4.58)	39.94 (6.66)
Sweden	39.25 (6.28)	n/a	39.25 (6.28)
Netherlands	35.79 (5.37)	36.31 (5.75)	36.04 (5.53)
UK	42.77 (4.60)	43.32 (3.75)	43.06 (4.16)
Spain	43.29 (3.89)	41.14 (1.32)	42.22 (3.10)
France	39.67 (5.47)	40.72 (5.38)	40.21 (5.43)
Switzerland	39.10 (5.32)	40.96 (5.68)	38.99 (5.51)
Poland	41.68 (5.23)	41.26 (4.26)	41.47 (4.89)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 7. Mean (SD) system usability scale-therapist (SUS-T) scores across country-sites in b-CBT

Country	**b-CBT** (n=444)
Germany	27.98 (1.26)
Sweden	27.67 (7.68)
Netherlands	25.94 (1.90)
UK	28.59 (2.34)
Spain	34.77 (2.24)
France	26.09 (2.28)
Switzerland	27.75 (2.35)
Poland	30.51 (2.26)

Abbreviations: blended-cognitive behaviour therapy; SUS-T, system usability scale- therapist b-CBT.

eTable 8. Mean (SD) of WAI-SR-C composite and subscale scores (goals, task, bond) at 3-month assessments in the full sample (n=943) and the subgroup sample (n=400)

	Full trial sample (n=8 country-sites)			**Subset sample (n=4 country-sites)**		
	b-CBT (n=476)	TAU (n=467)	Total (n=943)	b-CBT (n=200)	TAU (n=200)	Total (n=400)
WAI-SR-C						
Composite	47.09 (7.65)	41.55 (9.66)	44.56 (9.05)	46.83 (7.73)	44.22 (7.57)	45.52 (7.75)
Goals	16.14 (2.93)	13.81 (3.72)	15.09 (3.51)	15.83 (2.98)	14.49 (3.02)	15.16 (3.07)
Task	14.39 (3.05)	12.52 (3.86)	13.54 (3.56)	14.76 (2.87)	14.18 (2.98)	14.47 (2.94)
Bond	16.56 (2.97)	15.21 (3.51)	15.94	16.24 (3.03)	15.55. (2.82)	15.89 (2.95)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-C, working alliance inventory-short revised-client.

eResults 2. Results of sensitivity analysis using complete case analysis (with missing data), which includes: means and SDs for working alliance (therapist and client) and system usability, and linear regression models.

Table 9. Mean (SD) unimputed WAI-SR-T composite and subscale scores (goals, task, and bond) across treatment group

WAI-SR-T scores	b-CBT (n=168)	TAU (n=172)	Total (n=340)
Composite	41.35 (5.72)	41.88 (5.53)	41.62 (5.62)
Goals	12 (2.17)	11.82 (2.22)	18.20 (2.25)
Task	11.42 (2.10)	11.54 (2.27)	11.91 (2.19)
Bond	18.12 (2.34)	18.28 (2.17)	11.48 (2.19)

Abbreviations: b-CBT, blended cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-T, working alliance inventory-short revised-therapist.

Table 10. Mean (SD) unimputed WAI-SR-T scores across country-sites and treatment group

Country	b-CBT (n=444)	TAU (n=439)	Total (n=340)
Germany	37.27 (7.36)	43.08 (5.42)	38.66 (7.20)
Sweden	39.32 (6.59)	n/a	39.32 (6.59)
Netherlands	36.05 (5.73)	35.57 (5.89)	35.81 (5.78)
UK	43.41 (4.83)	44.08 (4.00)	43.75 (4.41)
Spain	44.72 (3.57)	41.50 (4.95)	44.52 (3.66)
France	40 (6.52)	40.69 (6.33)	40.39 (6.38)
Switzerland	39.29 (5.43)	41.00 (5.80)	40.13 (5.62)
Poland	41.76 (5.46)	41.26 (5.33)	41.54 (5.37)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-T, working alliance inventory-short revised-therapist.

Table 11. Mean (SD) SUS-T unimputed scores across country-sites and treatment group

Country	b-CBT (n=444)
Germany	27.98 (1.23)
Sweden	27.70 (8.04)
Netherlands	26 (1.72)
UK	28.47 (1.25)
Spain	34.21 (2.26)
France	27.35 (2.23)
Switzerland	27.88 (2.40)
Poland	30.61 (2.30)
Pooled	28.84 (2.62)

Abbreviations: b-CBT, blended-cognitive behaviour therapy; TAU, treatment as usual; WAI-SR-T, working alliance inventory-short revised-therapist.

Table 12. Mean (SD) unimputed WAI-SR-C composite and subscale scores (goals, task, and bond) across treatment group

WAI-SR-C scores	b-CBT (n=168)	TAU (n=172)	Total (n=340)
Composite	47.43 (10.18)	46.13 (9.53)	47.78 (9.86)
Goals	16.10 (3.73)	14.59 (3.78)	15.68 (3.78)
Task	15.30 (3.66)	14.96 (3.58)	15.12 (3.61)
Bond	16.03 (3.75)	15.17 (3.50)	15.94 (3.61)

Abbreviations: b-CBT, blended cognitive behaviour therapy; TAU, treatment as usual, WAI-SR-T, working alliance inventory-short revised-client.

Treatment assignment as a predictor for WAI-SR-T scores

Treatment assignment did not significantly predict WAI-SR-T scores across four country-sites for composite and all subscale scores (eTable 13).

Association between post-treatment PHQ-9 scores and WAI-SR-T scores

In the b-CBT group, WAI-SR-T composite, goals, and task scores were significantly associated with post-treatment PHQ-9 scores, in which lower PHQ-9 scores were associated with higher WAI-SR-T total, goals and task scores. WAI-SR-T bond scores were not significantly associated with PHQ-9 scores. See eTable 14 for model summaries.

Association between post-treatment PHQ-9 and WAI-SR-T scores, adjusting for WAI-SR-C scores

In the b-CBT arm, the nested LRM indicates that adding WAI-SR-T (composite, goals and task scores) (step 2), to WAI-SR-C (composite, goals and task scores) (step 1), as an additional predictor for PHQ-9 scores at 3-months, explained an additional 1% of the variance in PHQ-9 scores. eTable 15 summarises the findings from all models.

Testing the interaction between WAI-SR-T and SUS-C on the relationship between WAI-SR-T and PHQ-9

The interaction between WAI-SR-T and SUS-C on the association between WAI-SR-T scores and client PHQ-9 at 3-months was not significant for models with WAI-SR-T composite scores (*b*=-0.019 [95% CI: -0.04 to 0.00], *P*=0.060), the goals (*b*=-0.035 [95% CI: -0.08 to 0.01], *P*=0.239), and task (*b*=-0.030 [95% CI: -0.08 to 0.02], *P*=0.237) subscale scores. A significant interaction was however found for bond subscale scores (*b*=-0.062 [95% CI: -0.12 to 0.00], *P*=0.038). eFigure 2. shows a trend for an inverse association between composite bond WAI-SR-T and PHQ-9 scores among those with higher SUS-C scores.

eTable 13. Adjusted linear regression models of treatment assignment as a predictor for WAI-SR-T scores. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-T (outcome)	*B* (95% CI)	*P V*alue
Model 1		
Composite	-0.48 (-1.85 to 0.89)	.495
Model 2		
Goals	-0.20 (-0.73 to 0.34)	.470
Model 3		
Task	-0.08 (-0.61 to 0.45)	.755
Model 4		
Bond	-0.11 (-0.66 to 0.44)	.699

Abbreviations: *B*, unstandardized beta; 95% CI, 95% confidence intervals; PHQ-9, patient health questionnaire-9, WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 14. Adjusted linear models of association between post-treatment client PHQ-9 and WAI-SR-T scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-T(outcome)	*B* (95% CI)	*P* value
Composite	-0.14 (-0.22 to -0.06)	.001
Goals	-0.35 (-0.55 to -0.14)	.001
Task	-0.42 (-0.63 to -0.21)	<.001
Bond	-0.12 (-0.35 to-0.11)	.314

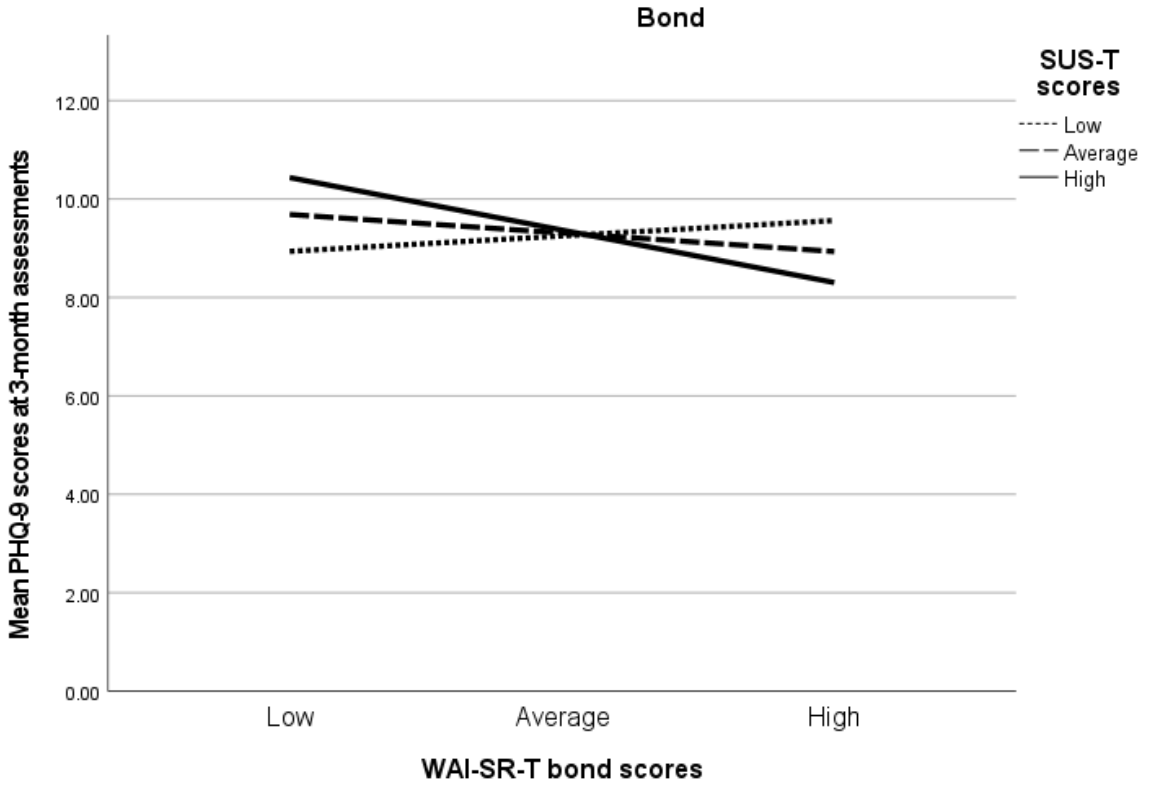
Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 15. Nested linear regression models of associations between PHQ-9 scores and WAI-SR-C scores in step 1 and WAI-SR-T scores in step 2 in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

Variables		Composite		Goals		Task		Bond	
		B (CI 95)	*P* Value	*B* (CI 95)	*P* Value	*B* (CI 95)	*P* Value	*B* (CI 95)	*P* Value
Step 1									
	Constant	4.14 (0.38 to 8.66)	.072	2.60 (1.39 to 7.31)	.191	4.51 (0.66 to 8.37)	.022	2.36 (-2.22 to 6.94)	.311
	WAI-SR-C	-0.09 (-0.17 to -0.02)	.010	-0.21 (-0.40 to -0.01)	.042	-0.35 (-0.53 to -0.18)	<.001	-0.15 (-0.35 to 0.06)	.103
Step 2									
	Constant	6.61 (1.09 to 12.12)	.019	4.77 (0.15 to 9.39)	.043	6.27 (2.01 to 10.53)	<.004	3.79 (2.86 to 10.43)	.262
	WAI-SR-C	-0.07 (-0.15 to -0.01)	.066	-0.12 (-0.33 to -0.09)	.245	-0.27 (-0.47 to -0.08)	<.006	-0.14 (-.34 to 0.07)	.182
	WAI-SR-T	-0.10 (-0.22 to -0.03)	.217	-0.31 (-0.60 to -0.03)	.031	-0.29 (-0.60 to -0.02)	.062	-0.09 (-0.40 to 0.21)	.559

Composite: $R^2 = .28$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.127); Goals: $R^2 = .27$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.031); Task: $R^2 = .31$ for step 1: $\Delta R^2 = .01$ for step 2 (ps. =.062); Bond: $R^2 = .27$ for step 1: $\Delta R^2 = .00$ for step 2 (ps. =.559).

Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client; WAI-SR-T, working alliance inventory-short revised-therapist.



eFigure 2. Multiple line graph of the interaction between SUS-T on WAI-SR-T bond scores on the association between WAI-SR-T bond and client PHQ-9 scores at 3-month assessments in b-CBT.

Legend**:** PHQ-9, patient health questionnaire-9; SUS-T, system usability scale-therapist; WAI-SR-T, working alliance inventory-short revised-therapist.

eResults 3: Results of sub-group analyses involving four country-sites (i.e., France, Poland, Switzerland & UK) that compared b-CBT with face-to-face CBT using linear regression models.

Association between post-treatment PHQ-9 scores and WAI-SR-T scores

In the b-CBT arm, higher WAI-SR-T task subscale scores was significantly associated with lower PHQ-9 scores. Composite scores and the goals and bond subscale scores were not significantly associated with post-treatment PHQ-9 scores (See *eTable 23* for model summaries).

Association between post-treatment PHQ-9 and WAI-SR-T scores, adjusting for WAI-SR-C scores

In the b-CBT arm, WAI-SR-T composite and all subscale scores (goals, task, bond) were not associated with PHQ-9 scores at 3-months, when controlling for WAI-SR-C composite and all subscale scores. *eTable 24* summarises the findings from all models.

Testing the interaction between WAI-SR-T and SUS-T on the relationship between WAI-SR-T and PHQ-9

The interaction between WAI-SR-T and SUS-T on the association between WAI-SR-T composite scores and client PHQ-9 at 3-months was not significant for WAI-SR-T composite scores (*b*=-0.03 [95% CI: -0.04 to 0.10], *P*=0.40), and the goals (*b*=-0.05 [95% CI: -0.34 to 0.43], *P*=0.13), task (*b*=-0.15 [95% CI: -0.02 to 0.32], *p*=0.09) and bond (*b*=-0.07 [95% CI: -0.03 to 0.11], *p*=0.45) subscale scores.

eTable 16. Adjusted linear models of association between post-treatment client PHQ-9 and WAI-SR-T scores in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

WAI-SR-T (outcome)	B (95% CI)	*P* value
Composite	-0.13 (-0.29 to 0.02)	.093
Goals	-0.31 (-0.70 to 0.08)	.116
Task	-0.41 (-0.81 to -0.00)	.048
Bond	-0.16 (-0.58 to 0.25)	.434

Abbreviations: 95% CI, 95% confidence intervals; B, unstandardized beta; b-CBT, blended-cognitive behavioural therapy; PHQ-9, patient health questionnaire-9; WAI-SR-T, working alliance inventory-short revised-therapist.

eTable 17. Nested linear regression models of associations between PHQ-9 scores and WAI-SR-C scores in step 1 and WAI-SR-T scores in step 2 in b-CBT. Composite and subscale (goals, task, bond) scores are independent models

Variables		Composite		Goals		Task		Bond	
		B (CI 95)	P Value	*B* (CI 95)	P Value	*B* (CI 95)	P Value	*B* (CI 95)	P Value
Step 1									
	Constant	14.07 (8.33 to19.81)	<.001	11.26 (5.99 – 16.53)	<.001	13.73 (8.43 to 19.03)	<.001	12.37 (6.88 to 17.86)	<.001
	WAI-SR-C	-0.16 (-0.26 to -0.06)	.001	-0.32 (-0.58 to -0.06)	.017	-0.47 (-0.73to-0.21)	.001	-0.36 -0.61 to -0.10)	.006
Step 2									
	Constant	16.08 (8.43 to 23.73)	<.001	12.69 (6.52 to 18.86)	<.001	15.15 (9.02 to 21.28)	<.001	14.06 (4.98 to 23.13)	.003
	WAI-SR-C	-0.15 (-0.25 to 0.05)	.005	-0.28 (-0.55 to 0.00)	.051	-0.43 -0.71 to -0.15	.003	-0.35 -0.61 to -0.09)	.008
	WAI-SR-T	-0.06 (-0.22 to 0.10)	.433	-0.183 (-0.59 to 0.22)	.377	-0.19 (-0.61 to 0.23)	.364	-.096 (-0.51 to 0.31)	.645

Model 1: R^2 = .25 for step 1: ΔR^2 = *.00* for step 2 (ps. =<.433); Model 2: R^2 = .23 for step 1: ΔR^2 = *.00* for step 2 (ps. =.377); Model 3: R^2 = .26 for step 1: ΔR^2 = *.00* for step 2 (ps. =.364); Model 4: R^2 = .23 for step 1: ΔR^2 = *.00* for step 2 (ps. =.645).

Abbreviations: 95% CI, 95% confidence intervals; *B*, unstandardized beta; PHQ-9, patient health questionnaire-9; WAI-SR-C, working alliance inventory-short revised-client; WAI-SR-T, working alliance inventory-short revised-therapist.

Appendix 18. Dissemination

To date, the findings of my thesis have been disseminated through the following activities.

Peer-reviewed publications

The results of the client qualitative interviews that was used to adapt the working alliance framework for a b-CBT setting were published in BMJ Open on September 23rd 2020 [47]. This framework was also tested in a Spanish sample of clients that were allocated to either unguided or minimally guided internet-based CBT (iCBT) programme for depression. This paper was published in Frontiers in Psychology, on 29th March 2023 [214]. The findings showed that all of the categories and sub-categories of the framework were endorsed, strengthening the studies reliability and validity. The results of the therapist qualitative interviews that outlined barriers and facilitators to fostering a working alliance in a b-CBT intervention was published in the British Journal of Psychiatrists (BJPsych) Open on 5th July 2022 [48]. The quantitative evaluation results of the client-rated working alliance in b-CBT were submitted to the Journal of Medical Internet Research (JMIR) and was under peer-review ahead of the submission of my thesis. All of the journals mentioned above are open access.

Oral presentations

The findings of my four papers were also presented at several academic forums. Below are selected external oral presentations targeted to diverse audiences.

November 2022. I co-organised the Innovation & Inclusion in Digital Mental Health Symposium with Birkbeck Centre for Interdisciplinary Research on Mental Health. This symposium explored how social inclusion can be placed at the centre of digital innovations in mental health. My presentation focused on how PPI can be harnessed to leverage person-centred innovation and the working alliance, that drew from experiences from my PhD. This event was recorded and live-tweeted. A publication piece-based on the event is in the process of being prepared by the co-organiser and I, and in collaboration with symposium speakers.

July 2022. I presented the findings of the therapist qualitative interviews that outlined the barriers and facilitators to fostering a working alliance as part of an early career forum on the Mental Health Promotion and Intervention in Occupational Settings (MENTUPP) consortium that aims to develop, implement, and evaluate a mental health intervention (which I am currently employed in).

January 2021. I presented at the Building Therapeutic Relationships Online event which was an interdisciplinary webinar hosted by Centre for Cultures of Reproduction, Technologies, and Health

(CORTH), Sussex University. My presentation involved drawing on the findings of my PhD both qualitative and quantitative evaluations of the working alliance in b-CBT to develop recommendations for empowering the working alliance in clinical practice.

November 2019. I was one of three students to be awarded a scholarship to travel to Japan to present at the Kyoto Short Course on Participatory Action Research. I presented my experiences and reflections of involving PPI to inform my thesis, and contributed to a panel discussion, to an audience of public health students. Following the short course, a summary of all presentations was disseminated in the London School of Hygiene and Tropical Medicine blog post.

July 2019. I presented the findings of the client qualitative interviews on a panel focused on 'relationships that are developed online', at the International Association for Relationship Research (IARR) conference which was held in Sussex University.

Posters

December 2019. I presented a poster summarising the findings from the client qualitative interviews at the annual MindTech Symposium, in which my poster was selected as one of three commendable posters

Copies of advertisements, images and emails associated with the events are provided below

Innovation and inclusion in digital mental health

Full schedule can be found here https://cirmh.bbk.ac.uk/events/innovation-inclusion-in-digital-mental-health/

Birkbeck UNIVERSITY OF LONDON

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Online symposium co-hosted by the Centre for Global Mental Health at LSHTM and Birkbeck Centre for Interdisciplinary Research on Mental Health

Innovation & Inclusion in Digital Mental Health: Histories and Futures

Thursday 17th Nov 2022 - 2:30-5:15 PM (GMT)
Webinar link: https://lshtm.zoom.us/j/92154278123

Programme

Panel 1: Social Inclusion
Arlinda-Pashoja (LSHTM & St Mary's)
Corrine Hendy (NIH Mind Tech)
Dixon Chibanda (LSHTM)
Ursula Read (Warwick)
Chair: Dan Robotham (McPin Foundation)

Panel 2: Person Centered Innovations & the Therapeutic Relationship
Asmae Doukani (LSHTM)
Hannah Zeavin (Indiana)
Sarah Markham (KCL)
TBC (Inuka Coaching)
Chair: Sarah Marks (BBK)

Panel 3: Envisioning the Future of Digital Innovations in Mental Health
Becky Inkster (Cambridge)
César Escobar-Viera (University of Pittsburgh)
Demi Fortson (Mendü)
Pattie Gonsalves (Sussex University)
Jasmin Pierre (The Safe Place)
Chair: Asmae Doukani (LSHTM)

CORTH Webinar: Building therapeutic relationship online

Building therapeutic relationships online:
how clinical interactions are changing as sexual and reproductive care goes digital

CORTH Webinar Series
Friday 29th January 2021, 9am to 4pm

Introduction and Keynote

09.15-09.30 – **Welcome from the seminar organisers and the context for digital sexual health care in the UK and beyond**
Maya Unnithan, University of Sussex
Paula Baraitser, SH:24

09.30-10.30 – **Keynote + discussion**
The future of digital health care: theories and methods
Deborah Lupton, University of New South Wales, Sydney

10.30-11.00 – **Break**

Themed Session 1:
Showing Care in Digital Environments

11.00-11.15 – **Showing care in online sexual health services**
Paula Baraitser, SH:24
Maya Unnithan, University of Sussex

11.15-11.30 – **The tears you missed: exploring telehealth psychology consults during the Covid-19 crisis in Australia**
Leanne Downing, University of New South Wales, Sydney

11.30-11.45 – **Negotiating the therapeutic alliance in online CNT**
Asmae Doukani, London School of Tropical Medicine and Hygiene

11.45-12.00 – **Showing care by automated text message**
Caroline Free, London School of Tropical Medicine and Hygiene

12.00-12.30 – **Discussion**

12.30-14.00 – **Break**

Themed Session 2:
More Than Digital / More Than Human

14.00-14.15 – **It takes too long: the slowness of care through WhatsApp in a Kenyan digital health service**
Faith Anne Nyagichuhi Mararo, Jojo, Kenya

14.15-14.30 – **Enacting digital healthcare: how spaces and boundaries come to matter**
Catherine Will and Ulla McKnight, University of Sussex

14.30-14.45 – **More than human collaborations to treat genital herpes and warts**
Paula Baraitser, SH:24

14.45 - 15.15 – **Trading off convenience and care in emergency contraception provision** (TBC)

15.15 - 15.30 – **Discussion**

Close and next steps
Maya Unnithan, University of Sussex
Paula Baraitser, SH:24

Short Course on Participatory action research, Kyoto

Short Course on Participatory Action Research

November 21-22 (Th, Fri) 9:00～17:00
Venue: 1st floor, Small Seminar Room,
Science Frontier Laboratory Building, Medical Campus

Participatory Action Research (PAR) aims to deliver goal-oriented action that follows as a result of the research. This short course introduces basic theory and methods of PAR as well as the implementation strategy of PAR in the field of public health. This Short Course is for students and researchers who are new to PAR. It is a great opportunity to gain knowledge about how to conduct PAR research. The lectures will be conducted in English.

DAY 1: November 21
Basic Theory and Methods of PAR

Theory and Philosophy of PAR

PAR Methodologies

Case Example of PAR:
Engaging the Elderly in PAR

Group Work

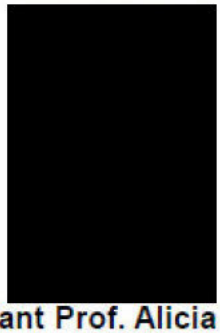
DAY 2: November 22
Implementation Strategies of PAR

Thinking Critically about Participation

Case Example of PAR:
Young People with Sickle Cell

Student Research Presentations:
(3 students from LSHTM)

Prof. Pranee Liamputtong
Western Sydney University
The editor of "Participatory Qualitative Research Methodologies in Health". She has authored over 300 books, book chapters, and publications.



Assistant Prof. Alicia Renedo
Lead researcher of DEPTH, London School of Hygiene and Tropical Medicine

Please Register / Make Inquiry from the Website:
https://forms.gle/bYhvK68p1wbKwGyL8

Register here!

Organized by Kyoto University School of Public Health - SGU International Office

LSHTM blog post about participatory workshop at Kyoto University

https://blogs.lshtm.ac.uk/depth/2019/12/11/trip-report-lshtm-participatory-research-workshop-at-kyoto-university/

International Association for Relationship Research (IARR)

2019 “Applied Relationship Science” Mini-Conference - July 18-21, Brighton, UK.

Confirmation email. Schedule is no longer available

Asmae Doukani

From: ErisUnleashed Support <support@erisunleashed.com>
Sent: 11 May 2019 06:21
Subject: IARR Brighton 2019 Schedule

Congratulations on being accepted as a presenter at the 2019 IARR Brighton Mini-conference. We are pleased to announce that the conference schedule has now been published. You can view the conference online at the following link: https://iarrconference.org/conference-schedule/. Please note that, although the conference schedule has been drafted, there might be some slight modifications made closer to the conference.

If you have not registered for the conference, you may do so at anytime by clicking on the following link: : https://tinyurl.com/brightoniarr2019. Please note that early registration closes on 31 May 2019 and late registration closes on 30 June 2019. We will not be able to take registration fees or fees for the social events onsite. Thus, you must register prior to 1 July 2019.

Also, if you have yet to book your accommodation at one of the hotels or halls of residence that we have negotiated favourable rates, you may do so by clicking on the following link: https://tinyurl.com/AccommodationBrighton. These rates may not be guaranteed for much longer, so make your accommodation booking soon.

Over the coming weeks we will be posting additional information, including a map of the campus for digital access throughout the conference. You will also be able to search for individual presentations by the name of the presenter and be able to download a user friendly version of the conference program.

The conference platform also allows for the integration of social media links for your presentation and to your professional accounts. If you would like to have your presentation tagged, please submit your requested hashtag to support@erisunleashed.com and they will be posted. You can also send your social media contact information for FaceBook, LinkedIn, Twitter, Instagram, Skype, and of course e-mail. This information will then appear with your speaker information on the conference site. This information is completely optional and can be removed upon your request.

If you have any questions or comments, please forward them to support@erisunleashed.com.

2019 Mini IARR Conference on Applied Relationship Conference Program Committee: Michelle Luke (Chair), Cassandra Alexopoulos, Kathy Carnelley, Kate Cavanagh and Erica Hepper

Kind Regards,
Support Service

MindTech symposium (2019) poster and photo of winning poster

Toward a conceptual framework of the working alliance in a blended cognitive behavioural therapy intervention

Doukani, A[1]., Free, C[1]., Michelson, D[2]., Smith[1], S., Araya, R[3]., Montero-Marin, J[4]., Cerga-Pashoja, A[1]., & Kakuma, R[5]

London School of Hygiene and Tropical Medicine[1], University of Sussex[2], Kings College London[3] & Dharamsala Institute of Mindfulness and Psychotherapy [4]

1. BACKGROUND

The working alliance **(WA)** as defined by Bordin[1] is:

"A formation between the client seeking change and the therapist...that incorporated a mutual understanding and agreement about change **goals** and the necessary **tasks** to move forward these goals along with the establishment of **bonds** to maintain the partners' work" [1, pg. 13].

Rationale:
- WA has been found to be the most consistent predictor for positive therapeutic outcomes in face-to-face formats of psychotherapy [2].
- Despite the digitisation of mental health care, WA has not been theoretically examined in blended (therapist plus computerised program) cognitive behavioural therapy **(b-CBT)** [3].

Aim (Post-service user involvement):
To examine and adapt Bordin's [1] WA in a b-CBT intervention for depression.

2. METHODS

Step 1: Service user involvement (SUI) enlisted at the onset of the project informed:
- which format of CBT to explore WA in (i.e., bended instead of computerised CBT only)
- participant qualitative interview topic guide.

Step 2: Participant individual semi-structured qualitative interviews.
- Ninteen participants were recruited from the b-CBT arm of the E-Compared trial (which evaluated the cost-effectiveness of b-CBT) [4].
- Interview topics were guided by Bordin's[1] theory of WA and SUI input.
- Data was transcribed and analysed using thematic analysis with a constant comparative method, to derive latent themes at a psychological level [5].
- The final conceptual framework was reviewed to ensure that each theme represented a 'therapeutic process' and not a 'treatment outcome', using pre-defined

3. FINDINGS

Four **multi-faceted** themes pertaining to WA demands in b-CBT were identified:

Aligns with Bordin's[1] theory

THEME 1: BOND
A healthcare provider with good interpersonal competencies in aid of building a trusting working relationship with the service-user.

THEME 2: GOALS
Collaborative efforts between the service-user and the healthcare provider to appropriately identify what the service-user hopes to achieve through therapy.

THEME 3: TASK
The selection of acceptable therapeutic activities that address service-user goals and the availability of responsive support from the healthcare provider.

New

THEME 4: DIGITAL HEURISTICS
A range of therapy engagement facilitators that promote self-directed discovery.

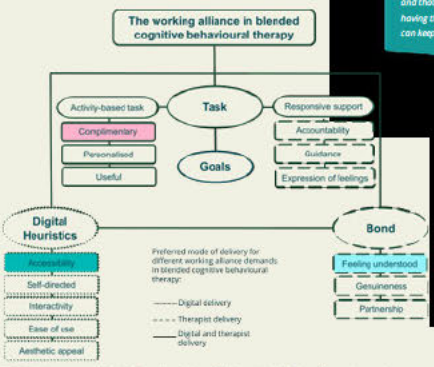


Fig1: Participant reported working alliance demands in a blended cognitive behavioural therapy intervention.

4. CONCLUSION

To our knowledge, this study is the first to offer:
- a preliminary conceptual framework of WA demands in b-CBT
- insights of how the human therapist and digital resources can effectively be deployed to meet WA needs in b-CBT.

The findings can be used to promote WA in technological design and clinical practice, thereby promoting engagement in similar b-CBT interventions.

Future research should examine the relationship between the WA in b-CBT and clinical outcomes in b-CBT interventions.

Acknowledgements

I would like to thank the E-compared consortium for supporting my PhD and the eleven Patient and Public Involvement advisors whose input shaped the methodology of the project, including Abé Chekh-Dove El-Ghassani, Michael Clarke, Paul H Ware, Dr Serah Markham and Tibby Stodel. I would also like to express my gratitude to Shamalla Usmani who co-facilitated the SUI focus groups.

Email: Asmae.Doukani@lshtm.ac.uk Twitter:@asmae.doukani

References

1.Bordin, E. S. The generalizability of the psychoanalytic concept of the working alliance. Psychother. Theory, Res. Pract. 16, 252–260: (1979).

2.Lambert, M. J. Psychotherapy outcome research: implications for integrative and eclectic therapists. In Handbook of psychotherapy integration (ed. John C Norcross & Marvin R Goldfried) (Basic Books, (1992).

3.Torous, J. & Hsin, H. Empowering the digital therapeutic relationship: virtual clinics for digital health interventions. npj Digit. Med. 1, 16: (2018).

4. 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).

5. Corbin J, Strauss A. Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory. Fourth. London: SAGE Publications: (2008).

6. Llewelyn S, Macdonald J, Aafjes-van Doorn K. Process–outcome studies. In: APA handbook of clinical psychology: Theory and research (Vol 2): (2016).

E-COMPARED

CENTRE FOR GLOBAL MENTAL HEALTH

Improving Health Worldwide • www.lshtm.ac.uk

Picture of commended poster