



Salisbury, C. J., O'Cathain, A., Edwards, L. P., Thomas, C. L., Gaunt, D. M., Hollinghurst, S. P., Nicholl, J., Large, S., Yardley, L., Lewis, G., Foster, A., Garner, K., Horspool, K., Man, M.-S., Rogers, A., Pope, C. J., Dixon, P. C., & Montgomery, A. A. (2016). Effectiveness of an integrated telehealth service for patients with depression: a pragmatic randomised controlled trial of a complex intervention. *Lancet Psychiatry*, 3(6), 515-525. [https://doi.org/10.1016/S2215-0366\(16\)00083-3](https://doi.org/10.1016/S2215-0366(16)00083-3)

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
[10.1016/S2215-0366\(16\)00083-3](https://doi.org/10.1016/S2215-0366(16)00083-3)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via Elsevier at <http://www.sciencedirect.com/science/article/pii/S2215036616000833>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Effectiveness of an integrated telehealth service for patients with depression: a pragmatic randomised controlled trial of a complex intervention



Chris Salisbury, Alicia O’Cathain, Louisa Edwards, Clare Thomas, Daisy Gaunt, Sandra Hollinghurst, Jon Nicholl, Shirley Large, Lucy Yardley, Glyn Lewis, Alexis Foster, Katy Garner, Kimberley Horspool, Mei-See Man, Anne Rogers, Catherine Pope, Pdraig Dixon, Alan A Montgomery



Summary

Background Many countries are exploring the potential of telehealth interventions to manage the rising number of people with chronic disorders. However, evidence of the effectiveness of telehealth is ambiguous. Based on an evidence-based conceptual framework, we developed an integrated telehealth service (the Healthlines Service) for chronic disorders and assessed its effectiveness in patients with depression. We aimed to compare the Healthlines Depression Service plus usual care with usual care alone.

Methods This study was a pragmatic, multicentre, randomised controlled trial with participants recruited from 43 general practices in three areas of England. To be eligible, participants needed to have access to the internet and email, a Patient Health Questionnaire 9 (PHQ-9) score of at least 10, and a confirmed diagnosis of depression. Participants were individually assigned (1:1) to either the Healthlines Depression Service plus usual care or usual care alone. Random assignment was done by use of a web-based automated randomisation system, stratified by site and minimised by practice and PHQ-9 score. Participants were aware of their allocation, but outcomes were analysed masked. The Healthlines Service consisted of regular telephone calls from non-clinical, trained health advisers who followed standardised scripts generated by interactive software. After an initial assessment and goal-setting telephone call, the advisers called each participant on six occasions over 4 months, and then made up to three more calls at intervals of roughly 2 months to provide reinforcement and to detect relapse. Advisers supported participants in the use of online resources (including computerised cognitive behavioural therapy) and sought to encourage healthier lifestyles, optimise medication, and improve treatment adherence. The primary outcome was the proportion of participants responding to the intervention (defined as PHQ-9 <10 and reduction in PHQ-9 of ≥5 points) at 4 months after randomisation. The primary analysis was based on the intention-to-treat principle without imputation and all serious adverse events were investigated. This trial is registered with Current Controlled Trials, number ISRCTN 14172341.

Findings Between July 24, 2012, and July 31, 2013, we recruited 609 participants, randomly assigning 307 to the Healthlines Service plus usual care and 302 to usual care. Primary outcome data were available for 525 (86%) participants. At 4 months, 68 (27%) of 255 individuals in the intervention group had a treatment response compared with 50 (19%) of 270 individuals in the usual care group (adjusted odds ratio 1·7, 95% CI 1·1–2·5, $p=0\cdot019$). Compared with usual care alone, intervention participants reported improvements in anxiety, better access to support and advice, greater satisfaction with the support they received, and improvements in self-management and health literacy. During the trial, 70 adverse events were reported by participants, one of which was related to the intervention (increased anxiety from discussing depression) and was not serious.

Interpretation This telehealth service based on non-clinically trained health advisers supporting patients in use of internet resources was both acceptable and effective compared with usual care. Our results provide support for the development and assessment of similar interventions in other chronic disorders to expand care provision.

Funding National Institute for Health Research (NIHR).

Copyright © Salisbury et al. Open Access article distributed under the terms of CC BY.

Introduction

The growing prevalence of chronic disorders is a challenge to the capacity of health-care systems, which are mainly based on face-to-face consultations between patients and doctors. There is international interest in the potential of technology to enable individuals to manage their own health problems, reducing the need to make appointments

with health professionals. These technologies, broadly termed telehealth, include telephone support, messaging, internet-based approaches, and remote monitoring. Some interventions can be automated and supported by non-clinically trained staff, which could expand provision and increase access to care. UK health policy envisages telehealth becoming mainstream.¹ In the USA, the

Lancet Psychiatry 2016

Published Online

April 27, 2016

[http://dx.doi.org/10.1016/S2215-0366\(16\)00083-3](http://dx.doi.org/10.1016/S2215-0366(16)00083-3)

See Online/Comment

[http://dx.doi.org/10.1016/S2215-0366\(16\)30039-6](http://dx.doi.org/10.1016/S2215-0366(16)30039-6)

Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Bristol, UK (Prof C Salisbury MD, C Thomas PhD, L Edwards PhD, S Hollinghurst PhD, K Garner PhD, M-S Man PhD, P Dixon PhD); School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK (Prof A O’Cathain PhD, Prof J Nicholl DSc, A Foster MPH, K Horspool MSc); Bristol Randomised Trials Collaboration, School of Social and Community Medicine, University of Bristol, Bristol, UK (A A Montgomery PhD, D Gaunt MSc); NHS England South (Wessex), Southampton, UK (S Large PhD); Department of Psychology, University of Southampton, Southampton, UK (Prof L Yardley PhD); Division of Psychiatry, University College London, London, UK (Prof G Lewis PhD); Faculty of Health Sciences, University of Southampton, Southampton, UK (A Rogers PhD, C Pope PhD); and Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK (A A Montgomery)

Correspondence to: Prof Chris Salisbury, Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Bristol BS8 2PS, UK c.salisbury@bristol.ac.uk

Research in context

Evidence before this study

There is much scientific literature about specific telehealth interventions for different chronic disorders. Before developing the Healthlines intervention, we did a meta-review of existing systematic reviews. We searched MEDLINE, Embase/AMED, PsycInfo, Web of Science, Database of Abstracts of Reviews of Effects (DARE), and The Cochrane Library between Jan 1, 2005, and March 31, 2010, for relevant systematic reviews. We used combinations of search terms for systematic reviews, telehealth, or telemedicine and a list of important chronic disorders (appendix p 13). We concluded that, although many studies had been done, many of these were of poor quality, with small sample sizes, methodological limitations, short-term follow-up, and insufficient theoretical basis for interventions. This conclusion was supported by a more recent evidence synthesis that showed evidence of publication bias and concluded that the evidence base for telehealth for chronic disorders is “on the whole weak and contradictory”. We supplemented these reviews with a meta-review of existing systematic reviews of telehealth for depression, focusing on which technologies seemed to work best for which groups of patients. These reviews provided support for telephone-based and computerised-interventions for depression, especially internet interventions based on cognitive behavioural therapy (CBT), although limitations and inconsistencies in the evidence base were again notable.

Some evidence suggested that professional support could improve the effectiveness of computerised CBT. More recent reviews reinforce these conclusions. Although there is much policy enthusiasm for telehealth programmes, few large pragmatic trials of such programmes have been done with real-world implementation and a broad range of patients.

Added value of this study

Our trial builds on previous evidence by testing a new model of care that combines the use of various telehealth tools supported by non-clinically trained staff. Our study provides robust support for the potential role of an integrated telehealth approach to support patients with depression in primary care. Our results showed that the Healthlines Depression Service increased the proportion of patients achieving a treatment response and also led to improvements in anxiety, self-management, patient satisfaction, and access to health care.

Implications of all the available evidence

Telehealth interventions for chronic disease can lead to small but meaningful improvements for patients. Basing the intervention design on a coherent conceptual model and including multiple evidence-based approaches in combination is likely to enhance effectiveness. The promising findings from this study justify developing similar interventions for other chronic disorders.

Veterans Health Administration has enrolled more than 50 000 patients in a home telehealth programme, and the Renewing Health Consortium is testing telehealth programmes in nine European countries.

Despite this enthusiasm for telehealth, evidence of benefit is ambiguous and inconsistent, in part due to insufficient theoretical underpinning for many interventions.^{2,3} Systematic reviews in different disorders have shown benefits from specific technologies in selected patients, but few studies have investigated their effectiveness in large-scale, real-world implementation.² Furthermore, the focus on specific applications is of limited value because their use cannot be considered in isolation from the health-care system. Technology-based solutions have frequently been introduced without incorporation into existing models of service provision. The NHS Five Year Forward View proposes that what is needed is so-called combinatorial innovation—an approach that combines different technologies and changed ways of working to transform care delivery.⁴

We developed a new model of care to improve management of people with chronic disease based on making the best use of various technologies in combination, supported by non-clinically trained staff and integrated with the health-care system. This approach incorporates recognised strategies to improve management for chronic disease, use of technology to

implement those strategies in ways that reduce the need for face-to-face contact with clinicians, use of specific telehealth tools which have the best evidence of effectiveness, and use of technology to ensure integration with primary care. The aim is to improve access to care, expand care provision without relying on clinical staff, deliver more effective treatment, and improve self-management, leading to improved patient outcomes.

This paper describes a trial of this approach in the example of depression. Depression affects 3% of adults in the UK, is a chronic or relapsing disorder in about half of those affected, accounts for about a quarter of primary care consultations, and has substantial adverse effects on quality of life.⁵ There is evidence from systematic reviews in favour of telehealth interventions for depression, including those delivered by telephone⁶ or the internet.^{7–10} However, more than half of patients drop out of online therapy,⁹ and therapist support alongside internet-based interventions increases effectiveness and improves retention of participants.^{7,9,10}

Through a programme of research, including literature reviews,¹¹ qualitative research,¹² and a survey of patient views,¹³ we developed an evidence-based conceptual model for effective use of telehealth to improve management of chronic disorders—the Telehealth in CHronic disease (TECH) model (appendix p 1).¹⁴ Building on the Chronic Care Model,¹⁵ the TECH model

See Online for appendix

proposes that telehealth programmes need to address engagement of patients and health providers, promotion of self-management behaviours, optimisation of treatment, and care coordination, and they need to be provided in partnership with usual primary care providers. We used the TECH model to design and assess telehealth interventions (The Healthlines Service) for two exemplar common chronic disorders: depression and raised cardiovascular risk. In this trial, we aimed to assess the effectiveness of the Healthlines Service plus usual care compared with usual care alone for patients with depression in a large-scale, real-world application.

Methods

Study design and participants

This study was a pragmatic, multicentre, randomised controlled trial. Participants were recruited in three areas of England (around Bristol, Sheffield, or Southampton). The trial was approved by the National Research Ethics Service Committee South West–Frenchay (Reference 12/SW/0009). The study protocol has been reported previously.¹⁶ Readers interested in obtaining further information about the intervention materials should refer to the study website.

Participants were recruited from 43 general practices, which covered populations with various sociodemographic characteristics. Inclusion criteria were a score on the Patient Health Questionnaire 9 (PHQ-9)¹⁷ of at least 10 points and a confirmed diagnosis of depression on the Clinical Interview Schedule-Revised (CIS-R) scale,¹⁸ being aged 18 years or older, and having access to a telephone, the internet, and email. Participants were excluded if they were currently receiving therapy or case management from a mental health worker; had given birth in the previous 12 months; had a history of major bipolar disorder, psychotic illness, dementia, severe learning disability, or substance dependency; were receiving palliative care; had a significant suicide risk; or were unable to communicate verbally in English. Potentially eligible participants were also excluded if their general practitioner (GP) deemed that participation would cause distress (eg, because of a recent bereavement).

Potentially eligible participants were identified via searches of computerised general practice records for patients who had consulted a doctor for depression or low mood, or who had been prescribed antidepressants within the previous 2 months. We asked GPs to screen the list to remove patients with known exclusion criteria. A random sample of potentially eligible patients in each practice were sent postal information about the study and a PHQ-9 questionnaire. Patients who expressed an interest in the study and had a PHQ-9 score of at least 10 were screened by researchers over the telephone to confirm eligibility, including use of the CIS-R to confirm a diagnosis of depression. Eligible patients were asked to complete a baseline questionnaire and consent form,

either online or by post. If respondents indicated suicidal ideas during assessment of eligibility we asked their GP to assess whether they should be excluded from the trial.

Randomisation and masking

Participants who consented to participate were individually randomly allocated (1:1) to either the intervention plus usual care group or the usual care alone group. Allocation was done with an automated web randomisation system developed independently by the Bristol Randomised Controlled Trials Collaboration (Bristol, UK). Randomisation was stratified by location (Bristol, Sheffield, or Southampton) and minimised by general practice and baseline PHQ-9 depression score (10–14, 15–19, ≥ 20). Participants were notified of their allocation by email. Participants were aware of their assignment to the intervention or control groups. Outcome data were collected by participant self-report or electronic download from general practice computer records, and the trial statisticians analysed the outcomes masked to allocation.

Procedures

This was a complex intervention incorporating use of technologies supported by non-clinically trained staff to address each of the components of the TECH model. To apply the model to a specific clinical disorder, we sought to identify telehealth tools that had some evidence of effectiveness in that disorder and that could be used to implement the strategies within the TECH model. Therefore the specific telehealth tools varied for the different exemplar disorders, but were delivered by the Healthlines Service within a common intervention framework (shown for depression in the appendix [p 2]).

The intervention was originally provided by staff from NHS Direct, which, until March 2014, provided various telehealth services through a national network of call centres and a website. After NHS Direct closed in March, 2014, the Healthlines Service was transferred to Solent NHS Trust. The Healthlines Service was based on regular telephone calls from a health adviser who was supported by interactive software. The advisers were not clinically qualified but had experience working for NHS Direct and had a further 3 weeks of training in health coaching, motivational interviewing, antidepressant drug treatment, use of a computerised cognitive behavioural therapy (CBT) programme, and the Healthlines telephone support software. With the help of scripts generated by the interactive software, the advisers supported participants in addressing their own health goals and directed them to relevant online resources, including reliable health information, interactive programmes, and relevant apps and widgets (eg, to help with increasing exercise). The advisers emailed links to appropriate websites to participants or sent them the information by post.

For the study website see <http://www.bristol.ac.uk/healthlines/>

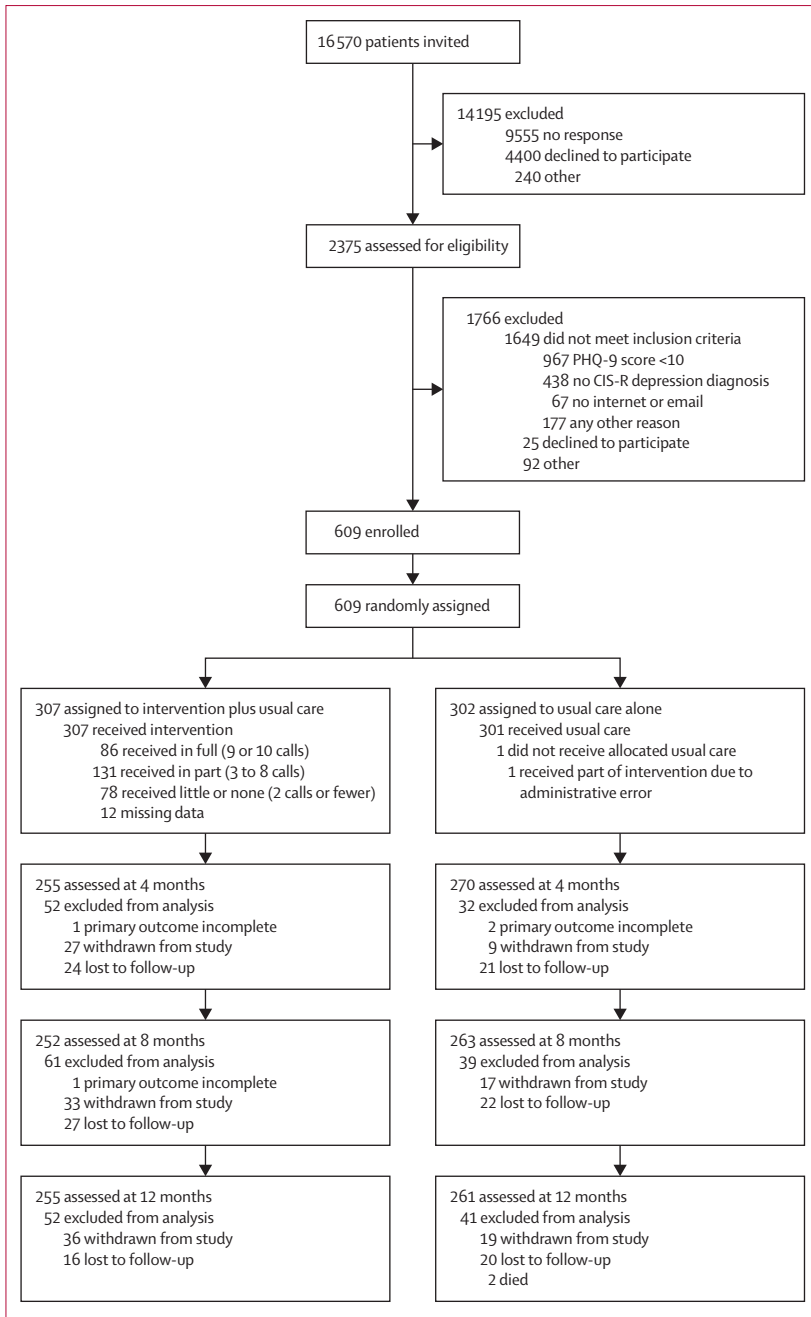


Figure 1: Trial profile
 Primary outcome incomplete indicates patients who did not answer enough questions in their Patient Health Questionnaire-9 to allow calculation of a valid score.

The web portal also provided information about depression, links to relevant patient-led organisations and a link to Big White Wall, which is a digital mental health network that includes a clinically moderated online forum.

After an initial assessment and goal-setting telephone call, the advisers called each participant on six occasions roughly equally spaced over 4 months, and then made up to three more calls at roughly two month intervals to provide reinforcement and to detect relapse. As well as providing support in use of the CBT programme (online or in book form), the telephone scripts included modules covering the monitoring of depression symptoms, drug treatment, medication adherence, exercise, and alcohol use. To ensure coordination with primary care, the advisers sent regular progress reports to participants' GPs by email and copied them to participants via the Healthlines portal. In cases of inadequate treatment response, the advisers contacted participants' GPs to recommend escalation of medication, enclosing a summary of current treatment guidelines.⁵ This approach was based on our aim to support, rather than to undermine, the work of the participants' main primary care providers. Each participant was telephoned by the same adviser on each occasion when possible, since we had identified that it was important to avoid an anonymous call-centre approach to promote participant engagement.¹¹ Photographs of the advisers were provided on the Healthlines web portal to enhance the sense of personal care. To facilitate access to care, the Healthlines Service was available from 1000 h to 2000 h on weekdays and from 1000 h to 1400 h on Saturdays.

NHS Direct was closed down towards the end of the trial, therefore delivery of the intervention was paused for 2 months while it was transferred to Solent NHS Trust. Two-fifths of participants had a gap in service provision during this transfer and some did not receive the full number of intended phone calls before the end of their 12 month follow-up period.

Outcomes

The primary outcome was the proportion of participants responding to the intervention, defined as a PHQ-9¹⁷ score of less than 10 and a reduction in PHQ-9 of at least 5 points, 4 months after randomisation. Secondary outcomes were PHQ-9 as a binary outcome at 8 and 12 months and as a continuous outcome at 4, 8, and 12 months; anxiety (GAD-7);²¹ quality of life (EQ-5D-5L);²² satisfaction with treatment received and with amount of support received (patient satisfaction); perceived access to care; self-management skills and self-efficacy (HeiQ);²³ use of telehealth interventions; medication adherence (Morisky);²⁴ health literacy (eHEALs);²⁵ and perceptions of care coordination (Haggerty).²⁶ We pre-specified questions about internet use and experience but did not analyse these questions in order to reduce the number of secondary outcomes. These secondary outcomes were

For the Big White Wall see <http://www.bigwhitewall.com>

Participants were given access to a Healthlines web portal, which linked to several resources, including the Living Life to the Full Interactive (LLTTFi) programme. This interactive multimedia programme delivers computerised CBT-based treatment for depression through six self-directed sessions, to be completed roughly every two weeks.¹⁹ Alternatively, participants could choose to follow similar material in book form.²⁰

chosen to assess the effect of the intervention on the various components of the underlying TECH model. At baseline, we also obtained details of socio-demographic characteristics and current treatment for depression. All measures were collected through patient questionnaires, completed online or by post, at baseline and at 4, 8, and 12 months after randomisation. We attempted to follow up non-respondents by email, telephone, and post. Participants were offered the option of completing just the primary outcome during their second reminder, which could have been by post, email or phone. After 12 months, we collected data from computerised general practice records about consultations and prescriptions for antidepressants. We obtained data about use of the intervention from Healthlines Service records. All potential serious adverse events were investigated. Adverse events were mainly detected as part of the collection of data with respect to resource use during the 12 month follow-up period, either collected within the patient questionnaires or during the review of participants' medical records in primary care at the end of the trial. We collected data about any hospital attendance or new or recurrent serious medical events recorded in primary care records during the 12 month period.

Statistical analysis

We chose the sample size pragmatically, taking into account the size of effect that would be likely to affect practice and that might be feasible. Assuming a 30% response to treatment in the control group and 20% attrition, 300 participants in each group would provide 80% power (α of 5%) to detect a difference of 13% and 90% power (α of 1%) to detect a difference of 18%.

We used descriptive statistics to compare baseline characteristics of trial participants by allocated group. If we detected important imbalances between the intervention and control groups, these variables were included in regression models in sensitivity analyses of the primary outcome. We fitted all regression models with maximum likelihood estimation, apart from the regression models that used multiply imputed data, for which we used QR decomposition.

We did the primary analysis with a mixed-effects logistic regression model adjusted by the stratification and minimisation variables of site (categorical), baseline value of the outcome (continuous), and general practice (categorical, included as a random effect). In the primary analysis, we included all participants with complete data in accordance with their allocated treatment, based on the principle of intention to treat without imputation. We investigated the robustness of the primary analysis to different methods of imputing missing outcome data: simple imputation that assumed no treatment response or multiple imputation (appendix p 5).²⁷ We also investigated the effect of omitting GP practice as a random effect, and adjusting for time between randomisation and follow-up and variables imbalanced between the groups at baseline.

	Usual care alone (n=302)*	Intervention plus usual care (n=307)*
Demographic		
Age (years)	50.0 (12.8)†	49.1 (12.9)‡
Female	204/302 (68%)	213/307 (69%)
White	292/301 (97%)	300/306 (98%)
Employment situation		
Full-time employment	92/299 (31%)	88/303 (29%)
Part-time employment	39/299 (13%)	56/303 (18%)
Full-time education	2/299 (1%)	5/303 (2%)
Unemployed	13/299 (4%)	14/303 (5%)
Unable to work due to long-term illness/disability	78/299 (26%)	73/303 (24%)
Unable to work due to carer responsibilities	2/299 (1%)	4/303 (1%)
Fully retired from work	44/299 (15%)	40/303 (13%)
Looking after the home	10/299 (3%)	13/303 (4%)
Doing something else	19/299 (6%)	10/303 (3%)
Occupation (most recent or current)		
Administrative or secretarial occupations	51/262 (19%)	49/270 (18%)
Associate professional or technical occupations	37/262 (14%)	35/270 (13%)
Elementary occupations	21/262 (8%)	19/270 (7%)
Managers or senior officials	32/262 (12%)	41/270 (15%)
Personal services	28/262 (11%)	27/270 (1%)
Process, plant, and machine operatives	11/262 (4%)	15/270 (6%)
Professionals	35/262 (13%)	42/270 (16%)
Sales and customer services	35/262 (13%)	29/270 (11%)
Skilled trades	12/262 (5%)	13/270 (5%)
Highest education qualification achieved		
Degree or higher degree	84/298 (28%)	68/303 (22%)
A levels or equivalent	54/298 (18%)	63/303 (21%)
GCSEs/O levels or equivalent	119/298 (40%)	130/303 (43%)
No qualifications	41/298 (14%)	42/303 (14%)
Accommodation		
Own accommodation or buying with mortgage	162/300 (54%)	179/307 (58%)
Part-rent or rent accommodation	124/300 (41%)	118/307 (38%)
Live rent free	14/300 (5%)	10/307 (3%)
Index of multiple deprivation	18.0 (13.0)§	18.3 (12.8)‡
Clinical data		
Previously treated for depression	258/276 (93%)	269/295 (91%)
PHQ-9 score	16.7 (4.7)†	17.1 (4.5)‡
GAD-7 score	12.4 (5.0)¶	13.5 (4.6)
Categorised with mild depression from CIS-R	52/302 (17%)	39/307 (13%)
Categorised with moderate depression from CIS-R	148/302 (49%)	165/307 (54%)
Categorised with severe depression from CIS-R	102/302 (34%)	103/307 (34%)
Taking antidepressants	258/288 (90%)	251/289 (87%)
Data are n/N (%) or mean (SD). GCSE=General Certificate of Secondary Education. PHQ-9=Patient Health Questionnaire 9. GAD-7=Generalised Anxiety Disorder scale. CIS-R=Clinical Interview Schedule-Revised scale. *Denominators vary because of missing data. †n=302. ‡n=307. §n=301. ¶n=298. n=304.		
Table 1: Baseline characteristics		

By fitting interaction terms between trial groups and subgroup variables, we investigated whether any effect of the Healthlines intervention differed by subgroups defined at baseline by sex, age, PHQ-9 score, severity of depression, or use of antidepressant medication.

To estimate the effect of the Healthlines intervention at 12 months when received as intended, we described compliance as little or none (two telephone calls or fewer), partial (three to eight calls), or full (nine or ten calls). We estimated the complier-average causal effect (CACE) with principal stratification in two ways, classifying partial compliers as either non-compliers or full compliers.

We did repeated measures analyses of the primary outcome, as both a binary and continuous outcome, using appropriate mixed-effect regression models, including general practice as a random effect, participants as random intercepts, and assuming an independent covariance structure. We investigated whether the between-group difference changed over time by fitting an interaction between trial group and follow-up timepoint. In the absence of any such interactions, we report the average between-group effect across 12 months.

Secondary outcomes were analysed in a similar manner to the primary analysis. We estimated between-group effects with linear, logistic, or binomial mixed-effect regression models, adjusted for stratification and minimisation variables and continuous value of the outcome at baseline (if appropriate). Participants were analysed as randomised, without imputation of missing data. We did no sensitivity analyses for secondary outcomes. To reduce the number of statistical comparisons, we estimated between-group differences for secondary outcomes only at the 12 month follow-up timepoint. We described serious adverse events by study group.

We did analyses using Stata version 13.1. The trial was overseen by an Independent Trial Steering Committee and an Independent Data Monitoring Committee, who agreed a statistical analysis plan before analysis. Two patient and public representatives actively contributed as members of the Trial Steering Committee. The trial is registered with Current Controlled Trials, number ISRCTN 14172341.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had

full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants were recruited and randomly assigned to study groups between July 24, 2012, and July 31, 2013. Of 2375 participants assessed for eligibility, 1649 (69%) did not meet eligibility criteria, mainly because they did not meet the diagnostic criteria for depression (1405 [85%] of 1649 patients not meeting the eligibility criteria). Of the 726 eligible participants, 609 participants were randomly assigned, with 307 assigned to intervention plus usual care and 302 assigned to usual care alone (figure 1). Primary outcome data were obtained for 255 (83%) participants in the intervention group and 270 (89%) in the usual care group. We retained 516 (85%) participants until the final 12 month follow-up assessment.

Table 1 shows baseline characteristics of participants who entered randomisation. Most participants had severe and enduring depression. Of patients with data available, 205 (34%) were classified as severely depressed at baseline, 527 (92%) had previously been treated for depression, and 509 (88%) were currently taking antidepressant medication. The intervention and control groups were mostly well balanced, although there were small differences in work status, education, accommodation, depression severity, and use of antidepressants.

Analysis of the primary outcome showed that 68 (27%) of 255 participants in the intervention group responded to treatment at 4 months, compared with 50 (19%) of 270 participants in the control group (adjusted odds ratio [OR] 1.7, 95% CI 1.1–2.5, $p=0.019$; table 2). This 8% difference between groups in the proportion of participants responding to treatment is equivalent to a number needed to treat of 12. This result was robust to sensitivity analyses (appendix p 6). No evidence suggested that the intervention was differentially effective for any subgroups defined by baseline characteristics.

The proportion of participants who responded to treatment increased in both arms at 8 and 12 months (table 2). Although the between-group difference seemed to diminish with increasing duration of follow-up, there was no evidence of an interaction between treatment group and timepoint ($p_{\text{interaction}}=0.402$). Therefore, we estimated an overall treatment effect from all follow-up data at 4, 8, and 12 months in two repeated measures analyses, binary and continuous. This suggested a positive average effect of the intervention over the 12 month follow-up period (binary response to treatment $p=0.035$). Mean PHQ-9 scores also decreased over time for both groups (table 3), with no evidence of an interaction between treatment group and timepoint ($p_{\text{interaction}}=0.345$). A repeated measures analysis of continuous PHQ-9 scores provided evidence of a small overall treatment effect ($p=0.045$).

	Usual care	Intervention plus usual care	Adjusted odds ratio (95% CI)	p value
4 months	50/270 (19%)	68/255 (27%)	1.7 (1.1–2.5)	0.019
8 months	61/263 (23%)	75/252 (30%)	1.4 (1.0–2.2)	NC
12 months	86/261 (33%)	95/255 (37%)	1.2 (0.9–1.8)	NC
Average of 4, 8, and 12 month effects*	1.6 (1.0–2.6)	0.035

Data are n/N (%) unless otherwise stated. All analyses are adjusted by site (Bristol, Sheffield, or Southampton) and baseline PHQ-9 score. GP practice is included as a random effect. NC=not calculated at individual timepoints; analysis plan specified repeated measures analysis. *Based on a repeated measures analysis that was additionally adjusted by follow-up timepoint as a categorical variable.

Table 2: Repeated measures analysis of treatment response as a binary outcome

	Usual care		Intervention plus usual care		Adjusted difference in means (95% CI)	p value
	Patients with data available	Unadjusted mean (SD)	Patients with data available	Unadjusted mean (SD)		
PHQ-9 score (continuous outcome)						
Baseline	302	16.7 (4.7)	307	17.1 (4.5)	..	NA
4 months	270	13.8 (6.2)	255	13.3 (6.1)	-0.8 (-1.8 to 0.1)	NC
8 months	263	13.4 (6.2)	252	12.4 (6.2)	-1.2 (-2.2 to -0.3)	NC
12 months	261	11.9 (6.4)	255	11.6 (6.2)	-0.5 (-1.5 to 0.5)	NC
Average of 4, 8, and 12 month effects*	-0.8 (-1.6 to 0.0)	0.045
Generalised anxiety (GAD-7) ²¹	237	9.2 (5.8)	223	8.7 (5.5)	-1.1 (-2.0 to -0.2)	0.019
Quality of life (EQ-5D-5L) ²²	227	0.564 (0.30)	219	0.569 (0.30)	-0.003 (-0.04 to 0.04)	0.896
Satisfaction with treatment†‡	184	3.3 (0.9)	193	3.7 (0.9)	0.5 (0.3 to 0.6)	<0.001
Difficulties with obtaining access to care†‡	232	4.2 (1.9)	216	4.5 (1.9)	0.3 (0.0 to 0.6)	0.038
Satisfaction with amount of support received†‡	177	2.1 (0.9)	185	2.6 (0.8)	0.6 (0.4 to 0.7)	<0.001
Self-management skills and self-efficacy (heiQ) ²³	235	2.4 (0.9)	221	2.5 (0.9)	..	
Physical activity† (heiQ health-directed behaviour scale)	237	2.4 (0.9)	221	3.0 (0.5)	0.1 (<0.0 to 0.2)	0.118
Self-monitoring and insight†	238	2.6 (0.6)	221	2.7 (0.6)	0.1 (0.0 to 0.2)	0.005
Constructive attitudes and approaches†	239	2.6 (0.5)	221	2.8 (0.5)	0.0 (-0.1 to 0.1)	0.480
Skill and technique acquisition†	238	2.8 (0.6)	220	2.9 (0.6)	0.2 (0.1 to 0.2)	0.001
Health services navigation†	179	3.4 (0.9)	173	3.2 (1.1)	0.2 (0.1 to 0.3)	<0.001
Adherence to antidepressant medication (Morisky) ²⁴ †	235	3.7 (0.8)	220	3.9 (0.8)	-0.1 (-0.2 to 0.1)	0.511
Health literacy (eHEALS) ²⁵ †	174	..	0.2 (0.1 to 0.4)	<0.001
Care coordination (Haggerty) ²⁶	176	3.1 (2.2)	179	3.5 (2.4)	..	
Role clarity and coordination†	236	3.1 (1.0)	219	3.2 (1.0)	-0.1 (-0.2 to 0.1)	0.361
Evidence of a care plan†	230	3.2 (1.2)	210	3.1 (1.2)	0.3 (-0.1 to 0.8)	0.173
Overall experience of organisation of health care†	0.1 (-0.1 to 0.3)	0.247
Self-organisation of health care†	0.0 (-0.2 to 0.2)	0.841

All analyses are adjusted by site (Bristol, Sheffield or Southampton), baseline outcome (if measured) and baseline PHQ-9 score. GP practice is included as a random effect. PHQ=patient health questionnaire. heiQ=Health Education Impact Questionnaire. NC=not calculated at individual timepoints; analysis plan specified repeated measures analysis. NA=not applicable. *Based on a repeated measures analysis that was additionally adjusted by follow-up timepoint as a categorical variable. †Higher score is more positive (fewer access difficulties, greater satisfaction). ‡Based on scales generated before the main trial analysis using principal components analysis and incorporating questions taken from existing validated questionnaires or constructed for this research.

Table 3: Secondary outcomes and measures used to assess them

Table 3 shows the findings for the secondary outcomes, except for use of telehealth interventions, which is shown in the appendix (p 7). The intervention was associated with improvements in anxiety, as assessed with the GAD-7 instrument.²¹ It was also associated with improvements in several measures of self-management skills and attitudes and improved health literacy.²⁵ Participants in the intervention group expressed greater satisfaction with access to health care, treatment, and amount of support they received. There was no evidence of improved adherence with antidepressant medication or improved care coordination (table 3) or that participants made more use of other health-related technologies (appendix p 7). For ease of presentation, table 3 only shows data about secondary outcomes after 12 months' follow-up. Details of findings after 4 and 8 months are available in the appendix (p 8).

Use of the intervention varied considerably, with some participants dropping out after a few calls while others completed the complete course of telephone calls. Figure 2 shows the number of Healthlines encounters with intervention participants out of a maximum of

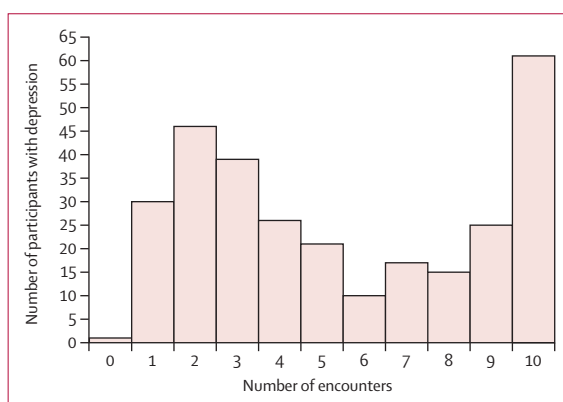


Figure 2: Distribution of Healthlines telephone encounters from 295 patients
Data about use of the intervention were missing for 12 participants who received the intervention.

ten encounters. The median number of encounters was five (IQR 2–9, 295 participants had available data), mean encounter duration was 18.5 min (SD 12.7), and there was a total of 1972 encounter calls.

	PHQ-9 response at 12-month follow-up		Partial compliers classified as non-compliers	Partial compliers classified as full compliers
	Usual care	Intervention plus usual care		
No intervention received (0–2 encounters started)	86/261 (33%)	16/52 (31%)
Partial intervention received (3–8 encounters started)	..	42/111 (38%)
Full intervention received (9–10 encounters started)	..	36/86 (42%)	1.9 (0.99–3.48)	1.3 (0.87–1.95)

Data are n/N (%) or unadjusted odds ratio (95% CI). We estimated the effect among compliers at 12 months because this was the scheduled duration to receive the entire intervention. Three participants who never received the Healthlines intervention and one participant who only received an unscheduled non-encounter call are categorised as receiving none of the intervention. 12 participants had missing encounter data.

Table 4: Complier-average causal effect analysis at 12 months

Only 86 (28%) of 307 of participants in the intervention group received at least nine of the potential maximum of ten telephone encounters. Table 4 shows the crude estimated effect at 12 months among compliers, after classifying partial compliers in the intervention group as either non-compliers or full compliers. The results suggest an increase in effect when compliance is defined as completion of most or all of the Healthlines encounters.

Use of different components of the intervention also varied. Generally, sustained usage was low, although some individuals used the resources extensively. Out of 285 participants in the intervention group with valid data, 237 chose to use the online computerised CBT programme (LLTFi) and 53 chose to follow the book (eight individuals used both). Of those choosing LLTFi, 204 participants logged on to the website and completed a median of two (IQR 0–5) of the seven modules. 66 participants who logged on did not complete the first module. 98 participants registered with Big White Wall and logged on to the website at least once. The median number of logins was two (range 1–104), the median number of interactions (posts) was zero (range 0–49), and the time spent on the site was 0.30 h (range 0.00–11.17).

In a prespecified exploratory analysis of the process of care, participants in the intervention group had slightly more primary care consultations during 12 months (mean 15.4, SD 11.0) than did those in the control group (mean 14.3, SD 12.5; adjusted incidence ratio 1.07, 95% CI 0.96–1.19, $p=0.22$). There were no differences between the intervention and control groups in the proportion of participants who had been prescribed an antidepressant during the trial, the number of changes in antidepressant type or dose, or the number of participants who were taking an antidepressant at follow-up (appendix p 11).

During the course of the trial, 70 adverse events were reported by participants (36 in the usual care group and 34 in the intervention group), of which one was related to the intervention (increased anxiety from talking about depression) and was not serious (appendix p 12). Two patients died (one due to COPD and one due to throat cancer), both in the usual care group.

Discussion

This report describes a large pragmatic trial of the Healthlines depression service, a novel approach to the delivery of health care through a combination of various technologies to improve treatment and self-management, supported by lay staff, and integrated with the health-care system. The intervention was clinically effective, leading to improved response to treatment at 4 months' for participants receiving the intervention plus usual care compared with those receiving usual care alone, and the size of the effect is important, with a number needed to treat of 12. Furthermore, compared with participants who received usual care alone, participants who received the intervention reported reduced anxiety, improved access to health support and advice, greater satisfaction with the treatment and the amount of help they received, and improvements in self-management attitudes and skills.

The effect of the intervention was greatest after 4 months of follow-up, and the difference between the intervention and usual care groups narrowed with time as both groups improved. After 12 months of follow-up, evidence suggested no benefit from the intervention, although an average benefit existed for the whole 12 month follow-up period. Therefore, the main effect of the intervention in terms of depression was increased speed of recovery, which is nevertheless important. However, only a few participants fulfilled our criteria for response to treatment, whether they received the intervention or usual care, and the mean PHQ-9 score was more than 10 in both groups at all timepoints, suggesting substantial residual symptoms. Notably, many participants had severe and enduring depression when they were recruited to the trial, most were taking antidepressants, and most remained symptomatic at the end of the trial. These results suggest that many participants had so-called treatment-resistant depression, which is unsurprising, since this pattern of a long history of depression and poor treatment response is typical of patients managed in primary care. More than three-quarters of patients treated with antidepressants in primary care for at least 6 weeks have clinically significant

residual symptoms because of complex reasons such as insufficient effect of or intolerance to medication, non-adherence, and undertreatment.²⁸ This evidence is consistent with the notion that depression is often a chronic disease and shows the challenge of improving care for patients with treatment-resistant depression.

Management options for treatment-resistant depression include changes of medication, increased dosage, addressing of non-adherence, or addition of psychological therapy. This Healthlines intervention was designed to address all of these issues, for example through strategies to promote adherence, offering computerised CBT, and sending guidance to GPs about changes to medication. Our data suggest that the proposed mechanisms of action were only partly achieved, with no evidence of improved medication adherence or that GPs were more active in changing medication. Many participants only used some components of the intervention to a small extent, and only a few received the full course of telephone consultations that formed the core of the intervention. However, some participants engaged with the intervention extensively, and our analysis suggested that adherence to the intervention was associated with enhanced effectiveness.

Therefore, it is likely that the main mechanisms of effect were the support and motivation received from the Healthlines advisers to improve self-management, along with the addition of computerised CBT to existing drug treatment. To improve effectiveness of the intervention, exploration of ways to improve communication with primary care will be necessary to improve medication optimisation. Such exploration might be easier outside of a research context once the intervention is well established and has been normalised within the health-care system. To improve patient engagement, prescreening might be beneficial to target the intervention at those who would be most interested in using this approach.

Findings from systematic reviews^{6–10} have suggested positive effects on patient outcomes from various specific telehealth interventions for depression, although some investigators have pointed out methodological limitations in the evidence base, including the abundance of small feasibility studies, assessment of a small range of outcomes, and only short-term follow-up. Another systematic review⁸ described the evidence for internet-supported treatment for depression as promising but inconclusive. Several trials of computerised CBT for depression have had positive results, but these have had limitations and a high quality trial of two computerised CBT packages with regular telephone support showed no evidence of benefit from either package compared with usual GP care.²⁹ Very few pragmatic trials have been done to study system-level telehealth interventions for depression that integrate various technologies and new ways of working implemented by non-clinically trained staff. Our study helps to fill this evidence gap.

The most similar previous study, which was done in the USA, was based on a so-called collaborative care model. Care managers were provided with a web-based clinical decision-support system, but the intervention did not make use of any other telehealth approaches.³⁰ The adjusted odds ratio for treatment response was 1.9 (95% CI 1.09–3.45) at 6 months follow-up, similar to the estimate of treatment response at 4 months in this UK-based Healthlines trial (1.7, 95% CI 1.1–2.5). Several studies of other collaborative care interventions have been done that often involve telephone follow-up from case managers, but have not included the integrated use of internet or other telehealth resources, which is a defining characteristic of the Healthlines intervention. A Cochrane review³¹ estimated that the risk ratio for response from collaborative care for depression was 1.32 (95% CI 1.22–1.43) in the short term (0–6 months) and 1.31 (95% CI 1.17–1.48) in the medium term (6–12 months). The findings from our trial are similar to these results, but slightly more positive (the observed adjusted odds ratio at 4 months follow-up equates to a risk ratio of 1.5, 95% CI 1.1–1.9).

This trial has several strengths, including a large sample size, inclusion of participants with a confirmed diagnosis of depression, the high proportion of participants retained, and recruitment from multiple sites. The study is highly pragmatic, testing a new approach to care based on telehealth, which could be quickly and easily rolled out nationally. The intervention was carefully developed with an evidence-based conceptual model that helps us to explore causal mechanisms and provides a framework for development and evaluation. Alongside the trial, we did parallel process and economic assessments that will be reported separately.

The study also has several limitations. First, only a small proportion of those patients sent information about the trial expressed interest in participating. Targeting of the initial mailing to the population of patients meeting our severity criteria for depression was not possible. Therefore, we cannot establish how many of the individuals who did not respond to the invitation would not have been eligible because they did not have depression or would not meet severity criteria and how many were not interested in the intervention or did not wish to participate in this research study. Absence of interest or ability to use the intervention is not necessarily a threat to external validity, because we recognise that telehealth interventions are not necessarily suitable or of interest to everyone. However, if those responding to the invitation to participate in the research are unrepresentative, the findings might not be generalisable. If the intervention was implemented widely, it is possible that people with different characteristics or severity of depression would take it up, but whether the benefit would be greater or less than that we observed is impossible to know. This problem of low recruitment is common to other large trials of depression in primary

care, which have recruited patients by use of similar methods.^{28,32} In this trial, once eligibility had been confirmed, the proportion of eligible individuals who agreed to participate was high (84%).

Another limitation is the high proportion of participants who received less than a full course of encounters with the health adviser. This problem is also common in other telehealth interventions for depression.⁹ In this trial, the missed encounters might have occurred for various reasons; some individuals chose not to continue with the telephone calls (possibly because they got better), some became uncontactable, and others missed encounters because of the closure of NHS Direct. These findings might help to explain the positive benefit seen when response to treatment (based on the PHQ-9 score) was treated as a binary outcome, yet minimal change seen when the PHQ-9 score was treated as continuous. This result suggests that a proportion of individuals benefited from the Healthlines service, but many people did not, which would be consistent with the finding that one group of individuals dropped out of the service after just two or three encounters and another group completed the course and with the finding that those who completed the course gained most benefit. A further limitation was that, although the overall retention was high, the retention rate differed slightly between the intervention and usual care arms. However, multiple imputation of missing primary outcome data had no effect on the findings, so we think that it is unlikely that differential attrition could explain our results.

Our findings show that it is feasible and effective to provide a scalable intervention for depression delivered by non-clinically trained advisers working with computerised algorithms and encouraging people to make use of the wide range of help available from the internet. Such an intervention makes it possible to substantially expand provision of care without being limited by the availability of clinically trained staff, which would help to meet the pressing need to expand services for common mental health problems. Although the absolute benefit from this intervention in terms of clinical outcomes is small, the number of patients with the potential to benefit is very large and the results are sufficiently promising to justify further development of the intervention to improve its acceptability and effectiveness. Further research should explore the benefits of interventions based on a similar model for other chronic disorders.

Contributors

CS, AO'C, SH, JN, SL, LY, GL, AR, CP, and AAM developed the protocol for the study, obtained funding, provided methodological advice and supervised the conduct of the trial. CS led protocol development and the funding application, acted as chief investigator with overall responsibility for the conduct of the trial, and led the drafting of the Article. AO'C supervised the conduct of the trial in Sheffield. CT, M-SM, and LE acted as trial managers, coordinating the conduct of the trial across the centres. LE, AF, KG, and KH recruited patients and did the follow-up, data collection, and data entry. DG developed the statistical analysis plan and did the statistical analysis. PD contributed to the statistical analysis. SL coordinated development and delivery of the intervention with NHS

Direct. AAM supervised the statistical analysis. All authors contributed to decision making throughout data collection, analysis, interpretation, and reporting and approved the final version of this manuscript.

Declaration of interests

CS, GL, AO'C, and JN act as members of various boards for the National Institute for Health Research (NIHR) but were not on the board that commissioned this project. The other authors declare no competing interests.

Acknowledgments

This report summarises independent research funded by the NIHR under its Programme Grant for Applied Research (Grant Reference Number RP-PG-0108-10011). The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the NIHR, the NHS or the Department of Health. We thank all the patients, health care professionals, Health Information Advisers, and other NHS Direct staff who contributed time and effort to make this trial possible. We are grateful to Dr Sarah Williams at Solent NHS Trust who took over responsibility for hosting the intervention when NHS Direct closed and Steve Bellerby, who managed implementation of the Healthlines software at both Trusts. We thank the members of the Trial Steering and Data Monitoring Committees, particularly Michelle McPhail and Anne Jacob who were Patient and Public representatives. We thank the Big White Wall and Living Life to the Full Interactive for use of these programmes, as well as providing anonymised data on participant usage. We acknowledge Tom Fahey and Simon Brownsell who were applicants on the research programme grant but not directly involved in this trial. We thank Chris Williams for advising about intervention development and contributing to the training of the advisers. We are grateful to the Primary Care Research Network (now, NIHR Clinical Research Network) for assisting us with general practice recruitment. We wish to acknowledge the work of Frederika Collihole, Richard Campbell, Ben Davies, Lorna Duncan, Diane Beck, and Janet Cooke who supported participant recruitment, data entry and trial administration. This study was designed and delivered in collaboration with Bristol Randomised Trials Collaboration, a UKCRC Registered Clinical Trials Unit in receipt of NIHR Clinical Trials Unit support funding. Copyright of the Healthlines telephone algorithms is held by Solent NHS Trust. The Living Life to the Full Interactive programme (copyright Media Innovations Limited) and the Big White Wall (copyright BigWhiteWall Ltd) were used with permission.

References

- 1 NHS England. Technology Enabled Care Services (TECS). 2015. <http://www.england.nhs.uk/ourwork/qual-clin-lead/tecs/> (accessed April 14, 2015).
- 2 Wootton R. Twenty years of telemedicine in chronic disease management—an evidence synthesis. *J Telemed Telecare* 2012; 18: 211–20.
- 3 Flodgren G, Rachas A, Farmer Andrew J, Inzitari M, Shepperd S. Interactive telemedicine: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*, 2015. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002098.pub2/abstract> (accessed Dec 30, 2015).
- 4 Five Year Forward View 2014. <https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf> (accessed Dec 30, 2015).
- 5 National Institute for Health and Care Excellence. Depression in adults: the treatment and management of depression in adults. CG902009. <http://www.nice.org.uk/CG90> (accessed Oct 8, 2015).
- 6 Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: a meta-analysis. *Clin Psychol (New York)* 2008; 15: 243–53.
- 7 Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cogn Behav Ther* 2009; 38: 196–205.
- 8 García-Lizana F, Muñoz-Mayorga I. Telemedicine for depression: a systematic review. *Perspect Psychiatr Care* 2010; 46: 119–26.
- 9 Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clin Psychol Rev* 2012; 32: 329–42.
- 10 Saddichha S, Al-Desouki M, Lamia A, Linden IA, Krausz M. Online interventions for depression and anxiety—a systematic review. *Health Psychol Behav Med* 2014; 2: 841–81.

- 11 Vassilev I, Rowsell A, Pope C, et al. Assessing the implementability of telehealth interventions for self-management support: a realist review. *Implement Sci* 2015; **10**: 59.
- 12 Segar J, Rogers A, Salisbury C, Thomas C. Roles and identities in transition: boundaries of work and inter-professional relationships at the interface between telehealth and primary care. *Health Soc Care Community* 2013; **21**: 606–13.
- 13 Edwards L, Thomas C, Gregory A, et al. Are people with chronic diseases interested in using telehealth? A cross-sectional postal survey. *J Med Internet Res* 2014; **16**: e123.
- 14 Salisbury C, Thomas C, O’Cathain A, et al. Telehealth in CHronic disease: mixed-methods study to develop the TECH conceptual model for intervention design and evaluation. *BMJ Open* 2015; **5**: e006448.
- 15 Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. *Manag Care Q* 1996; **4**: 12–25.
- 16 Thomas CL, Man M-S, O’Cathain A, et al. Effectiveness and cost-effectiveness of a telehealth intervention to support the management of long-term conditions: study protocol for two linked randomized controlled trials. *Trials* 2014; **15**: 36.
- 17 Kroenke K, Spitzer R, Williams JW. The PHQ-9 validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606–13.
- 18 Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol Med* 1992; **22**: 465–86.
- 19 Williams C, Wilson P, Morrison J, et al. Guided self-help cognitive behavioural therapy for depression in primary care: a randomised controlled trial. *PLoS One* 2013; **8**: e52735.
- 20 Williams C. Overcoming depression and low mood: a five areas approach. 3rd edn. London, UK: Hodder Arnold, 2009.
- 21 Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med* 2006; **166**: 1092–97.
- 22 EuroQol Group. EQ-5D-5L User Guide. http://www.euroqol.org/fileadmin/user_upload/Documents/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf (accessed March 31, 2016).
- 23 Osborne RH, Elsworth GR, Whitfield K. The Health Education Impact Questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. *Patient Educ Couns* 2007; **66**: 192–201.
- 24 Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; **24**: 67–74.
- 25 Norman DC, Skinner AH. eHEALS: The eHealth Literacy Scale. *J Med Internet Res* 2006; **8**: e27.
- 26 Haggerty JL, Roberge D, Freeman GK, Beaulieu C, Breton M. Validation of a generic measure of continuity of care: when patients encounter several clinicians. *Ann Fam Med* 2012; **10**: 443–51.
- 27 Altman DG. Missing outcomes in randomized trials: addressing the dilemma. *Open Med* 2009; **3**: e51–53.
- 28 Wiles N, Thomas L, Abel A, et al. Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: the CoBaIT randomised controlled trial. *Health Technol Assess* 2014; **18**.
- 29 Gilbody S, Littlewood E, Hewitt C, et al. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *BMJ* 2015; **351**: h5627.
- 30 Fortney JC, Pyne JM, Edlund MJ, et al. A randomized trial of telemedicine-based collaborative care for depression. *J Gen Intern Med* 2007; **22**: 1086–93.
- 31 Archer J, Bower P, Gilbody S, et al. Collaborative care for depression and anxiety problems. *Cochrane Database Syst Rev* 2012; **10**: CD006525.
- 32 Richards DA, Hill JJ, Gask L, et al. Clinical effectiveness of collaborative care for depression in UK primary care (CADET): cluster randomised controlled trial. *BMJ* 2013; **347**: f4913.