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Improving Distress in Dialysis (iDiD): A feasibility two arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without telephone support for psychological distress in haemodialysis patients

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Abstract

Introduction: Psychological distress is common in End-Stage Renal Disease (ESRD) and is associated with poorer health outcomes. Cognitive-behavioural therapy (CBT) is recommended in UK clinical guidelines for the management of depression in people with long-term conditions (LTCs). Online CBT based treatments offer a pragmatic solution for under-resourced renal services. However the application CBT treatment principles to the psychosocial needs of ESRD patients requires a degree of tailoring to ensure appropriate application. This study seeks to explore the feasibility and acceptability of implementing a two-arm parallel randomised controlled trial (RCT) of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in haemodialysis patients.

Methods: Patients will be screened for depression and anxiety whilst attending for their haemodialysis treatments. We aim to recruit sixty adult haemodialysis patients who meet criteria for mild to moderately severe symptoms of depression and/or anxiety will be individually randomised using a computer generated 1:1 sequence ratio with allocation concealment by automated email to patients on completion of their online baseline questionnaire. Patients will be randomised to either online CBT with telephone support from a therapist (intervention arm) or online CBT with no telephone support (control arm). Outcomes include feasibility and acceptability data on rates of recruitment, randomisation, retention, and treatment adherence. We will also explore change in self-report measures of depression (Patient Health Questionnaire-9), anxiety (Generalised Anxiety Disorder-7), quality of life (Euro-QoL), service use (client service receipt inventory), and illness cognitions (brief illness perception questionnaire). A qualitative process evaluation will also be conducted.

Ethics and dissemination: An NHS research ethics committee approved the study. Data from this study will provide essential information for the design and testing of further interventions to ameliorate distress in dialysis patients and will be of interest to patients the renal multi-disciplinary team.

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Keywords: End-stage renal disease, haemodialysis, cognitive-behavioural therapy, psychological distress, online therapy, online treatment, computerised therapy

Introduction

End-stage renal disease (ESRD) is a chronic condition that permanently affects kidney function (1). Without treatment with renal replacement therapy (e.g. dialysis or transplantation) a person's physical health would rapidly deteriorate because of the build-up of toxins and waste products in the body (2). In 2013, 56,940 adults in the UK were receiving renal replacement therapy (3) accumulating direct physical health care costs of £27, 000 per patient, per year (4). The treatment of ESRD is not only costly but burdensome for patients, requiring adherence to dialysis regimens, prescribed medications, diet and fluid restrictions, and regular attendance at health care appointments (5).

Psychological distress is common in ESRD, with an estimated prevalence of 39% among people in receipt of dialysis (6). When psychological distress co-occurs alongside ESRD higher rates of mortality (7) and health care utilisation (8) are observed. The application of UK clinical guidelines for psychological distress management in chronic physical health problems specifically to people with ESRD is fraught with difficulties (9). First, the safety and efficacy of pharmacotherapy in managing psychological distress among people with ESRD remains unclear, because of a lack of robust randomised controlled trials (10). Second, whilst talking therapies likely offer a safer alternative to pharmacotherapy because they target non-biological causal pathways, reducing the potential for contraindicated treatments, their efficacy in the ESRD population is largely unknown. Only two small scale, non-UK based, randomised controlled trials (RCTs) have examined the efficacy of cognitive behavioural therapy (CBT) relative to usual care among haemodialysis patients (11, 12). Both trials found CBT was effective in reducing psychological distress. These findings are consistent with larger scale RCTs of CBT treatments for depression in people with coronary heart disease (13).

However the NHS has limited resources to allow the demand for CBT therapist time to be met adequately. A practical approach to address this problem is to implement a stepped care health service delivery model (14). Within this model a person suffering from psychological distress is initially offered the "least restrictive" evidence based treatment

available, for example, guided self-help treatment materials in the form of treatment manuals or computer therapy packages. Individuals begin their treatment with low-intensity interventions unless their distress is deemed too severe to benefit from the type of minimal intervention offered. The concept "least restrictive" means that there is decreased treatment burden for patients, but equally health services can treat a larger volume of patients, by offering less intensive treatment interventions. If necessary a patient is "stepped up" to receive more intensive treatments to manage their distress after the initial low-intensity treatment.

Guided self-help CBT treatments are effective in the management of psychological distress in people with (15) and without co-morbid physical health conditions (16). Furthermore, on-line/computerised self-help resources offer a greater degree of personalisation, presenting only information that is relevant to the needs of the patient based on their responses to specific questions. This allows better management of informational needs and encourages active engagement, thus fostering a sense of personal control from the patient (17). Indeed, in people without physical health conditions, online/computerised guided self-help treatments have largely demonstrated equivalence with face-to-face psychological interventions in terms of their clinical effectiveness (depression and anxiety) (18) and degree of adherence to treatment sessions (19). The degree of efficacy of online self-help interventions for improving symptoms of distress among people with chronic physical health conditions remains mixed (20). Overall, self-help interventions that included a CBT treatment model effectively reduced distress (20).

However there are a number of factors that determine the efficacy of online/computerised self-help treatments. One moderating factor is whether support is provided by a health care professional. Dovetailing online/computerised self-help treatments with support from health care professionals improves outcomes and prevents treatment drop-out (21, 22). The type of support provided is also important. Studies that provided technical/administrative support to overcome practical barriers with online/computerised self-help treatments have demonstrated poorer clinical outcomes compared with studies that used qualified therapists or health care professionals trained to deliver psychological treatments (22). However, the difference of effect was statistically non-significant but this was likely because of an absence of statistical power not an absence of effect per se. A recent RCT explored the

efficacy of online CBT with weekly technical/motivational support telephone calls from a non-clinician for the management of depression and compared it with usual GP care (23). Its findings confirmed that providing patients with access to online CBT with only technical support had no added benefit on depression outcomes compared with GP usual care.

It seems likely that access to a skilled therapist is especially important in the context of co-morbid mental and physical health conditions because of the potential for treatment antagonisms, whereby the effective management of a person's mental health has the potential to dysregulate the management of physical health or vice versa (24). However, individual differences can also determine a person's perceived need for support from a health care professional. A qualitative meta-synthesis of online/computerised therapies for depression and anxiety identified conflicting user experiences (25). Positive experiences included feelings of empowerment, independence, and anonymity, whilst negative experiences included perceived treatment burden from the online/computerised treatments and feelings of isolation because of a lack of human interaction.

Given that the evidence points to the efficacy of online/computerised treatments with therapeutic support for the management of psychological distress in people with and without physical LTCs; it remains uncertain whether these findings apply to the management of psychological distress in UK NHS haemodialysis treatment settings. An online CBT treatment intervention designed to manage psychological distress in people on haemodialysis has the potential to offer both a pragmatic and effective treatment for the management of psychological distress in ESRD. This study seeks to explore the feasibility and acceptability of implementing a two arm parallel RCT of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in people receiving haemodialysis treatments within a stepped care health service delivery framework.

Background to the study

The development of the improving distress in dialysis (iDiD) online CBT treatment involved a multi-disciplinary team of health psychologists, clinical psychologists, psychiatrists, nephrologists, and six patient and public involvement representatives. The preliminary content of the website was initially determined by self-help resources used to manage

adjustment outcomes in LTCs implemented in previous trials by one of our authors (RMM) (26-28). In addition, a literature review of the correlates of distress in dialysis was used to develop an ESRD specific CBT treatment model (29). The content of each online treatment session was first drafted on paper and reviewed by the research team. Once approved by the research team, patient representatives provided feedback on the relevance and ease of understanding of the information and CBT intervention techniques described in each of the treatment sessions. Any issues raised within each session were incorporated into the development of subsequent sessions. The informational and CBT content was then uploaded onto an online platform using LifeGuide software (30). Advice was given from (LY) regarding how to tailor information and CBT intervention techniques shown to individuals based on their responses to specific questions/options on the website. This allowed the generation of an interactive online therapy tool that was responsive to the needs of patients. The presentation and navigation through the website was tested using patient representatives and "think-aloud" techniques. This process occurred iteratively so that comments on early sessions could be incorporated into the design of subsequent sessions.

The website includes a total of seven sessions. The content of each session is summarised in Table 1. For more detailed information about the cognitive-behavioural content of the sessions see our distress in dialysis CBT treatment model (29). Patients are encouraged to complete one session per week and each session was designed to last approximately one hour in duration. In brief, the first two sessions are psycho-educational providing specific information about ESRD, its management and the potential for this to impact on mood. Patients generate their own personal model of distress consisting of ESRD specific triggers, feelings, thoughts, behaviours, and physical symptoms. The remaining four sessions target components from the patients self-generated personal model of distress including: implementing positive coping strategies for dealing with emotions (e.g. acceptance, exposure, expression), thought challenge techniques, problem solving, behavioural activation, sleep, and assertiveness skills training for managing difficult social relationships. At the end of each online session, patients are encouraged to set a goal to complete over the next week. A variety of goals are displayed relevant to the content shown in the online session the patient is working on. After selecting a goal, the patient is encouraged to make an action plan. All goals are stored to a specific "My tasks" area on the website. Each time

the patient logs onto the website they are asked to review their progress with their goals. The "My tasks" function allows patients to track their progress as they work through the website and store any information they have found particularly useful. The final session concentrates on relapse prevention where patients reflect on the skills they have learnt over the six sessions and generate action plans to sustain these behaviours moving forward.

Objectives

The following aims will be addressed as part of the feasibility and acceptability study of a parallel RCT of online CBT with therapist led telephone support vs online CBT without telephone support, delivered within a stepped care framework among outpatient haemodialysis patients with co-morbid psychological distress.

1. To assess the feasibility and acceptability of screening all patients who attend for haemodialysis. Patients will be screened for depression and anxiety using standardised measures presented on iPADs. The presence of psychological distress is often not identified by non-mental health trained clinicians (31). Implementing screening questionnaires for psychological distress in medical settings can promote its detection (32) and ultimately the provision of mental health care. We will quantify number of people who agree to be screened.
2. To explore rates of recruitment and retention into the trial.
3. To examine willingness to be randomised to either the intervention arm (with telephone support) or control arm (with no telephone support) by recording participant reasons for non-consent into the study (if disclosed).
4. To explore the level of adherence to online treatment sessions and telephone support calls (intervention arm only).
5. To explore the potential efficacy of an on-line intervention with therapist led telephone support in reducing psychological distress when compared with website alone to inform the planning of a future full-scale trial to detect clinically meaningful change in psychological distress outcomes.

6. To examine if change in quality of life differs between the intervention group (online intervention plus therapist led telephone support) and control group (online intervention only)
7. To provide a preliminary assessment of the cost-effectiveness of the intervention.
8. To examine the pre-post difference in ESRD illness cognitions and whether their effect differs between the intervention and control arm (online intervention only).
9. To qualitatively explore patient perceptions of the acceptability and usability of the website and telephone support calls and identify areas of improvement for future interventions.

Methods

Design

A two parallel armed randomised controlled trial (RCT) with participants randomised using a 1:1 ratio computerised algorithm at the level of the individual and a nested qualitative study.

Setting and participants

Participants will be recruited from haemodialysis units at Guy's and St Thomas' hospital (London, UK).Participants will be eligible for inclusion if:

1) Aged 18 years or over and receive hospital haemodialysis three-times weekly.
2) They have mild to moderately severe depressive symptoms (based on PHQ-9 (33) scores of 5 to 19; a self-report measure of depression) and/or presence of mild to moderate anxiety symptoms (based on GAD-7 (34) scores of 5-14).
3) They speak English sufficiently well to engage with screening tools.
4) They have a basic understanding of how to use the Internet and an email address.

Participants will be ineligible if:

1) They currently receive active treatment for depression and/or anxiety. We consider active treatment, as any current psychological treatments (talking therapies) or receipt of a new anti-depressant and/or anti-anxiety medication. A medication is considered new if commenced three months prior to the completion of the depression and anxiety screening questionnaire. A participant will become eligible

for the study once three months has elapsed from commencing their anti-depressant and/or anti-anxiety medication.

2) They have a severe mental health disorder, for example, psychosis, bi-polar disorder.
3) They have active suicidal thoughts, as indicated by a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself".
4) They have evidence of addiction to alcohol or drugs.

A participant will be withdrawn from the study if:

1) There are safety concerns in relation to their physical or mental health.
2) The participant chooses to withdraw from the study.
3) A patient's level of psychological distress deteriorates.

Flow of recruitment and participant timeline

Participants will be identified for inclusion using web-based screening questionnaires routinely used as part of the Integrating Mental and Physical healthcare: research, training and services (IMPARTS) initiative at Guy's and St Thomas' hospital (35). Face-to face screening will occur by a renal dialysis nurse or a member of the research team. Participants consenting to the screen will be assessed for depression and anxiety using the PHQ-9 (36) and GAD-7 (34) respectively. The PHQ-9 is a nine item self-report questionnaire deemed acceptable for the identification of depression in medical care settings, including specialist settings (32). Likewise, the GAD-7, is a self-report seven item questionnaire with evidenced criterion validity for the detection of generalized anxiety disorder (34). The patient will complete the web-based questionnaires either alone or with the assistance of a renal nurse/researcher. Whilst completing the screening questionnaire, patients will be asked to give their permission (yes/no) for a member of the research team to contact them about the present study.

Results from the screening questionnaires are uploaded onto the patient's electronic medical record, which will be checked by the nursing team/researcher for immediate risk. Risk is defined as a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself". If suicidal ideation is detected then a risk assessment will be performed to determine the immediacy of referral to either liaison

psychiatry or renal clinical psychology. Level of risk will be assessed in line with the IMPARTS risk assessment protocol. This includes enquiring about degree of suicidal ideation and level of hopelessness, whether active plans are present, enquiring about the patient's history of suicidal attempts, recent life stressors, protective factors, and degree of social support. The outcome of the risk assessment will be immediately discussed with either the renal clinical psychologist or liaison psychiatrist and a management plan will be put into place.

All anonymised screening results will be securely emailed from the IMPARTS database to the iDiD research team, on a weekly basis. A stratified stepped care model, according to the criteria outlined in Figure 1 will be applied to the anonymised data to identify potentially eligible participants for the study. The stratified stepped-care approach assigns individuals to treatments of varying intensity based on the severity of their symptoms (37). PHQ-9 scores within the range of 5-19, are considered indicative of mild to moderately severe symptoms of depression (36). Likewise, GAD-7 scores within the range of 5 to 14 indicate the presence of mild to moderately severe anxiety (34). Individuals with mild to moderately severe symptoms of depression and/or anxiety will be considered appropriate for treatment with the iDiD online CBT treatment and for inclusion in this study. Individuals with moderate to severe depression (PHQ-9 score ≥ 20) and/or anxiety (GAD7 score ≥15) or individuals with evidence of current suicidal ideation are considered inappropriate for the iDiD online CBT intervention. These patients will be referred and managed by either the renal clinical psychology team or liaison psychiatry. Finally, any individuals who are identified as having current suicidal ideation and severe depression (PHQ-9 score ≥ 20) will receive an urgent referral to liaison psychiatry.

Individuals who meet the criteria for mild to moderately severe symptoms of depression and/or anxiety will have their data de-anonymised providing they give us consent to contact them about the study. These potential participants will be screened against the remaining inclusion/exclusion criteria during weekly referral meetings with the research and clinical team. If they remain eligible then a researcher will approach the participant whilst they attend for dialysis to explain the study with the participant information sheet. Participants will be given a minimum of 24 hours to establish if they would like to take part.

All patients with mild to moderately severe symptoms of depression and/or anxiety who either: i) do not meet our remaining study inclusion criteria, ii) choose not to consent into the study, or iii) do not provide consent for us to approach them about the study, will be provided with the option of receiving usual care follow-up from the renal clinical psychology team. Usual care includes a face-to-face clinical assessment followed by a tailored psychological treatment intervention. Patients who decline psychological treatment will be issued with the renal clinical psychology service contact details and will be provided with advice on how to contact the team should they become concerned about their emotional health in the future.

As discussed above, patients who screen positive for moderate to severe symptoms of depression and/or anxiety (PHQ-9 score ≥ 20 and/or GAD7 score ≥15) will receive an automatic referral to the renal clinical psychology team. If upon clinical assessment by the renal clinical psychologist a moderate to severely depressed and/or anxious patient is deemed appropriate for the iDiD self-help study, then they will be "stepped down" for approach by the iDiD research team. Likewise, the research team will be informed by the renal clinical psychology team of any patients who meet the iDiD study inclusion criteria and declare an interest in the study despite initially stating during screening that they did not want to be contacted by the study team.

Participants who consent to take part in the study will be issued with an iDiD study identification number. A researcher will attend the dialysis unit and help the patient to sign-up to the iDiD online CBT treatment using an iPAD. At sign-up participants will be asked to enter their personal email address and select a password for use each time they logon. At the point of sign-up participants will also be asked to enter their NHS number (supplied to them by the researcher) to ensure that multiple iDiD accounts are not registered by the same participant. Participants will then receive a confirmatory email with a link to the iDiD website. After signing up, participants will complete the baseline questionnaires online. If baseline questionnaires are not completed, then participants will receive two reminder emails and an assistance based telephone call/visit at the dialysis unit. Participants will be informed of their randomisation process outcome immediately after completing the online baseline questionnaire. Participants will also receive an email confirming their treatment allocation. We anticipate the participant's journey through the study will last approximately

six months as summarised in Figure 2. We expect a period of one month to elapse from the point of screening to randomisation. Once participants are randomised, both groups will be able to access the iDiD website for a period of 12 weeks before being prompted to complete the follow-up questionnaires via email. The email will also advise participants that their access to the iDiD website is ending within a few weeks and to print off any information they have found helpful from the "My tasks" tab of the website. Two reminder emails and an assistance based telephone call/visit will occur over a period of three weeks if the follow-up questionnaires remain incomplete. After 20 weeks participants will receive an email thanking them for their participation in iDiD study. Access to the iDiD website will no longer be available after this time. On completion of the three months follow-up questionnaires a subsample of participants will be asked to complete a qualitative interview. We will follow-up participants for a period of approximately six months post their randomisation date to complete the interview.

Randomisation, allocation concealment, and blinding

Participants will be randomised to iDiD online CBT plus telephone support or iDiD online CBT only condition using Lifeguide software (a computerised random number generator with a 1:1 ratio). Because the randomisation sequence is automated by Lifeguide in real-time the allocation sequence is concealed from researchers. All baseline questionnaires will be completed online prior to randomisation. Participants will be randomised at the individual level. The trial co-ordinator will also receive an automated email informing them of the outcome of the randomisation procedure to identify participants who require telephone support calls during the trial. The researcher conducting the qualitative interviews will also be unblinded at follow-up to ensure that appropriate questions are asked in relation to telephone support calls. The statistician will remain blinded to treatment allocation.

Trial Intervention

All participants have access to the iDiD online CBT website (treatment content outlined in Table 1 and described in detail in our ESRD CBT Treatment Model (29)). Participants will be advised in the participant information sheet to logon to the website once a week. Participants will also receive weekly reminder emails to encourage engagement with the website. iPADs will be available for participants to use during their dialysis sessions.

iDiD online CBT website plus therapist led telephone support (Intervention arm)

Participants in the intervention arm of the trial will receive three 30 minute telephone support calls at weeks two, four, and six from a psychological wellbeing practitioner and a member of the research team (JH) who has a PhD in health psychology and has trained and worked as a psychological wellbeing practitioner (PWP). Psychological wellbeing practitioners typically work in primary care mental health service teams as part of the UK IAPT initiative (38). PWPs are trained to deliver low-intensity CBT based treatments including: cognitive restructuring, behavioural activation, problem solving, medication management, exposure therapy, and sleep management. The purpose of the telephone support calls are to promote engagement with the website and support the patient in collaboratively developing goals to work on using the resources and information available to them on the website. At the start of each telephone call the PWP will set an agenda with the participant and end the telephone call with a summary of the telephone support call and a shared goal for the participant to work towards. The first telephone support call is scheduled for when the participant should have completed online their own personal model of distress. The PWP will develop a shared understanding of the participants source of distress, provide empathy, reinforce with the participant the relationships between thoughts, feelings, and behaviours, and inform participants of the content the website which is likely most applicable to them as they continue to move forward with the website. The PWP and patient will develop a goal to work towards prior to their next telephone call.

The second telephone support call will provide an opportunity for the PWP to review with the participant their progress on their self-generated goals, work through a particular cognitive-behavioural intervention technique selected by the patient, and close the session with a shared goal to work towards with the help of the website in advance of the final telephone support call. The final telephone support call will follow a similar format to that of the second call except the telephone session will end with a relapse prevention plan. The plan will be generated collaboratively with the patient. All telephone support calls will be audio-recorded to provide intervention fidelity checks and for self-reflection during clinical supervision.

Clinical supervision

JH was trained to deliver the telephone support calls using role played sessions with feedback from RMM. Ongoing supervision will be provided by a renal clinical psychologist (AC). During supervision audio-recorded sessions will be listened to. Shared reflection on the PWPs telephone session will be discussed in line with the core competency framework for delivering psychological therapies in long-term conditions (39). Shared goals will be identified for the PWP to work towards over the course of the study. Supervision will also be an opportunity for case management. The PWP will discuss their proposed treatment plan in response to the first telephone support call and degree of patient progress at each supervision session. If a patient needs to be stepped up to receive more intensive psychological treatments then this will be initiated by the research team and managed by the renal clinical psychologist.

iDiD online CBT website with no telephone support (control arm)

Participants allocated to the control arm of the study will receive their usual renal care in addition to having access to the website. Usual care for individuals with ESRD managed with haemodialysis includes attending for dialysis three times per week for up to five hours at a time. Participants can be referred or self-refer into the renal clinical psychology service or primary care mental health service if their symptoms of depression and/or anxiety increase. We will ask participants in the three-month follow-up questionnaire whether they have commenced any new treatments for mental health since starting the study and this will be statistically accounted for.

Outcomes

Data collection and feasibility outcomes

Because this is a feasibility study our primary focus is to collect data on the feasibility and acceptability of the trial design and intervention by collecting descriptive data on *recruitment and retention rates and willingness to be randomised* according to CONSORT trial guidelines (40). We will also examine *adherence* to the online intervention and telephone support calls (intervention arm only). The degree of adherence to the online intervention will be automatically recorded by the Lifeguide software. We will calculate descriptive values for the mean number of sessions completed, the number of participants

who complete all sessions, the number of participants who complete 80% or more sessions, and the number of participants who complete each session (e.g. session 1, 2, 3 etc). Degree of adherence to the telephone call (intervention arm only) will be recorded by the psychological wellbeing practitioner. The following values will be calculated: mean number of telephone calls completed, number of participants who complete all telephone calls, number who complete 1 or more telephone call, number of participants who complete telephone sessions 1, 2, and 3 respectively, and mean duration of telephone calls across all three telephone support calls. In addition to a qualitative interview (described below) patients will be asked to self-report their experience of using the iDiD website at three months follow-up. The open-ended questions will enquire about: i) how useful they found the iDiD website and ii) whether they found the website easy to use. Participants will also be given the option to add any further comments.

Self-reported patient outcomes will also be collected via the iDiD website at baseline and three months follow-up. The assessment schedule completed by patients is summarised in Table 2 and described below.

- Continuous self-report measure of depression: PHQ-9(36) (described in detail above, scale range from 0 to 27, high scores indicate greater depressive symptoms)
- Continuous self-report measure of anxiety: (GAD-7) (34) (described in detail above, scale 0 to 21, high scores indicate greater anxiety symptoms).
- The five item EuroQoL (EQ-5D) (41) includes a five item measure of health status across the following domains: mobility, ability to self-care, ability to continue with activities (i.e. work, social life), pain, and anxiety and depression. In addition it has a visual analogue scale ranging from 0 to 100 where a person is asked to rate their overall health. The EQ-5D is recommended by NICE for use in cost-effectiveness evaluations (42).
- The Client Service Receipt Inventory (CSRI) (43) collects retrospective data on service use across the following five domains: i) background and client information (i.e. hospital admissions and discharge, frequency of GP visits, medications), ii) accommodation and living situation, iii) employment history, earnings, and other personal resources, iv) service receipt (i.e. hospital appointments, home help), and v)

receipt of informal care from caregivers. This information will be used in our cost-effectiveness evaluations.

- The brief illness perception questionnaire (BIPQ) (44) will assess participants self-reported beliefs about their ESRD and will provide an indication of whether participants beliefs about their ESRD change in response to clinical intervention. This information will be assessed at baseline and follow-up.
- Satisfaction with care will be evaluated using a 2-item scale that asks participants to rate their degree of satisfaction with the care they receive for their physical and mental health on a five-item Likert response scale. This information will be assessed at baseline and follow-up.
- Serious adverse events will be directly enquired about using self-report at follow-up only according to good clinical practice guidelines. Participants will be asked whether they have experienced any adverse events since starting the study choosing from a list of five options. If participants indicate they have experienced adverse events then they will be asked for details. In addition participants will be asked if they have experienced any adverse health effects since starting the study and encouraged to elaborate where needed.
- Treatments for depression and/or anxiety: Two brief self-report questions at follow-up will ask participants if they have received any pharmacological or psychological treatments for their depression and/or anxiety in addition to the iDiD website since starting the study.

Socio-demographic and clinical characteristics

Socio-demographic characteristics including: gender, age, ethnicity, home environment (marital status, housing situation, number of dependents) and level of education will be collected at baseline only via self-report. Likewise, clinical characteristics including: dialysis vintage and treatment history for depression and anxiety will be self-reported by patients at baseline.

Number and type of co-morbidities will be extracted from notes at baseline only. The following clinical outcomes and covariates will be extracted from notes at baseline and

follow-up: Kt/V (dialysis treatment adequacy), haemoglobin, serum albumin, C reactive protein, serum potassium levels, interdialytic weight gain, serum phosphate levels.

Qualitative interviews

Qualitative interviews with a sub-group of participants over the phone will be conducted post-intervention (three months) by a researcher who has not been involved in their treatment. These interviews will explore whether the intervention met patient expectations, positive and negative opinions about the website, whether patients felt they gained any benefit from using website, its personal relevance to them, and its acceptability as a treatment. A minimum of ten participants will be purposively sampled across a range of socio-demographic and clinical characteristics (e.g. treatment group, age, gender, ethnicity, dialysis vintage, degree of adherence to the intervention, degree of improvements in outcomes from the intervention). Interviews will continue until data saturation occurs. The outcomes of these qualitative interviews will help to revise our theoretical understanding of distress in dialysis and update the content of the intervention accordingly, in line with current medical research guidelines for process evaluations (45). Interviews will be transcribed verbatim and an inductive thematic analysis will be performed.

Sample size

The aim of this study is to explore the feasibility of implementing our trial procedures and to inform a power calculation for a future randomised controlled trial. We have calculated the sample size required based on the margins of error associated with the recruitment. The approximate size of the Guy's and St Thomas' dialysis population is 600 patients, in which we expect to be able approach 400. Assuming a conservative uptake rate of 50%, 200 patients will be screened with approximately 40% meeting the inclusion criteria (the estimated prevalence of depression symptoms in HD patients; see Palmer et al, 2013). If we assume 50% of those eligible will consent to be randomised a sample size of approximately 66 would allow us to estimate the true population consent rate with a 5% margin of error and a 95% confidence level.

Analysis plan

To examine the feasibility and acceptability of our screening, recruitment, retention, and randomisation process (objectives 1-3), we will quantify the flow of participants through the

study using frequencies and percentages in accordance with the consort flow diagram (40) shown in Figure 2. We will also record and quantify reasons for non-consent, exclusion, and drop-out for each stage of the study. We will examine degree of adherence to the intervention and telephone support calls (where applicable) using descriptive statistics (objective 4).

We will also perform an *exploratory* intention to treat mixed models analysis blind to treatment group on the following self-report outcomes at three months follow-up: depression, anxiety, and quality of life (objective 5 & 6). Variability in these patient outcomes will help to inform a future power calculation for a full-scale trial.

Service costs will be calculated by combining service use data with appropriate unit costs (46). These will be added to the costs of the intervention which will be based on development costs and the time spent providing telephone support. Costs will be compared between the two groups and cost-effectiveness assessed by combining the costs with the primary outcome measures and quality adjusted life years (QALYs) in the form of incremental cost-effectiveness ratios (ICERs). Uncertainty around the ICERs will be addressed using cost-effectiveness planes and acceptability curves (objective 7). We will also perform an exploratory process analysis using intention to treat mixed models to establish whether illness cognitions changed in response to the online intervention and whether differences occurred between the intervention and control group (objective 8). Qualitative interviews will be transcribed verbatim and analysed using thematic analysis to allow the feasibility and acceptability of the online intervention and telephone support calls to be explored (objective 9).

Ethics

This study has ethical approval from the NHS research ethics committee (14/LO/1934) and is sponsored by King's College London.

Data collection and management

The IMPARTS screening interface, developed by Teleologic Ltd, is web-based and installed on the server configuration already in use at King's College Hospital NHS Foundation Trust (KCH) for Teleologic specialty systems and has been extended to Guy's & St Thomas'

Hospitals NHS Foundation Trust. The patient logs on to the system with their unique Hospital Number. Their screening results are outputted to the documents folder of the Electronic Patient Record via the most secure wifi network within each NHS Trust. In addition, the system writes to a SQL Server database with documented table schema that is available for reporting and interrogation within the acute trusts' firewalls.

All quantitative outcomes are measured via online questionnaires that participants will access via iDiD website. The information is stored on a secure server associated with the Lifeguide program at the University of Southampton. The website prompts the participant when data is missing. Study data can only be downloaded from the server by members of the research team who are granted password access. All data will be confidentially stored in accordance with the data protection act (47) and King's College London data management procedures.

Formal committee

A trial management team will meet regularly to discuss the overall running of the study including: rates of recruitment, adherence to the protocol, safety and confidentiality of patients. All serious adverse events related to the study will be reported to the study sponsor, ethics committee, and, Guy's and St Thomas' research and development department.

Discussion

Psychological distress is common in people with ESRD. However, studies examining the efficacy of either pharmacological or psychological interventions for the management of distress in dialysis are limited. Likewise, access to psychological treatment interventions tailored to the specific psycho-social stresses associated with ESRD is problematic. An online CBT treatment designed specifically to manage distress in dialysis, offers a pragmatic solution to under-resourced health services, which are advised to offer integrated mental and physical health care treatments.

This is the first study to examine whether it is feasible to implement a RCT of online CBT with telephone support vs online CBT without telephone support within a stepped care framework, to secondary care haemodialysis patients with co-morbid distress. Indeed, it will

identify unique challenges that occur in the dialysis population in the recruitment and retention of patients for a treatment intervention designed to manage their distress alongside an already burdensome ESRD treatment regimen. Likewise, the study will be able to simultaneously examine the acceptability of this treatment to patients in terms of whether its content was relevant and useful. In addition, the utility of the online mode of delivery with or without telephone support will be examined. We anticipate that the results of this trial will substantially inform the design of a future large scale trial powered to detect the efficacy of online CBT treatments for the management of distress in dialysis.

Trial Status

The study commenced recruitment in February 2015. Recruitment will continue until February 2016 with the last patient's follow-up in May 2016.

Funding: This work was funded by Guy's and St Thomas' charity (GSTT, grant number: EFT130206).

List of abbreviations

CBT, Cognitive behavioural therapy; ESRD, End-stage renal disease; ICERS, incremental cost-effectiveness ratios; iDiD, Improving distress in dialysis; QALYs, Quality Adjusted Life Years; RCT, Randomised Controlled Trial

Competing Interests: None to declare

Authors Contributions:

Study design: All authors

Intervention development: JH, RMM, DG, AC, LY, JC:

Statistical analysis plan: PM, JC.

All authors contributed to writing the protocol.

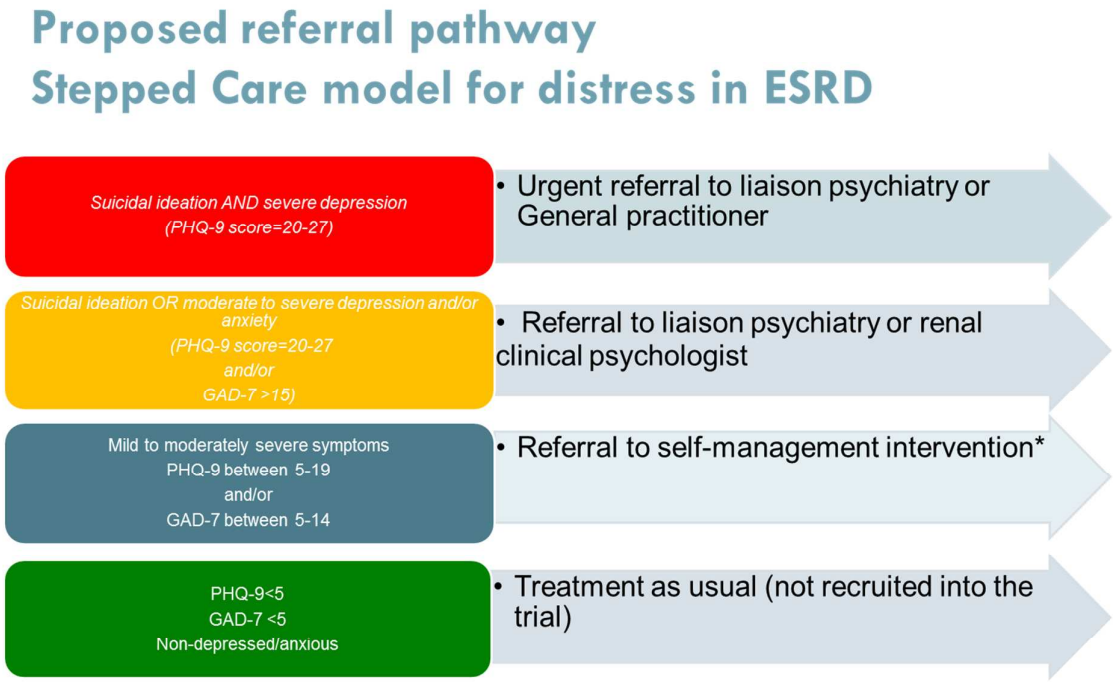

Figure 1: Stratified stepped care referral pathway for managing psychological distress among individuals attending for haemodialysis

Figure 2: Flow of participants through the study

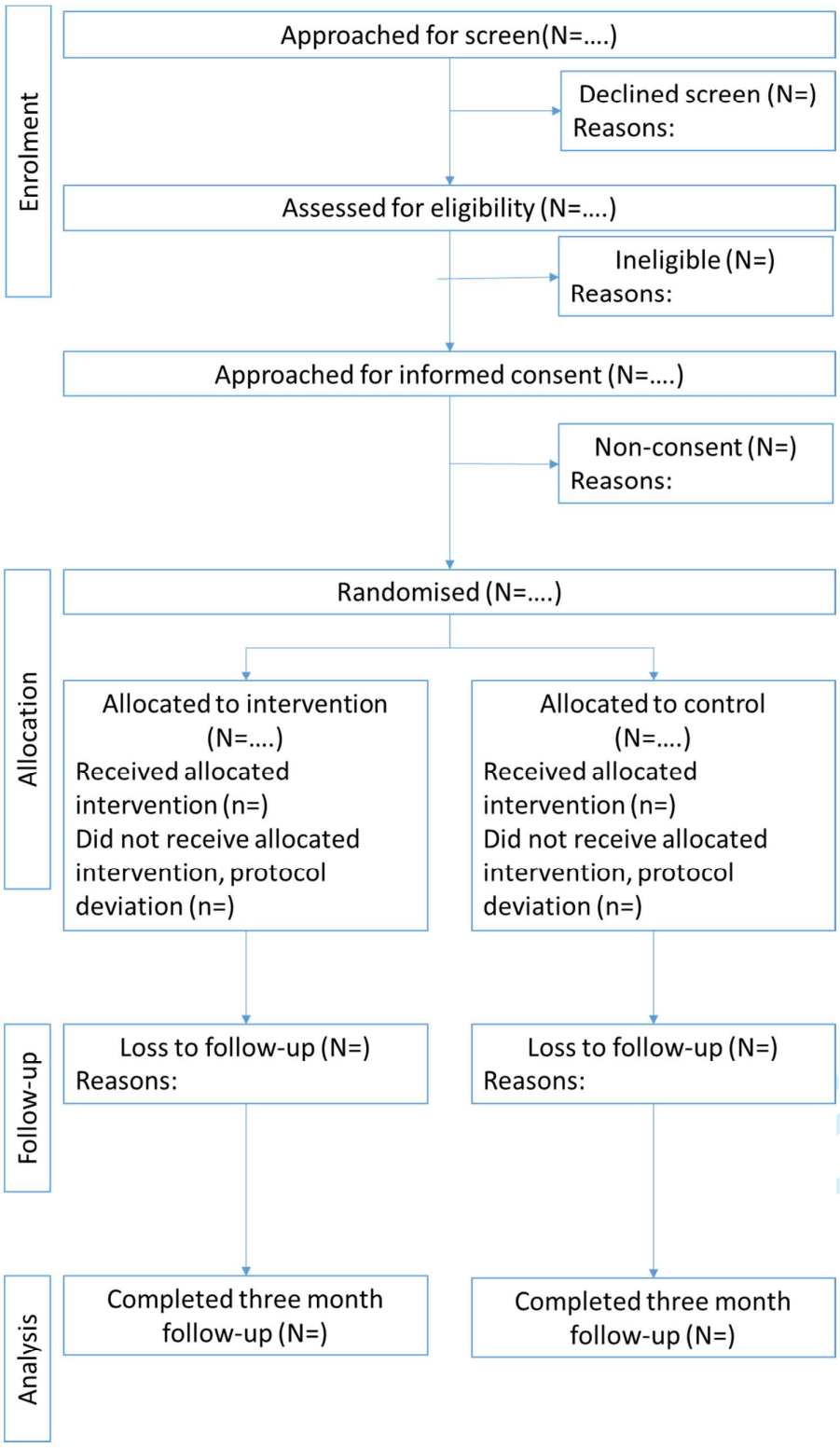

Table 1: Summary of iDiD online treatment sessions

Session	Content
1. What is end-stage renal failure?	-Psycho-education including information about: -ESRD and its treatment -Expectation management about the effectiveness of dialysis treatments and its psycho-social consequences. -Explaining the rationale for specific ESRD treatments (i.e. improving physical health) and psychological interventions (i.e. improving emotional health)
2. Why do I feel distressed?	-Recap on information learnt about in session 1 -Self-generation of a personal model of distress. Patients self-identify their own vicious cycle to improve their understanding of the inter-relationships between ESRD specific stressors (triggers), feelings, thoughts, behaviours, and physical symptoms. *Between session task:* Recap on the content of session 2 by re-reading the session.
3. Dealing with my negative feelings	-Recap on information learnt about in session 2 -Recap on the reinforcing relationship between unhelpful coping behaviours and the maintenance of psychological distress. -Examples provided of positive emotion regulation strategies including: acceptance, relaxation, expression, exercise, behavioural activation, behavioural experiments, graded exposure, tips for improving the quality of sleep. *Between session task:* Selection of a helpful coping

	strategies for managing negative emotions before completion of next online session.

4. Tackling unhelpful thoughts about end-stage renal disease	-Recap on information learnt about in session 3 -Provide examples of unhelpful thoughts typical in people with ESRD, information about the identification of unhelpful thoughts using thought records, and provide examples of how to challenge and gradually alter unhelpful thinking styles. *Between session task:* Encourage patients to continue working on their goals from session three and complete a thought record sheet if relevant to their personal needs.
5.Goal setting and problem solving	-Recap on information learnt about in session 4. -Explain the rationale for "SMART" goals and how to use the technique. Link with activity monitoring and action planning. -Explain the seven steps to problem solving technique. Use to foster confidence that participants are implementing the best possible solution to challenging situations. *Between session task:* Encourage participants to continue working on their goals from previous sessions that they find useful and relevant and if feasible implement: i) "SMART" goal techniques, ii) action planning, or iii) seven steps to problem solving approach.
6. Managing difficult social relationships	-Recap on information learnt about session 5 -Provide case examples of social situations people with ESRD find challenging (i.e. dealing with medical professionals). -Describe what assertiveness is and how behaving assertively can improve how you feel in social situations

	that are perceived as stressful. Provide case examples of how others have behaved assertively in ESRD specific social contexts to allow participants to adapt for their own use. -Encourage patients to think about their social support network and whether they are making ideal use of their social networks or is there scope to improve their social networks. *Between session tasks:* Prepare potential assertive responses to stressful social situations and/or consider social support networks and how to optimise them.
7. Progress recap and preparing for the future	-Recap on the progress made over the previous six sessions by encouraging patients to reflect on their new skills and achieved goals. -Generation of action plans to continue using skills and thinking about what skills they can implement when an acute stressful situations arises.

Table 2: Schedule of assessments

Assessment	Time		
	Screening	**Baseline**	**3 months**
PHQ-9	x	x	x
GAD-7	x	x	x
EQ-5D		x	x
Client Service Receipt Inventory		x	x
Socio-demographics		x	
Clinical characteristics		x	
Biological clinical outcomes		x	x
Self-reported adverse events			x
Self-reported treatments for depression and anxiety during the study			x
Brief illness perception questionnaire		x	x
Satisfaction with care		x	x
Experience of using the iDiD website			x

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Improving Distress in Dialysis (iDiD): A feasibility two arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without therapist led telephone support for psychological distress in haemodialysis patients

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Improving Distress in Dialysis (iDiD): A feasibility two arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without therapist led telephone support for psychological distress in haemodialysis patients

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Abstract

Introduction: Psychological distress is common in End-Stage Renal Disease (ESRD) and is associated with poorer health outcomes. Cognitive-behavioural therapy (CBT) is recommended in UK clinical guidelines for the management of depression in people with long-term conditions (LTCs). Access to skilled therapists competent in managing the competing mental and physical health demands of ESRD is limited. Online CBT treatments tailored to the needs of the ESRD population offers a pragmatic solution for under-resourced services. This study examines the feasibility and acceptability of implementing a two-arm parallel randomised controlled trial (RCT) of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in haemodialysis patients.

Methods: Patients will be screened for depression and anxiety whilst attending for their haemodialysis treatments. We aim to recruit sixty adult haemodialysis patients who meet criteria for mild to moderately severe symptoms of depression and/or anxiety. Patients will be randomised individually (using a 1:1 computerised sequence ratio) to either online CBT with therapist telephone support (intervention arm) or online CBT with no therapist (control arm). Outcomes include feasibility and acceptability descriptive data on rates of recruitment, randomisation, retention, and treatment adherence. Self-report outcomes include measures of depression (Patient Health Questionnaire-9), anxiety (Generalised Anxiety Disorder-7), quality of life (Euro-QoL), service use (client service receipt inventory), and illness cognitions (brief illness perception questionnaire). A qualitative process evaluation will also be conducted. The statistician will be blinded to treatment allocation.

Ethics and dissemination: An NHS research ethics committee approved the study. Data from this study will provide essential information for the design and testing of further interventions to ameliorate distress in dialysis patients. Any amendments to the protocol will be submitted to the NHS committee and study sponsor.

Keywords: End-stage renal disease, haemodialysis, cognitive-behavioural therapy, psychological distress, online therapy, online treatment, computerised therapy

Trial registration: ClinicalTrials.gov Identifier-NCT023528702

Funder: This work was funded by Guy's and St Thomas' charity (GSTT, grant number: EFT130206).

Strengths and limitations of this study

- This protocol provides a framework for the design and evaluation of an online cognitive-behavioural therapy treatment for the management of co-morbid distress and end-stage renal disease.
- First feasibility study to evaluate cognitive-behavioural therapy using online pragmatic delivery methods in a UK NHS haemodialysis setting.
- Recruitment from a single UK NHS site may hinder generalisabilty of feasibility outcomes.
- Patient treatment preferences are not accounted for.

Introduction

End-stage renal disease (ESRD) is a chronic condition that permanently affects kidney function (1). Without renal replacement therapy (e.g. dialysis or transplantation) a person's physical health would rapidly deteriorate because of the build-up of toxins and waste products in the body (2). In addition to renal replacement therapy patients are required to attend regular clinical appointments, take multiple medications and adhere to rigid dietary and fluid restrictions (3).

Psychological distress is common in ESRD with an estimated prevalence of 39% among people in receipt of dialysis compared with a prevalence of 27% in patients with chronic kidney disease (stages 1-5) (4). Co-morbid psychological distress and ESRD is associated with higher rates of mortality (5) and health care utilisation (6). The safety and efficacy of pharmacotherapy in managing psychological distress among people with ESRD remains unclear because of a lack of robust randomised controlled trials (7). Whilst talking therapies likely offer a safer alternative to pharmacotherapy, their efficacy in the ESRD population is largely unknown. Only two small scale, non-UK based, randomised controlled trials (RCTs) have examined the efficacy of cognitive behavioural therapy (CBT) relative to usual care

among haemodialysis patients (8, 9). Both trials found CBT was effective in reducing psychological distress. These findings are consistent with larger scale RCTs of CBT treatments for depression in people with coronary heart disease (10).

The NHS has limited resources to allow the demand for CBT therapist time to be met adequately. A practical approach to address this problem is to implement a stepped care health service delivery model (11). Within this model individuals begin with low-intensity interventions unless their distress is deemed too severe to benefit from the type of minimal intervention offered. Providing low-intensity treatments means that there is decreased treatment burden for patients, but equally health services can treat a larger volume of patients. If necessary a patient is "stepped up" to receive more intensive intervention if the initial low-intensity treatment did not improve outcomes.

Guided self-help CBT treatments are considered low-intensity interventions (12) and are effective in the management of psychological distress in people with (13) and without co-morbid physical health conditions (14). On-line/computerised self-help resources allow better management of the informational needs of patients and encourage active engagement with treatment by interacting with the online interface (15). Indeed, in people without physical health conditions, online/computerised guided self-help treatments have largely demonstrated equivalence with face-to-face psychological interventions in terms of their clinical effectiveness (depression and anxiety) (16) and degree of adherence to treatment sessions (17).

However there are a number of factors that determine the efficacy of online and computerised self-help treatments. One moderating factor is whether support is provided by a health care professional. Online/computerised self-help treatments with support from health care professionals improves outcomes and prevents treatment drop-out (18, 19). The type of support provided is also important. A recent RCT explored the efficacy of online CBT with weekly technical/motivational support telephone calls from a non-clinician for the management of depression and compared it with usual GP care (20). Its findings confirmed that providing patients with access to online CBT with only technical support had no added benefit on depression outcomes compared with GP usual care. Access to a skilled therapist is especially important in the context of co-morbid mental and physical health conditions

because of the potential for treatment antagonisms, whereby the effective management of a person's mental health has the potential to dysregulate the management of physical health or vice versa (21).

Given that the evidence points to the efficacy of online/computerised treatments with therapeutic support for the management of psychological distress in people with and without physical LTCs; it remains uncertain whether these findings apply to the management of psychological distress in UK NHS haemodialysis treatment settings. This study seeks to explore the feasibility and acceptability of implementing a two arm parallel RCT of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in people receiving haemodialysis treatments within a stepped care health service delivery framework.

Background to the study

The development of the improving distress in dialysis (iDiD) online CBT treatment involved a multi-disciplinary team of health psychologists, clinical psychologists, psychiatrists, nephrologists, and six patient and public involvement representatives. The preliminary content of the website was initially determined by self-help resources used to manage adjustment outcomes in LTCs implemented in previous trials by one of our authors (RMM) (22-24). In addition, a literature review of the correlates of distress in dialysis was used to develop an ESRD specific CBT treatment formulation and seven session protocol (25). In brief our CBT formulation recognises the unique acute and chronic stressors that occur in the dialysis population including: ESRD diagnosis, surgical procedures needed for vascular access site generation, loss of independence, changes in body and self-image, uncertainty about health and future, the unseen burden of kidney disease, and chronic illness self-management challenges-specifically managing thirst and food cravings, and dealing with health professionals. CBT intervention techniques for managing these illness specific stressors are then introduced in subsequent online treatment sessions. The content of each treatment session was first drafted on paper and reviewed by the research team. Patient representatives then provided feedback on the relevance and ease of understanding of the information and CBT intervention techniques described. Next the intervention content was uploaded onto an online platform using LifeGuide software (26). The presentation and navigation through the website was tested using patient representatives and "think-aloud"

techniques. This process occurred iteratively so that comments on early sessions could be incorporated into the design of subsequent sessions.

The intervention includes a total of seven sessions. The content of each session is summarised in Table 1. For more detailed information see our distress in dialysis CBT treatment formulation model (25)**.** Patients are encouraged to complete one session per week and each session was designed to last approximately one hour in duration.

Objectives

The following aims will be addressed as part of the feasibility and acceptability study of a feasibility parallel RCT of online CBT with therapist led telephone support vs online CBT without therapist support, delivered within a stepped care framework among outpatient haemodialysis patients with co-morbid psychological distress.

1. To assess the feasibility and acceptability of screening all patients who attend for haemodialysis. Patients will be screened for depression and anxiety using standardised measures presented on iPADs. The presence of psychological distress is often not identified by non-mental health trained clinicians (27). Implementing screening questionnaires for psychological distress in medical settings can promote its detection (28) and ultimately the provision of mental health care. We will quantify the number of people who agree to be screened.
2. To explore rates of recruitment and retention into the trial.
3. To examine willingness to be randomised to either the intervention arm (with telephone support) or control arm (no telephone support) by recording participant reasons for non-consent into the study (if disclosed).
4. To explore the level of adherence to online treatment sessions and telephone support calls (intervention arm only).
5. To explore the potential efficacy of an online intervention with therapist led telephone support in reducing psychological distress when compared with website alone. This will inform the planning of a future full-scale trial to detect clinically meaningful change in psychological distress outcomes.
6. To examine if change in quality of life differs between the intervention arm and control arm

7. To provide a preliminary assessment of the cost-effectiveness of the intervention.
8. To examine change in ESRD illness cognitions and whether their effect differs between the intervention and control arm.
9. To qualitatively explore patient perceptions of the acceptability and usability of the website and telephone support calls and identify areas of improvement for future interventions.

Methods

Design

A two parallel armed randomised controlled feasibility trial (RCT). Participants will be randomised, individually, using a 1:1 ratio computerised algorithm. A nested qualitative study will evaluate patient experience.

Setting and participants

Participants will be recruited from haemodialysis units at Guy's and St Thomas' hospital (London, UK).

Participants will be eligible for inclusion if:

1) Aged 18 years or over and receive hospital haemodialysis three-times weekly.
2) They have mild to moderately severe depressive symptoms (based on PHQ-9 (29) scores of 5 to 19; a self-report measure of depression) and/or presence of mild to moderately severe anxiety symptoms (based on self-report GAD-7 (30) scores of 5-14).
3) They speak English sufficiently well to engage with screening tools.
4) They have a basic understanding of how to use the Internet and an email address.

Participants will be ineligible if:

1) Currently receiving active treatment for depression and/or anxiety. Active treatment is defined as any current psychological treatment (talking therapies) or receipt of a new anti-depressant and/or anti-anxiety medication. A medication is considered new if commenced three months prior to the completion of the depression and anxiety screening questionnaire.

2) They have a severe mental health disorder, for example, psychosis, bi-polar disorder.
3) They have active suicidal thoughts, as indicated by a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself".
4) They have evidence of addiction to alcohol or drugs.

A participant will be withdrawn from the study if:

1) There are safety concerns in relation to their physical or mental health.
2) The participant chooses to withdraw from the study.
3) A patient's level of psychological distress deteriorates.

Flow of recruitment and participant timeline

Participants will be identified for inclusion using web-based screening questionnaires routinely used as part of the Integrating Mental and Physical healthcare: research, training and services (IMPARTS) initiative at Guy's and St Thomas' hospital (31). Participants consenting to the screen will be assessed for depression and anxiety using the PHQ-9 (32) and GAD-7 (30) respectively. The PHQ-9 is a nine item self-report questionnaire deemed acceptable for the identification of depression in medical care settings, including specialist settings (28). Likewise, the GAD-7, is a self-report seven item questionnaire with evidenced criterion validity for the detection of generalized anxiety disorder (30). Both the PHQ-9 and GAD-7 are routinely used in UK primary care Improving Access to Psychological Therapy (IAPT) sites (33) to monitor patient outcomes. The patient will complete the web-based questionnaires either alone or with the assistance of a renal nurse/researcher. Whilst completing the screening questionnaire, patients will be asked to give their permission (yes/no) for a member of the research team to contact them about the present study.

Results from the screening questionnaires are uploaded onto the patient's electronic medical record. Results will be checked by the nursing team/researcher for immediate risk. Risk is defined as a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself". If suicidal ideation is detected then a risk assessment will be performed to determine the immediacy of referral to either liaison psychiatry or renal clinical psychology. Level of risk will be assessed in line with the IMPARTS risk assessment protocol. This includes enquiring about degree of suicidal ideation and level

of hopelessness, whether active plans are present, enquiring about the patient's history of suicidal attempts, recent life stressors, protective factors, and degree of social support. The outcome of the risk assessment will be immediately discussed with either the renal clinical psychologist or liaison psychiatrist and a management plan will be put into place.

Anonymised screening results will be securely emailed from the IMPARTS database to the iDiD research team on a weekly basis. A stratified stepped care model, according to the criteria outlined in Figure 1 will be applied to the anonymised data to identify potentially eligible participants for the study. The stratified stepped-care approach assigns individuals to treatments of varying intensity based on the severity of their symptoms (34). PHQ-9 scores within the range of 5-19, are considered indicative of mild to moderately severe symptoms of depression (32). Likewise, GAD-7 scores within the range of 5 to 14 indicate the presence of mild to moderately severe anxiety (30). Individuals with mild to moderately severe symptoms of depression and/or anxiety will be considered appropriate for treatment with the iDiD online CBT program and for inclusion in this study. Individuals with severe depression (PHQ-9 score ≥ 20) and/or anxiety (GAD7 score ≥15) or individuals with evidence of current suicidal ideation are considered inappropriate for iDiD online CBT. These patients will be referred and managed by either the renal clinical psychology team or liaison psychiatry (when detected at the point of screen).

Individuals who meet the criteria for mild to moderately severe symptoms of depression and/or anxiety will have their data de-anonymised providing they give us consent to contact them about the study. These potential participants will be screened against the remaining inclusion/exclusion criteria during weekly referral meetings with the research and clinical team. If they remain eligible then a researcher will approach the participant whilst they attend for dialysis to explain the study with the participant information sheet. Participants will be given a minimum of 24 hours to establish if they would like to take part.

All patients with mild to moderately severe symptoms of depression and/or anxiety who either: i) do not meet our remaining study inclusion criteria, ii) choose not to consent into the study, or iii) do not provide consent for us to approach them about the study will be provided with the option of receiving usual care follow-up from the renal clinical psychology

team. Usual care includes a face-to-face clinical assessment followed by a tailored psychological treatment intervention or referral to an IAPT service.

As discussed above, patients who screen positive for severe symptoms of depression and/or anxiety (PHQ-9 score ≥ 20 and/or GAD7 score ≥15) will receive an automatic referral to the renal clinical psychology team. If upon clinical assessment by the renal clinical psychologist a severely depressed and/or anxious patient is deemed appropriate for the iDiD self-help study, then they will be "stepped down" for approach by the iDiD research team. Likewise, the research team will be informed by the renal clinical psychology team of any patients who meet the iDiD study inclusion criteria and declare an interest in the study despite initially stating during screening that they did not want to be contacted by the study team.

Participants who consent to take part in the study will be issued with an iDiD study identification number. A researcher will attend the dialysis unit and help the patient to sign-up to the iDiD online CBT treatment using an iPAD. At sign-up participants will be asked to enter their personal email address and select a password for use each time they logon. At the point of sign-up participants will also be asked to enter their NHS number (supplied to them by the researcher) to ensure that multiple iDiD accounts are not registered by the same participant. Participants will then receive a confirmatory email with a link to the iDiD website. After signing up, participants will complete the baseline questionnaires online. If baseline questionnaires are not completed, then participants will receive two reminder emails and an assistance based telephone call/visit at the dialysis unit. Participants will be informed of their randomisation process outcome immediately after completing the online baseline questionnaire. Participants will also receive an email confirming their treatment allocation. We anticipate the participant's journey through the study will last approximately six months as summarised in Figure 2. We expect a period of one month to elapse from the point of screening to randomisation. Once participants are randomised, both groups will be able to access the iDiD website for a period of 12 weeks before being prompted to complete the follow-up questionnaires via email. The email will also advise participants that their access to the iDiD website is ending within a few weeks and to print off any information they have found helpful from the "My tasks" tab of the website. Two reminder emails and an assistance based telephone call/visit will occur over a period of three weeks if the follow-up questionnaires remain incomplete. After 20 weeks participants will receive an email

thanking them for their participation in iDiD study. Access to the iDiD website will no longer be available after this time. On completion of the three month follow-up questionnaires a subsample of participants will be asked to complete a qualitative interview. We will follow-up participants for a period of approximately six months post their randomisation date to complete the interview.

Randomisation, allocation concealment, and blinding

Participants will be randomised to iDiD online CBT plus therapist led telephone support or iDiD online CBT only condition using Lifeguide software (a computerised random number generator with a 1:1 ratio). Because the randomisation sequence is automated by Lifeguide in real-time the allocation sequence is concealed from researchers. All baseline questionnaires will be completed online prior to randomisation. Participants will be randomised at the individual level. The trial co-ordinator will also receive an automated email informing them of the outcome of the randomisation procedure to identify participants who require telephone support calls during the trial. The researcher conducting the qualitative interviews will also be unblinded at follow-up to ensure that appropriate questions are asked in relation to telephone support calls. Because of the nature of the intervention patients will not be blind to their treatment allocation. Follow-up outcomes will be completed independently by participants when prompted by email unless the participant requires assistance. The statistician will remain blinded to treatment allocation.

Trial Intervention

All participants have access to the iDiD online CBT treatment (summarised in Table 1 and described in detail in our ESRD CBT formulation model (25)). Participants will be advised in the participant information sheet to logon to the website once a week. Participants will also receive weekly reminder emails to encourage engagement with the website. iPADs will be available for participants to use during their dialysis sessions.

iDiD online CBT website plus therapist led telephone support (Intervention arm)

Participants in the intervention arm of the trial will receive three 30 minute telephone support calls at weeks two, four, and six from JH who has a PhD in health psychology and is a trained psychological wellbeing practitioner (PWP). PWPs typically work in primary care mental health teams as part of the UK Improving Access to Psychological Therapies (IAPT)

initiative (33). PWPs deliver low-intensity CBT treatments including: cognitive restructuring, behavioural activation, problem solving, medication management, exposure therapy, and sleep management. The purpose of the telephone support calls are to promote engagement with the website and to support the patient in collaboratively developing goals to work on using the resources and information available to them on the website. At the start of each telephone call the PWP will set an agenda with the participant. The first telephone support call is scheduled for when the participant will have completed session two online. During session two the participant will have completed a self-assessment and developed their own personal model of distress. Thus during the first call the PWP will develop a shared understanding of the participants source of distress, provide empathy, reinforce with the participant the relationships between thoughts, feelings, and behaviours, and inform participants of the content the website which is likely most applicable to them as they continue to move forward with the website. The PWP and patient will develop a goal to work towards prior to their next telephone call.

The second telephone support call will provide an opportunity for the PWP to review with the participant their progress on their self-generated goals, work through a particular cognitive-behavioural intervention technique selected by the participant, and close the session with a shared goal to work towards with the help of the website in advance of the final telephone support call. The final telephone support call will follow a similar format except the telephone session will end with a relapse prevention plan. The plan will be generated collaboratively with the patient. All telephone support calls will be audio-recorded to provide intervention fidelity checks and for self-reflection during clinical supervision.

Clinical supervision

JH was trained to deliver the telephone support calls using role played sessions with feedback from RMM. Ongoing supervision will be provided by a renal clinical psychologist (AC). Shared reflection on audio-recorded sessions will be discussed in line with the core competency framework for delivering psychological therapies in long-term conditions (35). Shared goals will be identified for the PWP to work towards over the course of the study. Supervision will also be an opportunity for case management. The PWP will discuss their proposed treatment plan in response to the first telephone support call and degree of

patient progress at each supervision session. If a patient needs to be stepped up to receive more intensive psychological treatments then this will be initiated by the research team and managed by the renal clinical psychologist.

iDiD online CBT website with no telephone support (control arm)

Participants allocated to the control arm of the study will receive their usual renal care in addition to having access to the website. Usual care for individuals with ESRD managed with haemodialysis includes attending for dialysis three times per week for up to five hours at a time. Participants can be referred or self-refer into the renal clinical psychology service or primary care mental health service if their symptoms of depression and/or anxiety increase. We will ask participants in the three-month follow-up questionnaire whether they have commenced any new treatments for mental health since starting the study.

Outcomes

Data collection and feasibility outcomes

Because this is a feasibility study our primary focus is to collect data on the feasibility and acceptability of the trial design and intervention by collecting descriptive data on *recruitment and retention rates and willingness to be randomised* according to CONSORT trial guidelines (36). We will also examine *adherence* to the online intervention and telephone support calls (intervention arm only). The degree of adherence to the online intervention will be automatically recorded by the Lifeguide software. We will calculate descriptive values for the mean number of sessions completed, the number of participants who complete all sessions, the number of participants who complete 50% or more sessions, and the number of participants who complete each session. Degree of adherence to the telephone call (intervention arm only) will be recorded by the psychological wellbeing practitioner. The following values will be calculated: mean number of telephone calls completed, number of participants who complete all telephone calls, number who complete one or more telephone call, number of participants who complete telephone sessions one, two, and three respectively, and mean duration of telephone calls across all three telephone support calls. In addition to a qualitative interview (described below) patients will be asked to self-report their experience of using the iDiD website at three months follow-up. The open-ended questions will enquire about: i) how useful they found the iDiD website and ii)

whether they found the website easy to use. Participants will also be given the option to add any further comments.

Self-reported patient outcomes will also be collected via the iDiD website at baseline and three months follow-up. The assessment schedule completed by patients is summarised in Table 2 and described below.

- Continuous self-report measure of depression: PHQ-9 (32) (described in detail above, scale range from 0 to 27, high scores indicate greater depressive symptoms)
- Continuous self-report measure of anxiety: (GAD-7) (30) (described in detail above, scale range from 0 to 21, high scores indicate greater anxiety symptoms).
- The five item EuroQoL (EQ-5D) (37) includes a five item measure of health status across the following domains: mobility, ability to self-care, ability to continue with activities (i.e. work, social life), pain, and anxiety and depression. In addition it has a visual analogue scale ranging from 0 to 100 where a person is asked to rate their overall health. The EQ-5D is recommended by NICE for use in cost-effectiveness evaluations (38).
- The Client Service Receipt Inventory (CSRI) (39) collects retrospective data on service use across the following five domains: i) background and client information (i.e. hospital admissions and discharge, frequency of GP visits, medications), ii) accommodation and living situation, iii) employment history, earnings, and other personal resources, iv) service receipt (i.e. hospital appointments, home help), and v) receipt of informal care from caregivers. The CSRI was amended to make its content relevant to the needs of the dialysis population in collaboration with the trial health economist (PM) and Renal Consultant (DG).
- The brief illness perception questionnaire (BIPQ) (40) will assess participants self-reported beliefs about their ESRD. The BIPQ was developed and validated among patients with long-term conditions, including renal disease. This information will be assessed at baseline and follow-up. It will provide an indication of whether participants beliefs about their ESRD change in response to clinical intervention.
- Satisfaction with care will be evaluated using a 2-item scale that asks participants to rate their degree of satisfaction with the care they receive for their physical and

mental health on a five-item Likert response scale. This information will be assessed at baseline and follow-up.

- Serious adverse events will be directly enquired about using self-report at follow-up only, according to good clinical practice guidelines. Participants will be asked whether they have experienced any adverse events since starting the study choosing from a list of five options. If participants indicate they have experienced adverse events then they will be asked for details. In addition participants will be asked if they have experienced any adverse health effects since starting the study and encouraged to elaborate where needed.
- Treatments for depression and/or anxiety: Two brief self-report questions at follow-up will ask participants if they have received any pharmacological or psychological treatments for their depression and/or anxiety in addition to the iDiD website since starting the study.

Socio-demographic and clinical characteristics

Socio-demographic characteristics including: gender, age, ethnicity, home environment (marital status, housing situation, number of dependents) and level of education will be collected at baseline only via self-report. Clinical characteristics including: dialysis vintage and treatment history for depression and anxiety will be self-reported by patients at baseline.

Number and type of co-morbidities will be extracted from notes at baseline only. The following clinical outcomes and covariates will be extracted from notes at baseline and follow-up: Kt/V (dialysis treatment adequacy), haemoglobin, serum albumin, C reactive protein, serum potassium levels, interdialytic weight gain, and serum phosphate levels.

Qualitative interviews

Qualitative interviews with a sub-group of participants over the phone will be conducted post-intervention (three months) by a researcher who has not been involved in their treatment. These interviews will explore whether the intervention met patient expectations, positive and negative opinions about the website, whether patients felt they gained any benefit from using website, its personal relevance to them, and its acceptability as a treatment. A minimum of ten participants will be purposively sampled across a range of

socio-demographic and clinical characteristics (e.g. treatment group, age, gender, ethnicity, dialysis vintage, degree of adherence to the intervention, degree of improvements in outcomes from the intervention). Interviews will continue until data saturation occurs. The outcomes of these qualitative interviews will help to revise our theoretical understanding of distress in dialysis and update the content of the intervention accordingly, in line with current medical research guidelines for process evaluations (41). Interviews will be transcribed verbatim and an inductive thematic analysis will be performed.

Sample size

The aim of this study is to explore the feasibility of implementing our trial procedures and to inform a power calculation for a future randomised controlled trial. We have calculated the sample size required based on the margins of error associated with recruitment. The approximate size of the Guy's and St Thomas' dialysis population is 600 patients, in which we expect to be able approach 400. Assuming a conservative uptake rate of 50%, 200 patients will be screened with approximately 40% meeting the inclusion criteria (the estimated prevalence of depression symptoms in HD patients; see (4)). If we assume 50% of those eligible will consent to be randomised a sample size of approximately 66 would allow us to estimate the true population consent rate with a 5% margin of error and a 95% confidence level.

Analysis plan

To examine the feasibility and acceptability of our screening, recruitment, retention, and randomisation process (objectives 1-3), we will quantify the flow of participants through the study using frequencies and percentages in accordance with the consort flow diagram (36) shown in Figure 2. We will also record and quantify reasons for non-consent, exclusion, and drop-out for each stage of the study. We will examine degree of adherence to the intervention and telephone support calls (where applicable) using descriptive statistics (objective 4).

We will also perform an *exploratory* intention to treat mixed model analysis blind to treatment group on the following self-report outcomes at three months follow-up: depression, anxiety, and quality of life (objective 5 & 6). Variability in these patient outcomes will help to inform a future power calculation for a full-scale trial.

Service costs will be calculated by combining service use data with appropriate unit costs (42). These will be added to the costs of the intervention which will be based on development costs and the time spent providing telephone support. Costs will be compared between the two groups and cost-effectiveness assessed by combining the costs with the primary outcome measures and quality adjusted life years (QALYs) in the form of incremental cost-effectiveness ratios (ICERs). Uncertainty around the ICERs will be addressed using cost-effectiveness planes and acceptability curves (objective 7). We will also perform an exploratory process analysis using intention to treat mixed models to establish whether illness cognitions changed in response to the online intervention and whether differences occurred between the intervention and control group (objective 8). Qualitative interviews will be transcribed verbatim and analysed using thematic analysis to allow the feasibility and acceptability of the online intervention and telephone support calls to be explored (objective 9).

Ethics

This study has ethical approval from the NHS research ethics committee (14/LO/1934) and is sponsored by King's College London.

Data collection and management

The IMPARTS screening interface, developed by Teleologic Ltd, is web-based and installed on the server configuration at Guy's & St Thomas' Hospitals NHS Foundation Trust. The patient logs on to the system with their unique Hospital Number. Their screening results are outputted to the documents folder of the Electronic Patient Record via the most secure wifi network within each NHS Trust.

All quantitative outcomes are measured via online questionnaires that participants will access via iDiD website. The information is stored on a secure server associated with the Lifeguide program at the University of Southampton. The website prompts the participant when data is missing. Study data can only be downloaded from the server by members of the research team who are granted password access. All data will be confidentially stored in accordance with the data protection act (43) and King's College London data management procedures.

Formal committee

A trial management team will meet regularly to discuss the overall running of the study including: rates of recruitment, adherence to the protocol, safety and confidentiality of patients. All serious adverse events related to the study will be reported to the study sponsor, ethics committee and Guy's and St Thomas' research and development department.

Discussion

Psychological distress is common in people with ESRD. However, studies examining the efficacy of either pharmacological or psychological interventions for the management of distress in dialysis are limited. Likewise, access to psychological treatment interventions tailored to the specific psycho-social stresses associated with ESRD is problematic. An online CBT treatment designed specifically to manage distress in dialysis offers a pragmatic solution to under-resourced health services, which are advised to offer integrated mental and physical health care treatments.

This is the first study to examine whether it is feasible to implement a RCT of online CBT with telephone support vs online CBT without telephone support within a stepped care framework to secondary care haemodialysis patients with co-morbid distress. Indeed, it will identify unique challenges that occur in the dialysis population in the recruitment and retention of patients. Likewise, the study will be able to simultaneously examine the acceptability of this treatment to patients in terms of whether its content was relevant and useful. In addition, the utility of the online mode of delivery with or without telephone support will be examined. We anticipate that the results of this trial will substantially inform the design of a future large scale trial powered to detect the efficacy of online CBT treatments for the management of distress in dialysis.

Trial Status

The study commenced recruitment in February 2015. Recruitment will continue until February 2016 with the last patient's follow-up in May 2016. Outcomes will be disseminated at national and international conferences and in journal articles.

List of abbreviations

CBT, Cognitive behavioural therapy; ESRD, End-stage renal disease; ICERS, incremental cost-effectiveness ratios; iDiD, Improving distress in dialysis; QALYs, Quality Adjusted Life Years; RCT, Randomised Controlled Trial

Authors Contributions:

Study design: All authors

Intervention development: JH, RMM, DG, AC, LY, JC:

Statistical analysis plan: PM, JC.

All authors contributed to writing the protocol.

Sponsor: King's College London, Mr Keith Brennan (Keith.brennan@kcl.ac.uk)

Protocol version: Version 3: Date 11.05.15

Role of sponsor and funder

The funder and sponsor had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors.

Conflicts of interest:

None

Access to data: Data will be confidentially and securely stored for 7 years as per University policy. Anonymised aggregated data will be made available upon request to the corresponding author.

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Table 1: Summary of iDiD online treatment sessions

Session	Content
1. What is end-stage renal failure?	-Psycho-education including information about: -ESRD and its treatment. -Expectation management concerning the effectiveness of dialysis treatments and its psycho-social consequences. -The rationale for specific ESRD treatments (i.e. improving physical health) and psychological interventions (i.e. improving emotional

	health). -Normalising the experience of distress in the context of dialysis.
2. Why do I feel distressed?	-Recaps on information learnt about in session 1. -Self-generation of a personal model of distress. Patients self-identify their own vicious cycle to improve their understanding of the inter-relationships between ESRD specific stressors (triggers), feelings, thoughts, behaviours, and physical symptoms. *Between session task:* Recap on the content of session 2 by re-reading the session.
3. Dealing with my negative feelings	-Recaps on information learnt about in session 2. -Revision of reinforcing relationship between unhelpful coping behaviours and the maintenance of psychological distress. -Explanation of positive emotion regulation strategies including: behavioural activation, emotional expression, graded exposure, and tips for improving the quality of sleep. Patients are also informed of the value of acceptance, relaxation, and physical exercise. *Between session task:* Selection of a helpful coping strategy for managing negative emotions before completion of next online session.

4. Tackling unhelpful thoughts about end-stage renal disease	-Recaps on information learnt about in session 3. -Examples of unhelpful thoughts typical in people with ESRD provided. -Information and skill development on the identification of unhelpful thoughts using thought records. -Explanation of how to challenge and gradually alter unhelpful thinking styles by generating alternatives. *Between session task:* Continue working on goals from session three (if useful) and complete a thought record if relevant to their personal needs.
5.Goal setting and problem solving	-Recaps on information learnt about in session 4. -The rationale for "SMART" goals and how to use the technique is explained in depth. -Information about the value of activity monitoring, behavioural activation, and action planning. -Explanation of the seven steps to problem solving technique is introduced. Use to foster confidence in illness self-management. *Between session task:* Continue working on goals from previous sessions that remain useful and relevant. If applicable implement one of the following: i) "SMART" goal techniques, ii) activity monitoring/behavioural activation, or iii) seven steps to problem solving approach.
6. Managing difficult social relationships	-Recaps on information learnt about session 5 -Case examples of social situations people with ESRD find challenging (i.e. dealing with medical professionals)

	provided. -Introduction to assertiveness concept and its effects on physical and psychological health. -Case examples provided of how others behave assertively in ESRD specific social contexts to allow participants to adapt for their own use. -Reflection on social support network and whether there is scope to improve it to meet physical, emotional, and informational needs. *Between session tasks:* Continue working on goals from previous sessions that remain useful and relevant. If feasible/applicable implement: a potential assertive responses to a stressful social situation or reflect on social support networks and how to optimise them.
7. Progress recap and preparing for the future	-Recaps on the progress made over the previous six sessions by encouraging patients to reflect on their new skills and achieved goals. -Generation of action plans to continue using skills moving forward. Identification of a specific action plan to implement when an acute stressful situations arises.

675 Table 2: Schedule of assessments

Assessment	Time		
	Screening	**Baseline**	**3 months**
PHQ-9	x	x	x
GAD-7	x	x	x
EQ-5D		x	x
Client Service Receipt Inventory		x	x
Socio-demographics		x	
Clinical characteristics		x	
Biological clinical outcomes		x	x
Self-reported adverse events			x
Self-reported treatments for depression and anxiety during the study			x
Brief illness perception questionnaire		x	x
Satisfaction with care		x	x
Experience of using the iDiD website			x

Figure titles:

Figure 1: Stratified stepped care referral pathway for managing psychological distress among individuals attending for haemodialysis

Figure 2: Flow of participants through the study

Figure 1: Stratified stepped care referral pathway for managing psychological distress among individuals attending for haemodialysis

199x102mm (300 x 300 DPI)

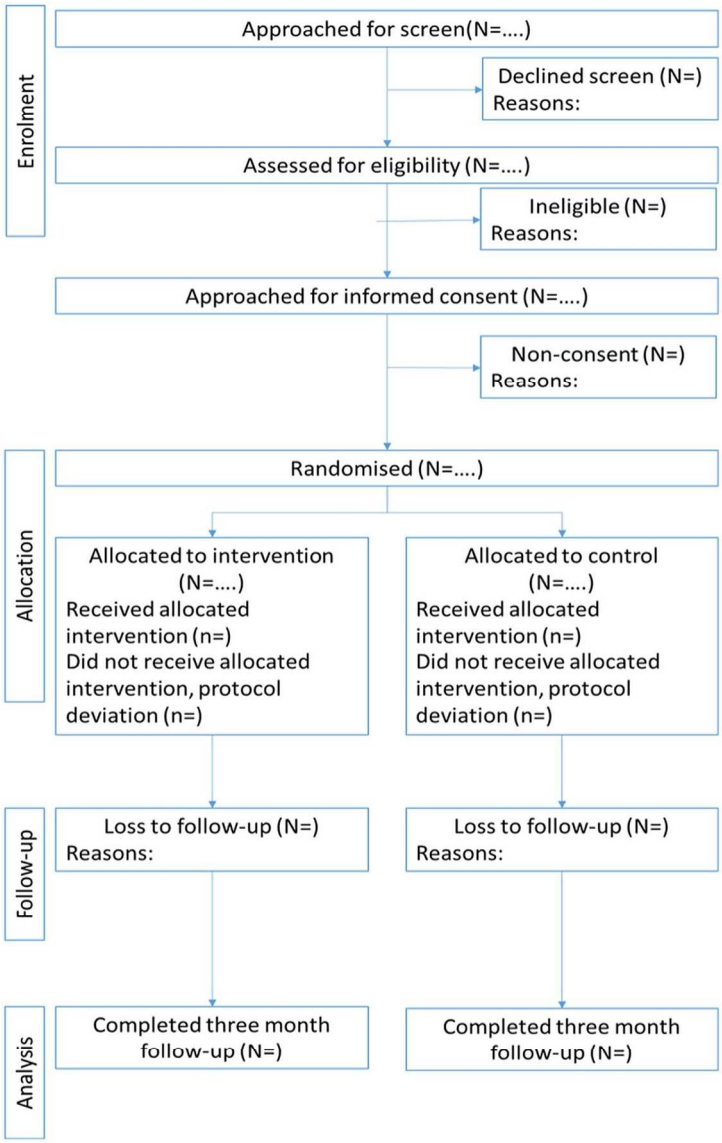

Figure 2: Flow of participants through the study
99x153mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__2_____
	2b	All items from the World Health Organization Trial Registration Data Set	Documented in trial registry (2a) & page 1_____
Protocol version	3	Date and version identifier	_3_____
Funding	4	Sources and types of financial, material, and other support	_3_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1_____
	5b	Name and contact information for the trial sponsor	_3_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__3_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_NA for feasibility study_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 to 6_____
	6b	Explanation for choice of comparators	5 to 6_____
Objectives	7	Specific objectives or hypotheses	7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 to 9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12 to 14_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11 and 13_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15 and 16 _____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9 to 13_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions12	12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 to 12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA as trial co-ordinator is not blind._____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9 to 11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9 to 11_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17 to 18_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17 to 18_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17 to 18_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA for feasibility study_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA for feasibility study _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA for feasibility study _____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2 and 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9 and 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA harms addressed according to King's indemnity insurance
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Adheres to NHS consent form_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this NA with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Improving Distress in Dialysis (iDiD): A feasibility two arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without therapist led telephone support for psychological distress in haemodialysis patients

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Improving Distress in Dialysis (iDiD): A feasibility two arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without therapist led telephone support for psychological distress in haemodialysis patients

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Abstract

Introduction: Psychological distress is common in End-Stage Kidney Disease (ESKD) and is associated with poorer health outcomes. Cognitive-behavioural therapy (CBT) is recommended in UK clinical guidelines for the management of depression in people with long-term conditions (LTCs). Access to skilled therapists competent in managing the competing mental and physical health demands of ESKD is limited. Online CBT treatments tailored to the needs of the ESKD population offers a pragmatic solution for under-resourced services. This study examines the feasibility and acceptability of implementing a two-arm parallel randomised controlled trial (RCT) of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in haemodialysis patients.

Methods: Patients will be screened for depression and anxiety whilst attending for their haemodialysis treatments. We aim to recruit sixty adult haemodialysis patients who meet criteria for mild to moderately severe symptoms of depression and/or anxiety. Patients will be randomised individually (using a 1:1 computerised sequence ratio) to either online CBT with therapist telephone support (intervention arm) or online CBT with no therapist (control arm). Outcomes include feasibility and acceptability descriptive data on rates of recruitment, randomisation, retention, and treatment adherence. Self-report outcomes include measures of depression (Patient Health Questionnaire-9), anxiety (Generalised Anxiety Disorder-7), quality of life (Euro-QoL), service use (client service receipt inventory), and illness cognitions (brief illness perception questionnaire). A qualitative process evaluation will also be conducted. The statistician will be blinded to treatment allocation.

Ethics and dissemination: An NHS research ethics committee approved the study. Data from this study will provide essential information for the design and testing of further interventions to ameliorate distress in dialysis patients. Any amendments to the protocol will be submitted to the NHS committee and study sponsor.

Keywords: End-stage kidney disease, haemodialysis, cognitive-behavioural therapy, psychological distress, online therapy, online treatment, computerised therapy

Trial registration: ClinicalTrials.gov Identifier-NCT023528702

Funder: This work was funded by Guy's and St Thomas' charity (GSTT, grant number: EFT130206).

Sponsor: King's College London, Mr Keith Brennan (Keith.brennan@kcl.ac.uk)

Protocol version: Version 3: Date 11.05.15

Role of sponsor and funder

The funder and sponsor had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript. The views expressed in this article are those of the authors.

Conflicts of interest:

None

Access to data: Data will be confidentially and securely stored for 7 years as per University policy. Anonymised aggregated data will be made available upon request to the corresponding author.

Strengths and limitations of this study

- This protocol provides a framework for the design and evaluation of an online cognitive-behavioural therapy treatment for the management of co-morbid distress and end-stage renal disease.
- First feasibility study to evaluate cognitive-behavioural therapy using online pragmatic delivery methods in a UK NHS haemodialysis setting.
- Recruitment from a single UK NHS site may hinder generalisabilty of feasibility outcomes.
- Patient treatment preferences are not accounted for. However such designs would be associated with increased costs, a prohibitive factor in the current study, and increase the potential for confounding factors.

Introduction

End-stage kidney disease (ESKD) is a chronic condition that permanently affects kidney function (1). Without renal replacement therapy (e.g. dialysis or transplantation) a person's physical health would rapidly deteriorate because of the build-up of toxins and waste products in the body (2). In addition to renal replacement therapy patients are required to attend regular clinical appointments, take multiple medications and adhere to rigid dietary and fluid restrictions (3).

Psychological distress is common in ESKD with an estimated prevalence of 39% among people in receipt of dialysis compared with a prevalence of 27% in patients with chronic kidney disease (stages 1-5) (4). Co-morbid psychological distress and ESKD is associated with higher rates of mortality (5) and health care utilisation (6). The safety and efficacy of pharmacotherapy in managing psychological distress among people with ESKD remains unclear because of a lack of robust randomised controlled trials (7). Whilst talking therapies likely offer a safer alternative to pharmacotherapy, their efficacy in the ESKD population is largely unknown. Only two small scale, non-UK based, randomised controlled trials (RCTs) have examined the efficacy of cognitive behavioural therapy (CBT) relative to usual care among haemodialysis patients (8, 9). Both trials found CBT was effective in reducing psychological distress. These findings are consistent with larger scale RCTs of CBT treatments for depression in people with coronary heart disease (10).

The NHS has limited resources to allow the demand for CBT therapist time to be met adequately. A practical approach to address this problem is to implement a stepped care health service delivery model (11). Within this model individuals begin with low-intensity interventions unless their distress is deemed too severe to benefit from the type of minimal intervention offered. Providing low-intensity treatments means that there is decreased treatment burden for patients, but equally health services can treat a larger volume of patients. If necessary a patient is "stepped up" to receive more intensive intervention if the initial low-intensity treatment did not improve outcomes.

Guided self-help CBT treatments are considered low-intensity interventions (12) and are effective in the management of psychological distress in people with (13) and without co-morbid physical health conditions (14). On-line/computerised self-help resources allow better management of the informational needs of patients and encourage active engagement with treatment by interacting with the online interface (15). Indeed, in people without physical health conditions, online/computerised guided self-help treatments have largely demonstrated equivalence with face-to-face psychological interventions in terms of their clinical effectiveness (depression and anxiety) (16) and degree of adherence to treatment sessions (17).

However there are a number of factors that determine the efficacy of online and computerised self-help treatments. One moderating factor is whether support is provided by a health care professional. Online/computerised self-help treatments with support from health care professionals improves outcomes and prevents treatment drop-out (18, 19). The type of support provided is also important. A recent RCT explored the efficacy of online CBT with weekly technical/motivational support telephone calls from a non-clinician for the management of depression and compared it with usual GP care (20). Its findings confirmed that providing patients with access to online CBT with only technical support had no added benefit on depression outcomes compared with GP usual care. Access to a skilled therapist is especially important in the context of co-morbid mental and physical health conditions because of the potential for treatment antagonisms, whereby the effective management of a person's mental health has the potential to dysregulate the management of physical health or vice versa (21).

Given that the evidence points to the efficacy of online/computerised treatments with therapeutic support for the management of psychological distress in people with and without physical LTCs; it remains uncertain whether these findings apply to the management of psychological distress in UK NHS haemodialysis treatment settings. This study seeks to explore the feasibility and acceptability of implementing a two arm parallel RCT of online CBT with (intervention arm) and without (control arm) therapist support to improve psychological distress in people receiving haemodialysis treatments within a stepped care health service delivery framework.

Background to the study

The development of the improving distress in dialysis (iDiD) online CBT treatment involved a multi-disciplinary team of health psychologists, clinical psychologists, psychiatrists, nephrologists, and six patient and public involvement representatives. The preliminary content of the website was initially determined by self-help resources used to manage adjustment outcomes in LTCs implemented in previous trials by one of our authors (RMM) (22-24). In addition, a literature review of the correlates of distress in dialysis was used to develop an ESKD specific CBT treatment formulation and seven session protocol (25)**.** In brief our CBT formulation recognises the unique acute and chronic stressors that occur in the dialysis population including: ESKD diagnosis, surgical procedures needed for vascular access site generation, loss of independence, changes in body and self-image, uncertainty about health and future, the unseen burden of kidney disease, and chronic illness self-management challenges-specifically managing thirst and food cravings, and dealing with health professionals. CBT intervention techniques for managing these illness specific stressors are then introduced in subsequent online treatment sessions. The content of each treatment session was first drafted on paper and reviewed by the research team. Patient representatives then provided feedback on the relevance and ease of understanding of the information and CBT intervention techniques described. Next the intervention content was uploaded onto an online platform using LifeGuide software (26). The presentation and navigation through the website was tested using patient representatives and “think-aloud” techniques. This process occurred iteratively so that comments on early sessions could be incorporated into the design of subsequent sessions.

The intervention includes a total of seven sessions. The content of each session is summarised in supplementary table 1. For more detailed information see our distress in dialysis CBT treatment formulation model (25)**.** Patients are encouraged to complete one session per week and each session was designed to last approximately one hour in duration.

Objectives

The following aims will be addressed as part of the feasibility and acceptability study of a feasibility parallel RCT of online CBT with therapist led telephone support vs online CBT without therapist support, delivered within a stepped care framework among outpatient haemodialysis patients with co-morbid psychological distress.

1. To assess the feasibility and acceptability of screening all patients who attend for haemodialysis. Patients will be screened for depression and anxiety using standardised measures presented on iPADs. The presence of psychological distress is often not identified by non-mental health trained clinicians (27). Implementing screening questionnaires for psychological distress in medical settings can promote its detection (28) and ultimately the provision of mental health care. We will quantify the number of people who agree to be screened.
2. To explore rates of recruitment and retention into the trial.
3. To examine willingness to be randomised to either the intervention arm (with telephone support) or control arm (no telephone support) by recording participant reasons for non-consent into the study (if disclosed).
4. To explore the level of adherence to online treatment sessions and telephone support calls (intervention arm only).
5. To explore the potential efficacy of an online intervention with therapist led telephone support in reducing psychological distress when compared with website alone. This will inform the planning of a future full-scale trial to detect clinically meaningful change in psychological distress outcomes.
6. To examine if change in quality of life differs between the intervention arm and control arm
7. To provide a preliminary assessment of the cost-effectiveness of the intervention.

8. To examine change in ESKD illness cognitions and whether their effect differs between the intervention and control arm.
9. To qualitatively explore patient perceptions of the acceptability and usability of the website and telephone support calls and identify areas of improvement for future interventions.

Methods

Design

A two parallel armed randomised controlled feasibility trial (RCT). Participants will be randomised, individually, using a 1:1 ratio computerised algorithm. A nested qualitative study will evaluate patient experience.

Setting and participants

Participants will be recruited from haemodialysis units at Guy's and St Thomas' hospital (London, UK).

Participants will be eligible for inclusion if:

1) Aged 18 years or over and receive hospital haemodialysis three-times weekly.
2) They have mild to moderately severe depressive symptoms (based on PHQ-9 (29) scores of 5 to 19; a self-report measure of depression) and/or presence of mild to moderately severe anxiety symptoms (based on self-report GAD-7 (30) scores of 5-14).
3) They speak English sufficiently well to engage with screening tools.
4) They have a basic understanding of how to use the Internet and an email address.

Participants will be ineligible if:

1) Currently receiving active treatment for depression and/or anxiety. Active treatment is defined as any current psychological treatment (talking therapies) or receipt of a new anti-depressant and/or anti-anxiety medication. A medication is considered new if commenced three months prior to the completion of the depression and anxiety screening questionnaire.
2) They have a severe mental health disorder, for example, psychosis, bi-polar disorder.

3) They have active suicidal thoughts, as indicated by a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself".
4) They have evidence of addiction to alcohol or drugs.

A participant will be withdrawn from the study if:

1) There are safety concerns in relation to their physical or mental health.
2) The participant chooses to withdraw from the study.
3) A patient's level of psychological distress deteriorates.

Flow of recruitment and participant timeline

Participants will be identified for inclusion using web-based screening questionnaires routinely used as part of the Integrating Mental and Physical healthcare: research, training and services (IMPARTS) initiative at Guy's and St Thomas' hospital (31). Participants consenting to the screen will be assessed for depression and anxiety using the PHQ-9 (32) and GAD-7 (30) respectively. The PHQ-9 is a nine item self-report questionnaire deemed acceptable for the identification of depression in medical care settings, including specialist settings (28). Likewise, the GAD-7, is a self-report seven item questionnaire with evidenced criterion validity for the detection of generalized anxiety disorder (30). Both the PHQ-9 and GAD-7 are routinely used in UK primary care Improving Access to Psychological Therapy (IAPT) sites (33) to monitor patient outcomes. The patient will complete the web-based questionnaires either alone or with the assistance of a renal nurse/researcher. Whilst completing the screening questionnaire, patients will be asked to give their permission (yes/no) for a member of the research team to contact them about the present study.

Results from the screening questionnaires are uploaded onto the patient's electronic medical record. Results will be checked by the nursing team/researcher for immediate risk. Risk is defined as a score of greater than one on the depression PHQ-9 item "Thoughts that you would be better off dead, or of hurting yourself". If suicidal ideation is detected then a risk assessment will be performed to determine the immediacy of referral to either liaison psychiatry or renal clinical psychology. Level of risk will be assessed in line with the IMPARTS risk assessment protocol. This includes enquiring about degree of suicidal ideation and level of hopelessness, whether active plans are present, enquiring about the patient's history of

suicidal attempts, recent life stressors, protective factors, and degree of social support. The outcome of the risk assessment will be immediately discussed with either the renal clinical psychologist or liaison psychiatrist and a management plan will be put into place.

Anonymised screening results will be securely emailed from the IMPARTS database to the iDiD research team on a weekly basis. A stratified stepped care model, according to the criteria outlined in Figure 1 will be applied to the anonymised data to identify potentially eligible participants for the study. The stratified stepped-care approach assigns individuals to treatments of varying intensity based on the severity of their symptoms (34). PHQ-9 scores within the range of 5-19, are considered indicative of mild to moderately severe symptoms of depression (32). Likewise, GAD-7 scores within the range of 5 to 14 indicate the presence of mild to moderately severe anxiety (30). Individuals with mild to moderately severe symptoms of depression and/or anxiety will be considered appropriate for treatment with the iDiD online CBT program and for inclusion in this study. Individuals with severe depression (PHQ-9 score ≥ 20) and/or anxiety (GAD7 score ≥15) or individuals with evidence of current suicidal ideation are considered inappropriate for iDiD online CBT. These patients will be referred and managed by either the renal clinical psychology team or liaison psychiatry (when detected at the point of screen).

Individuals who meet the criteria for mild to moderately severe symptoms of depression and/or anxiety will have their data de-anonymised providing they give us consent to contact them about the study. These potential participants will be screened against the remaining inclusion/exclusion criteria during weekly referral meetings with the research and clinical team. If they remain eligible then a researcher will approach the participant whilst they attend for dialysis to explain the study with the participant information sheet. Participants will be given a minimum of 24 hours to establish if they would like to take part.

All patients with mild to moderately severe symptoms of depression and/or anxiety who either: i) do not meet our remaining study inclusion criteria, ii) choose not to consent into the study, or iii) do not provide consent for us to approach them about the study will be provided with the option of receiving usual care follow-up from the renal clinical psychology team. Usual care includes a face-to-face clinical assessment followed by a tailored psychological treatment intervention or referral to an IAPT service.

As discussed above, patients who screen positive for severe symptoms of depression and/or anxiety (PHQ-9 score ≥ 20 and/or GAD7 score ≥15) will receive an automatic referral to the renal clinical psychology team. If upon clinical assessment by the renal clinical psychologist a severely depressed and/or anxious patient is deemed appropriate for the iDiD self-help study, then they will be "stepped down" for approach by the iDiD research team. Likewise, the research team will be informed by the renal clinical psychology team of any patients who meet the iDiD study inclusion criteria and declare an interest in the study despite initially stating during screening that they did not want to be contacted by the study team.

Participants who consent to take part in the study will be issued with an iDiD study identification number. A researcher will attend the dialysis unit and help the patient to sign-up to the iDiD online CBT treatment using an iPAD. At sign-up participants will be asked to enter their personal email address and select a password for use each time they logon. At the point of sign-up participants will also be asked to enter their NHS number (supplied to them by the researcher) to ensure that multiple iDiD accounts are not registered by the same participant. Participants will then receive a confirmatory email with a link to the iDiD website. After signing up, participants will complete the baseline questionnaires online. If baseline questionnaires are not completed, then participants will receive two reminder emails and an assistance based telephone call/visit at the dialysis unit. Participants will be informed of their randomisation process outcome immediately after completing the online baseline questionnaire. Participants will also receive an email confirming their treatment allocation. We anticipate the participant's journey through the study will last approximately six months as summarised in Figure 2. We expect a period of one month to elapse from the point of screening to randomisation. Once participants are randomised, both groups will be able to access the iDiD website for a period of 12 weeks before being prompted to complete the follow-up questionnaires via email. The email will also advise participants that their access to the iDiD website is ending within a few weeks and to print off any information they have found helpful from the "My tasks" tab of the website. Two reminder emails and an assistance based telephone call/visit will occur over a period of three weeks if the follow-up questionnaires remain incomplete. After 20 weeks participants will receive an email thanking them for their participation in iDiD study. Access to the iDiD website will no longer be available after this time. On completion of the three month follow-up questionnaires a

subsample of participants will be asked to complete a qualitative interview. We will follow-up participants for a period of approximately six months post their randomisation date to complete the interview.

Randomisation, allocation concealment, and blinding

Participants will be randomised to iDiD online CBT plus therapist led telephone support or iDiD online CBT only condition using Lifeguide software (a computerised random number generator with a 1:1 ratio). Because the randomisation sequence is automated by Lifeguide in real-time the allocation sequence is concealed from researchers. All baseline questionnaires will be completed online prior to randomisation. Participants will be randomised at the individual level. The trial co-ordinator will also receive an automated email informing them of the outcome of the randomisation procedure to identify participants who require telephone support calls during the trial. The researcher conducting the qualitative interviews will also be unblinded at follow-up to ensure that appropriate questions are asked in relation to telephone support calls. Because of the nature of the intervention patients will not be blind to their treatment allocation. Follow-up outcomes will be completed independently by participants when prompted by email unless the participant requires assistance. The statistician will remain blinded to treatment allocation.

Trial Intervention

All participants have access to the iDiD online CBT treatment (summarised in supplementary table 1 and described in detail in our ESKD CBT formulation model (25)). Participants will be advised in the participant information sheet to logon to the website once a week. Participants will also receive weekly reminder emails to encourage engagement with the website. iPADs will be available for participants to use during their dialysis sessions.

iDiD online CBT website plus therapist led telephone support (Intervention arm)

Participants in the intervention arm of the trial will receive three 30 minute telephone support calls at weeks two, four, and six from JH who has a PhD in health psychology and is a trained psychological wellbeing practitioner (PWP). PWPs typically work in primary care mental health teams as part of the UK Improving Access to Psychological Therapies (IAPT) initiative (33). PWPs deliver low-intensity CBT treatments including: cognitive restructuring, behavioural activation, problem solving, medication management, exposure therapy, and

sleep management. The purpose of the telephone support calls are to promote engagement with the website and to support the patient in collaboratively developing goals to work on using the resources and information available to them on the website. At the start of each telephone call the PWP will set an agenda with the participant. The first telephone support call is scheduled for when the participant will have completed session two online. During session two the participant will have completed a self-assessment and developed their own personal model of distress. Thus during the first call the PWP will develop a shared understanding of the participants source of distress, provide empathy, reinforce with the participant the relationships between thoughts, feelings, and behaviours, and inform participants of the content the website which is likely most applicable to them as they continue to move forward with the website. The PWP and patient will develop a goal to work towards prior to their next telephone call.

The second telephone support call will provide an opportunity for the PWP to review with the participant their progress on their self-generated goals, work through a particular cognitive-behavioural intervention technique selected by the participant, and close the session with a shared goal to work towards with the help of the website in advance of the final telephone support call. The final telephone support call will follow a similar format except the telephone session will end with a relapse prevention plan. The plan will be generated collaboratively with the patient. All telephone support calls will be audio-recorded to provide intervention fidelity checks and for self-reflection during clinical supervision.

Clinical supervision

JH was trained to deliver the telephone support calls using role played sessions with feedback from RMM. Ongoing supervision will be provided by a renal clinical psychologist (AC). Shared reflection on audio-recorded sessions will be discussed in line with the core competency framework for delivering psychological therapies in long-term conditions (35). Shared goals will be identified for the PWP to work towards over the course of the study. Supervision will also be an opportunity for case management. The PWP will discuss their proposed treatment plan in response to the first telephone support call and degree of patient progress at each supervision session. If a patient needs to be stepped up to receive

more intensive psychological treatments then this will be initiated by the research team and managed by the renal clinical psychologist.

iDiD online CBT website with no telephone support (control arm)

Participants allocated to the control arm of the study will receive their usual renal care in addition to having access to the website. Usual care for individuals with ESKD managed with haemodialysis includes attending for dialysis three times per week for up to five hours at a time. Participants can be referred or self-refer into the renal clinical psychology service or primary care mental health service if their symptoms of depression and/or anxiety increase. We will ask participants in the three-month follow-up questionnaire whether they have commenced any new treatments for mental health since starting the study.

Outcomes

Data collection and feasibility outcomes

Because this is a feasibility study our primary focus is to collect data on the feasibility and acceptability of the trial design and intervention by collecting descriptive data on *recruitment and retention rates and willingness to be randomised* according to CONSORT trial guidelines (36). We will also examine *adherence* to the online intervention and telephone support calls (intervention arm only). The degree of adherence to the online intervention will be automatically recorded by the Lifeguide software. We will calculate descriptive values for the mean number of sessions completed, the number of participants who complete all sessions, the number of participants who complete 50% or more sessions, and the number of participants who complete each session. Degree of adherence to the telephone call (intervention arm only) will be recorded by the psychological wellbeing practitioner. The following values will be calculated: mean number of telephone calls completed, number of participants who complete all telephone calls, number who complete one or more telephone call, number of participants who complete telephone sessions one, two, and three respectively, and mean duration of telephone calls across all three telephone support calls. In addition to a qualitative interview (described below) patients will be asked to self-report their experience of using the iDiD website at three months follow-up. The open-ended questions will enquire about: i) how useful they found the iDiD website and ii) whether they found the website easy to use. Participants will also be given the option to

add any further comments.

Self-reported patient outcomes will also be collected via the iDiD website at baseline and three months follow-up. The assessment schedule completed by patients is summarised in Table 1 and described below.

- Continuous self-report measure of depression: PHQ-9 (32) (described in detail above, scale range from 0 to 27, high scores indicate greater depressive symptoms)
- Continuous self-report measure of anxiety: (GAD-7) (30) (described in detail above, scale range from 0 to 21, high scores indicate greater anxiety symptoms).
- The five item EuroQoL (EQ-5D) (37) includes a five item measure of health status across the following domains: mobility, ability to self-care, ability to continue with activities (i.e. work, social life), pain, and anxiety and depression. In addition it has a visual analogue scale ranging from 0 to 100 where a person is asked to rate their overall health. The EQ-5D is recommended by NICE for use in cost-effectiveness evaluations (38).
- The Client Service Receipt Inventory (CSRI) (39) collects retrospective data on service use across the following five domains: i) background and client information (i.e. hospital admissions and discharge, frequency of GP visits, medications), ii) accommodation and living situation, iii) employment history, earnings, and other personal resources, iv) service receipt (i.e. hospital appointments, home help), and v) receipt of informal care from caregivers. The CSRI was amended to make its content relevant to the needs of the dialysis population in collaboration with the trial health economist (PM) and Renal Consultant (DG).
- The brief illness perception questionnaire (BIPQ) (40) will assess participants self-reported beliefs about their ESKD. The BIPQ was developed and validated among patients with long-term conditions, including renal disease. This information will be assessed at baseline and follow-up. It will provide an indication of whether participants beliefs about their ESKD change in response to clinical intervention.
- Satisfaction with care will be evaluated using a 2-item scale that asks participants to rate their degree of satisfaction with the care they receive for their physical and mental health on a five-item Likert response scale. This information will be assessed at baseline and follow-up.

- Serious adverse events will be directly enquired about using self-report at follow-up only, according to good clinical practice guidelines. Participants will be asked whether they have experienced any adverse events since starting the study choosing from a list of five options. If participants indicate they have experienced adverse events then they will be asked for details. In addition participants will be asked if they have experienced any adverse health effects since starting the study and encouraged to elaborate where needed.
- Treatments for depression and/or anxiety: Two brief self-report questions at follow-up will ask participants if they have received any pharmacological or psychological treatments for their depression and/or anxiety in addition to the iDiD website since starting the study.

Socio-demographic and clinical characteristics

Socio-demographic characteristics including: gender, age, ethnicity, home environment (marital status, housing situation, number of dependents) and level of education will be collected at baseline only via self-report. Clinical characteristics including: dialysis vintage and treatment history for depression and anxiety will be self-reported by patients at baseline.

Number and type of co-morbidities will be extracted from notes at baseline only. The following clinical outcomes and covariates will be extracted from notes at baseline and follow-up: Kt/V (dialysis treatment adequacy), haemoglobin, serum albumin, C reactive protein, serum potassium levels, interdialytic weight gain, and serum phosphate levels.

Qualitative interviews

Qualitative interviews with a sub-group of participants over the phone will be conducted post-intervention (three months) by a researcher who has not been involved in their treatment. These interviews will explore whether the intervention met patient expectations, positive and negative opinions about the website, whether patients felt they gained any benefit from using website, its personal relevance to them, and its acceptability as a treatment. A minimum of ten participants will be purposively sampled across a range of socio-demographic and clinical characteristics (e.g. treatment group, age, gender, ethnicity, dialysis vintage, degree of adherence to the intervention, degree of improvements in

outcomes from the intervention). Interviews will continue until data saturation occurs. The outcomes of these qualitative interviews will help to revise our theoretical understanding of distress in dialysis and update the content of the intervention accordingly, in line with current medical research guidelines for process evaluations (41). Interviews will be transcribed verbatim and an inductive thematic analysis will be performed.

Sample size

The aim of this study is to explore the feasibility of implementing our trial procedures and to inform a power calculation for a future randomised controlled trial. We have calculated the sample size required based on the margins of error associated with recruitment. The approximate size of the Guy's and St Thomas' dialysis population is 600 patients, in which we expect to be able approach 400. Assuming a conservative uptake rate of 50%, 200 patients will be screened with approximately 40% meeting the inclusion criteria (the estimated prevalence of depression symptoms in HD patients; see (4)). If we assume 50% of those eligible will consent to be randomised a sample size of approximately 66 would allow us to estimate the true population consent rate with a 5% margin of error and a 95% confidence level.

Analysis plan

To examine the feasibility and acceptability of our screening, recruitment, retention, and randomisation process (objectives 1-3), we will quantify the flow of participants through the study using frequencies and percentages in accordance with the consort flow diagram (36) shown in Figure 2. We will also record and quantify reasons for non-consent, exclusion, and drop-out for each stage of the study. We will examine degree of adherence to the intervention and telephone support calls (where applicable) using descriptive statistics (objective 4).

We will also perform an *exploratory* intention to treat mixed model analysis blind to treatment group on the following self-report outcomes at three months follow-up: depression, anxiety, and quality of life (objective 5 & 6). Variability in these patient outcomes will help to inform a future power calculation for a full-scale trial.

Service costs will be calculated by combining service use data with appropriate unit costs (42). These will be added to the costs of the intervention which will be based on development costs and the time spent providing telephone support. Costs will be compared between the two groups and cost-effectiveness assessed by combining the costs with the primary outcome measures and quality adjusted life years (QALYs) in the form of incremental cost-effectiveness ratios (ICERs). Uncertainty around the ICERs will be addressed using cost-effectiveness planes and acceptability curves (objective 7). We will also perform an exploratory process analysis using intention to treat mixed models to establish whether illness cognitions changed in response to the online intervention and whether differences occurred between the intervention and control group (objective 8). Qualitative interviews will be transcribed verbatim and analysed using thematic analysis to allow the feasibility and acceptability of the online intervention and telephone support calls to be explored (objective 9).

Ethics

This study has ethical approval from the NHS research ethics committee (14/LO/1934) and is sponsored by King's College London.

Data collection and management

The IMPARTS screening interface, developed by Teleologic Ltd, is web-based and installed on the server configuration at Guy's & St Thomas' Hospitals NHS Foundation Trust. The patient logs on to the system with their unique Hospital Number. Their screening results are outputted to the documents folder of the Electronic Patient Record via the most secure wifi network within each NHS Trust.

All quantitative outcomes are measured via online questionnaires that participants will access via iDiD website. The information is stored on a secure server associated with the Lifeguide program at the University of Southampton. The website prompts the participant when data is missing. Study data can only be downloaded from the server by members of the research team who are granted password access. All data will be confidentially stored in accordance with the data protection act (43) and King's College London data management procedures.

Formal committee

A trial management team will meet regularly to discuss the overall running of the study including: rates of recruitment, adherence to the protocol, safety and confidentiality of patients. All serious adverse events related to the study will be reported to the study sponsor, ethics committee and Guy's and St Thomas' research and development department.

Discussion

Psychological distress is common in people with ESKD. However, studies examining the efficacy of either pharmacological or psychological interventions for the management of distress in dialysis are limited. Likewise, access to psychological treatment interventions tailored to the specific psycho-social stresses associated with ESKD is problematic. An online CBT treatment designed specifically to manage distress in dialysis offers a pragmatic solution to under-resourced health services, which are advised to offer integrated mental and physical health care treatments.

This is the first study to examine whether it is feasible to implement a RCT of online CBT with telephone support vs online CBT without telephone support within a stepped care framework to secondary care haemodialysis patients with co-morbid distress. Indeed, it will identify unique challenges that occur in the dialysis population in the recruitment and retention of patients. Likewise, the study will be able to simultaneously examine the acceptability of this treatment to patients in terms of whether its content was relevant and useful. In addition, the utility of the online mode of delivery with or without telephone support will be examined. We anticipate that the results of this trial will substantially inform the design of a future large scale trial powered to detect the efficacy of online CBT treatments for the management of distress in dialysis.

Trial Status

The study commenced recruitment in February 2015. Recruitment will continue until February 2016 with the last patient's follow-up in May 2016. Outcomes will be disseminated at national and international conferences and in journal articles.

List of abbreviations

CBT, Cognitive behavioural therapy; ESKD, End-stage renal disease; ICERS, incremental cost-effectiveness ratios; iDiD, Improving distress in dialysis; QALYs, Quality Adjusted Life Years; RCT, Randomised Controlled Trial

Authors Contributions:

Study design: All authors

Intervention development: JH, RMM, DG, AC, LY, JC:

Statistical analysis plan: PM, JC.

All authors contributed to writing the protocol.

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675 Table 1: Schedule of assessments

Assessment	Time		
	Screening	**Baseline**	**3 months**
PHQ-9	x	x	x
GAD-7	x	x	x
EQ-5D		x	x
Client Service Receipt Inventory		x	x
Socio-demographics		x	
Clinical characteristics		x	
Biological clinical outcomes		x	x
Self-reported adverse events			x
Self-reported treatments for depression and anxiety during the study			x
Brief illness perception questionnaire		x	x
Satisfaction with care		x	x
Experience of using the iDiD website			x

Figure titles:

Figure 1: Stratified stepped care referral pathway for managing psychological distress among individuals attending for haemodialysis

Figure 2: Flow of participants through the study

Figure 1: Stratified stepped care referral pathway for managing psychological distress among individuals attending for haemodialysis

199x102mm (300 x 300 DPI)

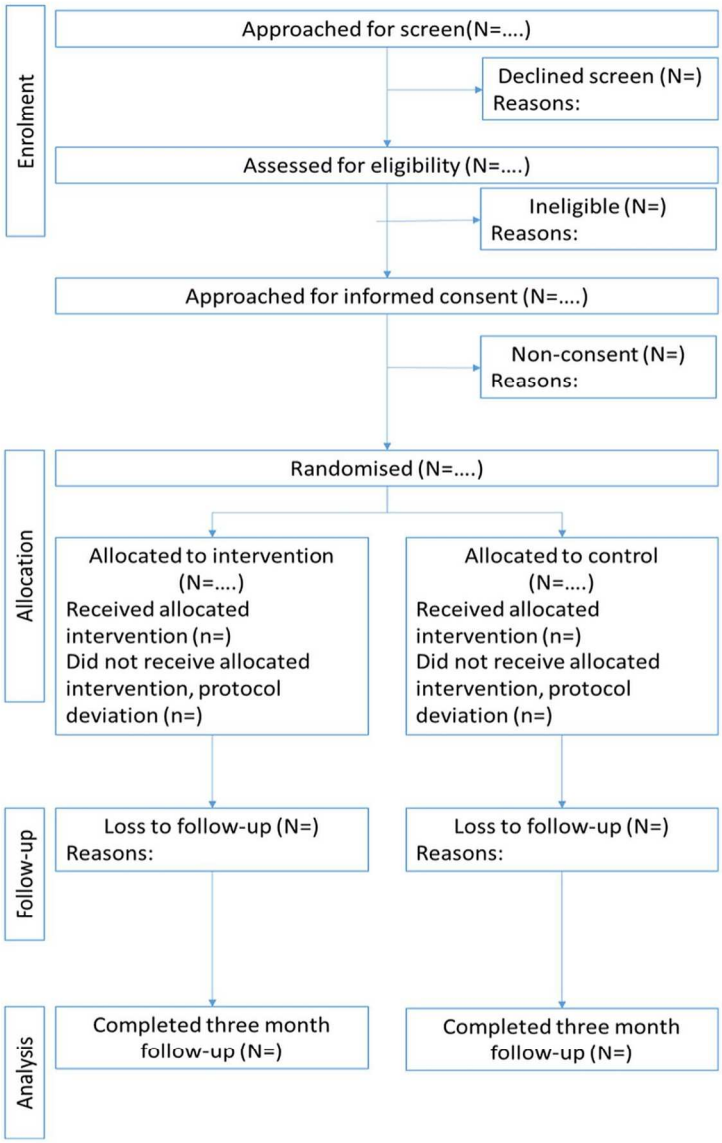

Figure 2: Flow of participants through the study
99x153mm (300 x 300 DPI)

Supplementary table 1: Summary of iDiD online treatment sessions

Session	Content
1. What is end-stage renal failure?	-Psycho-education including information about: -ESKD and its treatment. -Expectation management concerning the effectiveness of dialysis treatments and its psycho-social consequences. -The rationale for specific ESKD treatments (i.e. improving physical health) and psychological interventions (i.e. improving emotional health). -Normalising the experience of distress in the context of dialysis.
2. Why do I feel distressed?	-Recaps on information learnt about in session 1. -Self-generation of a personal model of distress. Patients self-identify their own vicious cycle to improve their understanding of the inter-relationships between ESKD specific stressors (triggers), feelings, thoughts, behaviours, and physical symptoms. *Between session task:* Recap on the content of session 2 by re-reading the session.
3. Dealing with my negative feelings	-Recaps on information learnt about in session 2. -Revision of reinforcing relationship between unhelpful coping behaviours and the maintenance of psychological distress. -Explanation of positive emotion regulation strategies including: behavioural activation, emotional expression, graded exposure, and tips for improving the quality of sleep. Patients are also informed of the value of acceptance, relaxation, and physical exercise. *Between session task:* Selection of a helpful coping strategy for managing negative emotions before completion of next online session.

4. Tackling unhelpful thoughts about end-stage renal disease	-Recaps on information learnt about in session 3. -Examples of unhelpful thoughts typical in people with ESKD provided. -Information and skill development on the identification of unhelpful thoughts using thought records. -Explanation of how to challenge and gradually alter unhelpful thinking styles by generating alternatives. *Between session task:* Continue working on goals from session three (if useful) and complete a thought record if relevant to their personal needs.
5.Goal setting and problem solving	-Recaps on information learnt about in session 4. -The rationale for "SMART" goals and how to use the technique is explained in depth. -Information about the value of activity monitoring, behavioural activation, and action planning. -Explanation of the seven steps to problem solving technique is introduced. Use to foster confidence in illness self-management. *Between session task:* Continue working on goals from previous sessions that remain useful and relevant. If applicable implement one of the following: i) "SMART" goal techniques, ii) activity monitoring/behavioural activation, or iii) seven steps to problem solving approach.
6. Managing difficult social relationships	-Recaps on information learnt about session 5 -Case examples of social situations people with ESKD find challenging (i.e. dealing with medical

	professionals) provided. -Introduction to assertiveness concept and its effects on physical and psychological health. -Case examples provided of how others behave assertively in ESKD specific social contexts to allow participants to adapt for their own use. -Reflection on social support network and whether there is scope to improve it to meet physical, emotional, and informational needs. *Between session tasks:* Continue working on goals from previous sessions that remain useful and relevant. If feasible/applicable implement: a potential assertive responses to a stressful social situation or reflect on social support networks and how to optimise them.
7. Progress recap and preparing for the future	-Recaps on the progress made over the previous six sessions by encouraging patients to reflect on their new skills and achieved goals. -Generation of action plans to continue using skills moving forward. Identification of a specific action plan to implement when an acute stressful situations arises.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__2_____
	2b	All items from the World Health Organization Trial Registration Data Set	Documented in trial registry (2a) & page 1_____
Protocol version	3	Date and version identifier	_3_____
Funding	4	Sources and types of financial, material, and other support	_3_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_1_____
	5b	Name and contact information for the trial sponsor	_3_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__3_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_NA for feasibility study_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 to 6_____
	6b	Explanation for choice of comparators	5 to 6_____
Objectives	7	Specific objectives or hypotheses	7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 to 9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12 to 14_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11 and 13_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15 and 16 _____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9 to 13_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions12	12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9 to 12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA as trial co-ordinator is not blind._____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9 to 11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9 to 11_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17 to 18_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17 to 18_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17 to 18_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA for feasibility study_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA for feasibility study _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA for feasibility study _____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2 and 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9 and 10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA harms addressed according to King's indemnity insurance
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Adheres to NHS consent form_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this NA with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.