This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE STUDY

Cognitive Behaviour Therapy for Depersonalisation-Derealisation Disorder (CBT-f-DDD): A feasibility study

SHORT STUDY TITLE / ACRONYM

CBT-f-DDD

PROTOCOL VERSION NUMBER AND DATE

6.4

27.10.22

RESEARCH REFERENCE NUMBERS

IRAS Number:	314923
SPONSORS Number:	H-1809b
FUNDERS Number:	NIHR202201

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:10/05/2022

Priscilla Essuman

.....

Name (please print):

Priscilla Essuman

.....

Position:

Sponsorship Manager.....

Chief Investigator:

Signature: .....  Date:10/05/22

Name: (please print):

.....Dr Elaine Hunter.....

LIST of CONTENTS

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Study Co-ordinator	Same as Chief Investigator above
Sponsor	CAMDEN AND ISLINGTON NHS FOUNDATION TRUST of St. Pancras Hospital, 4 St. Pancras Way, London, Greater London, United Kingdom, NW1 0PE Sponsor.noclor@nhs.net 0203 317 3034
Joint-sponsor(s)/co-sponsor(s)	N/A
Funder(s)	National Institute of Health Research, Central Commissioning Facility, Grange House, 15, Church Street, Twickenham, TW1 3NL. Tel: 020 8843 8000. Fax: 020 8843 8001. Email: ccf@nihr.ac.uk
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Committees	**Trial Steering Committee** Chair: Professor Paul Salkovskis (paul.salkovskis@hmc.ox.ac.uk) Clinician/Researcher: Dr Emma Cernis (emma.cernis@psych.ox.ac.uk) PPI representative: Mr Chris Leslie (chrissleslie@gmail.com) **Independent Data Monitoring and Ethics Committee** Chair: Dr Susannah Pick (Susannah.pick@kcl.ac.uk)

	Statistician: Dr Dominic Stringer (dominic.stringer@kcl.ac.uk) PPI representative: Ms Jordan Downey (jordandowney19@gmail.com) **Patient Advisory Group** Andreas Pantazopoulos (andreas.pantazopoulos@gmail.com) Leanne Sturrock (leannesturrock@gmail.com) Lindsay Dunsmore (lindunsmore@icloud.com)

STUDY SUMMARY

Study Title	Cognitive Behaviour Therapy for Depersonalisation-Derealisation Disorder (CBT-f-DDD): A feasibility study
Internal ref. no. (or short title)	CBT-f-CBT
Study Design	A CBT-f-DDD manual and workshop will be developed and generic NHS CBT therapists from inner and outer London Trusts will be trained. Eligible participants (n=60) will be randomised to receive either 6 months of CBT-f-DDD or standard care. Assessments will be conducted at four time points: eligibility, start and end of intervention, and 12-month follow-up. Mixed-method measures of feasibility and acceptability will be collated and evaluated from both participants and clinicians, to assess recruitment, eligibility and attrition rates; resources needed; power calculations; therapist adherence to CBT-f-DDD; and participant and therapist satisfaction and acceptability. Public and patient involvement is intrinsic at every stage of the study. There are 3 phases of the study which will last 28 months overall. Phase 1 (4 months) will consist of participant recruitment, the development of the CBT-f-DDD manual and delivery of the workshop for clinical staff. In Phase 2 (12 months), there will be ongoing recruitment and participants will be given either 6 months of CBT-f-DDD or standard care. In Phase 3 (12 months) 12-month follow-ups will be conducted using quantitative and qualitative methods. Data analysis, write up and dissemination will be carried out.
Study Participants	People who meet diagnostic criteria for Depersonalisation-Derealisation Disorder

Planned Size of Sample (if applicable)	To recruit 60 in total to allow for 40 completers (20 in each arm of the study).
Follow up duration (if applicable)	N/A
Planned Study Period	28 months
Research Question/Aim(s)	This project has 4 aims: 1) to fill the demonstrable gap in effective treatments for DDD by undertaking a feasibility RCT of CBT-f-DDD to define the parameters to inform a future efficacy trial (RCT), 2) disseminate specialist CBT-f-DDD skills to generic NHS clinicians, 3) to evaluate a manualised protocol, training workshop and clinical supervision, and 4) determine whether CBT-f-DDD can be conducted within a typical NHS setting with generic CBT therapists given a brief training in DDD.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	
	NIHR
	UCL
	Camden and Islington NHS Foundation Trust
	Barnet Enfield and Harringay NHS Trust

ROLE OF STUDY SPONSOR AND FUNDER

The sponsor is responsible for the study design, conduct of the study, data analysis and interpretation, writing of manuscripts and dissemination of results. The sponsor will make the final decisions regarding any of these aspects of the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Steering Groups

1) Trial Management Group

This includes all members of the research team who meet monthly (fortnightly during recruitment phase) to discuss all aspects of management of the trial such as recruitment, personnel, randomisation etc

Dr Elaine Hunter (e.hunter@ucl.ac.uk): Joint Principal Investigator (Chief Investigator)

Professor Anthony David (anthony.s.david@ucl.ac.uk): Joint Principal Investigator

Professor Glyn Lewis (glyn.lewis@ucl.ac.uk): co-investigator

Dr Nicola Morant (n.morant@ucl.ac.uk): co-investigator

Dr Rafael Gafoor (r.gafoor@ucl.ac.uk): co-investigator

Dr Elena Pizzo (e.pizzo@ucl.ac.uk): co-investigator

Mr Joe Perkins (jp@joeperkins.co.uk): co-investigator/ PPI representative

Ms Nicola Dalrymple (nicola.dalrymple@candi.nhs.uk): Research Assistant

Research Assistant 2 (to be recruited later in project)

2) Trial Steering Committee

This is an independent team from the investigators who operate on behalf of the funders to oversee the study and have power to stop the trial if they deem this necessary. First meeting to be convened before entry of first patient and frequency to be determined by TSC chair. The TSC and IDMEC committees will be given charters which will allow the Chairperson (who will be NIHR approved) to adjust the membership of the committees as necessary during the conduct of the study. The NIHR will be kept informed of all changes to the TSC and IDMEC committees.

Chair: Professor Paul Salkovskis (paul.salkovskis@hmc.ox.ac.uk)

Clinician/Researcher: Dr Emma Cernis (emma.cernis@psych.ox.ac.uk)

PPI representative: Mr Chris Leslie (chrissleslie@gmail.com)

3) Independent Data Monitoring and Ethics Committee

This is an independent team from the investigators who operate on behalf of the funders. The IDMEC sees unblinded data and meets to provide reports to the TSC. First meeting to be convened before entry of first patient and frequency to be determined by IDMEC chair.

Chair: Dr Susannah Pick (Susannah.pick@kcl.ac.uk)

Statistician: Dr Dominic Stringer (dominic.stringer@kcl.ac.uk)

PPI representative: Ms Jordan Downey (jordandowney19@gmail.com)

4) Patient Advisory Group

Independent group of people with lived experience of the condition. Meetings of the PAG will be held every two months throughout the study to have on-going involvement with recruitment, intervention, analysis and interpretation. Activities of the PAG will include reviewing trial materials (e.g. information sheets, consent forms), involvement in designing qualitative interview topic guides, and providing a lived experience perspective on trial processes.

Andreas Pantazopoulos (andreas.pantazopoulos@gmail.com)

Leanne Sturrock (leannesturrock@gmail.com)

Lindsay Dunsmore (lindunsmore@icloud.com)

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Dr Rafael Gafoor – co-applicant (r.gafoor@ucl.ac.uk)

Mr Joe Perkins – co-applicant/ PPI representative (jp@joeperkins.co.uk)

Dr Elena Pizzo – health economics advisor (e.pizzo@ucl.ac.uk)

Ms Nicola Dalrymple – research assistant (nicola.dalrymple@candi.nhs.uk)

Patients, service users, and/or their carers, or members of the public have been involved at all stages of the study. In terms of the study protocol, the Co-PI supervised a service audit of CBT-f-DDD using a semi-structured survey of 45 service users and their referrers to evaluate experiences of assessment and therapy. This identified therapy components of most value to service users. This information has been incorporated in the current study design.

The Co-PI's are involved with the national charity for DDD *'Unreal'* as, respectively, founding member/trustee and ambassador. The Charity is a co-applicant, with Mr Perkins as the named representative. We have already conducted pre-award activities by setting up a Patient Advisory Group (PAG) of people with lived experience (PWLE) of DDD who were recruited through the charity 'Unreal'. An initial meeting of this group reviewed an earlier proposal and gave feedback on the acceptability of the proposed measure and procedures. It was also suggested that a nominal fee toward travel costs should be included to encourage participants to take part in assessments, and for out of London participants to attend regular therapy sessions. These changes have been incorporated into the current study design. Another PAG meeting reviewed study documents and their suggestions were integrated into the content and design of the documents.

PPI is built into our research in three ways:

1. PWLE of DDD will co-present in the training for clinicians alongside the co-PI to give a service user perspective on the experience and impact of DDD.
2. Meetings of the PAG will be held every two months throughout the study. Activities of the PAG will include reviewing study materials (e.g. information sheets, consent forms); input into designing qualitative interview topic guides; providing a lived experience perspective on recruitment and trial processes; and contributing to the interpretation of qualitative and quantitative findings.
3. At the end of the study, the PAG and members of the charity *Unreal* will be involved with dissemination activities targeted to service user and stakeholder groups more broadly.
    a. An online dissemination event will be co-delivered with PWLE of DDD from the Charity to the 447 people who currently receive a regular newsletter, as well as the ~2000 subscribers across the Charity's social media platforms.

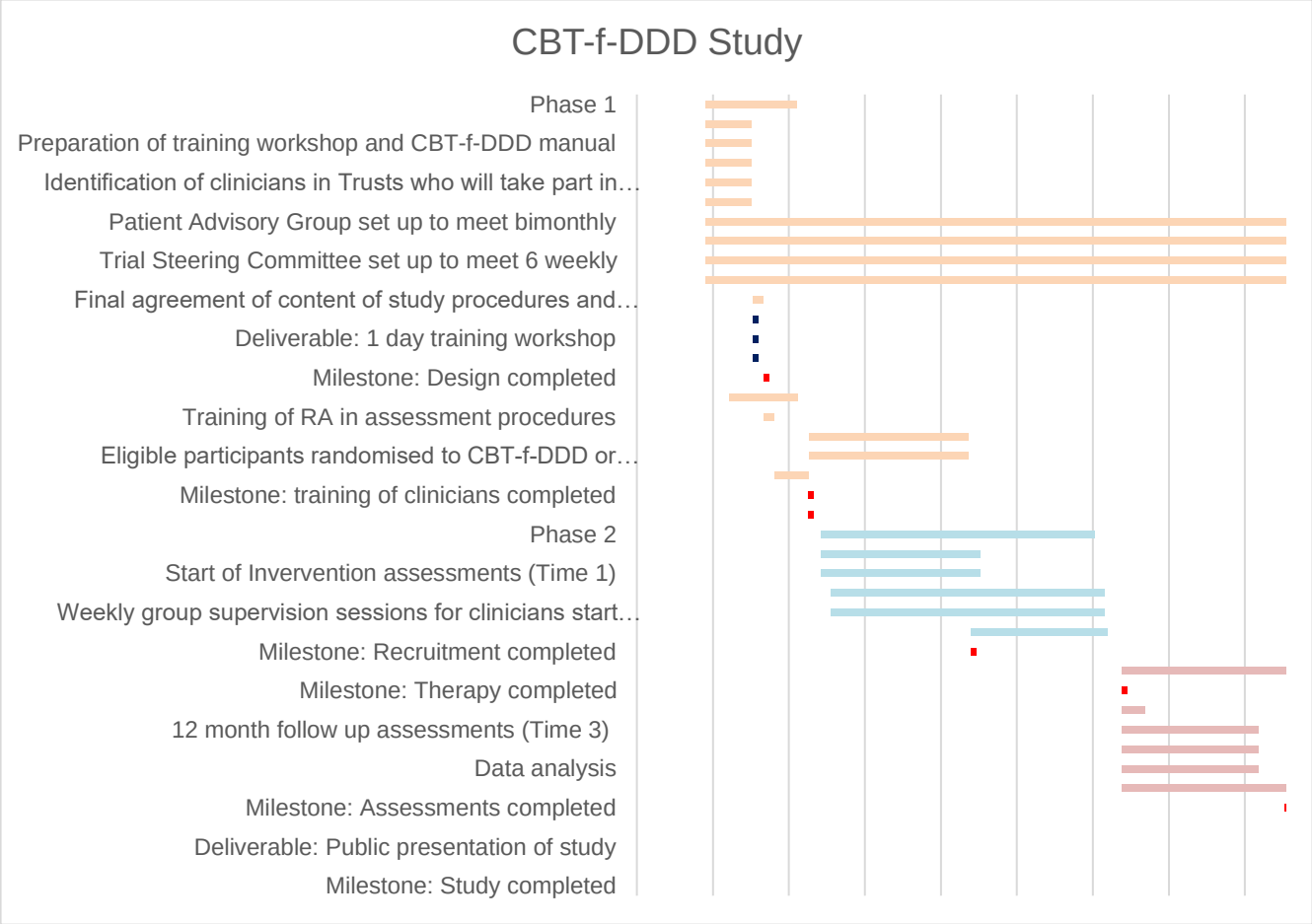
b. A plain English summary of the findings will be made available on the Charity's website.
c. The Charity has been successful in raising awareness of DDD via media coverage and will use the results to do the same for treatments for DDD via press and social media targeted at PWLE and the public.
d. The Charity will also liaise directly with clinical organisations such as the Royal College of General Practitioners and the Royal College of Psychiatrists to raise awareness of CBT as a possible intervention for DDD.
e. There have been discussions in the Ministry of Health about the lack of research on evidence-based treatments for DDD and the Charity will liaise with their contacts here to lobby for greater service provision within the NHS if the results appear promising.
f. Clinical audiences will be reached with a conference presentation at the annual CBT conference of the BABCP as well as via written publications.

KEY WORDS: Cognitive Behaviour Therapy
Dissociative disorders
Depersonalisation Derealisation Disorder

STUDY FLOW CHART

Task	Start date	Duration (days)
Phase 1	01-Dec-21	120
Preparation of materials in study e.g. consent forms, assessments etc	01-Dec-21	60
Preparation of training workshop and CBT-f-DDD manual	01-Dec-21	60
Awareness raising of recruitment starting in C&I and BEH NHS Trusts	01-Dec-21	60
Identification of clinicians in Trusts who will take part in the study	01-Dec-21	60
Awareness raising of recruitment starting with Unreal Charity	01-Dec-21	60
Patient Advisory Group set up to meet bimonthly	01-Dec-21	840
Trial Management Group set up to meet monthly	01-Dec-21	840
Trial Steering Committee set up to meet 6 weekly	01-Dec-21	840
Independent Data Monitoring and Ethics Committee set up to meet 6 weekly	01-Dec-21	840
Final agreement of content of study procedures and materials by PAG	01-Feb-22	14
Deliverable: study materials (e.g. assessments, questionnaires)	01-Feb-22	7
Deliverable: 1 day training workshop	01-Feb-22	7
Deliverable: Manualised protocol for CBT-f-DDD	01-Feb-22	7
Milestone: Design completed	15-Feb-22	7
NHS ethical approval application with submission following PAG approval	01-Jan-22	90
Training of RA in assessment procedures	15-Feb-22	14
Recruitment of participants and Eligibility assessments (Time 0)	15-Apr-22	210
Eligible participants randomised to CBT-f-DDD or standard care	15-Apr-22	210
CBT-f-DDD half-day training workshops for clinicians delivered	01-Mar-22	45
Milestone: training of clinicians completed	15-Apr-22	7
Milestone: Ethics approved	15-Apr-22	7
Phase 2	01-May-22	360
Eligible participants allocated to CBT-f-DDD therapists	01-May-22	210
Start of Invervention assessments (Time 1)	01-May-22	210
CBT-f-DDD therapy sessions start (12-18 sessions within 6-month window)	15-May-22	360
Weekly group supervision sessions for clinicians start with Co-PI (clinicians to attend fortnightly)	15-May-22	360
End of therapy assessments (Time 2) and questionnaire about experiences of treatment	15-Nov-22	180
Milestone: Recruitment completed	15-Nov-22	7

Phase 3	01-Jun-23	300
Milestone: Therapy completed	01-Jun-23	7
Therapist qualitative interviews regarding training, therapy and supervision	01-Jun-23	30
12 month follow up assessments (Time 3)	01-Jun-23	180
Participant qualitative interviews on experiences of therapy	01-Jun-23	180
Data analysis	01-Jun-23	180
Writing up of study	01-Jun-23	300
Milestone: Assessments completed	01-Jan-24	7
Deliverable: Academic manuscripts and presentation of study	15-Feb-24	7
Deliverable: Public presentation of study	15-Feb-24	7
Dissemination events to public and professionals	15-Feb-24	45
Milestone: Study completed	21-Mar-24	7



STUDY PROTOCOL

Cognitive Behaviour Therapy for Depersonalisation-Derealisation Disorder (CBT-f-DDD): A feasibility study

1 BACKGROUND

Depersonalisation-Derealisation Disorder (DDD) is a distressing mental health condition where a person has a profound sense of disconnection and unreality about themselves and the world[1]. Systematic reviews of the prevalence of DDD in community surveys estimate it to be around 1-3%, which is similar to rates of schizophrenia or obsessive-compulsive disorder, with higher prevalence rates of DDD (~20%) found in people in contact with mental health services, usually in combination with other disorders [2,3]. However, there is a huge gap between true prevalence rates and clinical diagnosis and chronic under-diagnosing of DDD has undoubtedly contributed to the widely held but erroneous assumption that DDD is rare. Consequently, there has been an under-funding of research into effective treatments, with what there is of an evidence base being mostly produced by the applicants and 1 or 2 other groups worldwide. There is currently no NICE guidance on treatments for DDD [4]. Recent lobbying of parliament achieved formal acknowledgement of the urgent need for more research [5].

CBT is the most widespread talking therapy used in the NHS with effectiveness demonstrated across a wide range of conditions[4.] CBT seeks to identify cognitive (i.e. thoughts and thinking processes), emotional and behavioural factors that might perpetuate symptoms and seeks to find more helpful alternatives. Although the basic cognitive and behavioural theory of emotion and behaviour remains the same, adaptations of CBT to different disorders take account of what are the most relevant areas to address in therapy [6].

In systematic reviews of the existing evidence of treatment for DDD, the strongest evidence is for CBT that has been adapted for the condition, with little benefit demonstrated from a variety of medications and other therapy modalities [7]. There have been two uncontrolled studies of consecutive referrals to a tertiary specialist clinic which were undertaken by the co-PIs [8,9]. In the first of these, we treated 21 participants most with longstanding severe symptoms which had not responded to medication or talking therapies, with a mean of 13 individual CBT sessions. There was a significant reduction in state DDD symptom severity at post-treatment and six-month follow up (mean difference of 12.6 (s.d. = 19.5), with 29% of participants no longer meeting diagnostic criteria at the end of therapy, in addition to a significant reduction in the severity of general dissociation, anxiety, depression and general functioning. A recent analysis of outcomes of 36 participants from the same clinic, as yet unpublished, has replicated these initial findings [9]. Significant improvements on trait DDD symptoms (mean difference of 40.4 (s.d. = 69.7) were found after a mean of 18 sessions of CBT, with additional significant reductions in anxiety and depression symptoms.

However, there were several methodological limitations to these studies: participants were not randomised and compared to a control group; the sample sizes were small; participants were only recruited from one tertiary specialist clinic and therefore may not be typical of those in generic primary and secondary care setting; and a small number of clinicians delivered the intervention. It is not possible therefore to know if the key ingredient for change was CBT-f-DDD and whether these results can be generalised to other NHS settings. However, given the chronic nature of DDD, these results are still promising even though they are uncontrolled.

2 RATIONALE

This project has 4 aims: 1) to fill the demonstrable gap in effective treatments for DDD by undertaking a feasibility RCT of adapted Cognitive Behaviour Therapy (CBT) for DDD (CBT-f-DDD) to define the parameters to inform a future efficacy trial (RCT), 2) disseminate the specialist CBT-f-DDD skills to generic NHS clinicians, 3) to evaluate a manualised protocol, training workshop and clinical supervision, and 4) determine whether CBT-f-DDD can be conducted within a typical NHS setting with generic CBT therapists given a brief training in DDD.

DDD has not had the same level of research into effective treatments as have other disorders with similar prevalence rates. There is only one specialist clinic for DDD in the UK, with another clinic which accepts DDD referrals, and only three clinical psychologists who have experience in regularly treating people with DDD. Both clinics are based in London, which given CBT is usually offered on a weekly basis, makes it difficult for those living outside the capital to attend. Moreover, these services are funded on a cost-per-case basis that means people with DDD need to obtain specialist funding from their local Clinical Commissioning Group to be able to be seen by specialist services, even for an assessment, and this can take months, and sometimes years, to obtain. Once funding has been obtained there is an additional delay with long waiting lists due to lack of specialist clinicians.

3 THEORETICAL FRAMEWORK

The proposed feasibility RCT addresses the aim of the RfPB research call by:

1. Defining the feasibility and acceptability parameters for a subsequent larger scale efficacy RCT for CBT adapted for DDD. We will determine the pooled standard deviation for the follow up score of the primary outcome variables as well as the correlation with the outcome scores at the end of the study period. These data, along with the mean clinically important difference (MCID) will be used in the sample size calculation for a fully powered subsequent study.
2. Enabling more clinicians to be trained in working with DDD, and for the expertise that has been developed in specialist DDD services to be disseminated via training and regular case supervision to those working in standard primary and secondary care. This will test whether the results in effectiveness in CBT-f-DDD obtained to date in specialist services can be generalisable to standard, generic, NHS services, in inner and outer London regions allowing greater access to DDD-specific treatment for those with the condition, without the need to refer to overstretched tertiary services.
3. We will evaluate whether it is possible to develop a manualised protocol and train CBT therapists with a half-day workshop to be able to adapt their current skills to work effectively with DDD. If this is effective, it will allow for widespread training of CBT therapists nationwide to enable more local treatment for DDD to be offered.
4. Evaluating whether CBT-f-DDD is effective in the treatment of symptoms and associated sequelae. Given the paucity of high-quality studies into treatments for DDD, this will be of huge benefit both for those with the condition, as well as clinicians (and ultimately the NHS).

4 RESEARCH QUESTION/AIM(S)

A) To undertake a feasibility RCT of adapted Cognitive Behaviour Therapy (CBT) for DDD (CBT-f-DDD) to define the parameters to inform a future efficacy trial (RCT) and to perform a within-trial economic evaluation to compare the costs and outcomes of the intervention group versus the standard care group,

B) disseminate the specialist CBT-f-DDD skills to generic NHS clinicians,

C) to evaluate a manualised protocol, training workshop and clinical supervision, and

D) determine whether CBT-f-DDD can be conducted within a typical NHS setting with generic CBT therapists given a brief training in DDD.

4.1 Objectives

OBJECTIVES

A1). Assess the referral rates from generic referrals to local primary and secondary mental health services in inner and outer London NHS Trusts, as well as those self-identified via a national charity specifically for those with DDD, '*Unreal*'[10], where the study will be advertised. Eligibility rates will also be calculated.
A2). Assess participant acceptability of randomisation, assessment processes and measures, as well as retention rates and satisfaction with treatment using quantitative and qualitative methods.
A3). Determine the pooled standard deviation of the clinical outcome (Cambridge Depersonalisation Scale[11]) so that a sample size calculation can be carried out for an RCT.
A4). Assess the costs of training for CBT for DDD, the costs of delivering the intervention (CBT for DDD) and the cost of the standard care (no CBT). We will identify and measure health service usage and quality of life to estimate the incremental cost per QALY associated with the intervention.
B1). Train up to 20 NHS generic CBT therapists in CBT-f-DDD via a training workshop and consolidate the application of theory into clinical practice via treatment of at least one client with DDD with regular clinical case supervision.
C1). Develop a manualised protocol for treatment.
C2). Assessing the training of generic CBT therapists in CBT-f-DDD with a half-day workshop.
C3). Monitor therapy progress and evaluate the effectiveness of supervision via therapist feedback.
D1) Evaluate the feasibility of delivering CBT-f-DDD within a standard NHS setting

4.2 Outcomes

<u>Outcomes collected to establish the feasibility, health economic evaluation, and acceptability of conducting a future effectiveness RCT including:</u>

- Recruitment/ eligibility data
    - Number of referrals from each source, numbers ineligible, reasons for ineligibility, rates and reasons for refusal to be included in the study. A minimum of 12 participants in each arm for feasibility studies has been suggested for pilot studies[12] which would require recruiting 29 eligible participants in total (including 20% drop out estimate).
- Attrition rates and reasons for withdrawing throughout the study, follow-up rates
- Sample characteristics to check representativeness of the sample
    - Descriptive demographic data including participants' age, gender, ethnicity, education, employment status.
    - Clinical characteristics including age of onset of DDD, duration, co-morbid diagnoses, previous treatments for DDD, type and dosage of current medication.
- Resources needed to complete CBT-f-DDD
    - Length of time required for RAs to complete assessments and collect and analyse data (from research assistant time sheets), CBT attendance rates (from electronic patient

records), and the amount and nature of supervision required (from Co-PI supervision notes).

- Health economics evaluation
    - Baseline data on health service usage using The Client Service Receipt Inventory[13] which collects information on participants' use of health and social care services, living situation, income, employment and benefits, NHS and private costs. Quality of Life will be assessed using the EQ5D5L[14]. These data will be collected at baseline (time 1 assessment), after treatment (time 2 assessment) and at 12-month follow up (time 3 assessment).
- Power calculations
    - We will determine the pooled standard deviation for the baseline score of the primary outcome variable, as well as the correlation with the outcome scores at the end of the study period. These data, along with the mean clinically important difference (MCID), will be used in the sample size calculation for a fully powered subsequent study.
- Therapist adherence to CBT-f-DDD (fidelity)
    - Records of session content, participants' engagement with CBT-f-DDD, and homework tasks completed (all from therapist post session checklists) will be monitored. Also, a random sample of 10% of audio-recorded therapy sessions will be evaluated using standardised CBT protocols for adherence to the CBT model[15] as well as an adapted CBT-f-DDD checklist.
- Participant acceptability (collected via end of intervention questionnaire and semi-structured interviews at Time 3)
    - Acceptability of assessment procedures and measures.
    - Acceptability of CBT-f-DDD including aspects of the treatment found helpful and unhelpful, perceived impact of the intervention, and satisfaction with the intervention and therapists.
- Therapist acceptability (collected via semi-structured interviews at Time 3)
    - Satisfaction with training and supervision, confidence in delivering CBT-f-DDD, views of the intervention's value and perceived impact, and perceived feasibility of delivery in standard clinical settings.

5 STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYIS

This project will use a two arm individually randomised (RCT), single blinded to assessor, design to test the feasibility and acceptability of conducting a future RCT of individual CBT for DDD compared to standard care.

Participant Journey

Suitable referrals will undertake an eligibility assessment (Time 0) and if suitable for inclusion, they will be randomised to either CBT-f-DDD or standard care. They will be assessed again at the start of intervention (Time 1) and then offered either weekly sessions of individual CBT, or standard care, within a 6-month intervention window. Depending on how frequently they attend the CBT-f-DDD therapy, number of sessions will vary from a required minimum of 12 to a possible 24. At the end of the intervention period both groups will be assessed again (Time 2). After a further 6 months (i.e. 12 months since Time 1 assessment) they will be assessed again for the final time (Time 3).

Phase 1 (Months 1-4): Recruitment and Training of Therapists

Ethical approval will be sought, and fully informed, written consent will be obtained from those patients recruited to the trial. Participants will be identified by local clinicians based on eligibility criteria, will be provided with participant information sheets and will be asked for consent to be contacted by the research team. Clinicians will then contact the research team with the potential participants' information. If consent to contact is granted, potential participants will be assessed for eligibility and a range of standard measures will be completed (Eligibility assessment, Time 0 assessment) by a research assistant who will not be involved in the delivery of the intervention. During Phase 1, the manualised intervention will be completed, and the final version agreed with the Patient Advisory Group. This will be made available for bona fide researchers and NHS services.

Training of Therapists

The training of the CBT therapists will take place in half-day workshops. We have agreement from the relevant Heads of Services that NHS therapists across services at C&I and BEH will attend the training in order to be able to take on one or more cases of DDD (i.e. 0.1 WTE or more) following the training. As this is a feasibility study, we will be examining whether a half-day training would be sufficient to provide these knowledge and skills. All NHS clinicians will be qualified and have existing CBT skills and experience, so the training workshop will aim to help clinicians understand DDD and to demonstrate the adaptation of existing CBT skills to work with this specific disorder. This will allow clinicians to build upon existing CBT skills. We will enquire about whether CBT therapists included in the study are accredited with the British Association of Behavioural and Cognitive Psychotherapists (BABCP) and we will be collecting this data. All clinicians will receive a hard copy of the training manual to accompany the training with additional materials and reading.

We envisage having a relatively large number of therapists with a small trial caseload to reduce the burden on services and to maximise the number of therapists who will benefit from training and specialist supervision. We have estimated this will equate in total to the cost of 2.2 WTE therapists to complete the CBT intervention on 20 participants, including attrition. Written consent will be obtained from therapists recruited to the trial prior to their involvement in the study. These therapists will be involved in the study for the period of 6 months of the delivery of the intervention, plus training and report writing time of another 1 month, although if this may be longer if therapists see more than one client in succession. In addition to the initial training, the co-Principal Investigator (Hunter) will offer weekly group specialist supervision to the participating therapists, who will be asked to attend on a fortnightly basis. Therapists will audio record all their therapy sessions, with consent from patients, to check adherence to CBT protocol (i.e., a random 10% of recordings will be listened to and rated according to the standardised CBT scale CTS-R[15]).

Phase 2 (Months 5-16): On-going Recruitment and Intervention

At the end of Phase 1, participants will be assessed again (Start of Intervention, Time 1 assessment). Randomisation lists will have been created by the independent statistician (Dr Louise Marston – UCL Primary Care & Population Health) prior to recruitment to the study, and they will be delivered to the recruitment sites by sealed envelope method. All participants and study staff will not be blinded apart from Dr Rafael Gafoor, who is the principal statistician for the study. Dr Gafoor will be unblinded at the end of the study.

Those in the CBT arm will be offered weekly therapy over a 6-month period, up to a maximum of 24

sessions. A minimum of 12 sessions is needed to be categorised as having completed a suitable 'dose' of therapy. Those in the standard care arm will be asked to keep a record of the type and frequency of their appointments with clinical services and treatments offered. This can be supplemented with information provided by their key worker, if applicable.

At the end of the intervention participants will be assessed again (End of Intervention, Time 2 assessment). In addition, participants in both groups will complete a brief questionnaire about their experiences of treatment, including acceptability and impact. In the standard care arm, this will allow for an assessment of participants' views of what was received and the acceptability of this to compare to those in the intervention arm. When therapists have completed intervention delivery for all their cases, they will be invited to participate in a qualitative interview to explore their views on the acceptability, feasibility and perceived impact of training, therapy delivery and supervision.

Phase 3 (Months 17-28): 12-month follow up quantitative data collection, qualitative data collection, analysis of all data, writing up and dissemination and planning for substantive study.
12-month follow up (12-month follow-up, Time 3 assessment) quantitative data will be collected from participants in both the CBT-f-DDD and standard care arms. Following this, a random sample of participants from both arms (n=20) will be invited to an individual semi-structured interview conducted in person, or by phone or videoconference, about their experiences of treatment and its impact. We will also aim to interview any participants who dropped out the interventions arm of the trial, in order to understand reasons for drop out and whether these relate to intervention acceptability issues. However, we recognise that recruitment of these people may be challenging. Dissemination of the findings will take place within the Charity, NHS partners and UCL, through conference presentations, as well as in written peer-reviewed publications. Participants will have the option of requesting study results upon completion by ticking a box in the consent form, and a Plain English Summary will be made available on the Unreal charity website, of which participants will be informed. Upon completion of the study, participants will also receive £10 for their participation.

Standardised outcome measures used to assess their acceptability and feasibility in a future trial (in terms of measures' content and data collection procedures*, including*

- Primary outcomes: Feasibility and acceptability outcomes (listed below, including recruitment/eligibility data, attrition rates and follow up rates)
- Secondary outcomes: Depersonalisation: CDS[11], Dissociation: DES [16], Depression: PHQ [17], Anxiety: GAD [18], Co-morbidity: CIS-R[21], Functioning: Work and Social Adjustment scale (WASA [19]), and a global rating of change question (i.e. "do you feel better?"), Health Economic outcomes: Client Service Receipt Inventory [13] and Quality of Life (EQ5D5L [14])

Plan for analyses
Unblinded results will be discussed in closed sessions of the TMG, and IDMEC from which Dr Gafoor will be excluded. Unblinded interim results will be generated (if necessary) by Dr Louise Marston and circulated to other members of the team as required. Unblinded results will be made available to the IDMEC for each sitting if requested by the Chair of the committee.

Analyses of quantitative data will be primarily descriptive. Descriptions of continuous data, including clinical data and sample characteristics, will be analysed using means, standard deviations (SD) and medians. Frequencies and proportions will used to analyse categorical clinical or demographic variables. The means, SDs, and change scores of participant-level data from Time 0 to Time 3

assessments will be examined to see if changes in key outcomes occurred in the expected direction.

Qualitative data from interviews with therapists and participants will be transcribed and analysed using thematic analysis within NVivo software (supervised by co-applicant Dr Morant). Transcribing will be carried out using an encrypted audio device for the audio recording, which will be stored securely within the NHS setting. This will not have any personal contact details but be assigned a research code. Transcription of this audio recording will be done by a professional external agency (e.g., Transcription Divas) who have an over-arching contract with UCL that covers all the GDPR issues (as outlined in the collaboration agreement between UCL and C&I). These audio files will be destroyed at the end of the project.

As well as providing an in-depth exploration of treatment experiences and perceived impacts (from both provider and recipient perspectives), analysis will be structured to produce clear summaries of feasibility and acceptability issues as reported by therapists and participants. These will inform therapy and trial process modifications in advance of an efficacy trial.

<u>Outcomes collected to establish the feasibility and acceptability of conducting a future effectiveness RCT including:</u>

- Recruitment/ eligibility data (Time 0 & Time 1 assessment)
    - number of referrals from each source, numbers ineligible, reasons for ineligibility, rates and reasons for refusal to be included in the study. A *minimum* of 12 participants in each arm for feasibility studies has been suggested for pilot studies which would require recruiting 29 eligible participants in total (including 20% drop out estimate).
- Health Economic outcomes: Client Service Receipt Inventory and Quality of Life (EQ5D5L) (Time 0, 2 & 3 assessments)
- Attrition rates and reasons for withdrawing throughout the study, follow-up rates (Time 1-3 assessments)
- Sample characteristics (Time 0 assessment) to check representativeness of the sample
    - Descriptive demographic data including participants' age, gender, ethnicity, education, employment status
    - Clinical characteristics including age of onset of DDD, duration, co-morbid diagnoses, previous treatments for DDD, type and dosage of current medication
- Resources needed to complete CBT-f-DDD
    - Length of time required for RAs to complete assessments and collect and analyse data (from research assistant time sheets), CBT attendance rates (from electronic patient records), and the amount and nature of supervision required (from Co-PI supervision notes)
- Power calculations
    - We will determine the pooled standard deviation for the baseline score of the primary outcome variable as well as the correlation with the outcome scores at the end of the study period. These data, along with the mean clinically important difference (MCID) will be used in the sample size calculation for a fully powered subsequent study
- Therapist adherence to CBT-f-DDD (fidelity)
    - Records of session content, participants' engagement with CBT-DDD, and homework tasks completed (all from therapist post session checklists). Also, a random sample of 10% of audio-recorded therapy sessions will be evaluated using standardised CBT

protocols (standardised CBT rating scale used: CTS-R) for adherence to the CBT model[39] as well as an adapted CBT-f-DDD checklist.

- Participant acceptability (collected via end of intervention questionnaire and semi-structured interviews at Time 3)
    - Acceptability of assessment procedures and measures.
    - Acceptability of CBT-f-DDD including aspects of the treatment found helpful and unhelpful, perceived impact of the intervention, and satisfaction with the intervention and therapists.
- Therapist acceptability (collected via semi-structured interviews)
    - Satisfaction with training and supervision, confidence in delivering CBT-DDD, views of the intervention's value and perceived impact, and perceived feasibility of delivery in standard clinical settings.

6 STUDY SETTING

Participant recruitment will take place via NHS Mental Health Trusts. Two sites have been identified and agreed upon at the moment (with the potential for more to be identified at a later stage if necessary):

1. An inner London mental health trust (Camden and Islington NHS Foundation Trust (C&I))
2. An outer London mental health trust (Barnet, Enfield and Haringey Mental Health NHS Trust (BEH))

We appreciate the importance of recruitment to the success of the study, and this will be a priority for the research team. We predict the CBT-f-DDD training offered in the study to the clinicians in both NHS trusts will increase identification of DDD for NHS clinical staff and aid recruitment. We will also provide an infographic on DDD symptoms for other staff not involved in the training, to raise awareness. Posters and handouts about the study will be left in patient waiting areas. We will advertise the study on the Trust's intranet and have a section of the Unreal Charity's website dedicated to information about the study.

Two brief screening questions are highly effective in identifying symptoms of DDD, and we hope to include these within primary care, Increasing Access to Psychological Therapy (IAPT) assessments, and secondary care clinicians, so these symptoms may be identified. At the start of the study, the CI and RA will attend as many team meetings as possible in both trusts from whom we will be recruiting participants, to give a brief talk about the study. The RA will then continue to follow up these teams to ask about potential patients who might be suitable.

Active recruitment will be over a six-month period from 15.4.22 to 22.11.22 where we will need to recruit 8-10 participants per month into the study to meet our recruitment target.

The two NHS trusts listed will be our primary recruitment sites, where clinicians will be the first point of contact for potential participants and will aid in identification and recruitment. There is a potential for including more NHS trusts at a later stage. If further recruitment is required, we will recruit from PIC sites across London NHS primary care settings, particularly IAPT services. PIC sites will be given a short presentation about the study and provided with a local information pack.

Additionally, we will advertise the study through websites and other promotional materials of the co-

applicant charity, *Unreal*, website. People who are interested in participating can then contact the research team to ask for more information on the study or to volunteer to participate in the study. Participants who self-refer in this way would be provided with a participant information sheet and, if interested in participating and eligible to do so, would be taken through the consent process either through remote means (e.g., via videoconferencing) or by being invited to the research site (NHS trust, e.g., C&I or BEH). It will be made clear to potential participants who self-identified that they will be referred to the NHS trust for the duration of their participation in the study, as the intervention would be delivered by the NHS trusts. No information about participants will be collected and no research activities will be held within the charity. *Unreal* will be used solely as a platform to advertise the study.

For participants recruited outside of the NHS setting, who are eligible and have given consent to take part, we will involve their GPs and/or mental health teams, to gain information relevant to risk, current prescribed medication and use of services.

Assessments can also be conducted via video-conferencing methods or telephone should the participant prefer this and/or if there are further governmental restrictions due to Covid-19. Following recruitment, we will be starting randomisation to either CBT-f-DDD or standard care. The setting for the intervention arm will depend on participant and/or therapist preference and can be conducted face-to-face or via video-conferencing. The CI will be meeting fortnightly with therapists to provide group supervision. This will be done either in a face-to-face setting or remotely via video-conferencing. Clinicians and participants will be invited after the end of the intervention, at Time 3, to take part in semi-structured interviews relating to their experience of therapy. This again will be conducted either face-to-face or via video-conferencing methods, subject to restrictions or preferences.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

Participants must be aged between 16 and 75 and have symptoms of Depersonalisation and/or Derealisation currently meeting DSM5 criteria for Depersonalisation-Derealisation Disorder. This will be determined by the following two questions: “Over the last two weeks, how often have you had the experience of:

a) Experiences of unreality, detachment, or being an outside observer with respect to one's thoughts, feelings, sensations, body, or actions (e.g., perceptual alterations, distorted sense of time, unreal or absent self, emotional and/or physical numbing). [Depersonalisation]
0=not at all; 1=several days; 2=more than half the days; 3=nearly everyday

b) Experiences of unreality or detachment with respect to surroundings (e.g., individuals or objects are experienced as unreal, dreamlike, foggy, lifeless, or visually distorted). [Derealisation]
0=not at all; 1=several days; 2=more than half the days; 3=nearly every day.

Total score = (a+b). Scores <3 = mild-moderate severity DDD. Scores >=3 = moderate-severe severity DDD

Comorbidity with anxiety and/or depressive disorders will be not be an exclusion criterion. Any gender,

ethnicity or socio-economic background will be included. Participants will be within reasonable travelling distance of London in order to attend assessments and therapy sessions in person.

7.1.2 Exclusion criteria

Exclusion criteria are:

(i) people having previously had CBT specifically for DDD.
(ii) where there are co-morbid current diagnoses of a) psychosis spectrum disorder, b) substance dependence, c) intellectual disability, d) cognitive impairment due to head injury or organic disorder, e) PTSD.
(iii) participants lacking capacity to consent to take part in the study.
(iv) insufficient proficiency in English language to engage in CBT.
(v) requiring special communication needs arrangements.
(vi) people who are not registered with a GP.
(vii) Those with depersonalisation and/or derealisation symptoms which score below clinical severity (i.e., total score of 0-2) in response to the diagnostic questions.
(viii) Participants involved in other research studies involving mental or physical health research (including drug trials).

7.2 Sampling

7.2.1 Size of sample

As this is a feasibility study there is no formal sample size calculation. A *minimum* of 12 participants in each arm (a minimum of 24 participants in total completing the study) has been suggested for pilot studies, which would require recruiting 29 eligible participants in total (including 20% dropout estimate).

We aim for 20 participants in each arm completing the trial with follow up data, as we believe this will give us a final sample large enough to assess the practicalities of recruitment and intervention delivery, standard deviations of the main outcome measure and a sufficient range of age and gender to inform a future study since it is of the same order as our highly cited original observational study. To allow for an estimated drop out, which will be confirmed by the feasibility study, we will recruit a *maximum* number of 60 participants in total. Feasibility of recruitment is one of the key parameters of the trial and the larger the sample size the more reliable will be the power calculation for any future outcome study. Consequently, 60 participants would provide better statistical power, 40 would provide good power, and 24 would be the *minimum* number of participants required for accurate results. There will not be people recruited unnecessarily, as recruitment numbers will contribute towards the aims of the feasibility study.

To meet our relatively conservative aim of 20 participants completing the trial in each arm we will need a recruitment rate of 5-10 participants a month during the 6-month period between starting active recruitment on 15.4.22 and when recruitment closes on 22.11.22. Data from a tertiary NHS service managed by the co-PI where clients had needed to have CCG funding approved had an average of one referral per week, so we are reasonably confident that when this barrier is removed, we will be able to recruit at the required rate.

7.2.2 Sampling technique

The sample will consist primarily of all eligible patients with DDD within primary and secondary mental health services in the NHS Trusts within the recruitment period of the study. We aim to recruit a *maximum* of 60 participants with a diagnosis or symptoms meeting diagnostic criteria for DDD from NHS Mental Health Trusts. We have identified two participating NHS sites currently – Camden and Islington NHS Foundation Trust and Barnet, Enfield and Haringey Mental Health NHS Trust – with the potential for more sites to be identified at a later time, if necessary for boosting recruitment numbers. Recruited participants will be identified by local clinicians, or self-identified and referred to the Trusts if not already patients of said Trusts, and formally recruited to the study by the research assistant.

If further recruitment is required, we will recruit from PIC sites across London NHS primary care settings, particularly IAPT services. PIC sites will be given a short presentation about the study and provided with a local information pack.

We will also advertise the study through the UK charity for DDD (Unreal.org.uk), whereby people who self-identify can contact the research team should they be interested in participating. These potential participants would then be invited to the NHS sites or to remote meetings (via video-conferencing or telephone) for completing consent and assessment processes, and they would be under the care of the NHS sites for the duration of their participation in the study if eligible and willing to take part. No information will be collected via *Unreal* regarding eligible participants and no other research activity will be conducted on these sites, as they only serve as advertisement platforms for the study.

7.3 Recruitment

Recruitment will be facilitated through raising awareness of DDD symptoms via the specialist CBT-f-DDD training. An infographic about the key symptoms that will be provided to all clinicians in the Trust and posters and handouts will be left in patient waiting areas. We will advertise the study on the Trusts' intranet. Local clinicians will identify potentially suitable participants in their NHS clinical settings and will approach them to provide a participant information sheet and to gain consent to be contacted by the research team. The research assistant will regularly attend referral meetings in the services included in the study, and approach clinicians to enquire about suitable cases. We will seek to include two screening questions in primary and secondary care assessments.

7.3.1 Sample identification

Clinicians in primary and secondary care services within the NHS Mental Health Trusts will identify potentially suitable participants, check whether they meet the inclusion criteria, and make the initial approach including giving them a Participant Information Sheet with details about the study. The local clinicians will ask for permission to share the potential participants' personal data and consent to be contacted by the research team, and if consent is given, the local clinician will pass the potential participants details to the research team. The RA will follow this up with the potential participant to see if they are interested in taking part and to obtain informed consent. Once this has been given, the RA will undertake the baseline eligibility assessment (time 0). This means that clinicians will help identify potential participants, while the RA will be the one formally recruiting participants should they be eligible.

The sample will consist primarily of all eligible patients with DDD within primary and secondary mental health services in the NHS Trusts within the recruitment period of the study. We have identified two trusts (C&I and BEH) who will participate, with the potential for more sites to be included at a later time, if necessary for boosting recruitment numbers. If further recruitment is required, we will recruit from PIC sites across London NHS primary care settings, particularly IAPT services. PIC sites will be given a short presentation about the study and provided with a local information pack. Participants will be identified from PIC databases by the practice managers. The practice managers will use relevant search terms to identify potential participants from these databases and seek consent from these potential participants to be contacted by the research team. The latter will contact participants to provide a PIS and allow them a minimum of 24h to consider the information provided. Potential participants will be contact and will be able to ask any questions about the study and if they would like to take part, they will be taken through the consent process to participate in the study. Once this has been given, the RA will undertake the baseline eligibility assessment (time 0).

We will also advertise the study through the UK charity for DDD (*Unreal*), whereby people who self-identify can contact the research team should they be interested in participating. These potential participants would then be invited to the NHS sites or to remote meetings (via video-conferencing or telephone) for completing consent and assessment processes, and they would be under the care of the NHS sites for the duration of their participation in the study if eligible and willing to take part. No information will be collected via *Unreal* regarding eligible participants and no other research activity will be conducted on these sites, as they only serve as advertisement platforms for the study.

Contribution to travel costs for participants

Participant activities (n=3)	**Number of participants required**	**Number of assessments/ sessions per person**	**Contribution per assessment**	**Cost per participant**	**Cost to funder (all at 80%)**
Contribution to travel costs for non-London based participants to attend therapy sessions	10 (based on 33% recruitment via Charity)	Mean of 14 sessions (minimum of 12 sessions of CBT but up to 16)	£10	£140	1,120
Contribution to all participants' travel cost to attend quantitative assessments	60	4	£10	£40	1,920
Contribution to participants' travel costs to attend post	20	1	£10	£10	160

therapy qualitative interviews					
				Sub-total for participant activities	3,200

7.3.2 Consent

Patient consent

Informed consent will be obtained prior to the participant undergoing any activities that are specifically for the purposes of the study. Once the potential participant has been informed about the study by their local clinician and either contacted the research directly or given permission for their personal data to be passed to the research team, the latter will undertake the process of gaining informed consent. This will involve:

- A discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research, about the nature and objectives of the study and possible risks associated with their participation
- The presentation of written material (e.g., information leaflet and consent documents) which will have been approved by the REC, local regulatory requirements and legal requirements
- The opportunity for potential participants to ask questions about the study and their involvement
- Assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. In our assessment of capability, the participant will:
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision
    - be able to make a free choice
    - be capable of making this particular decision at the time it needs to be made
    - be able to communicate their decision and the reasons why they made it
    - *If capacity to consent is lost during the study, the participant will become ineligible to continue in the study. This will be discussed with them and their local clinicians.*

If consent is withdrawn during the study and the participant no longer wishes to take part in the research, no further data will be collected, but the data collected up to the point of withdrawal from the study will be kept. This will be made explicit on the consent form and participant information sheet.

The PI and members of the research team have been trained in consent procedures via the GCP training and both research assistants will undertake GCP training also.

Staff consent

Written informed consent will be sought from the clinical staff who take part in the study as CBT therapists. They will be asked to give their consent to participate in the study and take part in the training, collect demographic and data regarding their clinical experience, to be audio recorded in qualitative interviews, and to have their therapy sessions audio-recorded so that they can be rated using standardised CBT rating scales (CTS-R [15]).

8 ETHICAL AND REGULATORY CONSIDERATIONS

Full NHS ethics via the Integrated Research Application System (IRAS) will be sought and obtained prior to any data collection. Local NHS approval regarding feasibility will be sought from the sponsor, and "Local Capacity and Capability" will be confirmed by the sponsor prior to the start of the study at the NHS site.

This is not a high-risk study and we are not expecting there to be any inherent risks within the study. However, we are aware that within any therapy there is the potential that discussion of past difficult events may cause distress to the participant. All interventions will be carried out by qualified and trained NHS clinicians who will also be receiving regular specialised supervision by the CI and will be able to raise any concerns within this.

Potential participants will have randomisation explained to them during the consent process. Randomisation into the standard care arm of the study may cause some distress to the participant who may perceive this as missing out on a new intervention. If this is the case, the research team will explain that comparison between a new intervention and standard care is a necessary part of a randomised controlled trial and as we do not yet know if the intervention arm of the study will be effective, we are not denying participants a known benefit and therefore this remains ethically valid. This will also be made clear in the participant information sheet, informing of the 50% chance to be allocated to either arm of the trial.

Data collection will uphold the dignity of the participants as they will have individual meetings with a research assistant and so will have privacy and the opportunity to discuss any concerns. Participants will be invited to give feedback on their experiences at all stages of the study.

8.1 Assessment and management of risk

We do not expect this study to be high risk. However, we have undertaken a Research Risk Assessment and a Data Protection Impact Assessment to identify potential risks in order to mitigate against these as much as possible in advance.

Risk to Study

The research team have set up an appropriate data management plan. There will be a central Trial Management File which contains all the key documents. A delegation log has been completed. Staff have been trained in Good Clinical Practice. The design and methodology have been peer reviewed as part of the NIHR application process. Careful consideration has been given to recruitment with a range of sites to recruit from. The number of staff employed on the project and the resources available are sufficient to complete the research. The research team are highly experienced in carrying out research. Senior clinical staff in both NHS trusts have agreed to be part of the study.

Disclose of risk of self-harm/harm to others

All patients will provide information about their local team and GP. It is possible that participants may disclose potential risk to themselves or to others during any of the assessment interviews or on the measures completed (e.g., the item relating to thoughts of self-harm on the PHQ). The research assistants will be trained in risk assessment by the CI, and a senior clinical member of the research team will be available at all times to respond to any query that the research assistants may have regarding risk.

The consent form will clearly state that if any risk of harm to the patient or others is identified, that the research team will tell the participants' GP or local clinician of any identified risks to themself or others, including elderly or vulnerable adults or children that arise during the study, within the earliest possible time frame. It has been made explicit also on the Participant Information Sheet that, if any risk is disclosed, it might be necessary to inform the appropriate agencies. Participants will be current clients within NHS services, and we will provide local clinicians with the information from the participant as soon as possible and request an urgent risk assessment to be carried out within the NHS. If we are concerned about any potential delay to this risk assessment (e.g., local clinicians cannot be contacted immediately and the participant cannot ensure their safety), a member of the research team will accompany the participant to the nearest A&E and remain with them until they are seen by liaison mental health teams.

Risk due to Covid-19

We will follow government guidance and local NHS trust guidance to ensure that all face-to-face contacts between participants in the research and the research team meet with current advice to ensure covid security during the study. Patient participants will be given the option to undertake all/any assessments and/or therapy sessions via videoconferencing if they would prefer this.

Similarly, the training and/or supervision clinicians will be offered remotely if current circumstances prevent these being delivered in a face-to-face setting.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service (NHS REC) for the study protocol, informed consent forms and other relevant documents e.g., advertisements.

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained. The Chief Investigators will produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

For studies involving the NHS:

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

- Amendments to the study may be requested to the TMG by other committees based on data collected from the study.
- The decision to amend the protocol will be agreed with the TMG and whether an amendment is substantial or non-substantial.
- Authorizations for any amendments will be then sought from the sponsor, who will classify the amendment and authorize it before seeking regulatory approval.
- Substantial amendments will be submitted to the REC and the study paused until these have been approved.
- The protocol will be updated accordingly with a new version number to ensure the most recent protocol version is used.

8.3 Peer review

The study has already been peer reviewed by the National Institute for Health Research (NIHR) during the application process.

8.4 Patient & Public Involvement

The Co-PI supervised a service audit of CBT-f-DDD using a semi-structured survey of 45 service users and their referrers to evaluate experiences of assessment and therapy. This identified therapy components of most value to service users. This information has been incorporated in the current study design.

The Co-PI's are involved with the national charity for DDD *'Unreal'* as, respectively, founding member/trustee and ambassador. The Charity is a co-applicant, with Mr Perkins as the named representative. We have already conducted pre-award activities by setting up a Patient Advisory Group (PAG) of people with lived experience (PWLE) of DDD who were recruited through the charity 'Unreal'. An initial meeting of this group reviewed an earlier proposal and gave feedback on the acceptability of the proposed measure and procedures. Their suggestions included ways of promoting retention in the Standard Care participant group such as by offering for their assessment summaries to be shared with their local team and for them to be invited to *Unreal*'s monthly peer-support groups. It was also suggested that a nominal fee toward travel costs should be included to encourage participants to take part in assessments, and for out of London participants to attend regular therapy sessions. These changes have been incorporated into the current study design. Moreover, following a more recent PAG meeting, study documents, forms, and questionnaires were reviewed by PAG members. Their suggestions have also been incorporated in the documentation.

Two co-applicants have recently conducted a focus group and an online survey about PWLE of DDD's experiences of therapy in collaboration with *Unreal* [20]. The survey of 102 respondents found that 25% of cases waited more than 7 years from the onset of DDD symptoms to receive a diagnosis. Moreover, 54% found the non-specific treatment they were offered either not at all or only of limited help. Only 7% of those with DDD received CBT for their symptoms. These results indicate the urgent need for more people with DDD to be offered timely diagnosis and DDD-specific treatment to reduce the impact of symptoms and to save NHS resources. These findings will inform the final content of the intervention by increasing clinicians' awareness of the symptoms to aid diagnosis and offering disorder-specific training and supervision.

PPI is built into our research in three ways:

1. PWLE of DDD will co-present in the training for clinicians alongside the co-PI to give a service

user perspective on the experience and impact of DDD

2. Meetings of the PAG will be held every two months throughout the study. Activities of the PAG will include reviewing study materials (e.g. information sheets, consent forms); input into designing qualitative interview topic guides; providing a lived experience perspective on recruitment and trial processes; and contributing to the interpretation of qualitative and quantitative findings.
3. At the end of the study, the PAG and members of the charity *Unreal* will be involved with dissemination activities targeted to service user and stakeholder groups more broadly.
    a. An online dissemination event will be co-delivered with PWLE of DDD from the Charity to the 447 people who currently receive a regular newsletter, as well as the ~2000 subscribers across the Charity's social media platforms.
    b. A plain English summary of the findings will be made available on the Charity's website.
    c. The Charity has been successful in raising awareness of DDD via media coverage and will use the results to do the same for treatments for DDD via press and social media targeted at PWLE and the public.
    d. The Charity will also liaise directly with clinical organisations such as the Royal College of General Practitioners and the Royal College of Psychiatrists to raise awareness of CBT as a possible intervention for DDD.
    e. There have been discussions in the Ministry of Health about the lack of research on evidence-based treatments for DDD and the Charity will liaise with their contacts here to lobby for greater service provision within the NHS if the results appear promising.
    f. Clinical audiences will be reached with a clinical workshop and conference presentation at the annual CBT conference of the BABCP as well as via written publications.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. The clinicians will be able to raise any issues during regular supervision. Any breaches will be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.

8.6 Data protection and patient confidentiality

The data controller will be C&I as the sponsors of the study and the research team will work within C&I's Standard Operating Procedures for data protection and patient confidentiality. All investigators and study site staff will have completed the Trust's data protection mandatory training and will keep up to date with this for the duration of the study. The research team has undertaken a Data Protection Impact Assessment and worked with C&I's Information Governance Team to ensure compliance with local policies. The research team will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Randomisation lists will be created by the independent statistician (Dr Louise Marston – UCL Primary Care & Population Health) prior to recruitment and they will be delivered to the recruitment sites by sealed envelope method. The trial statistician, Dr Gafoor, will have no involvement in the generation or use of these lists.

The data that will be collected from patients will include personal data (i.e., name, address, postcode, date of birth, GP practice, local clinician information, phone number, email address, NHS number) and sensitive data (health data, ethnicity, religion, gender identification). Only members of the research team who are also NHS staff in C&I will have access to this information. All participants in the research study will be allocated a unique numerical identifier. There will be a document that has only this numerical identifier with the patient personal and contact details (name, address, postcode, phone number, date of birth, NHS number, GP details, local NHS service and local clinician contact information) but with **no** other sensitive personal data. This document will be encrypted and kept securely and separately from any other research data on an NHS computer on an NHS site. NHS computers will be password protected and secure. Sensitive data collected as part of the research study (i.e. health data relevant to the study outcomes, ethnicity, religion and sexual orientation) will be kept completely separate to any identifiable personal data, using only the numerical code assigned to each participant and in this way will be anonymised. Whilst it would be possible to link the numerical code to the identifiable data collected if having access to the relevant information, we have put technical and organisational measures in place to ensure that linking data are held separately. Documents containing identifiable data and/or linkage to unique numerical identifier will be kept on encrypted, password-protected NHS computers, on drives with access restricted to only a limited number of staff. These data will be kept for the minimum amount of time necessary for subsequent contact, and will be destroyed after the minimum period, as described below.

Pseudoanonymised data is defined as data that has no personally identifiable information (such as names, address, date of birth) but could have any potential for being identifiable. Pseudoanonymised data will be collected during this research to ascertain the outcomes of the study (health data) and to ensure we have a representative sample in the research (age/ethnicity/gender identification). Pseudoanonymised data will be shared with other members of the research team for the purposes of quantitative and qualitative analysis. To ensure data protection, these pseudoanonymised data will be kept completely separate from any personal contact information and only a unique research code number will be assigned to these data. Fully anonymised data (i.e., only statistics on groups) will be used in any publications from the research findings. Withdrawal of participant consent or loss of capacity to consent during the study will result in no further data being collected for the study. This information will be explicit in the consent form and participant information sheet and will be verbally explained to participants and clinicians as well before any information is collected.

All data held will be kept securely on NHS system files using encrypted digital files within password protected folders and storage media. Hard copies (e.g., consent forms) may be kept in locked cabinets on the NHS sites, in secure rooms, as arranged by the Sponsor. Access to anonymised sensitive data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis, which will include members of the research team:

[1,2] Dr Elaine Hunter, Co-Chief investigator, Senior Research Fellow, UCL

[1,2] Ms Nicola Dalrymple, Research Assistant, C&I

[1,2] Professor Glyn Lewis, Co-investigator, Head of the Department of Academic Psychiatry, UCL
Professor Anthony David, Co-Chief investigator, Professor and Director, Institute of Mental Health, UCL

Dr Nicola Morant, Co-investigator, Associate Professor, Department of Academic Psychiatry, UCL

Dr Rafael Gafoor, Co-investigator, Medical statistician, Department of Applied Health Research, UCL
Dr Elena Pizzo, Co-investigator, Principal Research Fellow & Health Economist, UCL
Mr Joe Perkins, Board Member of the charity Unreal and PPI co-investigator

[1] Will have access to patient identifiable information. Others will only have access to anonymised data.[2] Also have contracts/honorary contracts within C&I

Anonymised data will be sent to the Research Steering Committee and the Independent Data Monitoring and Ethics Committee. Data confidentiality will be preserved when the data are transferred outside the immediate research team to the RSC and IDMEC via anonymisation and password protection.

Audio recordings for qualitative data collection of patient and staff interviews will be made on encrypted recording devices and stored securely within the NHS setting. A professional transcription service (e.g., Transcription Divas) who have an over-arching contract with UCL (as outlined in the collaboration agreement between UCL and C&I) that covers all the GDPR issues, will be employed for this study. These audio files will be destroyed at the end of the project. There will be no video recording required in the study.

The data will be stored for the minimum duration needed, which will be the duration of the study and the required minimum duration post publication of 7 years for pseudoanonymised data and 20 years for completely anonymised data. The data custodian will be the chief investigator. The data controller will be the Sponsoring Organisation.

8.7 Indemnity

Indemnity for all aspects of the research design will be provided by UCL. A certificate of this will be submitted for ethical approval. For the clinical management of the study NHS indemnity will be provided by C&I as the sponsor of the research. For the conduct of the study, indemnity will be provided via the two NHS sites: C&I and BEH. No cover for non-negligent harm will be provided.

8.8 Access to the final study dataset

Access to the final study dataset will be limited to the minimum number of individuals necessary for quality control, audit, and analysis, which will be members of the research team only and members of the Research Steering committee and Independent Data Monitoring and Ethics Committee. However, access will also be permitted to site investigators if a formal request describing their plans is approved by the steering group. Given these data could have potential for identification of participants the final study dataset will not be available to others beyond the immediate research team and committees. However, the details of the statistical analysis and the analysis of transcripts will be made more widely available.

9 DISSEMINATION POLICY

9.1 Dissemination policy

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared. The full study report can be accessed on the research page website of the Unreal Charity. The participating investigators will have rights to publish the results of the study data and NIHR as the funding body will be acknowledged within the publications. Given these data could have potential for identification of participants, the final study dataset will not be available to others beyond the immediate research team and committees. However, the CBT-for-DDD treatment manual, details of the statistical analysis and the analysis of transcripts will be available to researchers and clinicians following publication of the results. We will produce both an academic conference presentation and will publish our findings in relevant journals.

A Plain English Summary will be made available on the Unreal website and can be made available by request to participants by selecting this option on their consent forms. We will use media links through the charity to publicise the study in the wider population and in doing so raise awareness of DDD as well as available treatments via print and other media.

9.2 Authorship eligibility guidelines and any intended use of professional writers

All members of the research team will be authors of the final study report and included in any conference presentation and journal articles.

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11. APPENDICES

11.1 On-site clinician and therapist information packs

A) Clinician Recruitment packs containing:

1) Study summary with inclusion and exclusion criteria
2) Contact details of research team
3) Clinician checklists for eligibility data (e.g. number of people meeting criteria for the study), recruitment data (e.g. number of people informed about study, reasons for refusals), attrition rates (drop outs and reasons for withdrawing)
4) Patient information sheets

B) Therapist packs containing:

1) CBT-for-DDD workshop presentation and manual
2) Checklist of session content
3) Rating of participants' engagement with CBT in session and with homework tasks
4) Consent for audio recordings with participants

11.2 Appendix 2 – Schedule of Procedures

Procedures	Assessment Time points

	Eligibility assessment: Time 0	Start of intervention: Time 1	End of intervention: Time 2	Follow up: Time 3	
Informed consent	X				
Assessment of inclusion and exclusion criteria	X				
Demographic information	X				
DDD current symptoms and symptom history	X			X	
Assessment of co-morbid diagnoses (CIS-R and semi-structured interview) and history of these, including current medication	X			X	
Clinical Measures (CDS, DES, PHQ, GAD, WASA)	X	X	X	X	
Health economics measure (Client Service Receipt Inventory) and quality of life measure (EQ5D)	X		X	X	
Global rating of change question			X	X	
Participant acceptability questionnaire about experiences of treatment (both arms)			X		
Clinician acceptability qualitative interview about experiences of training, supervision and therapy delivery			X		
Participant acceptability qualitative interview (including drop outs) about experiences of therapy				X	

11.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	6.4	27.10.2022	Nicola Dalrymple	Name and email change from previous research assistant to current research assistant

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the sponsor for approval prior to submission to the REC.