Camden and Islington NHS
NHS Foundation Trust

PHASE 3. COMMUNITY NAVIGATOR TRIAL
PROTOCOL V2.0, 9th November 2022

Camden and Islington NHS
NHS Foundation Trust

FUNDED BY
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Priment™ Clinical Trials Unit

Full title of trial	Randomised controlled trial of the Community Navigator programme to reduce loneliness and depression for adults with treatment resistant depression in secondary mental health services
Short title	The Community Navigator Trial
Version and date of protocol	Version 2.0, 09 November 2022
Sponsor:	Camden and Islington NHS Foundation Trust
Sponsor protocol number	TBC
Funder (s):	NIHR HTA Programme
ISRCTN no:	13205972
Intervention(s):	Community Navigator Programme – social intervention for treatment resistant depression, in addition to Treatment as Usual
Standard/Control/Treatment as usual:	Control group receiving treatment as usual
Phase of trial	Phase III
Sites(s)	Multi-site

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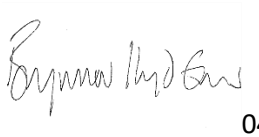
PROTOCOL VERSION HISTORY

Version Number	Date	Protocol Update Finalised By (insert name of person):	Reasons for Update
1.0	04 FEB 2022	Theodora Stefanidou	Finalised after CTU and Sponsor's review
2.0	09 NOV 2022	Gergely Bartl	Additional study promotion and recruitment detail added in section 9.2

SIGNATURES

The Chief Investigator and Priment have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, GCP, the UK Data Protection Act (2018), any applicable EU/UK amended acts to the Data Protection regulation, the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research , Priment's SOPs, and other regulatory requirements as amended.

Chief investigator Dr Bryn Lloyd-Evans	 04/02/2022	
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2 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
AR	Adverse Reaction
BAME	Black, Asian and Minority Ethnic
CBT	Cognitive Behavioural Therapry
CMHT	Community Mental Health Team
CI	Chief Investigator
CIS-R	Clinical Interview Schedule-Revised
CRF	Case Report Form
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
DJG-6	6-item De Jong Gierveld Loneliness Scale
DI	Designated Individual
DISC	Discrimination and Stigma Scale
DMEC	Data Monitoring and Ethics Comittee
EQ-5D-5L	EuroQol EQ-5D 5 level (EQ-5D-5L)
EU	European Union
GAD-7	General Anxiety Disorder Assessment
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Research Authority
ICD-10	International Classification of Diseases 10th Revision
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LSNS-6	Six-item Lubben Social Network Schedule
MIS	Four-item Multiple Identities Scale

NHS R&D	National Health Service Research & Development
NIHR HTA	National Institute of Health Research Health Technologies Assessment Programme
PHQ-9	Patient Health Questionnaire – Mental Health Disorders
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality adjusted life year
QC	Quality Control
QPR	Questionnaire on the Process of Recovery
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REQOL	Recovering Quality of Life
B-RSES	Brief Rosenberg self—esteem scale
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TRD	Treatment Reistant Depression
TSC	Trial Steering Committee
(ULS-8)	University Of California, Los Angeles Loneliness Scale

3 TRIAL PERSONNEL

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4 SUMMARY

Objectives: We will evaluate an innovative social intervention for people with treatment-resistant depression (TRD) in secondary care. People with TRD are severely and enduringly unwell, only partially helped by current treatments and often extremely lonely. We propose a randomised controlled trial (RCT) of the Community Navigator programme [1], which has been manualised and tested in an NIHR-funded feasibility trial [2]. This programme of support will include receiving support from a 'Community Navigator', who will work with the participating service users to increase their social activities and community engagement. The focus of the programme is to reduce loneliness. This is the intended means to reduce depression, our primary trial outcome, and achieve other health and social benefits. Further aims are: to determine the cost-effectiveness of the Community Navigator programme, and to explore its perceived impact, how benefits were achieved, and key considerations for its provision in NHS settings.

Type of trial: A Phase III, single (researcher) blind, randomised controlled, multi-site trial with two arms in people with TRD

Trial design and methods: In an individual RCT, we will test the effectiveness of the Community Navigator programme in reducing depression for people with TRD using secondary mental health services in four NHS Trusts in England. 306 service users will be randomly allocated to the programme of support from a Community Navigator or to a control group. The experimental group will receive, in addition to treatment as usual, up to 10 sessions of 1:1 support from a Community Navigator and attendance at up to four participant group "meet-ups" over an eight-month period. To help develop social connections as part of the goals of the intervention, participant will receive some financial re-embursement to cover costs incurred. Both the experimental and the control group will receive routine care with the control group also receiving an

	information booklet about local social resources. Assessment interviews will be performed at consent, at 8 months and at 14 months. Depression and loneliness data will be collected additionally at 4- and 11-month follow-ups. **Internal pilot progression criteria:** During the first six months of recruitment we have built in an internal pilot with progression criteria based on recruitment and engagement rates. Our continuation criteria require recruitment of 4.8 participants per site per month.This results in 29 participants recruited per site (116 in total) during the six-month pilot period: a rate which, sustained over the full 16 month recruitment period, yields 77 participants per site as planned. In response to feedback from the funding committee, we added an additional continuation criterion to assess feasibility of the delivery of the intervention. Among the participants recruited within the first five months of the study and randomised to the treatment group – i.e. those who have been enrolled in the study for at least one month at the Month 6 end-of-pilot point, we will monitor the proportion who have either: i) Already been treated per protocol, or ii) Who remain actively engaged in treatment. The Steering Committee and Funders will review progress against continuation criteria after the first six months of recruitment. **Qualitative studies:** We will collect qualitative data from intervention participants and providers at two stages: a) During the internal pilot (months 10-15), to understand any barriers to trial recruitment and intervention engagement; and b) later in the trial after the 8 month follow-up (months 18-33) to explore experiences of the programme and how perceived benefits were achieved, and to identify core and local contextual factors affecting delivery of the programme in an NHS context.
Trial duration per participant:	14 months
Estimated total trial duration:	33 months from enrolment of first participant in the internal pilot recruitment phase to final contact with last participant in the trial phase – from Months 10-39 of the study. **Months 10-15**: internal pilot recruitment phase; **Months 10-25**: Participant recruitment; **Months 10-33**: Intervention delivery; **Months 18 – 33**: 8-months follow-up; **Months 24-39**: 14-month follow-ups due; Month 39-42: final 14-month follow-ups completed within 3 months of due date.
Planned trial sites:	Multi-site (4 sites planned initially)

Total number of participants planned:	306 participants
Main inclusion/exclusion criteria:	We will recruit adults with TRD using Community-based secondary mental health services Inclusion criteria: 1. Age 18+ 2. Meet ICD-10 diagnostic criteria for depression assessed using the Clinical Interview Schedule - Revised (CIS-R) interview 3. Have had at least two reported courses of anti-depressants without symptom remission, confirmed by the participant 4. Score of 2 or more on 6-item De Jong Gierveld Loneliness Scale (DJG-6) Exclusion Criteria: 1. Are due to be discharged from the mental health team within the trial intervention period (8 months) 2. Currently using mental health inpatient services 3. Identified by involved clinicians or clinical records as having a primary diagnosis of a serious mental illness other than TRD, defined as schizophrenia or other non-mood psychotic disorders (ICD codes F20-29) or bipolar disorder (ICD code F31) 4. Lacks capacity to consent to participate 5. Does not understand English well enough to give informed consent and engage with the study intervention 6. Has a care coordinator who supervises the Community Navigators
Statistical methodology and analysis:	**Statistics:** Data will be analysed using the intention to treat principle with complete cases. The primary outcome, PHQ-9 score at 8 months follow up, will be analysed using a multilevel model accounting for clustering in the intervention arm using a random effect of navigator and adjusting for baseline PHQ-9 score and site using fixed effects. Secondary outcomes will be analysed using analogous methods. **Health Economics:** The primary economic analysis will be the incremental cost per quality adjusted life year (QALY) gained of Community Navigators plus routine care compared to routine care over 14 months from a health and social care cost perspective,

using the EQ-5D-5L to calculate QALYs. Secondary analyses will calculate QALYs using the ReQoL and from a wider cost perspective.

Qualitative: Our overarching approach to analysis will be reflexive and thematic. At each stage, we will adopt analysis approaches that fit our data, supported by NVivo12 software. We will use findings from this analysis to review our recruitment processes, the intervention logic model and develop a guide for future delivery of the programme in the NHS. An analysis group will include representation from PPI team members, the study peer researcher, and co-applicants.

5 BACKGROUND AND RATIONALE

About a third of people with depression are not helped by anti-depressants with appropriate treatment protocols and can be termed "treatment resistant" [3, 4]. Specialist psychological treatments are also of limited benefit for many in this group: symptom remittance was achieved for less than half the participants in a recent trial of CBT for TRD [5]. Among people with TRD in observational studies, only 20-30% recover over a few years [6]. For people with TRD whose illness is already protracted, only about 40% recover over 10 years' follow-up [7]. Those with the most severe, complex and enduring difficulties are supported by specialist mental health services. In a recent UK trial, optimised medical and psychological support for TRD from specialist teams provided minimal additional benefit compared to routine secondary care [8]. Our completed feasibility trial confirmed the high levels of clinical and social need in our secondary care TRD trial target population: participants were typically unemployed, single, met clinical thresholds for severe depression and anxiety, and were extremely lonely [2]. More research and new types of support are urgently needed for this clinical group.

The social determinants of depression [9,10], including the important role of social relationships [11,12], have long been identified, yet we lack established social interventions of known effectiveness. Loneliness, defined as the subjectively experienced gap between desired and actual social relationships [13], is an independent predictor of recovery from depression [14]. People with depression have tenfold increased odds of loneliness compared to the general population [15] and are commonly extremely lonely [16]. Yet support with social relationships and loneliness is often overlooked in mental health services [17] and we lack well-developed, effective programmes [18]. Loneliness offers a promising, novel intervention target for improving outcomes for people with TRD. Our study addresses a gap in evidence regarding theory-driven and potentially effective social interventions for TRD that would act via a different mechanism from the pharmacological and psychological treatments currently available. Our intervention could help mental health services provide genuinely biopsychosocial care for an important clinical group who are not adequately helped by current treatments.

A systematic review of interventions for subjective or objective social isolation was published in mental health in November 2019 (Johson and Lloyd Evans 2019)[18]. Three research databases (Medline, Web of

Science and PsycINFO) were searched combining terms for: subjective and objective social isolation, mental disorders, and trials. The review retrieved 19 trials of interventions for subjective social isolation (loneliness, or the conceptually related outcome perceived social support). Of 16 trials which compared an active intervention with routine care, one of two which used a supported socialisation intervention reported positive results for subjective social isolation, compared to two of four trials of cognitive approaches, and none which used other or mixed approaches. No trials involved a TRD population or a contemporary UK care context. The review concluded that more trials are required to determine effective interventions for subjective social isolation.

In this context, the promising findings from the Community Navigators feasibility study are of high interest: the direction and magnitude of effect suggested for loneliness and depression outcomes [2] were consistent with the hypothesis that the programme could be effective for these outcomes in a TRD client group. Our proposed trial will address an identified knowledge gap and provide robust evidence about the effectiveness of a loneliness intervention for depression in TRD.

Readiness of the Community Navigator programme for a trial

The successfully completed feasibility trial [2] established four key things: i) There is high interest in a Community Navigator programme and it is possible to recruit participants with TRD in secondary mental health care (40/65 people we approached were recruited within 4 months and we achieved an inclusive, diverse sample: 36% of participants were from Black, Asian and Minority Ethnic (BAME) communities; ii) Trial retention and outcomes data collection are feasible (we collected complete follow-up data for 35/40 participants – 88%); iii) The intervention can be delivered as intended and is acceptable to participants (participants attended a mean of 7 sessions with the navigator; 80% completed a network map and connections plan as intended); iv) The feasibility trial was not designed to evaluate effectiveness, but the direction and magnitude of effect for outcomes, including our proposed primary outcome of depression, were consistent with the hypothesis that the programme can help reduce loneliness and depression for people with TRD [2]. Qualitative feedback also indicates that participants valued the support and found it helpful in developing their social connections and improving their mood, they were also understanding of the effort required as addressing loneliness is challenging, and that the programme was welcomed by clinical teams at participating services. NIHR HTA can therefore be confident that a trial of this programme can be delivered, which will provide high quality evidence regarding the effectiveness of a novel and much needed intervention.

5.1 ASSESSMENT AND MANAGEMENT OF RISK

The potential risks anticipated from the assessments and study intervention, and plans for how these will be mitigated or managed, are detailed in the table below.

Name of Intervention/ Assessments/ design and Methods/	Potential risk	To whom	Risk Management

trial Population			
Study assessments	Distress from reflection on upsetting topics (e.g. loneliness)	Participants	What the study involves will be clearly explained to participants in the study information sheet and by researchers, and written informed consent will be taken before participants join the study. The study researcher will check with participants that they are aware their participation is voluntary and they can elect to withdraw from the study, or stop or pause the interview at any point. The outcome measures and interview schedules will be developed after consultation with the study patient and public involvement (PPI) group that will consist of people with lived experience of depression and anxiety. Questionnaires, survey questions and interview topics guides will be reviewed by the trial PPI group before finalisation of the protocol and any considered difficult or upsetting will be omitted or replaced.
	Lone working risks of harm	Researchers	Trial participants will have been screened for risk by clinicians in the relevant service before being contacted about participation in the study: We will seek and follow advice from the referring healthcare team about any risk or safety considerations about where a participant could be seen (e.g. could mean no home visits). University lone working policies will be adhered to at all times and a lone-working protocol including check-in arrangements for researchers will be developed for the study. Study researchers will inform colleagues in advance of any home visits to service users and will check in with colleagues afterwards. The study CIs will be contactable by phone by research assistants at all times, if advice or immediate debrief are needed. Research assistants will be given clear information about appropriate NHS clinical services to contact, and direction to contact emergency services if appropriate, in the event of any immediate concerns about a participant's or others' safety.
Community Navigator intervention	Risk of distress if plans to increase social contact prove too challenging or unsuccessful, or if the intervention otherwise proves unhelpful.	Participants	Risks from the study intervention: Community Navigators will be employed through the NHS Trusts participating in the study, which will be responsible for their training, supervision and management, and ensuring they work in a professional and helpful manner. The study team will take these additional steps to ensure participants' safety:

			a) Serious adverse events relating to trial participants will be monitored and reviewed, in accordance with the trial protocol and as advised by the Trial Steering Committee (TSC) and Data Monitoring and Ethics Comittee (DMEC), the Clinical Trials Unit and the sponsors. b) Study researchers will seek feedback from Community Navigators and their clinical supervisors and participants about the acceptability of the programme and any barreirs to participation during the internal pilot phase of the study. Findings will be shared with the TSC, and their advice sought about any requirement to modify the study procedures or the intervention, or pause the study, in the event of concerns. c) Study participants are provided with contact details for the research team, including CIs, and independent complaints bodies, should they wish to voice any concerns about the study or the intervention at the time. Participants will remain under the care of NHS clinical services and receiving standard care throughout the trial intervention, so expert help and support with any distress or anxiety generated by participation in the study will be readily available.
Community Navigator intervention	Lone working	Navigator	NHS lone working and safety policies will apply; Navigators will be provided with regular supervision within participating NHS sites.
Community Navigator Intervention	Inconsistency or non compliance to the delivery of the intervention	Researcher	We will work to ensure cosnsitent delivery of the trial intervention as intended in the following ways: i) Community Navigators will be provided with a bespoke training programme in delivering the intervention by the trial team before they start to work with participants. Wherever possible, their clinical supervisors from NHS sites will attend some of the training to, to familiarise themselves with the programme and be briefed about supervisory expectations.

			ii)There will also be an intervention manual provided which the Community Navigators will follow to ensure consistency in the delivery. iii) Community Navigators will be provided with regulargroup supervision and additional 1:1 supervision if required within the participating NHS site. This will include advice and support with delivering the intervention as per training and the manual. iv) The study team will seek early feedback from participants, Navigators and their supervisors in the internal pilot phase of the study, through a survey and qualitative interviews. This will explore any barriers to delivering the programme as intended, which will inform the focus and content of "top-up" training days provided to the Navigator teams by the research team during the trial intervention period. Intervention delivery will be monitored and is detailed in section 10.5 of this protocol.
Design and Methods	Data Breaches may occur due to: - post/email being received/read by unintended recipients - transfer of paper versions of the intervention and case report forms - digital storage and transfer of identifiable data - lack of data security of the digital intervention database.	Researcher, Participant, Organisation	All staff working on the trial will be training in GCP and have undergone Information Governance and GDPR training. Site initiation will also be carried out prior to commencing recruitment and sites and will cover data protection principles GCP and Data protection training of staff will also be checked at initiation. A Data Privacy Impact Assessment will be completed and the study will be registered with the sponsor's data protection department. We will use a web-based randomisation and clinical data management system for recording CRF data (Red Pill), which is provided by a company called Sealed Envelope Ltd. Sealed Envelope has been assessed by PRIMENT CTU to ensure that adequate processes are in place and are being followed for quality management, software development and data security purposes. The Red Pill service has been inspected by MHRA for GCP compliance, and there is a Master agreement and Data Processing agreement in place between UCL and Sealed

			Envelope to ensure compliance and agreement with clinical trial regulations and data protection laws. Any data that is collected that contains Personal Idenifiers such as name, address ,NHS numbers will be stored in UCL Data Safe Haven which has been certified to the ISO27001 information security standard and conforms to NHS Digital's Information Governance Toolkit. Any data that is to be shared outside of UCL will be anonymised and PRIMENT guidance on data sharing will be followed.
Design and Methods	This is a rater blinded study and therefore there is a risk of accidental unblinding and potential bias.	Researcher	There is a small risk that researcher carrying out assessment may become unblinded accidently by trial participants or unblinded research teams. We will minimise this risk by the following: Those carrying out the assessments will be separate to researchers delivering the intervention to preserve the blind. Blinded assessors will remind participants at each stage that they must not discuss their intervention with their assessor. The database will be set up to restrict access to details of treatment to only those who are unblinded. If an assessor does become unblinded we will make a note of this and ask an alternative assessor to complete future outcome measures for this participant.
COVID-19 Transmission	Risk of transmission between research team and participants and there is the potential risk that in this population, participants may be more vulnerable to death and morbidity due to COVID-19.	Participants and Researchers	We follow all government and local site COVID-19 guidance and procedures. This may include staff taking regular lateral flow tests prior to any visits, adhering to visiting policies at sites, wearing masks, social distancing, and hand hygiene. The intervention is designed to be delivered primarily through face to face contact, but 1:1 and group meetings could all be arranged remotely if required to meet participants' needs and preferences. Where practical and feasible and, in keeping with participants' preferences, we will also conduct remote data collection at scheduled visits.

6 OBJECTIVES

Primary: The study is designed to test our primary hypothesis: that people with TRD in specialist mental health services who are randomised to be offered the Community Navigator programme in addition to routine care, will be less depressed, measured using the PHQ-9 scale, at eight-month (end-of-treatment) follow-up, compared to a control group receiving routine care and an information booklet about local social resources.

Secondary: We will also test hypotheses that, compared to controls, the intervention group will be less depressed at 14 months (six months after end-of-treatment) follow up, and less lonely, less anxious, with better personal recovery at 8 and 14-month timepoints.

Further: We will also aim to determine the cost-effectiveness of the Community Navigator programme, and to explore its perceived impact, how benefits were achieved, and key considerations for its provision in NHS settings.

7 TRIAL DESIGN

7.1 OVERALL DESIGN

This is a rater-blind, randomised controlled trial with two arms. Each participant receiving the study intervention will receive up to ten 1:1 meetings with a Community Navigator over a 6-month period. Participants receiving the intervention will be invited to attend up to four "meet-ups" open to all participants, running alongside the intervention, facilitated by the Community Navigators. Participants will receive the study intervention in addition to routine care from a specialist community mental health team (CMHT). The control group will receive routine CMHT care plus written information about local social resources. Routine care for both trial groups includes reviews by a psychiatrist and, typically, regular meetings with a care coordinator and where indicated, psychological therapy. Assessments will be performed by blinded researchers at the time of consent (baseline), 8-month (end of treatment) and 14 month (six months after end of treatment). Baseline measures will be performed at the screening visit. Additonal depression and loneliness ratings will be collected through a self-completed online form or through a phone or video call with a study researcher at 4 and 11 months.

For a schematic diagram of the overall trial design please see Consort Diagram at Appendix 1.

We will collect qualitative data from intervention participants and providers at two stages: a) Qualitative study 1: during the internal pilot, to understand any barriers to trial recruitment and intervention engagement, using an online survey (Qualitative study 1a) and semi-structured interviews (Qualitative study 1b); and b) Qualitative study 2: later in the trial, using semi-structured interviews to explore experiences of the programme and how perceived benefits were achieved, and to identify core and local contextual factors affecting delivery of the programme in an NHS context. This will inform development of guidance to support future scale-up in the event of a positive trial result. Participant interviews will be conducted by a study peer researcher with lived experience of mental health difficulties, who will also lead the analysis. The PPI group will be actively involved, supporting the development of qualitative

interview guides, study recruitment materials and synthesis of findings. Please see Section 11 and Section 15 for a description of the qualitative studies and analysis.

8 INTERVENTION AND STANDARD/CONTROL/TREATMENT AS USUAL

Intervention: The programme offers participants up to 10 sessions of 1:1 support from a Community Navigator and attendance at four participant group "meet-ups" over a six-month period. Participants are expected to attend at least 3 sessions for the intervention to be considered to be delivered per protocol. It is designed to be delivered primarily through face to face contact, but 1:1 and participant group "meet-ups" could all be arranged remotely if required to meet participants' needs and preferences or Covid-19 restrictions. To help develop social connections as part of the goals of the intervention, participant will be able to access some financial re-embursement to cover costs incurred. This will help ensure that poverty, or delays with personal budgets or other forms of statutory assistance, are not insuperable barriers to enacting goals to address loneliness. A detailed intervention manual was developed during the completed feasibility trial [2] and will guide the Community Navigators and supervisors in this trial.

The frequency and timing of 1:1 meetings can be decided flexibly between the participant and the Community Navigator, to meet the participant's needs. Support will involve three stages:

a) The Community Navigator uses established processes to help people map their social world [19], visually mapping people, places and activities which are subjectively important to the person, and considering lapsed activities or contacts which the participant might want to resume, or new social groups or connections they might wish to develop. This mapping will be combined with exercises helping people to review and develop their current and desired sense of belonging to social groups. These are derived from a social identities intervention developed for the general population [20], and were adapted for our TRD population with the support of the developers during the feasibility trial [2].
b) This information is then used by the Community Navigator to help the participant develop a "personal connections plan", recorded using a bespoke chart developed in the feasibility study [2]. Participants develop goals for increasing their social connections, and are helped to break these goals down into steps, and identify personal resources and support within their network and community which can help them achieve their goals. Plans may involve engaging in new social groups and developing new contacts, or reconnecting with groups, friends or family; developing more meaningful social connections with people within existing social groups or activities that are valued and reinforce positive social identities.
c) Next, the Community Navigator Navigators will provide different types of social support [21] as appropriate to help participants enact their plans: this may include informational support [e.g. finding out about local groups or activities, or travel options to access them); practical support (e.g. using the budget; planning how a participant wants to introduce themselves in a social situation), or emotional support (e.g. going with a participant the first time to a new group, checking in with them after a phone call to a potential friend). Community Navigators will use solution-focused problem-solving approaches [22] to help participants break down goals into smaller steps if proving challenging. Participants' social network maps will be reviewed and any progress in developing social connections encouraged and celebrated. Community Navigators will at all times help participants to develop social connections which are sustainable without

long-term support from a Community Navigator; not befriending. For example, a Community Navigator would not typically accompany a participant several times to the same social group, as this support cannot be maintained after the end of the programme.

Group meet-ups will have an informal style and be lightly facilitated by the Community Navigators. They will encourage information-sharing about helpful local resources, experiences of developing connections and what has helped. Navigators will also introduce participants who may have points of connection (e.g. fellow dog-walkers), and potentially help facilitate a meeting as part of 1:1 support if participants are keen. Responding to qualitative feedback [2], we plan a "soft ending" to the programme which does not feel abrupt. Navigators will offer a telephone or video-call follow-up and one more group meet-up (the fourth of four available to each participant) after the ten 1:1 meetings, all to be completed before 8-month follow up.

Comparison: Both trial groups will receive routine care from a specialist community mental health team including reviews by a psychiatrist and, typically, regular meetings with a care coordinator and where indicated, psychological therapy. We will use information from participants and health records to describe routine care in detail and monitor use of NHS mental health services and any other local schemes aimed at promoting social participation. The Trial Manager will send control group participants written information, developed by the Community Navigator Teams, about local social prescribing services and social groups. Participants will be encouraged to consider these resources themselves, or discuss them with their care team. This constitutes a very low cost, low intensity comparator to the trial intervention, to test whether active, individualised support is superior to generic signposting.

8.1 CONCOMITANT MEDICATION

All participants will continue to receive treatment as usual, including any prescribed medications for mental health conditions. No interactions between the trial intervention and medications are anticipated. Participants will be prescribed a range of medications: we will rely on randomisation to address potential confounding. Only concomitant mental health medication will be recorded in the CRF and participant's medical notes/source data.

8.2 POST-TRIAL INTERVENTION ARRANGEMENTS

The Community Navigator programme is a time-limited intervention and will be completed for all participants during the trial. No arrangements are in place for retaining the Community Navigiators in employment after the end of the trial: this will be at the discretion of each participating NHS site.

9 SELECTION OF PARTICIPANTS

9.1 ELIGIBILITY OF TRIAL PARTICIPANTS

9.1.1 TRIAL PARTICIPANT INCLUSION CRITERIA

We will recruit adults with TRD using a participating mental health team.

Inclusion criteria:

1. Age 18+
2. Meet ICD-10 diagnostic criteria for depression assessed using the CIS-R interview [23]
3. Have had at least two reported courses of anti-depressants without symptom remission, confirmed by the participant
4. Score of 2 or more on DJG-6 loneliness scale [24]

9.1.2 TRIAL PARTICIPANT EXCLUSION CRITERIA

Exclusion Criteria:

1. Are due to be discharged from the mental health team within the trial intervention period (8 months)
2. Currently using mental health inpatient services
3. Identified by involved clinicians or clinical records as having a primary diagnosis of a serious mental illness other than TRD, defined as schizophrenia or other non-mood psychotic disorders (ICD codes F20-29) or bipolar disorder (ICD code F31)
4. Lacks capacity to consent to participate
5. Does not understand English well enough to give informed consent and engage with the study intervention
6. Has a care coordinator who supervises the Community Navigators

Exclusion criteria will be checked with the referring NHS staff member and with the participant during eligibility screening with the study researcher.

9.2 RECRUITMENT

Recruitment: Researchers will ask clinicians in participating teams or Clinical Research Network (CRN) staff in participating Trusts to identify potential eligible participants and ask them about willingness to talk to a researcher. Clinicians will review their caseloads to identify potential eligible participants. CRN staff will screen case registers and clinician caseloads in adherence with local Trust privacy notice permissions and consent to contact arrangements. A researcher will contact referred, potential participants, provide more information about the study and a written information sheet and answer questions, then seek informed consent. With the team's or clinician's approval, study researchers and/or clinical studies officers will also be available to talk topatients, where they would like to, who are attending clinic meetings with the community mental health teams, in order to provide information on the study. Participants who express an interest in participating following this contact will be provided further information by the study researchers as detailed in the informed consent procedure above.

Additional study promotion will also be carried out in order to make participation information available to a broad group of potentially eligible participants. The study poster and leaflet will be displayed in participating organisations including community mental health teams' offices and waiting areas. We will also publicise the study using the poster and leaflet in other community services which potential participants may use, including: participating NHS Trusts' other mental health services, community organisations (e.g. voluntary sector mental health services and other community groups or services) and GP surgeries in the study's catchment areas. The study leaflet and patient information sheet will also be made available on the study website, along with the study researchers' contact details for each site. We will make it clear on all study publicity that only people currently using participating mental health services can take part in the study. People who obtain study information from these sources can contact the study team directly to express interest in taking part, by calling or emailing the study researcher. In these circumstances, the study researcher would then contact the person's care team to check initial eligibility screening and the team's agreement for the person to be considered for the study, before proceeding with taking consent and further eligibility screening. In addition, where participating Trusts and/or mental health teams have details of service users who may be contacted with information on research participation, the local study team will arrange a mailout (post or email) to provide the study leaflet to potentially eligible participants. This contact will be made by the participating NHS Trust (clinical team, clinical studies officer or research department).

Those who provide consent will be screened for eligibility regarding depression diagnosis and loneliness using the structured CIS-R and DJG-6 tools, and previous anti-depressant use, before baseline measures are completed. Initial information about the study will usually be provided through a phone or video call, with a written information sheet posted or emailed to each potential participant. In collaboration with our PPI group, we will produce a leaflet to accompany this information, which will communicate key messages in plain English to appeal to the widest group of eligible participants as possible. Consent, eligibility screening and data collection will be by phone, video call or face-to-face meetings, as the participant prefers. Participants will only be enrolled in the trial and randomised to treatment or control group once consent and eligibility have been confirmed and baseline data have been collected.

At each site we will record the number of patients screened, approached and consented, and record reasons for non-eligibility, in order to produce a trial CONSORT diagram and help locate where in the recruitment process any barriers to recruitment are occurring. We will record key characteristics of recruited participants (e.g. age, gender, ethnicity, physical disabilities) and compare these with available routine service data for the patient group as a whole, to check the representativeness of our study sample. We will promptly consult our PPI group and the trial steering committee regarding adjustment to recruitment materials or additional strategies, in the event that any groups appear under-represented. A screening log will be kept and maintained to monitor recruitment.

Participant recruitment at a site will only commence when the trial has

1. Been initiated by the Sponsor (or its delegated representative), and
2. Issued with the 'Open to Recruitment' letter or Green Light letter from the Sponsor.

9.3 INFORMED CONSENT PROCEDURE

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be GCP trained, suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

Adequate time will be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after the person has been given the study documentation. It must be recorded in the source documents when the participant information sheet (PIS) has been given to the participant.

The study researcher will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to the participant giving consent by signing the consent form. Consent will not denote enrolment into trial.

For participants providing written consent face-to-face, the original signed consent form will be retained in the trial file at site and a copy placed in the medical/case notes. Where consent is obtained via videocall or telephone, the audio-recording will be stored securely at the university site and a record of the participan's consent made in their medical/case notes. A copy of the informed consent form will be given to the participant.

The PIS and consent form will be reviewed and updated if necessary throughout the trial (E.g: where new safety information becomes available). Participants will be re-consented if there have been any changes made to the patient information sheet before their next scheduled visit. Participants' capacity will be assessed before follow-up visits and documented in the medical notes and the trial database.

10 TRIAL PROCEDURES

10.1 PRE-TREATMENT ASSESSMENTS

Screening Visit:

The Following assessments will be done by researchers at the screening visit with potential participants, for whom the referring NHS site has confirmed they meet all eligibility criteria other than those listed below (see section 10.4 for more details on the assessment tools):

- Approach potential participants and provide PIS and obtain informed consent
- Clinical Interview Schedule-Revised (CIS-R) [23]
- Current loneliness: The DeJong Gierveld six-item Loneliness Scale (DJG-9) [24] yields a total score of 0-6, with a score of two an established cut-off for loneliness.

- Completion of at least two courses of anti-depressants, without full remission of symptoms

Baseline outcomes will be assessed at the screening visit and if not possible no more than 4 weeks after screening (day 0). Baseline outcomes are listed section 10.3.1. The assessments will be in a structured interview with a battery of measures and full details of the measure are described in section 10.4.

10.2 REGISTRATION / RANDOMISATION PROCEDURES

Following screening and baseline assessments, eligible participants will be randomised to a treatment group or a control group. We will use block randomisation stratified by site. Group allocation will be generated through an online randomisation system provided by a CTU-recommended service called "Sealed Envelope", and communicated to participants, clinical teams and Community Navigators by the non-blind Trial Manager or trial administrator. It will be set up, tested and validated following Priment SOPs.

10.3 SUBSEQUENT ASSESSMENTS AND PROCEDURES

10.3.1 VISIT SCHEDULE AND ASSESSMENTS

A schedule of all trial assessments and procedures is set-out in Appendix 1 and see section 10.4 for more details on the assessments listed below:

Table 1. Outcomes and timepoints

Timepoint	**Screening and Outcome Assessments**
Screening and Baseline (day 0)	Screening assessments • Clinical Interview Schedule – Revised (CIS-R) • De-Jong-Gierveld Loneliness Scale (DJG-6) • Confirmation of at least two courses of anti-depressants without symptom remission Baseline assessments completed with participant (if screening criteria are met) • Socio-demographic characteristics • Depression (PHQ-9) • UCLA Loneliness Scale (ULS-8) • General Anxiety Disorder (GAD-7) • Questionnaire on the Process of Recovery (QPR) • Four-item Multiple Identities Scale (MIS) • Brief Rosenberg self—esteem scale (B-RSES)

	• Discrimination and Stigma Scale (DISC) • Six-item Lubben Social Network Schedule (LSNS-6) • EuroQol EQ-5D 5 level (EQ-5D-5L) • Recovering Quality of Life (ReQoL) • Client Service Receipt Inventory (CSRI) • Daytime Activities Questionnaire • Self reported measure of expectiation and credibility of the intervention • Adverse Events and Concomittant mental health medication/treatment Data to be collected from patient health records (after trial enrolment) • Current diagnoses (ICD10 codes) • Mental health medication history • Mental health service use over the past 6 months (use of community and inpatient services)
4 months	• Depression (PHQ-9) • UCLA Loneliness Scale (ULS-8) • Questionnaire about support groups, social prescribing and other support activities (Daytime Activities Questionnaire) • Adverse Events
8 months (end-of-treatment)	Outcome assessments to be completed with the participant • Depression (PHQ-9) • UCLA Loneliness Scale (ULS-8) • General Anxiety Disorder (GAD-7) • Questionnaire on the Process of Recovery **(**QPR) • Four-item Multiple Identities Scale (MIS) • Brief Rosenberg self—esteem scale (B-RSES) • Discrimination and Stigma Scale (DISC) 4-item self-stopping sub-scale • Six-item Lubben Social Network Schedule (LSNS-6) • EuroQol EQ-5D 5 level (EQ-5D-5L) • Recovering Quality of Life (ReQoL) • Client Service Receipt Inventory (CSRI) • Daytime Activities Questionnaire • Adverse Events and Concomittant mental health medication/treatment Data to be collected from patient health records • Mental health medication (previous six months) • Mental health service use (previous six months)

11 months	• Depression (PHQ-9) • UCLA Loneliness Scale (ULS-8) • Questionnaire about support groups, social prescribing and other support activities (Daytime Activities Questionnaire)
14 months (6 months post-treatment)	Outcome assessments to be completed with the participant • Depression (PHQ-9) • UCLA Loneliness Scale (ULS-8) • General Anxiety Disorder (GAD-7) • Questionnaire on the Process of Recovery **(**QPR) • Four-item Multiple Identities Scale (MIS) • Brief Rosenberg self—esteem scale (B-RSES) • Discrimination and Stigma Scale (DISC) • six-item Lubben Social Network Schedule (LSNS-6) • EuroQol EQ-5D 5 level (EQ-5D-5L) • Recovering Quality of Life (ReQoL) • Client Service Receipt Inventory (CSRI) • Daytime Activities Questionnaire Data to be collected from patient health records • Mental health medication (previous six months) • Mental health service use (previous six months)

All trial assessments will be completed by study researchers using face-to-face meetings, video-conferencing or telephone interviews, led by participants' preference. All outcomes will be collected at 3 time points: at baseline, at 8 months (end of treatment) and at 14 months (six months after end-of-treatment). Assessments will be completed as soon as possible after, and within 3 months of the scheduled date. Depression and loneliness data will be collected additionally at 4- and 11-month follow-ups, either through a self-completed online form or through a phone or video call with a study researcher. The study researchers will send participants by email a link to an online questionnaire built using secure UCL Opinio software, inviting them to complete the measures online, or request a phone or video call if they prefer. Participants without working email addresses will be contacted by the study reseaarchers by phone. Participants' capacity will be assessed before follow-up visits and documented in the medical notes and the trial database. We will maintain blinding as completely as possible: only the trial manager, admin assistant and peer researcher will access participants' allocation status - and collect programme monitoring data about participants' receipt of the intervention – not the research assistants collecting follow-up data. Using self-report scales will further eliminate observer bias. Data will be entered in the "Sealed Envelope" secure online database with paper data stored at universities in line with GDPR requirements.

10.4 CLINICAL PROCEDURES AND SCREENING AND OUTCOME MEASURES

Socio-demographic characteristics: We will seek information about: participants age, gender, ethnicity, marital status, living arrangements, and depression and service use history.

Clinical Interview Schedule-Revised (CIS-R) [23]: This is a fully structured diagnostic instrument that was developed from an existing instrument, the Clinical Interview Schedule (CIS), which was designed for the use of clinically experienced interviewers such as psychiatrists. The CIS was revised and developed into a fully structured interview in order to increase standardisation and to make it suitable to be used by trained lay interviewers in assessing minor psychiatric morbidity in the community, general hospital, occupational and primary care research and generates diagnoses meeting ICD-10 criteria for depressive episodes.

The DeJong Gierveld six-item Loneliness Scale (DJG-9) [24]: To measure loneliness we will use the 6-item De Jong Gierveld Loneliness Scale which is a reliable and valid measurement instrument for overall, emotional, and social loneliness. It yields a total score of 0-6, with a score of two an established cut-off for loneliness.

Client Service Receipt Inventory (CSRI) : The Client Service Receipt Inventory (CSRI) is a tool used to collect information on the whole range of services and supports study participants may use. We will collect information about participants' accommodation, employment status and use of all physical health services using an adapted CSRI measure [25]. NHS mental health service use will be obtained from patient health records. Prescribed medications will be obtained from participant self-reports as well as mental health trust records, and we will seek permission to collect data from GP records if required to obtain complete information.

Mental Health Medical History: This will include use of mental health medication and services collected from patient health records.

Daytime Activities: This will include questions about support groups, social prescribing and other support activities.

UCLA Loneliness Scale – ULS-8 [26]: We will use the 8 item scale to measure loneliness, which has good established psychometric properties and has been used previously in mental health poppulations.

Generalised Anxiety Disorders Scale – GAD-7 [27]: To measure anxiety we will use GAD-7. The GAD-7 represents an anxiety measure based on seven items which are scored from zero to three. The whole scale score can range from 0 to 21 and cut-off scores for mild, moderate and severe anxiety symptoms are 5, 10 and 15 respectively.

Patient Health Questionnaire – PHQ-9 [28]: Our primary trial outcome is depression symptom severity and this will be measured by using the Patient Health Questionnaire – PHQ-9. This 9-item, self-report measure with good psychometric properties yields a total score from 0-27.

Lubben Social Network Schedule (LSNS) [29]: The Lubben Social Network Scale (LSNS) is one of the most widely used questionnaires to quantitively assess social network size and we will use the six-item Lubben Social Network Schedule to measure social network size.

Discrimination and Stigma Scale (DISC) [30]: The DISC is an interview-based scale which measures experiences of mental health-related discrimination ('being treated unfairly') in key areas of everyday life and social participation, including work, marriage, parenting, housing, leisure, and religious activities. To measure self-stigma we will be using the four-item self-stopping behaviours sub-scale from the Discrimination and Stigma Scale.

Multiple Identities Scale (MIS) [31]: We will also use established self-report scales to measure expected proximal intervention outcomes and multiple social identities by using the four-item Multiple Identities Scale [32];

Questionnaire on the Process of Recovery – QPR [32]: To measure personal recovery using the 15-item version.

Recovering Quality of Life (ReQoL) [33]: ReQoL is a new Patient Reported Outcome Measure (PROM) that has been developed to assess the quality of life for people with different mental health conditions. As part of our economic analysis we will assess preference based mental health related quality of life using the ReQoL [38].

Brief Rosenberg self—esteem scale (B-RSES) [34]: To measure self-efficacy we will use the 5-item Rosenberg self—esteem scale [33]. This is a reliable and valid measure of self-esteem using the five best items from the original 10-item Rosenberg scale.

EQ-5D-5L: is a standardised measure of health-related quality of life developed by the EuroQol Group to provide a simple, generic questionnaire for use in clinical and economic appraisal and population health surveys. EQ-5D-5L assesses health status in terms of five dimensions (with 5 levels in each dimension) of health and is considered a 'generic' questionnaire because these dimensions are not specific to any one patient group or health condition. As part of our economic analysis we will assess preference-based health related quality of life using using EQ-5D-5L [35].

Credibility and Expectancy questionnaire [37]: this is a six-item scale that measures treatment expectancy and credibility. We will use a single-item adapted version.

Trial safety monitoring is described in section 11. Monitoring of trial intervention delivery and compliance are described in section 10.5. Trial eligibility screening and outcme measures are described in section 10.1. The trial involves no other clinical procedures.

10.5 ASSESSMENT OF TRIAL INTERVENTION COMPLIANCE

Qualitative studies accompanying the trial are described in section 11. We will collect qualitative data from intervention participants and providers at two stages: a) during the internal pilot, to understand any barriers to trial recruitment and intervention engagement; and b) later in the trial to explore experiences of the programme and how perceived benefits were achieved, and to identify core and local contextual factors affecting delivery of the programme in an NHS context. This will inform development of guidance to support future scale-up in the event of a positive trial result. Participant interviews will be conducted by a study peer researcher who will also lead the analysis. The PPI group will be actively involved, supporting the development of qualitative interview guides, study recruitment materials and synthesis of findings.

Monitoring session content: Using procedures tested in the feasibility trial [2], the unblind trial manager or administrator will collect session logs from Community Navigators which describe the number and location of meetings with each participant and the content of the intervention delivered (e.g. how many participants developed a network map, and a personal connections plan). These will be used to assess the number of sessions attended by each participant and the extent to which the intervention was delivered as intended.

In line with the completed feasibility trial, a minimum of three meetings with the Community Navigator has been set for treatment per protocol.

Qualitative interviews with participants, Community Navigators and supervisors (described above) will be used to identify any contextual factors affecting the delivery of the intervention at each site. Our secondary outcome data collected at follow-up interviews (increased social contact and activity, reduced self-stigma, enhanced social identities, increased self-efficacy), and qualitative feedback from participants, will be used to explore how the intervention may reduce loneliness and depressive symptoms. We will thus use a mixed methods approach to understanding contextual factors, mechanisms of impact and fidelity of implementation, and how these may relate to programme outcomes, in line with established MRC guidance for evaluating complex interventions [38].

10.6 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

In consenting to participate in the trial, participants are consenting to trial treatment, assessments, follow-up and data collection.

Discontinuation of Trial Treatment for clinical reasons

A participant may be withdrawn from trial treatment whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- disease progression whilst on therapy
- unacceptable side effects or safety events
- intercurrent illness which prevents further treatment
- participants withdrawing consent to further trial treatment

Any alterations in the participant's condition which justifies the discontinuation of treatment in the site investigator's opinion.

Persistent non-compliance to protocol requirements.

The decision to withdraw a participant from treatment must be recorded in the CRF and medical/case notes/source documents, and the sponsor when required should be notified in writing.

In these cases participants remain within the trial for the purposes of follow-up for safety and or data analysis according to the treatment option to which they have been allocated.

Participant withdrawal from trial treatment

If a participant expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up and seek permission to allow use of routine follow-up data to be used for trial purposes. The importance of safety follow-up should be emphasised to the participant in the Participant Information Sheet.

The decision of the participant to withdraw from treatment must be recorded in the CRF and medical/case notes/source documents.

The participant may withhold their reason for withdrawal however, if the participant gives a reason for their withdrawal, this should be recorded.

Withdrawal of Consent to Data Collection

Participants who do not meet their Community Navigator or disengage after a single session will be contacted by site supervisors or the Trial Manager and offered a change of Navigator, wherever feasible. If a participant explicitly states they do not wish to contribute further data to the trial, their decision will be respected and recorded in their CRF and medical notes. If a participant states they wish to withdraw from the study completely, and for data already collected from them not to be used, this decision will also be respected and recorded and all data collected from or about this participant will be deleted. No other criteria for withdrawing a participant from the study are pre-planned. If concerns were raised by involved clinical services or others about whether continued participation in the study is in the participants' best interests, these concerns would be discussed promptly with the Clinical Trials Unit and the sponsors and a decision reached.

Loss to follow-up

If a participant moves from the area, it will not be possible to provide the trial intervention any further. However, study researchers will continue to use the participant's available contact details to complete follow up research interviews. If a participant is lost to follow-up at a site we will seek information from the involved mental health teams and the participant's GP as required to obtain information on the participant's status. We will seek consent from participants to do this in the PIS and consent form.

Our sample size calculation for the trial includes allows for a loss to follow up of 15% of participants, a conservative estimate based on our feasibility trial results [2]. An exclusion criterion is that participants are not due for discharge within the study intervention period, so nearly all our participants will remain in contact with mental health services during the follow-up period until the primary outcome time point (8 months), which will help ensure they are not lost to contact from the study team. We have built in mini data collection phone follow-up points at four and eleven months, which in part aim to promote engagement with and retention in the study, by limiting the amount of time participants have without contact from a researcher.

10.7 REPLACEMENTS

Participants who withdraw from the trial will not be replaced.

10.8 STOPPING RULES

The trial includes an internal pilot phase during the first six months of recruitment – Months 10 to 15, JUN-NOV-22. Continuation criteria are as follows:

	Red	Amber	Green
% threshold	50%	75%	100%
Recruitment rate (per site per month)	2	3	4
Number of sites open	2	3	4
Total number of participants	58	87	116
% treatment group participants engaged in treatment	50%	65%	80%

Our continuation criteria require recruitment of 4.8 participants per site per month. This results in 29 participants recruited per site (116 in total) during the six-month pilot period: a rate which, sustained over the full 16 month recruitment period, yields 77 participants per site as planned.

An additional continuation criterion assesses feasibility of the delivery of the intervention. Among the participants recruited within the first five months of the study and randomised to the treatment group – i.e. those who have been enrolled in the study for at least one month at the Month 15 end-of-pilot point, we will monitor the proportion who have either:

i) Already been treated per protocol, or

ii) Who remain actively engaged in treatment

Treatment per protocol is defined, as in the completed feasibility study [2], as a minimum three meetings with a Community Navigator. Current active engagement with treatment is defined as a participant having met their Community Navigator within the last month. All participants will still be within their six month intervention delivery time period at the Month 15 review point. Intervention delivery rates of 80%, 65% and 50% of treatment group participants engaged in treatment have been set as green, amber and red thresholds for this additional criterion.

If the trial does not meet all green thresholds at the end of Month 15, trial progress and plans for mitigating shortfalls in recruitment and retention will be reviewed by the TSC in Month 16 and the funders and sponsors in Month 17, who will recommend either continuing the trial with agreed mitigation plans, or stopping the trial and ending the study by end of Month 18.

No other stopping rules are planned, but study progress and safety monitoring will be reviewed by the Clinical Trials Unit, the sponsors, the DMEC and the TSC. The trial may be stopped before completion:

- On the recommendation of the TSC or DMEC
- On the recommendation of the sponsor, Priment CTU, the funder or CI

10.9 DEFINITION OF END OF TRIAL

The recruitment of the first trial participant is planned for JUN 2022. The final 14-month follow-up interview is due in NOV 2024. Allowing up to three months after this date to complete all follow up interviews, the final visit to the last participant will be completed by the end of FEB 2025. The expected duration of the trial is 33 months. The end of the trial is the date of the last vist of the last participant (14 month follow up of the last participant).

11 QUALITATIVE STUDIES

Qualitative study one- Exploring obstacles to recruitment and participation

Qualitative study 1a: In Months 10-15 – the internal pilot phase, we will run a brief, anonymous survey for all participants.

Participants: all trial participants recruited during the internal pilot phase of the trial (Months 10-15)

Procedures: All participants will be sent an email invitation to complete a survey online. Information about the survey will be included with the invitation email, and at the start of the online survey. Participants will check a consent box to agree to complete the survey, which will be self-completed anonymously. When participants want to take part to the survey but don't have access to the web, a paper copy of the survey will be posted to their preferred address in a pre-paid envelope.

Measures: The survey will include strcuctured and free-text questions asking about experience of the recruitment process and any areas where information was unclear or off-putting, and seeking recommendations for greater inclusivity in our messaging and approach. For those in the treatment group, we will ask about any barriers to engagement with the intervention. For the control group, we will ask about reaction to their allocation outcome and the information about local resources. Studies rarely ask participants to provide their expertise on recruitment, but this approach is consistent with our co-production ethos and we believe will add considerable value to the study ensuring recruitment to target is achievable.

Qualitative study 1b: During the internal pilot phase of the trial (Months 10-15), we will also conducted semi-structured qualitative interviews with treatment group participants, Community Navigators and their supervisors.

Participants: We will interview up to 20 people from the intervention group (five per site), prioritising any who disengage from the programme and seeking demographic diversity in our sample (gender, ethnicity and age). We will also seek to interview the three Community Navigators and their two supervisors at each site (n=20) either individually or in mini focus groups.

Measures: Semi-structured interview topic guides will be developed with our PPI team. These will further explore people's expectations of the programme from the recruitment process, obstacles to initial participation, and any barriers to subsequent engagement.

Analysis (Qualitative studies 1a and 1b): Analysis of the qualitative data collected in months 10-15 will proceed in two stages. We will provide rapid feedback to the programme team as soon as interviews and survey responses are provided, so that any adjustments to recruitment and the programme can be made as appropriate. The interview data will be analysed thematically as data is collected and coded during the familiarisation stage of the reflexive qualitative analysis process [39]. Survey data will be descriptively summarised be as soon as it closes to respondents. A short report will be produced for the study team and Trial Steering Committee. Second, a more in-depth analysis of interviews will involve more members of the study team, including our PPI group, to agree coding structures and discuss the synthesis process. We will use Nvivo-12 software to manage this analysis. This analysis will be timely too, so any new emerging insights can be considered by the programme team, but will also be developed into a publication.

Qualitative study two - programme delivery

Participants: We will interview at least 20 further intervention group participants (five per site) after 8-month, end-of-treatment follow-up (Months 18-33). We will sample purposively to achieve amaximum variation sample, including those who engaged fully and partially with the programme, a demographically diverse group and who have a range of scores on our primary outcome, depression at end-of-treatment. These will be different interviewees from study one. We will also seek to interview the Community Navigators and their superivsors at each site (maximum five interviews per site).

Procedures: As in Qualitative study 1b, a researcher will contact potential participants who had previously consented to be contacted about a qualitative interview, and provide more information about the qualitative study and a written information sheet and answer questions, then seek informed consent. Community Navigators and their supervisors at each site will likewise be contacted by a study researcher, provided with information and a written information sheet about the study, and to provide written informed consent before starting an interview. Interviews will be face to face, online or by phone depending on participant preferences, and interviewees will be reimbursed for participation with a shopping voucher as a gift of thanks. We will interview the two project supervisors together and the Community Navigators at each site, individually or together as they prefer, to ask about any factors affecting intervention take up or engagement from their perspectives (n=4 interviews per site maximum). All interviews will be audio-recorded and professionally transcribed.

Measures: Semi-structured interview topic guides will be developed. Interviews with participants will explore perceived impact of the programme, how benefits were achieved, and any factors relating to the participant's circumstances or the nature or context of the programme and how it was delivered which helped or hindered it from being a useful intervention. Interviews with Community Navigators and supervisors will explore what helped and hindered delivery of the programme as intended within an NHS context: to guide any refinement of recruitment processes or training or supervision procedures; and to develop implementation guidance.

Analysis: An analysis group will include representation from PPI group members, the study peer researcher, and co-applicants, including lived experience co-applicant TM. Our overarching approach to analysis will be thematic [39]. At each stage, we will adopt analysis approaches that fit our data, supported by NVivo12 software. We will use findings from this analysis to review the intervention logic model and develop a guide for future delivery of the programme in the NHS.

12 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to Priment pharmacovigilance SOPs.

12.10 DEFINITIONS for AE

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant administered a treatment/intervetnion and which does not necessarily have a causal relationship with the treatment/intervention. *Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a participant to whom a procedural intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention.*
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction	Any adverse event that: results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation**, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an inpatient admission, regardless of length of stay. **Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.**	
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is deemed to be 1. Related to the trial intervention AND 2. Unexpected (not listed in the protocol as an expected side effect of the intervention)
Important Medical Event	These events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.

12.11 RECORDING ADVERSE EVENTS

All adverse events will be recorded in the patient health records and source data in the first instance following consent and will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All adverse events will be recorded until the end of treatment point for each participant – i.e. 8 months after enrolment and randomisation.

Only Serious Adverse Events and any unexpected, study-related adverse events will be recorded in the CRF and SAE log. This social intervention is not invasive and participants may stop participating at any time.

12.12 EXPECTED SIDE EFFECTS

The following Events are expected and do not need reporting:

Testing Positive for Covid 19. Symptoms of COVID 19 are therefore expected and do not need reporting unless the symptoms are serious and result in hospitalisation.

Short-term increased anxiety or emotional discomfort are the only expected side effects from the study intervention. However, due to the nature of the participant group – people with severe and enduring depression, the following serious adverse events may be expected to occur for some participants, irrespective of their participation in the trial: admission to mental health acute care; attempted suicide; or suicide. Harm to others perpetrated by the participant, or any harm or threat of harm to the participant from the Community Navigator delivering the trial intervention, do constitute unexpected adverse events.

Disease progression is expected in some participants due to the nature of their condition and will be treated as expected events, unless the severty of the progression is unexpected.

Please note that if a patient experiences an adverse event that is not listed in this protocol then this should be classed as unexpected.

12.13 ASSESSMENTS OF SERIOUS ADVERSE EVENTS

Each adverse event will be assessed for severity, causalityand expectedness as described below. Where further information on the event is required that could potentially unblind binded staff e.g if the event requires expidited reporting to ethics, the unblind Trial Manager or Administrator will gather this information from the participants, involved clinical staff or case notes as appropriate. The site PI will make the final judgements about severity, causality and expectedness and this assessment will be done blinded.

Severity Category	**Definition**
Mild	The adverse event does not interfere with the participant's daily routine, and does not

	require further intervention; it causes slight discomfort.
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort.
Severe	Any adverse event that: 1. results in death, 2. is life-threatening*, 3. requires hospitalisation or prolongation of existing hospitalisation**, 4. results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect

Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form. The differentiated causality assessments will be captured in the trial specific AE database and the SAE form. The following categories will be used to define the causality of the adverse event:

Category	**Definition**
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for

	the event (e.g. the participant's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not assessable	Unable to assess on information available.

12.14 RELATED EVENTS

The assessment of the relationship between adverse events and the administration of the intervention is a decision based on all available information at the time of the completion of the case report form. If the event is a result of the administration of any of the research procedures then it will be classed as related.

12.15 EXPECTED EVENTS

If the event has been listed in the protocol as an expected side effect of the intervention then the event will be classed as expected. If the event is not listed or the severity of the listed event is not expected then it will be classed as unexpected. We are anticipating to pick up more expected SAEs in the intervention arm than in the control arm because intervention participants will have increased contact with the study team.

12.16 PROCEDURES FOR RECORDING AND REPORTING SERIOUS ADVERSE EVENTS AND SUSPECTED UNEXPECTED SERIOUS ADVERSE EVENTS

All serious adverse events (SAEs/SARs/SUSARs) will be recorded in the medical records and the CRF. Events reported prior to starting the intervention will be recorded in the medical history section and treated as pre-existing events and do not need to be recorded as and SAE unless the event worsened as a result of their participation on the trial.

All SAEs will be recorded for each participant from enrolment into the trial until end-of-treatment at Month 8. Pre-planned treatments involving hosptialisation will not be recorded in the CRF or require reporting.

All SAEs (except those specified in section 12.6 as not requiring reporting to the Sponsor), must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and the form will be preferably emailed to the Sponsor primentsafety@ucl.ac.uk, within 24 h of his / her becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Completed SAE forms must be sent within 24 hours of becoming aware of the event to Priment CTU

Email forms to primentsafetyreport@ucl.ac.uk and copying in the Sponsor sponsor.noclor@nhs.net

The reporting of adverse events to the ethics committee and sponsor will be completed according to Priment non-CTIMP safety management SOP or to any other specific requirements if the Sponsor of the trial is not UCL.

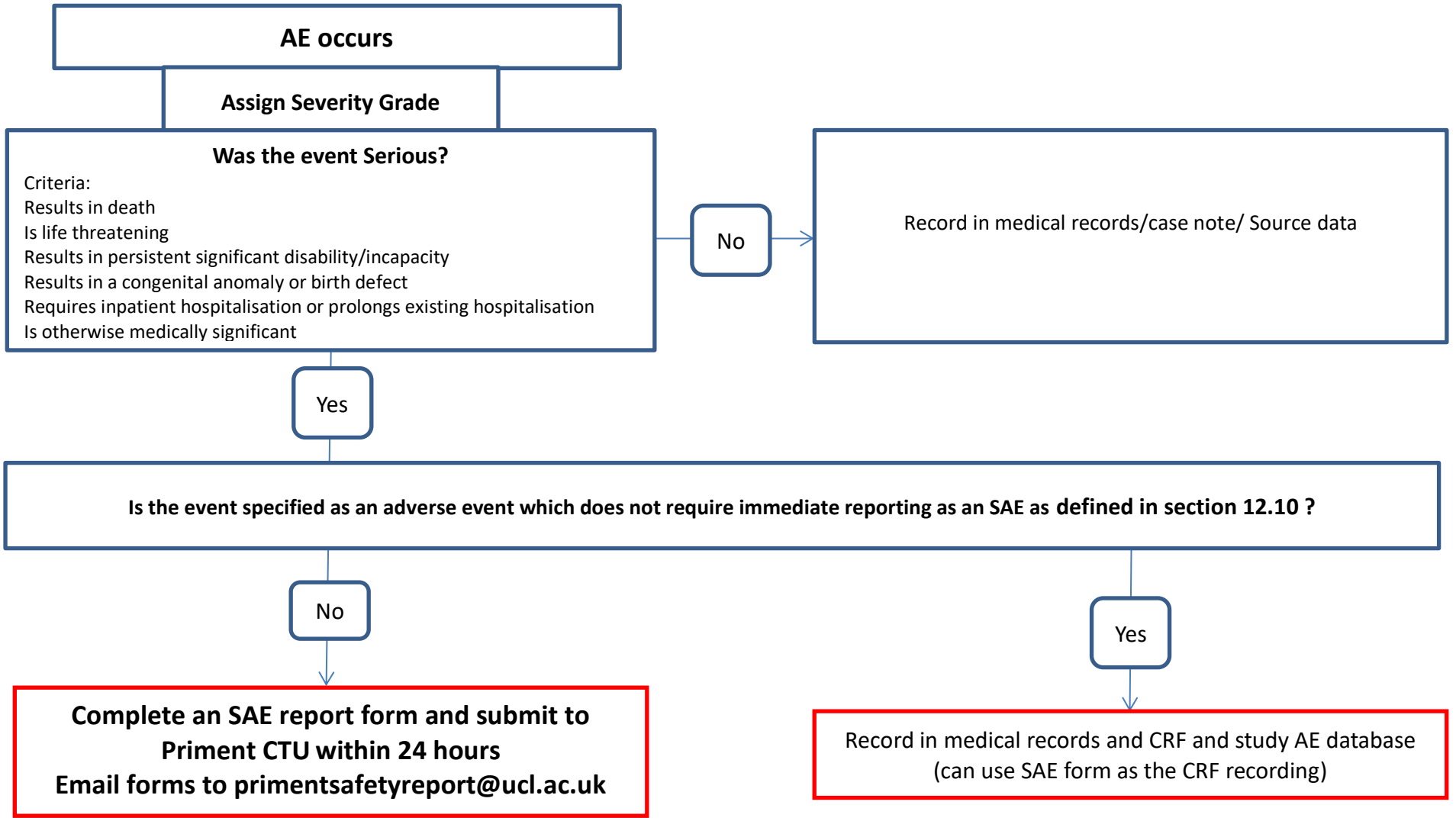
Priment CTU is responsible for reporting SUSARs to the ethics committee that approved the study. SUSARs that are fatal or life-threatening must be notified to REC within 7 days after the Chief Investigator has learned of them or within 15 calendar days of becoming aware of the event.

Follow-up SAE forms (clearly marked as follow-up) will be completed and emailed to Priment if further information becomes available.

The DMEC will also assume the role in periodically reviewing SAEs.

Camden and Islington NHS
NHS Foundation Trust

Flow Chart for SAE reporting



12.17 NOTIFICATION OF DEATHS

Only deaths that are assessed to be related to the Intervention will be reported to the sponsor. This report will be immediate.

12.18 REPORTING URGENT SAFETY MEASURES AND OTHER SAFETY EVENTS

If any urgent safety measures are taken, the CI shall immediately notify Priment of this measures, and in any event no later than 3 calendar days from the date the measures are taken. Written notification will be submitted within 3 calendar days to the relevant REC as in line with Priment SOP on Urgent Safety Measures.

12.19 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A "serious breach" is a breach which is likely to effect to a significant degree –

1. the safety or physical or mental integrity of the participants of the trial; or
2. the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

1. the conditions and principles of GCP in connection with that trial; or
2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of the breach.

Sites must record all protocol deviations on Priments protocol deviation log and file these in the site file. Sites must notify the CI, Priment and the sponsor of any deviations and these deviations will be filed in the TMF. Repeated frequent deviations may require immediate action and could potentially be classified as a serious breach. **PRM-SOP-006 Non Compliance To Study Protocol,Regulatory Requirements and Serious breaches of GCP or trial protocol** will be followed.

13 DATA MANAGEMENT

13.10 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

A data management plan will be created which will include details of the data collection tools, methods of completing case report forms, sign off of completed CRFs, source document identification and methods to maximise completeness of data collection.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

Data collected for the study will be entered in the medical/case notes/source documents in the first instance and then transcribed into the CRFs.

13.11 DATA COLLECTION AND HANDLING

All data will be collected and handled in accordance with Priment SOP Data Handling and the trial specific arrangements will be detailed in the data management plan.

The McPin Foundation is a non-profit organisation which facilitates user involvement in mental health research. It has an established track-record of working with NHS and university partners on nationally funded mental health research projects. A peer-researcher employed by the McPin Foundation will conduct qualitative interviews with participants who agree to this. An additional information sheet and consent form are provided for qualitative interview participants. The McPin peer researcher will access contact details for potential qualitative interview participants through the secure UCL DSH. All physical qualitative data (consent forms, paper transcripts) will be stored in secure cabinets at the McPin Foundation during the study. At the end of the study all physical data will be moved from McPin to UCL for archiving. Qualitative consent forms and data in electronic form (interview recordings) containing confidential personal data will be stored in UCL Data Safe Haven during the study and will be archived by PRIMENT at the end of the study. Data sharing agreements between the NHS sites, university partners and the McPin Foundation will be arranged by the sponsors and the Clinical Trials Unit before the start of the study.

13.12 TRIAL DATABASE

The CRFs will be entered into a web-based clinical data management system, Red Pill, provided by Sealed Envelope through Priment. Sealed Envelope has been assessed by Priment to ensure that adequate processes are in place and are being followed for quality management, software development and security. There will be an agreement in place between the sponsor and Sealed Envelope to ensure compliance and agreement with clinical trial regulations and data protection laws. It is good practice to make anonymised trial data set publicly available - at least on reasonable request. Our consent form explicitly includes this (item 4).

13.13 DATA OWNERSHIP

At the end of the trial the data belongs to the contractor, Camden and Islington NHS Foundation Trust, managed in accordance with its collaboration agreement with other involved parties.

14 STATISTICAL CONSIDERATIONS

14.10 OUTCOMES

14.10.1 PRIMARY OUTCOMES

We will collect all outcomes at baseline, 8-month (end-of-treatment) and 14-month (six months after end-of-treatment) follow-ups, and additional depression and loneliness ratings through phone or video calls at 4 and 11-months (see below Table 1).

Table 1. Participant data collection measures and time points

Measure	Baseline	4 months follow up	8 months follow up (End of treatment)	11 months follow up	14 months follow up
Screening measures					
CIS-R depression screening	✓				
DJG-6 Loneliness measure	✓				
Previous anti-depressant use	✓				
Primary outcome					
Depression severity (PHQ-9)	✓	✓	✓	✓	✓
Secondary outcomes					
Loneliness (ULS-8)	✓	✓	✓	✓	✓
Anxiety (GAD-7)	✓		✓		✓
Process of Recovery (QPR)	✓		✓		✓
Four-item Multiple Identities Scale (MIS)	✓		✓		✓
Brief Rosenberg self-esteem scale (B-RSES)	✓		✓		✓
Self-stigma (DISC-12 sub-scale)	✓		✓		✓
Lubben Social Network Schedule (LSNS-6)	✓		✓		✓
EuroQol EQ-5D 5 level (EQ-5D-5L)	✓		✓		✓
Recovering Quality of Life (ReQoL)	✓		✓		✓
Client Service Inventory (CSRI)	✓		✓		✓
Daytime Activities Questionnaire	✓	✓	✓	✓	✓
Self reported measure of expectiation and credibility of the intervention	✓				
Other measures					
Adverse events and Concomitant mental health medication/treatment	✓	✓ (Adverse Events only)	✓		

Our primary trial outcome, **depression symptom severity**, is measured by the Patient Health Questionnaire – PHQ-9. This 9-item, self-report measure with good psychometric properties yields a total score from 0-27.

14.10.2 SECONDARY OUTCOMES

We will use validated self-report scales to assess secondary outcomes, which will be confirmed following discussions with our PPI group and the Clinical Trials Unit. We will use the PHQ-9 measure to assess: i) the number of patients achieving a 20% reduction in PHQ-9 score; and ii) the number of patients who achieve remission of depressive symptoms, defined as a PHQ-9 score of <10. We propose to measure: **loneliness**: measured using the 8-item UCLA Loneliness Scale – ULS-8; **anxiety**: measured using the seven-item Generalised Anxiety Disorders Scale – GAD-7; **personal recovery:** measured using the 15-item Questionnaire on the Process of Recovery – QPR. We will also use established self-report scales to measure expected proximal intervention outcomes: **multiple social identities**, using four-item Multiple Identities Scale; **self-efficacy**, using the 5-item Brief Rosenberg self—esteem scale, **self-stigma** using the four-item self-stopping behaviours sub-scale from the DISC, **social network size**, using the six-item Lubben Social Network Schedule [35].

Economic analyses: We will assess preference-based **health related quality of life** using EQ-5D-5L [35] and preference based **mental health related quality of life** using the ReQoL [33]. We will collect information about participants' **accommodation, employment status and use of mental and physical health services**, using health records and an adapted CSRI measure [25].

14.11 SAMPLE SIZE AND RECRUITMENT

14.11.1 SAMPLE SIZE CALCULATION

We will recruit 306 participants. The standard calculation to detect a 0.4 standard deviation (sd) difference in PHQ-9 depression score between arms with 90% power and 5% alpha requires 132 participants per arm. Adjusting for baseline PHQ reduces the sample size by r2, where r is the correlation between baseline and follow-up outcome values [40]. Assuming a correlation of 0.5 and 15% attrition (informed by the feasibility trial [2]) results in a sample size of 117 participants per arm. Assuming four sites, three navigators per site, and an ICC for clustering by navigator of 0.05, results in a design effect of 1.6 (based on 13 participants per navigator). Inflating the sample size for clustering in the intervention arm only (to 188), then adjusting group sizes to be equal, produces a sample size of 153 participants per arm.

In response to peer review comments, we have checked the sample size calculation using simulation and have found that we do obtain 90% power, as calculated, when analysing the data using a mixed model with ML, treating each control subject as a cluster of size 1 (following Flight et al., 2016). However, as noted by the reviewer, the confidence interval coverage and Type I error are slightly improved by analysing the data using REML with the Kenward-Rogers adjustment. This results in a slight loss of power

but is the analysis we now intend to use. The power to detect a (standardised) difference of 0.4 is reduced to 87%, or equivalently, we have 90% power to detect a difference of 0.42. This still provides 90% power to detect a minimum clinically important difference on PHQ-9 between groups of about 2 points [42].

14.11.2 PLANNED RECRUITMENT RATE

The recruitment period for the trial will be 16 months. We will recruit 77 participants per site at a rate of just under five per month. This rate was achieved comfortably in the feasibility trial. We have considered access to sufficient teams and potential participants with each site, in discussions with participating NHS Trusts. There will be equal allocation between treatment arms, with 153 participants in the treatment group and 153 in a control group.

An internal pilot is built iin to the study for the first six months of participant recruitment (Months 10-15) – see section 10.8. Progress against continuatuion criteria will be reviewed by the TSC, the sponsors and the funders. This would allow study closure at 18 months if recommended. If our recruitment or intervention delivery rates fall within the amber "review" range, study referral, eligibility and participation rates, and qualitative data from a participant survey and interviews will be used to identify barriers to recruitment or intervention delivery and potential solutions.

14.12 STATISTICAL ANALYSIS PLAN

A summary of the statistical analysis is below. A more detailed statistical analysis plan will be produced by the statisticians and agreed with key members of the trial team prior to database lock. The analyses and subsequent reporting will be guided by the Consort recommendations [43]. The analysis for primary and secondary outcomes will be intention to treat. Analyses will be performed on a modified intention to treat basis, in which participants will analysed according to their allocated group using all available data for a given outcome and timepoint.

14.12.1 SUMMARY OF BASELINE DATA AND FLOW OF PARTICIPANTS

We will construct a Consort diagram to describe the flow of subjects through the study.

The baseline demographic and clinical characteristics of the participants will be summarised by randomised group and compared visually to assess whether balance has been achieved. Frequency and percentage within each category will be reported for categorical variables. Measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) will be reported according to distribution for continuous variables. No statistical tests will be performed. Any notable imbalances may lead to additional adjusted sensitivity analyses.

14.12.2 PRIMARY OUTCOME ANALYSIS

Statistical Analysis

The primary analysis of the PHQ-9 score at 8 months follow up (end-of-treatment) comparing intervention and control groups will use a mixed model (estimated using REML, with the Kenward-Roger adjustment) to perform an individual level analysis and will follow guidance [42] in adjusting for navigator clustering in the intervention arm only (random coefficient model): specifically, each control subject will be treated as a cluster of size 1. This model will also adjust for baseline PHQ-9 score and site using fixed effects. The estimated intervention effect will be reported with a 95% confidence interval and p value.

All modelling assumptions will be checked. In particular, a confirmatory analysis will be performed using the heteroscedastic model [42] which allows the residual variance for intervention and control groups to differ.

Withdrawals from the study, loss to follow up and other missing outcome data will be summarised seperately by randomised group. The primary analysis will be a complete case analysis. However, we will investigate whether there are any predictors of missingness. If any are found, these will be included in an adjusted analysis as a supportive analysis.

14.12.3 SECONDARY OUTCOME ANALYSIS

Statistical Analysis

The effect of the intervention on PHQ-9 score at 14-month (six months after end-of-treatment) follow up and secondary outcomes at 8 and 14 months will be assessed using analogous methods to those used for the primary outcome. P-values will not be reported for secondary analyses. The number and type of adverse events will be summarised by study arm.

Health Economics Analysis

Measurement of costs and outcomes: We will calculate the incremental cost per quality adjusted life year (QALY) gained of Community Navigators plus routine care compared to routine care over 14 months from a health and social care cost perspective, using the EQ-5D-5L to calculate QALYs. Secondary analyses will include (i) using the ReQoL to calculate QALYs; (ii) including wider societal costs such as productivity and absenteeism and use of voluntary services.

We will calculate the cost of delivering the Community Navigator intervention, including training and supervision based on activity reported by the community navigators. Unit costs for staff costs and Community Navigator costs will be taken from the Personal Social Services Resource Unit (PSSRU) [45]. We will collect all participants' mental health service use information from health records, including

contacts with community mental health staff and any use of inpatient or crisis services. Other health and social care resource use including primary care will be collected from an adapted CSRI at completed with researcher support at baseline, 8 months and 14 months asking about the past 6 months. The feasibility trial [2] identified that our TRD client group also had a range of physical health needs, so we will ask about planned and unplanned acute hospital resource use. Participants will be asked to report use of social prescribing schemes, befriending, peer support groups and other social clubs, organisation and voluntary sector groups as part of a bespoke questionnaire at baseline and each follow-up time-point to collect detailed information on any additional activities that might have occurred as a result of the intervention, with equicvalent information also collected for the arm receiving only routine care. Health and social care resource use will be costed using NHS reference costs [46] and PSSRU [45]. For wider societal costs we will ask about current employment status and for employed participants' time off work sick in the past 6 months, with additional absenteeism and presenteeism information collected using the Work Productivity Activity Impairment Questionnaire [47], incorporated into the CSRI. This will be costed using the human capital approach. Costs of voluntary services and accommodation will also be included in wider societal costs.

QALYS will be calculated using the EQ-5D-5L and appropriate UK tariff as the area under the curve adjusting for baseline [44]. EQ-5D-5L has been shown to be a valid and responsive measure for depression [48] although there is limited evidence for TRD. The use of the EQ-5D-5L is recommended in the National Institute for Health and Care Excellence [49] allowing for comparisons across disease areas. In the Community Navigators feasibility study [2], (noting very small patient numbers), patients in the intervention group had a 0.19 increase in utility compared to 0.05 in the control group, indicated that the EQ-5D-5L may be sensitive to a treatment effect. However, to address potential limitations with the EQ-5D-5L, we will also calculate QALYs using the ReQoL and its to be published tariff, a measure of mental health related quality of life.

We will report the mean incremental cost per QALY gained of the Community Navigator programme plus routine care, compared to routine care, over 14 months for all analyses. The denominator and numerator of the incremental cost per QALY gained will be calculated using regression analysis, accounting for baseline, site as a fixed effect and Community Navigator as a random effect. Other potential coefficients for inclusion will be considered as part of a health economics analysis plan signed off before database close. 95% confidence intervals, cost-effectiveness planes and cost-effectiveness acceptability curves will be calculated based on bootstrapped results. Assuming missing at random, we will use multiple imputation using chained equations to account for missing data. We will consider any potential missing not at random effects and sensitivity analyses for any uncertainty. All costs and consequences beyond 12 months will be discounted at a rate of 3.5% in line with NICE guidance.

14.12.4 SENSITIVITY AND OTHER PLANNED ANALYSES

Exploratory analyses will investigate whether the effect of the of the intervention on the primary outcome is affected by attendance at three or more meetings with Navigators (regarded as receipt of

the intervention per protocol) and whether there is a dose response effect of number of Navigator meetings. If adherence is an issue, a complier average causal effect (CACE) analysis will be considered.

The mediating effect of loneliness on depression will be explored across the five timepoints, main results permitting.

There are no planned subgroup analyses.

14.13 INTERIM ANALYSIS

Trial recruitment and intervention engagement will be monitored and continuation criteria reviewed during the internal pilot phase of the trial, as described in Section 13.2.2. We will also investigate whether the assumptions underlying the sample size calculation are reasonable (eg, the assumed correlation between baseline and follow up measurements of the primary outcome and associated reduction in required sample size). No other interim analyses are planned.

14.14 OTHER STATISTICAL CONSIDERATIONS

The analysis may deviate from the planned analysis described above depending on the distribution of the data, the extent of missing data and withdrawals, chance baseline imbalances and participant engagement with the intervention. Any deviations will be fully justified in the final report and any publications, as appropriate.

15 QUALITATIVE ANALYSIS PLAN

Qualitative study one: Analysis of the qualitative data collected months 10-15 will proceed in two stages. We will provide rapid feedback to the programme team as soon as interviews and survey responses are provided, so that any adjustments to recruitment and the programme can be made as appropriate. Audio-recordings of interviews will be professionally transcribed using a UCL-approved company. The interview data will be analysed thematically as data is collected and coded during the familiarisation stage of the qualitative analysis process [39]. Survey data will be descriptively summarised as soon as the survey closes to respondents. A short report will be produced for the study team and Trial Steering Committee. Second, a more in-depth analysis of interviews will involve more members of the study team, including our PPI group, to agree coding structures and discuss the synthesis process. We will use Nvivo-12 software to manage this analysis. This analysis will be timely too, so any new emerging insights can be considered by the programme team, but will also be developed into a publication.

Qualitative study two: Audio-recordings of interviews performed during months 18-33 will be professionally transcribed using a UCL-approved company. An analysis group will include representation from PPI group members, the study peer researcher, and co-applicants, including lived experience co-applicant TM. Our overarching approach to analysis will be thematic (Braun & Clarke, 2006). At each stage,

we will adopt analysis approaches that fit our data, supported by NVivo12 software. We will use these data to review the intervention logic model and develop a guide for future delivery of the programme in the NHS.

16 RECORD KEEPING AND ARCHIVING

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for a minimum of 10 years from the declaration of end of trial. The trial database will be archived by Priment CTU in line with priment SOPs.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

17 OVERSIGHT COMMITTEES

17.10 TRIAL MANAGEMENT GROUP (TMG)

The TMG will be responsible for overseeing the trial and key decisions will be discussed and agreed. The TMG will include the Chief Investigator, all the study co-applicants, the trial staff, along with an additional, independent lived experience PPI member. The group will meet monthly. Decisions and action points from meetings will be minuted and communicated to site PIs and researchers by the Trial Manager.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC and/or MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

17.11 TRIAL STEERING COMMITTEE (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the DMEC and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.
The TSC will be recruited and meet by Month 4 of the study – i.e. to allow any required revisions to the study protocol to be approved before the planned trial start in Month 10. TSC meetings will be scheduled regularly – at least annually - thereafter, in line with CTU advice. TSC membership has been reviewed and approved by the study funders. This group will provide independent oversight of the trial: representatives of the study funder and the sponsor will be invited to TSC meetings.

A TSC charter, using a CTU template, will be prepared and circulated before the first TSC meeting, and discussed and signed off at the meeting.

17.12 DATA SAFETY AND MONITORING BOARD (DMEC)

A DMEC will provide independent advice on data and safety aspects of the trial. A first DMEC meeting will be held by Month 4 of the study, .e. to allow any required revisions to the study protocol to be approved before the planned trial start in Month 10. Meetings of the Committee will be held at least annually to review trial safety data and progress. The DMEC is advisory to the TSC and can recommend premature closure of the trial to the TSC. DMEC membership has been reviewed and approved by the study funders.

A DMEC charter, using a CTU template, will be prepared and circulated before the first DMEC meeting, and discussed and signed off at the meeting.

18 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigators and institutions will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical/case notes/source documents.

19 ETHICS AND REGULATORY REQUIREMENTS

Priment CTU and the sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the HRA and an NHS research ethics committee, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s). The Memorandum of Undersatnding clarifies the sponsor's and PRIMENT CTU delegated responsibilities.

Before any site can enrol participants into the trial, the Chief Investigator/ Principal Investigator or designee will apply for local confirmation of capacity and capability. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approvals. All agreements must be approved by the Sponsor representative (Noclor on behalf of Camden & Islington NHs Foundation Trust) and will be submitted to the relevant regulatory body. Substantial amendments will not be implemented until the necessary approvals are obtained.This

does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Priment will ensure that the main REC are notified that the trial has finished. They will also notify the sponsor representative at sponsor.noclor@nhs.net. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply Priment with a summary report of the clinical trial, which will then be submitted to the main REC within 1 year after the end of the trial. The Sponsor representative will be copied into the submission of both reports.

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 trial is declared ended. The chief investigator will prepare the APR.

The CI will supply the Sponsor with a report of the clinical trial and a copy of the report will be submitted to the main REC, within 1 year after the end of the trial.

20 MONITORING REQUIREMENT FOR THE TRIAL

Priment CTU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

The degree of monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the trial.

A trial specific oversight and monitoring plan will be established for studies. The trial will be monitored in accordance with the agreed plan.

21 FINANCE

The study is funded by a research grant from the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA). The excess treatment costs of delivering the study intervention will be met by the participating NHS Trusts.

The CIs, PIs and trial management members have no financial conflicts of interests.

22 INSURANCE

The NHS indemnity scheme will cover the potential legal liability of the Sponsor arising from design, conduct and management of the study. Camden and Islington NHS Foundation Trust will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies

cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved.

23 PUBLICATION POLICY

This study is funded by the NIHR and it will be added to the NIHR Clinical Research Network Portfolio and will eligible for inclusion on the ISRCTN registry.

All proposed publications will be discussed with and reviewed by Priment CTU prior to publishing. Priment publication policy will be followed. This includes details on: Authorship guidelines, any details of publication restrictions and a process and timeframe for approving and submitting reports for dissemination.

Our study will provide high quality evidence about the effectiveness of a novel programme to address loneliness and reduce depression for people with TRD in secondary care. We will provide a final report for the funders in adherence to their requirements. We have included open access costs for four high quality scientific publications: the trial protocol, main results, qualitative investigation and health economics findings. We will co-produce a briefing document for policy makers, a guide to support future programme delivery in NHS settings, and articles in publications read by practitioners and commissioners (e.g. Community Care journal), and by service users (e.g. the National Survivor User Network newsletter). The PPI group will co-produce an infographic for participants and lay audiences. We will update the Community Navigator intervention manual and training manual (e.g. by making “how to” training videos), which will be publicly available throughout the course of the trial, to generate interest and to speed up knowledge transfer if warranted by trial findings.

The Study CI will draft a publications plan identifying proposed lead and included authors and timescales for publications. This will be discussed and agreed at study TMG meetings. Authorship will be based on ICMJE guidelines.

The lay participants will be asked during the consent process if they would like to receive a lay summary of the study findings. The study team will send a copy of the study findings to all interested participants when the study is over.

24 REFERENCES

1. Lloyd-Evans,B. Bone,J. Pinfold,V. et al. (2017) “The Community Navigator Study: A feasibility randomised controlled trial of an intervention to increase community connections and reduce loneliness for people with complex anxiety or depression” Trials 18 (1): 493

2. Lloyd-Evans,B. Frerichs,J. Stefanidou,T. et al (2020) “The Community Navigator Study: results from a feasibility randomised controlled trial of a programme to reduce loneliness for people with complex anxiety or depression” PLOS ONE May 29, 2020 https://doi.org/10.1371/journal.pone.0233535
3. Trivedi M, Rush A, Wisniewski S. et al. (2006) “Evaluation of outcomes with citalopram for depression using measurement- based care in STAR*D: implications for clinical practice” Am J Psychiatry 163: 28–40.
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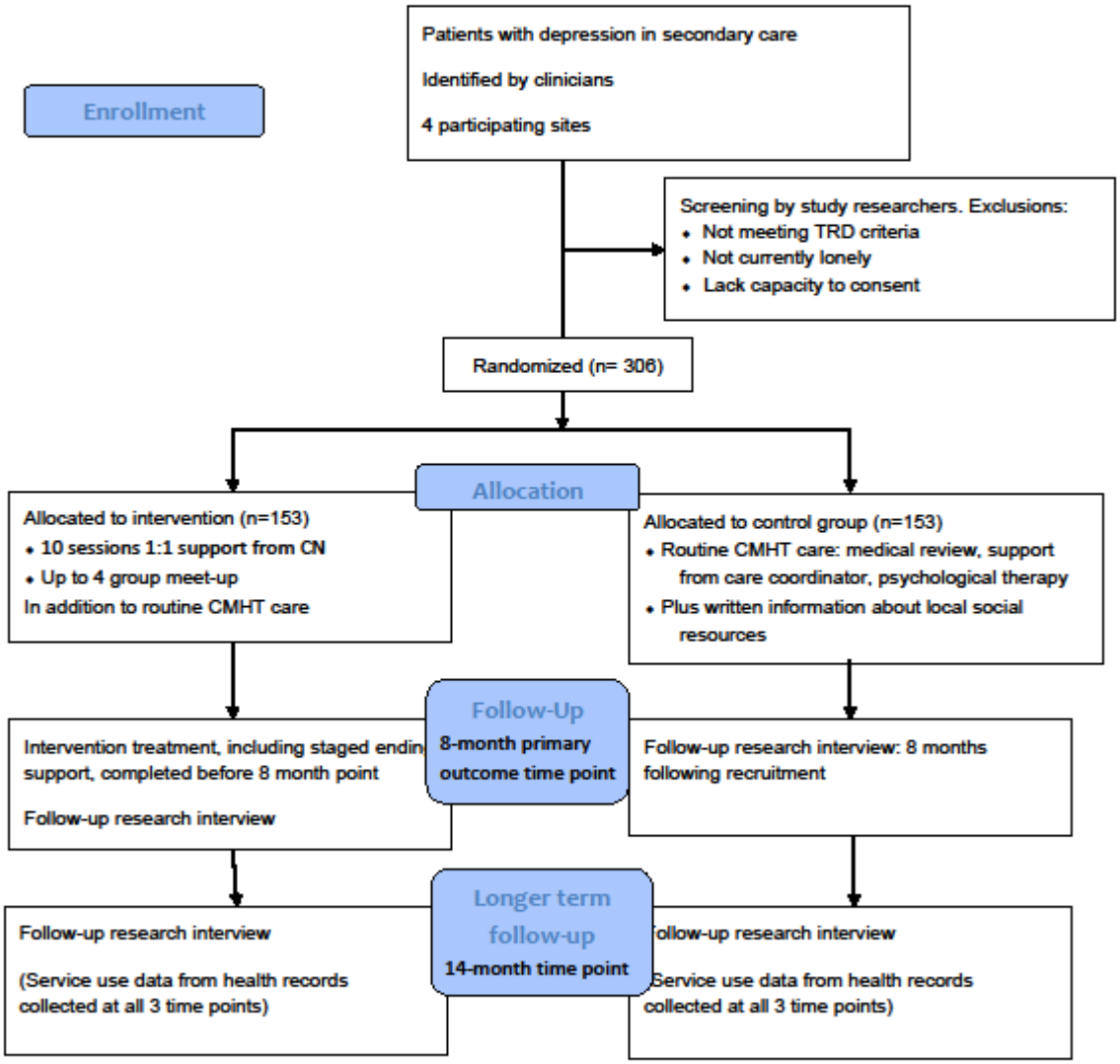
25 APPENDIX

CONSORT
TRANSPARENT REPORTING of TRIALS

COMMUNITY NAVIGATOR TRIAL CONSORT FLOW DIAGRAM



Appendix 2: Schedule of Assessments

	Screening	Treatment Phase		Follow-up	Final visit
Visit No:	1	2	3	4	5
	Screening and baseline assessment	4-month follow-up	8-month end-of-treatment follow-up	11-month follow-up	14-month (6 months post-treatment) follow-up
Window of flexibility for timing of visits:	n/a	+2 months	+3 months	+2 months	+3 months
Informed Consent	X				
Eligibility confirmation (CIS-R and DJG measures)	X				
Intervention credibility measure	X				
All outcome measures and service user information listed in s. 10.1	X		X		X
Depression (PHQ-9) and Loneliness (ULS-8) measures only	X	X		X	
Randomisation	X				
Trial Intervention/Treatment		X	X		
Adverse Events active monitoring	X	X	X		
Adverse events review	X	X	X	X	
Withdrawal	X	X	X	X	X

Appendix 3: List of supporting documents

Document type	Document Name	Version #	Date
Initial contact invitation script	Community Navigator Trial_script for initial approach	1.0	04FEB2022
Participant Information Sheeets (PIS)	Community Navigator Trial PIS	1.0	04FEB2022
	Community Navigator Trial_survey PIS and Consent Form	1.0	04FEB2022
	Community Navigator Trial_internal pilot qualitative interview study_trial participant PIS	1.0	04FEB2022
	Community Navigator Trial_internal pilot qualitative interview study_staff PIS	1.0	04FEB2022
	Community Navigator Trial_post-intervention qualitative interviews_trial participant PIS	1.0	04FEB2022
	Community Navigator Trial_post-intervention qualitative interviews_Community Navigator and supervisor PIS	1.0	04FEBb2022
Participant Consent Forms (CF)	Community Navigator Trial Consent form	1.0	04FEB2022
	Community Navigator Trial_qualitative interviews Consent Form_trial participants	1.0	04FEB2022
	Community Navigator Trial_qualitative interviews Consent Form_staff	1.0	04FEB2022
Data collection schedules	Community Navigator Trial_Eligibility Screening Participant Questionnaire	1.0	04FEB2022
	Community Navigators Trial_Baseline Participant Questionnaire	1.0	04FEB2022
	Community Navigator Trial_4 and 11 month Follow-up Participant Questionnaire	1.0	04FEB2022
	Community Navigator Trial_8 and 14 month Follow-up Participant Questionnaire	1.0	04FEB2022
	Community Navigator Trial_Baseline Data from health records	1.0	04FEB2022
	Community Navigator Trial_14 month data from health records	1.0	04FEB2022
	Community Navigator Trial_Session logs	1.0	04FEB2022
Qualitative topic guides and schedules	Community Navigator Trial_Anonymous online survey for internal pilot participants	1.0	04FEB2022
	Community Navigator Trial_Internal Pilot Qualitative Interviews_trial participant topic guide	1.0	04FEB2022

	Community Navigator Trial_Internal Pilot Qualitative Interviews_Community Navigator topic guide	1.0	04FEB2022
	Community Navigator Trial_Internal Pilot Qualitative Interviews_Supervisor topic guide	1.0	04FEB2022
	Community Navigator Trial_Post Intervention Qualitative Interviews_trial participant topic guide	1.0	04FEB2022
	Community Navigator Trial_ Post Intervention Qualitative Interviews_Community Navigator topic guide	1.0	04FEB2022
	Community Navigator Trial_ Post Intervention Qualitative Interviews_Supervisor topic guide	1.0	04FEB2022
Letters to involved clinical teams about participant's involvement in the trial	Community Navigator Trial_Letter to clinical Team	1.0	04FEB2022
	Community Navigator Trial_GP letter	1.0	04FEB2022
Other study documents	Community Navigator Trial_Leaflet	1.0	
	Community Navigator Trial_Referral form	1.0	04FEB2022
	Community Navigator Trial_DMEC Charter_signed	1.0	22.11.2021
	Community Navigator Trial_Trial Steeting Committee Charter_Signed	1.0	05.11.2021
	NIHR HTA_Funding letter	1.0	03SEPT2021
	NIHR HTA_Funder's Peer Reviews	1.0	20.10.2020
	Chief investigator's CV	1.0	Nov 2021
	SOeCAT Form	1.0	09.09.2020
	Organisation Information Document	1.0	31.11.2021
	Letter from sponsor (PDF of confirmation email)	1.0	07FEB2022
	Community Navigator Letter from Statistician	1.0	21.12.2021
	Community Navigators_PRIMENT CTU MOU	1.0	24.11.2021
	Summary of the study protocol in plain English	1.0	04FEB2022