TALKING WITH VOICES

NHS
Greater Manchester Mental Health
NHS Foundation Trust

Study Protocol

Title:	A novel dialogical therapy (Talking With Voices) in comparison to treatment as usual in adults with distressing and persistent auditory hallucinations: A randomised controlled trial to investigate the efficacy of a treatment strategy targeted at trauma-related mechanisms
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1. Signature Page

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

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

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

For and on behalf of the Study Sponsor:

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3. Abbreviations

BAME	Black, Asian and Minority Ethnic
CBTp	Cognitive behavioural therapy for psychosis
CFT	Compassion Focussed Therapy
CMHTs	Community mental health teams
DES-II	Revised Dissociative Experiences Scale
GMMH	Greater Manchester Mental Health NHS Foundation Trust
HRA	Health Research Authority
HVM	Hearing Voices Movement
iDMEC	Independent Data Monitoring and Ethics Committee
IMD	Index of Multiple Deprivation
KCTU	King's Clinical Trials Unit
MRC	Medical Research Council
NICE	National Institute of Health and Care Excellence
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant information sheet
PRU	Psychosis Research Unit
PSYRATS-AH	Psychotic Symptom Rating Scales–Auditory Hallucinations Subscale
QPR	Questionnaire About the Process of Recovery
RA	Research assistants
RCT	Randomised controlled trial
RDT	Research Delivery Team
REC	Research Ethics Committee
SAEs	Serious adverse events
SMHP	Serious mental health problems
SOP	Standard operating procedure
SURG	Service-User Reference Group
TALE	Trauma and Life Events Checklist
TAU	Treatment as usual
TSC	Trial Steering Committee
TwV	Talking With Voices
VH	Voice hearing

4. Abstract

Background: Hearing voices (‘auditory hallucinations’) is associated with a range of negative outcomes, including hospitalisation, suicidality, and impaired functioning. Approximately 70% of schizophrenia patients hear voices, and schizophrenia is one of the top 25 causes of disability worldwide. However, rates of voice hearing (VH) in other serious mental health problems (SMHP) are also high and show comparable phenomenological qualities, thus emphasizing a need for transdiagnostic treatment strategies. Currently, the main treatment approaches are antipsychotic medication and cognitive behavioural therapy (CBT), yet both have variable effectiveness and are often unavailable to those without a schizophrenia diagnosis. Furthermore, CBT does not consistently address the role of trauma in the onset and maintenance of VH. In response to these unmet needs, a feasibility/acceptability trial of a new dialogical intervention, Talking with Voices (TwV) was conducted. TwV involves a therapist speaking to the voice(s) while the client repeats its response verbatim, with the aim of promoting recovery and reducing voice-related distress. The TwV pilot trial (N=50) found excellent feasibility/acceptability data amongst participants with schizophrenia and demonstrated signals of positive change in measures of personal recovery (with a standardised effect size of 0.7) and in the ways people related to their voices. As a next step, we wish to evaluate the treatment mechanisms and clinical efficacy of TwV in a transdiagnostic population.

Aims and Objectives: We aim to establish TwV’s clinical efficacy in a multisite RCT for adults with SMHP who hear persistent, distressing voices; and to assess whether improved measures of personal recovery and negative impact of voices are mediated via key psychological mechanisms (improved relating to voices, and reductions in dissociation and negative self-beliefs). The objective is to recruit 296 participants (based on an effect size of 0.4) who will be randomised to either treatment (TwV + treatment as usual [TAU]) or control (TAU only).

Methods: Participants will be recruited from NHS secondary care services across 4 UK sites (Greater Manchester, London, Newcastle, and Oxford). The primary outcome is the total score on the Questionnaire About the Process of Recovery. Secondary outcomes will include overall voice severity and other relevant dimensions of VH and trauma sequalae. The primary analyses will use the linear mixed models to estimate the treatment policy estimand. The treatment window will be 8 months with mediational and outcome variables collected at baseline, 8 months (post-treatment) and 14 months.

Impact and Dissemination: The study will investigate the clinical efficacy of a novel intervention deliverable within the NHS, including data on key psychological processes that are potential treatment targets to ameliorate distressing voices in a transdiagnostic population. Long-term benefits include reducing the social and economic costs associated with VH; improving the efficacy/accessibility of evidence-based psychosocial interventions for SMHP; developing the workforce; and responding to the NHS’s Long-Term Plan for implementing personalised, trauma-informed care. Dissemination will occur via peer-reviewed articles, conference presentations, participant feedback, provision of the treatment manual, and engagement with the service-user community.

5. Background and Rationale

5.1. Why is this research needed now?

While voice hearing ([VH] the perception of speech with no objective source) is a common human experience, distressing voices are often reported by patients with a range of serious mental health problems (SMHP), including psychosis/schizophrenia (reported by up to 70% of individuals) (1), bipolar disorder (up to 62.8%) (2), depression (up to 40.6%)(2), and borderline personality disorder (up to 27%) (3). Incidence likewise appears high, with a recent survey of 1800 NHS patients diagnosed with non-affective psychosis finding that 48.2% heard voices saying things at least weekly (4). Correspondingly the impact of VH in these groups can be severe, including increased hospitalisation, suicidality, self-harm, and impaired social and occupational functioning (5–7). In turn schizophrenia, the condition with which VH is most closely associated, is classed as one of the top 25 causes of disability worldwide and is a significant economic burden in the UK, with total monetary costs estimated as £11.8 billion per year (8) and approximately 222,000 people being treated by the NHS for schizophrenia and schizophrenia-related disorders at any one time (9). Strikingly, however, it has been noted that there is little difference in clinical and phenomenological voice characteristics across these different SMHP diagnoses (10), emphasising the need and opportunity for transdiagnostic treatment strategies.

Given the toll of VH, there remains considerable scope for improving NHS care. Antipsychotics are a first-line treatment, yet a proportion of patients respond poorly (11), particularly those with a history of trauma exposure (12), and adverse effects often lead to reduced compliance (13). Indeed, a meta-analysis of 167 double-blind randomised controlled trials (RCTs) found only 23% of patients with schizophrenia had a ‘good’ response to antipsychotics (14). Likewise, cognitive behavioural therapy for psychosis (CBTp), the talking therapy recommended by the National Institute of Health and Care Excellence (NICE), is not associated with consistent improvements in VH (15), is not available to those with non-psychosis diagnoses, and may not specifically target voices during treatment. For example, a systematic review of 33 studies indicates only 24.8% of patients exhibit a ‘much improved’ reduction of positive psychotic symptoms, including VH, following CBTp (16). Both the presence and content of VH also demonstrate strong links with trauma (17–19) yet while the importance of personalised, trauma-informed care forms part of the NHS Long-Term Plan for mental health, this is not something consistently provided by CBTp. It is also clear that disparities exist in receipt of CBTp for those experiencing racial inequalities (20). As tackling SMHP is a current UK government priority, there is potential for a transdiagnostic psychological treatment to be implemented within the NHS, which in turn would rationalise training/supervision of staff and permit generalisation of skills across services while avoiding diagnostic ‘silos’ that prevent access. Given urbanicity and social adversity are associated with increased VH prevalence, providing treatments for implementation in groups with high rates of deprivation is particularly important, as is equity of access for different racial communities.

Taken together, it is clear distressed voice-hearers are in urgent need of more effective support, particularly evidence-based transdiagnostic strategies that can address the known role of trauma in VH (21). Specifically, therapies targeting traumatic sequelae which act as mechanisms in VH have the potential to improve outcomes, and this project will focus on the well-established trauma responses of dissociation, relating styles with voices, and negative self-beliefs, which have been found to mediate the trauma/VH relationship (22–25). In this regard, clinicians and patients differ in their views of recovery, with clinicians favouring symptom reduction while the latter prefer more holistic definitions of personal recovery (26), and our research has shown the emotional consequences of VH are strongly associated with such personal recovery (27).

5.2. What is the knowledge gap this research will address?

Talking With Voices (TwV) is based on a theoretical model of VH which uses direct verbal engagement with the voice(s) by a therapist to instigate a process of reconciliation and integration between hearer and voice (28), thereby aiming to resolve trauma-related dissociation, negative self-

beliefs, and problematic dynamics in the hearer/voice relationship with voices in a way not currently addressed by existing treatments. TwV's emphasis on relational aspects of working with VH, combined with its focus on the associations between voices, life events, and beliefs about oneself, additionally makes it distinct to existing approaches targeting VH, trauma, and dissociation (29–31). Databases (PubMed/MEDLINE, PsychINFO, Scopus) and trial registries (ClinicalTrials.gov, ISRCTN.com, bepartofresearch.nihr.ac.uk) were searched using terms synonymous for both VH and the treatment approach (voice hear* OR auditory hallucinat* AND dialo*OR talk* AND therap* OR treatment) to identify relevant research within the SMHP population. Three articles (a case report, a first-person account and a theoretical paper) were identified which discussed the application of Compassion Focussed Therapy (CFT) in relation to voice engagement; however, in addition to a lack of controlled evidence, the model does not involve direct dialogue with a therapist and instead focusses on developing an embodied compassionate self-identity, which "becomes the vehicle through which [the client] approaches therapeutic tasks, such as listening and talking to voices, engaging with traumatic childhood pain, and resolving emotional conflicts" (32). An additional narrative review (not identified during the search) (33) evaluated 12 CFT studies in populations with various mental health difficulties and concluded that more rigorous research designs are required before determining the direct contribution of CFT to recovery (in this regard, the one study directly referencing VH in its findings had a sample of 3) (34). A more robustly researched intervention is AVATAR (35), which has parallels to TwV by targeting relating styles with voices but uses digital representations instead of direct engagement. In a single site RCT, it demonstrated the utility of applying dialogical techniques and showed substantial effectiveness after 6 weeks of treatment compared to an active control (supportive counselling). However, the between-group differences were smaller and non-significant at 24 weeks. AVATAR is also not readily implementable in NHS settings due to the known challenges of scaling up digital therapeutics. Further, its benefits were found to be limited to VH and did not extend to the cognitive-affective processes we plan to target in TwV, nor broader personal recovery factors prioritised by patients.

TwV is a user-informed approach developed from the work of the Hearing Voices Movement (HVM), an international network of voice-hearers and their allies which has worked since the 1990s to promote more psychosocially focussed, recovery-oriented views of VH (36). However, despite its international impact, practices developed by the HVM have largely remained unevaluated, mostly due to the primacy it places on personal testimony and an "uneasy relationship" with traditional scientific methodology (36). Our proposal thus presents a valuable opportunity to combine these different traditions and perspectives. Existing limited data for TwV includes case examples (37–39), a concurrent multiple baseline design case series (n=15) (40), a small RCT (n=12) (41), and our NIHR-funded feasibility RCT (n=50) (42,43), all of which provided signals of efficacy with no emergent safety concerns. Our feasibility/acceptability pilot (outlined below) represents the most comprehensive evidence currently available and, consistent with the Medical Research Council (MRC) framework for developing and evaluating complex interventions, an efficacy evaluation is the next necessary step. As such, the proposed research aims to assess TwV in a multisite RCT comparing TwV + TAU vs. TAU only for adults with SMHP who report persistent, distressing voices. In addition, we aim to investigate if the therapy works as intended through improving relating styles with voices, dissociation, and self-beliefs.

5.3. Proof-of-concept

TwV adopts a theoretically-informed approach to target trauma-related psychological mechanisms in VH, with the aim of improving outcomes, given the known link between trauma and voice presence/content (17–19). Dissociation, a psychological response to trauma wherein emotional and cognitive systems become disconnected from one another, is strongly associated with VH (44), and has also been shown to mediate its relationship with trauma (45). Further, traumatic events are known to have an adverse impact on self-beliefs and relationships with others, which is hypothesised to shape negative VH content/beliefs and how one relates to the voices, which in turn can further exacerbate dissociation (22–24,46). Our TwV protocol (28) uses direct verbal

engagement from a therapist to instigate a process of reconciliation and integration between hearer and voice, thereby improving connection with emotions, self-concept, and interpersonal relating.

The HVM influence on TwV's development has ensured it was designed to provide a personalised intervention aligned with patient values; for example, being structured around subjective goals (47), holistic engagement with the experience of VH (5) and providing psychosocial support complimentary to medical approaches (48). Furthermore, it also corresponds with several key recommendations made by the International Consortium for Hallucination Research (49) for refining psychological therapies for VH, namely by 1) extending a focus on overall efficacy to understanding specific therapeutic processes, 2) a better targeting of psychological processes associated with VH, such as trauma, cognitive mechanisms, and personal recovery, and 3) using focused measurement of the intended outcomes of therapy.

5.3.1. Feasibility study

The current research plan is an expansion of the TwV pilot trial, which compared TwV + TAU with TAU alone amongst adults with a diagnosis of schizophrenia spectrum disorders (42,43). Owing to its co-produced nature, the intervention itself was not originally developed within the MRC framework for the development of complex interventions (50). However, subsequent pilot work, including manualisation of the therapy, was conducted according to the guidelines in order to establish the feasibility/acceptability of delivering TwV within the infrastructure of the NHS (including identifying key uncertainties and potential refinements). Consequently, the research programme is now positioned to progress to clinical evaluation.

The TwV pilot recruited to target (50/50; 100%), with excellent rates of treatment adherence (21/24 [87.5%] receiving ≥8 sessions) and retention (40/50 [80%] participants at 6-month follow-up). Withdrawals were likewise low, with only 1 participant withdrawing from the therapy arm and 2 from TAU. Although not powered to detect treatment effects, a statistically significant increase in perceived benevolence of the voice was observed (-3.93(SE 1.63); 95%CI: -7.27, -0.58; p=0.02) amongst participants receiving TwV, as well as a suggestion of increased personal recovery (-6.94(SE 4.41); 95%CI: -16.00, 2.12; p=0.13) and reduced dissociation (7.22(SE 7.17); 95%CI: -7.65, 22.08; p=0.33). In this regard our proposed primary outcome measure for the current trial, the Questionnaire About the Process of Recovery (QPR) (51), resulted in a between-group standard effect size of 0.7. In turn, there was a lower rate of serious adverse events (SAEs), including hospital admissions, in the therapy group relative to TAU, none of which were deemed trial-related by the combined Trial Steering Committee and Independent Data Monitoring and Ethics Committee (TSC-iDMEC).

Nested qualitative studies with both trial participants (52) and therapists (53) indicated several features of the intervention that were positively received. For participants, this included the opportunity to develop strategies to cope with hostile voices, the experience of a close therapeutic alliance, gaining new perspectives on voice utterances, discovering links between voice content and negative life events, and learning to relate to their voices in more constructive ways. In this regard, withdrawal rates can be in the region of 18% for therapies which include some element of aversive exposure, including treatments for post-traumatic stress (54) and direct work with voices (55), and from 20-24.5% in trauma-focussed therapies for psychosis patients (29). However, only 3/24 participants (12.5%) attended less than the 8 sessions constituting a therapeutic 'dose' of TwV, with only one participant (4.2%) dropping out of the therapy arm of the trial. Planned refinements to both recruitment procedures and treatment protocols have been made as a result of this analysis, including extending the therapy window and clarifying therapy aims in study informational materials. For therapists, in turn, TwV was felt to be a unique intervention that permitted an exploration of clients' VH experiences that was unavailable in other therapeutic models. Numerous examples were provided of acquiring and implementing new knowledge while augmenting/transferring existing skills, with therapists additionally referring to positive experiences of integrating both recruitment and therapy delivery within participants' existing healthcare teams. Several recommendations for therapist training and supervision were likewise derived from this work (53), which would be

implemented in the event of a definitive trial. Further, the results confirmed that CBTp therapists already experienced in working with voice-hearers were able to deliver the intervention without time-intensive training (8 days in total), which has positive implications for scalability.

Taken together, the pilot suggests that a larger trial of TwV would be acceptable and feasible to staff and service-users within the NHS, and that the expansion of the intervention into a transdiagnostic population may be of clinical benefit to those troubled by persistent, distressing VH. In this respect, analyses of both quantitative and qualitative data indicate long-term potential for enhancing service provision (a transferrable clinical model that utilises existing skills) and developing patient benefit (improved quality of life, improved rates of recovery, reduction in distressing VH).

6. Aims and Objectives

The project will be a rater-blinded, multisite, RCT assessing the clinical efficacy and mechanisms of a psychological therapy (TwV) for adults with SMHP who hear persistent, distressing voices, with the primary outcome being personal recovery assessed by the QPR (51) at 8 months (post-treatment).

6.1. Overall aim

The project will address the following principal research questions:

1. Is the psychological intervention TwV + TAU effective in improving personal recovery compared to TAU alone in adults with SMHP who hear persistent, distressing voices?
2. Are any identified treatment effects of TwV on recovery mediated by key mechanisms, specifically: improved relating with voices, reduced dissociation, and a reduction in negative self-beliefs.

6.2. Clinical efficacy aims

1. To establish the efficacy of TwV + TAU in improving measures of personal recovery compared to TAU alone when delivered to adults with SMHP who hear persistent, distressing voices.
2. To establish the efficacy of TwV + TAU in reducing the impact of distressing voices compared to TAU alone.
3. To establish the efficacy of TwV + TAU in reducing negative appraisals of voices and increasing positive appraisals of voices and helpful/functional responses towards voices compared to TAU alone.
4. To determine whether positive effects of TwV are detectable over a 14-month follow-up period.

6.3. Clinical efficacy hypotheses

1. TwV + TAU will result in improved measures of personal recovery at end of treatment (8-month follow-up) and 14-month follow-up compared to TAU alone.
2. TwV+TAU will lead to improvement in distressing voices at end of treatment compared to TAU alone.
3. TwV + TAU will lead to a reduction in negative appraisals of voices and increased positive appraisals of voices and helpful/functional responses towards voices at end of treatment compared to TAU alone.

6.4. Mechanistic aims

1. To examine the extent to which TwV + TAU impacts on measures of personal recovery via reductions in trauma-related psychological processes (dissociation and negative self-beliefs), and improvements in positive beliefs about voices and assertive relating skills with voices.

6.5. Mechanistic hypotheses

1. TwV + TAU will lead to reductions in dissociative symptoms and negative self-beliefs, and improvements in positive beliefs about voices and assertive relating skills with voices.
2. The mechanisms by which TwV + TAU leads to improvements in personal recovery is due to a reduction in dissociative symptoms and negative self-beliefs, and improvements in positive beliefs about voices and assertive relating skills with voices.

6.6. Research objectives

We intend to recruit 296 adults with SMHP who hear persistent and distressing voices from 4 NHS community-based, secondary care mental health services in the UK (Greater Manchester, London, Newcastle, and Oxford). Eligible participants will be randomised to either the treatment arm (TwV + TAU) or control arm (TAU alone) across 8 months. Outcome data will be collected at baseline, at 8 months (post-treatment) and at 14 months follow-up.

6.7. Deliverables from the project

The trial is designed to answer clinically significant hypotheses using the fewest number of participants, thereby maximising the use of resources and value for money. It will generate evidence for the clinical efficacy of a psychological therapy, deliverable within the NHS, that is intended to reduce the impact of persistent, distressing VH amongst adults with SMHP. The project will produce an updated therapy protocol, plus associated training materials, which will help facilitate effective implementation and sustainability within the NHS. Furthermore, the study will also provide data on the hypothesised treatment mechanisms for TwV, thereby offering potential improvements and refinements for future interventions which target distressing voices. In this regard schizophrenia, the diagnosis with which VH is most closely associated, is a significant economic burden in the UK, with total monetary costs estimated as £11.8 billion per year (8), and developing evidence-based interventions to support this population may contribute to sizeable savings for the health and social care budget.

7. Research Methods

7.1. Setting and context

The study will be an assessor-blinded, multisite RCT assessing the efficacy and mechanisms of a psychological therapy (TwV) for adults with SMHP who hear persistent and distressing voices. The 2 parallel arms will compare a psychological intervention (TwV) + TAU (treatment condition) to TAU alone (control condition). Assessment of outcome and mediational variables will take place at baseline, at 8 months (post-treatment) and at 14 months. In addition to TAU, participants randomised to the treatment arm will receive up to 26 weekly sessions of TwV of up to 1 hour duration, with an option for up to 4 booster sessions. The study will take place across 4 NHS community-based, secondary care mental health services in the UK: Greater Manchester, London, Newcastle, and Oxford. Independent, concealed randomisation will be performed via a web-based system using random permuted blocks, stratified by site and diagnosis, by King's Clinical Trials Unit ([KCTU] UKCRC registration 053).

7.2. Internal pilot progression criteria

Progress will be assessed after 13 months of recruitment and 5 months follow-up against pre-specified criteria. This will be subject to ongoing monitoring by the trial management group and reviewed by the TSC as necessary.

Table 1: Talking With Voices internal pilot progression criteria.

	Red		Amber		Green	
Threshold	**%**	**(N)**	**%**	**(N)**	**%**	**(N)**
Trial recruitment	≤59	(≤97)	60-99	(98-162)	100	(163)
Recruitment rate per month	≤59	(≤8)	60-99	(9-14)	100	(15)
Number of sites opened	≤50	(≤2)	70	(3)	100	(4)
Proportion receiving allocated intervention	≤59	(≤48)	60-99	(49-81)	100	(82)
Proportion with complete primary outcome data	≤84	(≤25)	85-99	(26-29)	100	(30)

7.3. Sample size

The trial is a partially nested design, with clustering due to therapists in the intervention arm and each participant in the control arm considered as a cluster of size 1. We allow for 14 therapists over the course of the trial, with an ICC=0.02, each therapist seeing an average of 9 participants and variation in the cluster size of 9 (assuming the cluster membership follows a Poisson process). To achieve 90% power to detect a between-group standard effect size (SES) of 0.4 at 8 months on the primary outcome measure (QPR), with 5% 2-sided significance level, and assuming a conservative correlation of 0.4 between the respective baseline and 8 month scores and 1:1 allocation ratio, we require 252 participants with outcome data in the analysis set. Allowing for a conservative 15% attrition (attrition was 10% in our pilot trial) requires 296 participants to be recruited. A recent study used an anchor-based method to establish the minimum important difference for the QPR and suggested that a difference of 4-5 points is a worthwhile target difference (74). Using a difference of 4.5 points, with a standard deviation of 11.5 (based on QPR scores from several of our SMHP trials) this equates to an SES of 0.4, as above. In our pilot trial, we observed an SES of 0.7.

7.4. Study population

The study population are adult users of mental health services with SMHP who hear persistent, distressing voices.

7.4.1. Inclusion criteria

1. Aged ≥16 years.
2. Heard voices for at least a year.
3. Scoring ≥1 on item 8 of the Psychotic Symptom Rating Scales–Auditory Hallucinations Subscale (PSYRATS-AH) (57).
4. Able to provide written informed consent.
5. Actively help-seeking in relation to distressing voices.
6. In contact with mental health services for ≥6 months.
7. Willing and able to communicate with their voices and relay what the voices say to a therapist.
8. Hear voices that are sufficiently personified to engage in dialogical work.

7.4.2. Exclusion criteria

1. At immediate risk of harm to self or others.
2. Currently receiving structured, individual psychological therapy.
3. Non-English speaking.
4. Primary diagnosis of alcohol/substance dependence or autism spectrum disorder.
5. Moderate/severe learning disability.
6. Organic cause for VH.
7. Homeless/of no fixed abode.

7.4.3. Withdrawal criteria

1. Participants who lose capacity to consent will be withdrawn from research procedures associated with the study.

A participant is free to withdraw from the trial if they wish to do so, without giving a reason and without affecting their care. A participant who chooses to withdraw from the intervention arm may continue with the research assessments if they wish. The researcher taking the withdrawal information should complete the Talking With Voices trial withdrawal form and provide this to the site lead and trial manager to update participant records. Participants who withdraw will not be replaced.

7.5. Recruitment method and consent process

We will utilise multiple recruitment methods, successfully applied on our other NIHR funded studies, to ensure the recruitment strategy provides maximum engagement of clinical services and outreach to all potentially eligible service-users. The initial recruitment approach will be as follows: 1) an engagement event with relevant teams and staff at each site to raise awareness of the study and 2) prior to the start of the study Principal Investigators (PIs) and the trial manager will establish contact with individual community mental health teams (CMHTs) with initial presentations slots at the start of the study. The PIs will support initial liaisons to ensure maximum support and engagement between the study and clinical teams.

The approach throughout the recruitment phase will focus on continued awareness and engagement with relevant services. We will achieve this by establishing regular contact between staff from the Clinical Research Network-funded Research Delivery Team (RDT), research assistants (RAs) and services and, where possible, we will agree attendance at the service referral meetings and/or physically locate the RA at the service base. Continued presence and awareness of the study will ensure fair access to all potential participants throughout the lifetime of recruitment by ensuring the CMHT have confidence in the study design and team. Where agreements are not in place to regularly attend referral meetings, we will approach service staff to organise individual case load reviews to identify all eligible participants. We will work closely with the RDT at each site and utilise their expertise and knowledge of engaging these services. Where in place, we will also utilise local NHS SOPs for delegation of screening and first contact from service staff to the RDT or Trust employed Research Assistants. We will provide all relevant staff members with recruitment materials to outline the study.

Referring healthcare staff will be requested to discuss the study with service-users in their caseloads who meet preliminary inclusion criteria and, in the event of potential participation, obtain verbal consent to be contacted by an RA. To aid this initial discussion, all potential participants will be provided with access to recruitment materials that explain the study rationale.. RAs will collect necessary referral information, then make telephone contact with the potential participant to further discuss the study and invite them to arrange an assessment appointment. For any intervention-specific questions, an option will be provided to speak with one of the trial therapists. In the case of self-referrals, RAs will request permission to contact a named healthcare provider to ascertain eligibility and other relevant referral details. Whenever possible, RAs will also screen potential participants during this call with the distress item (Q8) from the PSYRATS-AH, therefore avoiding taking up their time with an unnecessary in-person meeting in the event of being ineligible. Prior to taking written informed consent, all potential participants will be provided with the participant information sheet (PIS) and given at least 24 hours to consider the information and have any questions they might have answered before consenting. In the initial assessment meeting, RAs will clarify that the randomisation process is fully understood and reiterate that taking part is voluntary. Time will also be taken to address any additional questions/concerns. If the participant is happy to proceed, written consent will be obtained in line with requirements stipulated by the NRES Information Sheets and Consent Forms: Guidance for Researchers and Reviewers, Version 3.6.1, 2011(60) followed by completion of baseline assessments.

After eligibility has been confirmed within the trial team, the RA will contact the service user to inform them of the decision. Randomisations will be completed within 2 working days and the participant contacted by telephone and informed of their allocation. In the event of distress or

disappointment, an option to speak with a clinically qualified staff member will be made available. Letters will then be sent by the trial administrator to the participant, their GP and/or applicable healthcare workers.

7.6. Type and content of participant information materials

Co-applicants with lived experience of VH and SMHP will produce leaflets, posters and a PIS, utilising materials already employed during out pilot trial. Additional feedback will be sought from the Service User Reference Group (SURG), including identifying key questions they have about the study to ensure these are addressed within the informational materials (e.g., expectations, potential risks/benefits, and other factors influencing informed consent). We will seek guidance on how to address potentially distressing topics appropriately and sensitively (e.g., references to traumatic life events being embodied by voices), as well as developing a new document derived from previous PPI feedback that recommended creating a separate PIS specifically addressed to potential participant's voices.

To ensure we develop accessible materials, we will ensure research concepts (e.g., the research blind, randomisation) are explained in lay terminology. Where possible, materials will also utilise pictures/infographics. The content of the PIS will comply with the requirements set out by the National Research Ethics Service (NRES)(60). On request we will provide written material in other accessible formats such as large print, coloured paper, or in audio-recorded format for people with visual impairments.

7.7. Research methods to capture data from participants and their frequency

Assessment data will be collected by RAs, independent and blinded to allocation, using a self-report questionnaire for the primary outcome measure and a combination of self-report questionnaires and structured interviews for secondary measures and mediational variables. Training will be conducted with all assessors with arrangements in place for ensuring inter-rater reliability across sites. To aid with this process, assessments may be audio-recorded with participant permission to check on the quality and reliability of the assessment and scores. Audio recording will be carried out in line with the policy and procedures of the NHS site where the recording takes place.

After recruitment and baseline assessments are concluded, a follow-up assessment will take place at 8 months post-randomisation (end of treatment). Additional follow-up assessments will be performed at 14 months post-randomisation, dependent upon when participants were recruited into the trial (thus, the total follow-up period will vary from 14 months to 8 months, maximising the recruitment period and providing best value for money). In view of this, we anticipate 14-month follow-up data on the first 207 participants.

Participants will be provided with a thank you card at approximately 4- and 11-months post-randomisation in an effort to promote retention. Contact details for the trial team will be provided on the thank you card for participants who wish to get in touch to discuss their wellbeing, ask any questions, report concerns, or raise adverse events.

7.8. Study participant support

We will utilise protocols from our previous NIHR funded trials for supporting participants to minimise the potential for distress, as well as likelihood of drop-out. These approaches centre on minimising burden and ensuring appropriate care and encouragement throughout the assessment process. Our RAs will receive training in person-centred support and have access to regular supervision with clinically trained staff to ensure any distress that may arise throughout the assessments is appropriately addressed. The following approaches will be taken, including a standardised protocol for managing distress which was developed with service users: 1) offer of a supportive follow-up call with an RA within 48 hours of a research assessment to discuss any issues that may have arisen for them after completing the measures, 2) offer of a 'Helpline Numbers' card that will detail national and local helpline numbers; 3) ordering of outcome measures in priority, and reminders regarding choice to decline questions/measures; 4) offering choice regarding the modality (remote or face-to-

face) and endeavour to meet participants at the location of their choosing where possible (e.g., an option for least restrictive venues, such as participant homes or primary care settings); and 5) offering choice regarding the timing and length of the assessments, including taking breaks when required and the option of assessments spread across multiple occasions to minimise burden at any one time.

Existing treatments/services will not be withheld from participants in either arm of the trial, and they will be reminded of their right to freely withdraw from the study at any point without effecting their statutory care. All participants will further be provided with contact details for both local and central trial staff in the event of wishing to ask questions or raise concerns throughout the course of their involvement.

In the event of participants wishing to drop-out, a range of choices will be offered regarding both treatment and research procedure engagement. If they choose to completely withdraw from the study, then we will liaise with their healthcare team to try and ensure continued appropriate support is provided.

7.9. Methods for sharing study progress and findings with participants

Our team has a successful record of sharing study findings with participants and will utilise existing strategies to achieve this. This will include local, interactive dissemination events at the end of the trial as an opportunity for participants and their supporters to hear about the findings and provide feedback on the project. A plain-language summary of the main results will also be prepared and disseminated to any participants who wish to receive it. In the case of journal articles that are only available on subscription, provisions will be made as to whether participants may prefer to receive these in postal or electronic format. PPI will be integral to producing accessible research summaries, and where possible we will also employ infographics to present the results. To ensure maximum connection with participants, we will additionally host regular updates on the project website and provide all participants with a link to facilitate continued engagement with the study's progress.

7.10. Payments, rewards, and recognition for study participants

Participants will receive a token of appreciation in the form of a thank you card and a £20 payment per research assessment (£60 in total).

7.11. Equality, diversity, and inclusion for study participants

As part of our recruitment strategy, we plan to utilise and expand on existing work to ensure the study continues to reach under-served groups. Every person eligible to participate will be offered the same opportunity regardless of protected characteristics, and we will inspect data from each site to indicate the population characteristics of people with SMHP presenting to services with persistent, distressing voices. We will monitor recruitment in relation to the population characteristics of the study sample within our TSC and iDMEC and ensure that our SURG has appropriate representation of the study population. SURG's consultation will additionally be sought prior to the start of recruitment for specific recommendations on potential barriers and facilitators to engagement. In particular, feedback for our informational materials, recruitment approaches, and staff cultural competence will be reviewed.

We intend to conduct pilot work involving non-English speakers wherein participants excluded due to language barriers would receive the therapy without being randomised. However, due to a lack of validated outcome tools (including the primary outcome) in non-English languages, as well as the ethical and clinical restrictions of delivering a dialogical intervention via interpreters, we are unable to include participants in the trial who do not have sufficient command of English to complete assessment measures and/or engage with therapy. In terms of the former, the feasibility trial was not tested in non-English speaking participants, and the challenges this would entail when delivering TwV do not meet British Psychological Society Best Practice Guidelines when working with interpreters (61). However, this does not exclude people with English as a second language, and we will take every measure possible within the protocol and funding arrangements to engage this

group; for example, where spoken word is more accessible than written, we will provide materials in the latter.

In this regard, we found 34% of participants in our pilot trial did not identify as White, over twice as many as CBTp trials recruiting from the same geographic region (8.6%–14.2%) (42), and we intend to develop our outreach efforts to ensure continued diversity in ethnic representation, including seeking guidance from SURG regarding staff training and ensuring a culturally competent research team. Given racism and structural discrimination towards people from Black, Asian, and Minority Ethnic (BAME) communities may act as a barrier to engaging with the study due to understandable mistrust, we will also review equality and diversity issues regularly within our site meetings. We will also implement specific liaison with staff from CMHTs which demonstrate high engagement with BAME groups as part of our recruitment strategy, as well as liaising with NHS Chaplaincy and Spiritual Care services as part of intervention delivery (for example, seeking appropriate guidance from an imam when working with clients who identify their voices as jinn).

7.12. Randomisation

Following informed and written consent, eligible participants will be randomised within 2 working days. KCTU will support the development of the randomisation system, which we have used successfully in several multisite trials with the same trial statistician (Professor Emsley). Randomisation will be independent and concealed, using random permuted blocks stratified by site and diagnosis and administered via a study-specific web-based portal hosted by KCTU. Allocations will be made known by email to the Trial Manager (in order to monitor adherence to the randomisation algorithm), the Trial Administrator, trial therapists, site leads and CIs. The allocation will also be made known to participants by letter and phone call, and to relevant members of their healthcare team by letter. Blinding of the allocation code will be maintained for RAs until all outcome measures for all participants have been collected.

7.13. Protection against bias

In adherence with MRC guidelines (58), the following measures will be implemented. To protect against allocation bias, KCTU will independently prepare and hold a randomisation list using random permuted blocks; on completion of baseline assessments, RAs will then perform the randomisation utilising the web-based service. Trial administrators and/or therapists will then inform the participant. KCTU will be responsible for providing a study database, including automated checks on validity of data being entered, with procedures for data checking/cleaning also developed and implemented at each site. The primary database will not include any information about random allocation, which is contained in a separate system to protect against accidental unblinding. We will have a secondary database for entering unblinded information (e.g., adverse events, therapy information) that blinded researchers will not have access to.

The senior trial statistician will be unaware of individual participant's random allocations or group-level summary data split by arm throughout the course of the trial. The trial statistician will be blinded during the drafting of the Statistical Analysis Plan and become unblinded to the individual participant and group-level summary data at the preparation of the first closed iDMEC report (approximately 6 months after first participant recruitment). The investigators and research team will be blind to group-level summary data split by arm throughout the course of the trial.

Maintaining rater blindness to treatment allocation is crucial, and single-blind assessors will be blinded to treatment condition using a range of measures which we have successfully implemented in our previous trials. These will include separate offices for therapists and research staff, protocols for answering telephones (including reminders for participants, family members, and clinicians about the blind), protocols for message taking and secretarial support, separate diaries and pigeonholes, and data file security using passwords and encryption of randomisation information. A standard operating procedure (SOP) for maintaining, recording, and managing blinding will be developed to outline these procedures and will be reviewed by, and agreed with, our oversight committees. Each researcher will sign this SOP to confirm they understand and will comply with the protocols. Any

blind breaks will be recorded by the trial manager and reviewed by the Chief Investigator(s) for any patterns in unblinding. The iDMEC and TSC will also monitor unblindings and implement corrective action if necessary. There are only two follow-ups scheduled (at 8 months and 14 months, both after end of treatment), which will further reduce the risk of blind breaks by removing the opportunity for therapists and RAs to cross paths while visiting participants at their homes and/or when communicating with participants to arrange visits. All letters to participants and clinicians will contain a standardised statement about the need to maintain the single blinding process. In the event of blind breaks, we will identify independent assessors wherever possible to complete subsequent follow-ups (subject to any threats to participant engagement with follow-up). Finally, participant movement throughout the study will be documented at each stage, including all withdrawals and reasons for declining to participate.

Consistent with many investigators of psychological intervention trials, three team members (Branitsky, Corstens, Longden) have received occasional payment for conducting training workshops and/or lectures that address the TwV intervention either wholly or in part. To preserve transparency, these interests will be declared on all publications and other resulting outputs. There is also no intention to commercialise the therapy in the future (e.g., manuals will be made freely available without potential for financial gain), and any perception of competing interest/bias in trial management will be addressed through registration and publication of the protocol and utilising the integrity of KCTU procedures in addition to the measures outlined above. While development work for TwV has occurred at the Manchester site, the remaining centres are also fully independent of it and have an established record for developing/evaluating alternative interventions (e.g., CBTp, trauma-focussed CBTp, automated virtual reality therapy).

7.14. Recruitment and retention

While recruitment to target is a potential risk, data from Trust business intelligence services shows a potential pool of approximately 5466 individuals with a confirmed primary diagnosis of schizophrenia spectrum diagnoses (ICD-10: F20-F29) in the Greater Manchester site alone, and this will be considerably widened through the inclusion of a transdiagnostic sample. Additionally, all site leads have strong clinical links with relevant services for people with SMHPs, and all sites have extensive experience of liaison with clinical teams, the use of launch events for awareness raising, and liaison with voluntary sector organisations. We will further recruit an experienced trial manager to monitor recruitment targets on a weekly basis and implement problem-solving solutions for arising issues by drawing on existing expertise within the team. The local research networks additionally have Clinical Studies Officers, RAs, and Research Nurses with robust links with local services, and the research team has a strong history of successful collaboration with the networks to support recruitment to clinical trials. In this respect the TwV pilot recruited to 100% of its target (N=50), despite not receiving funding for a full-time RA, and we have had considerable past success with recruitment of people who experience SMHP as demonstrated by our strong track record of recruiting to psychological intervention studies (61–63).

Risk of attrition could also jeopardise the success of the internal pilot and the integrity of the definitive trial. Our sample size calculation would allow for an attrition rate of 15%; however, this is a conservative estimate, with attrition rates being 10% in our pilot trial. We will additionally employ evidence-based strategies to maximise retention and minimise loss to follow-up, such as assertive outreach approach to assessments, high quality training for RAs, and inclusion of crisis card provision and signposting in the assessment sessions.

8. Planned Interventions

The two parallel arms of this trial are a psychological intervention (TwV) + TAU (treatment condition) vs. TAU alone (control condition).

8.1. Treatment condition (TwV + TAU)

The proposed study will employ the treatment manual devised and refined during the TwV pilot (28), which utilises individualised formulations (referred to as 'constructs') to identify key psychosocial conflicts associated with VH and determine targeted treatment strategies and shared goals for relational change. An 8-month treatment window permits ≤26 sessions, with an option for up to 4 booster sessions to consolidate therapeutic gains. A range of interventions with associated milestones are delivered within the treatment timeframe (Table 2).

Table 2. Therapy phases and associated milestones for Talking With Voices.

Phases	Approximate session number	Therapy Milestones
Engagement & psychosocial education	1-2	Establishing client contact and explaining intervention Discussing experiences of, and beliefs about, hearing voices Normalising and destigmatising voice-hearing Psychosocial education focusing on the relationship between voice-hearing, life circumstances and negative emotions Establishing an alliance with the voices Commencing development of self-care and coping/grounding skills
Assessment & formulation	3-5	Developing a construct that encompasses all the voices a person hears Where applicable, explore renaming voices with less negative/derogatory names Based on the construct, have a shared understanding of 1) who or what the voices represent, and 2) what difficulties the voices represent
	6	Make a report of the construct and have a conversation about the report
	7	Reiterating therapy aims Planning which voices to speak with and the issues to explore Gaining voices' permission to dialogue Developing acceptable shared goals for dialogue Establishing the client's capacity to regain control and pre-agreeing a signal for ending the dialogue Identifying an ally within the client's social network and/or healthcare team to attend the final sessions
Dialogical work	8-23	Collaboratively setting between-session tasks Establishing boundaries for the voice via 'time-sharing' Encouraging voices to use therapy sessions as a space to express their own frustrations, rather than harassing the client during the week Achieving a direct dialogue with the voices Developing short replies/mantras that the client can use between sessions in response to the voices' concerns
Evaluation & consolidation	24-26	If desired/available, assist the client to access a local HVN peer-support group and provide signposting to relevant local services Handover session with identified family member and/or healthcare worker for support to take the work forward Create a collaborative summary of what was achieved during therapy and identify strategies/goals for the future (e.g., continue time-sharing, using respectful language, not obeying commands, self-soothing)

The manual adheres to general best-practice principles for psychological therapy with psychosis patients, including building collaborative relationships, developing shared goals, using inclusive language, validating individual experiences, and providing hope that recovery is possible (64). In turn, these principles underpin many of the specific values of TwV, which can be summarized as the following:

1. **A normalising approach:** VH is recognized as a common human experience that may cause distress but from which many people recover. Consistent with the ethos of the HVM, the concept of recovery is not solely defined by cessation of clinical symptoms as opposed

to reducing distress and promoting positive goals, with full recognition that individuals can live fulfilling lives as voice-hearers.
2. **A user-led intervention:** clients have a central role in determining the pace and goals of therapy and identifying the most useful strategies to cope with their experiences.
3. **A subjective interpretative framework:** therapists respect their clients' explanatory framework for understanding voices (e.g., trauma-based, spiritual, cultural) without insisting their clinical perspective is the correct one.
4. **Conceptualizing voices as representing parts of the self:** voices are considered a dissociative phenomenon which may often originate from traumatic events and/or reflect overwhelming emotion along with negative beliefs about oneself, other people, and the world. Correspondingly, voice content is seen as meaningful in the sense of drawing attention to unresolved distress.
5. **Facilitating a more peaceful hearer-voice relationship:** in signposting emotional vulnerabilities, voices can be seen as performing a 'protective' role in the sense that features like persecution or aggression are often masks for unresolved pain. Because attempts to suppress the voice will also suppress the emotions/beliefs which they embody, a complementary goal is therefore to help the voice communicate its purpose and needs in ways that are more constructive and respectful of the hearer.

Adherence checklists and electronic session records will be utilised to maximize fidelity to the manual, with any protocol divergences monitored during therapist supervision. Important treatment milestones will likewise be assessed and monitored and therapy sessions will be audio recorded for the purpose of fidelity to the intervention manual checks. Audio recording will be carried out in line with the policy and procedures of the NHS site where the recording takes place.

8.2. Control condition (TAU alone)

In the UK, TAU for SMHP is based on the Care Programme Approach and typically includes psychiatric medication, assignment of community-based health and social care staff, care coordination, access to rehabilitative services, and outpatient care. Referrers for participants in the TAU arm will not be requested to withhold any treatment throughout the duration of the trial, and all routine or additional treatments will be monitored. With the exception of emergent risk issues, TAU alone will also not involve liaison between researchers and the participants' healthcare teams.

9. Data Collection and Analysis

9.1. Assessment schedule and administration

After recruitment and baseline assessments are concluded, a follow-up assessment will take place at 8 months post-randomisation (end of treatment). Assessors will be trained in the use of all instruments to achieve a satisfactory level of inter-rater reliability and will be blind and independent to treatment group. Additional follow-up assessments will be performed at 14 months post-randomisation, dependent upon when participants were recruited into the trial (thus, the total follow-up period will vary from 14 months to 8 months, maximising the recruitment period and providing best value for money; we anticipate obtaining 14-month follow-up data on the first 207 participants). The window for collecting follow-up data will be two months.

Participants will be offered choices regarding length of assessments, including the option of breaks and multiple meetings. Assessment measures will be clearly prioritised so that the most important will be collected first to minimise missing data. We will have a standard protocol for managing any distress that is associated with the completion of measures, which we have successfully utilised in several trials and has been developed in collaboration with service users; this includes telephone contact within 2 working days of assessments to check on participant well-being.

9.2. Statistical analysis

We will report participant flow using the CONSORT 2018 extension for social and psychological intervention trials (65). Assessment of recruitment, drop-out and completeness of therapy will be summarised by descriptive statistics. The primary analyses will use the intention-to-treat population to estimate the treatment policy estimand. Statisticians will be unblinded after database lock as the statistical analysis needs to account for therapist effects in the TwV arm. No interim analysis is planned.

To test the primary hypothesis, we will fit a linear mixed model to the repeated measures of the QPR at 8 and 14 months, with fixed effects of randomization, time, time by randomization interaction, site, diagnosis, and baseline QPR, and random effects for participants and therapist. The treatment policy estimand will be estimated as the adjusted between-group mean difference from the model for each timepoint separately. All hypotheses for secondary outcomes will be analysed using linear mixed models for continuous outcomes and logistic mixed models for binary outcomes. Maximum likelihood estimation will allow for missing outcome data under a missing-at-random assumption, conditional on the covariates in the model.

To test treatment-effect mechanisms, mediation analysis will use parametric regression models to estimate the indirect effects of TwV on the mechanism measures and of mechanisms on primary and key secondary outcomes. Results will be reported using the AGrEMA guidelines (66).

9.3. Outcomes

Efficacy outcomes will assess overall personal recovery and impact/severity of VH, with additional clinically relevant outcomes of targeted psychiatric symptoms and functioning.

9.3.1. Primary outcome

The primary outcome will be the total score on the 15-item QPR at 8 months. The QPR was developed in collaboration with patients to assess personal recovery from psychosis, containing items that were initially derived from qualitative interviews about this topic. It has excellent reliability, validity, and sensitivity to change and is nationally adopted as a PROM for evaluation of early intervention for psychosis services, forming part of the Mental Health Services Data Set. Patients consistently prioritise personal recovery over specific symptom change (67) and the QPR has been cited (68) as the only measure of recovery that directly maps onto all 5 processes of the influential CHIME framework of personal recovery (69).

9.3.2. Secondary outcomes

Secondary outcomes will assess overall VH severity and other relevant dimensions of psychiatric distress and trauma sequalae.

1. The PSYRATS-AH (57), an interviewer-rated measure that assesses VH across 11 domains of phenomenology and impact.
2. The Voices Acceptance and Action Scale (70), a 12-item measure designed to assess acceptance-based attitudes and actions in relation to auditory and command hallucinations.
3. The Psychotic Symptoms Rating Scale: Multimodal Hallucinations, an unpublished scale adapted from PSYRATS-AH for assessing the presence and impact of non-auditory hallucinations.
4. The PTSD Checklist for DSM-5 (PCL-5) (71), a 20-item self-report measure that assesses the severity of a range of trauma-related symptoms.
5. The Trauma Voice Associations Questionnaire (73), a 16-item inventory which assesses connections between adverse life events and VH experiences.

The proposed mechanisms of action for TwV will also be measured with the following instruments:

1. Negative beliefs about the self will be assessed with The Brief Core Schema Scale (74), a 12-item self-report questionnaire.

2. Dissociative experience will be measured with the depersonalisation/derealisation subscale of The Revised Dissociative Experiences Scale (DES-II) (75), which contains 6 items scored for daily frequency.
3. Interactions with one's voices will be assessed with the Beliefs About Voices Questionnaire – Revised (76), a 35-item measure of beliefs about auditory hallucinations and emotional and behavioural reactions to them.
4. Assertiveness in response to one's voices will be assessed using the 15-item Approve – Voices Questionnaire (77).

All measures will be administered at baseline, at 8 months and at 14 months. Additional pharmacological and psychosocial treatments for mental health concerns, including hospitalisations, will also be monitored in both arms using a treatment documentation sheet.

9.3.3. Baseline characteristics

The Modified Trauma and Life Events Checklist (TALE) (72), a 21-item trauma screening tool for identifying clinically significant traumas in people with psychosis, will be administered as a baseline measure.

9.4. Termination criteria

The Sponsor may suspend or prematurely terminate the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons, such as when recommended by the iDMC. If suspicion of an unacceptable risk, including serious health threat to participants, arises during the clinical investigation, or when so instructed by relevant regulatory authorities, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed. The Sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. If, for any reason, the Sponsor suspends or prematurely terminates the investigation at an individual investigation site, the Sponsor shall inform the responsible regulatory authority as appropriate and ensure that relevant bodies are notified, either by the chief investigator(s) or by the Sponsor. If the suspension or premature termination was in the interest of safety the Sponsor shall inform all other principal investigators.

Access to or breaking the blinding code in the case of suspension or premature termination would be decided by the independent iDMC.

9.5. End of trial

The end of the trial is defined by the last visit to the last participant, which will occur in January 2026. The Sponsor, or delegated individual in the study team, must notify the NIHR of the end of the trial within 90 days of its completion.

10. Project Timetables and Recruitment Rate

Prior to the start of the study, work will commence to prepare the paperwork required for ethics, HRA, and NHS Capacity and Capability (C&C) approvals. Each site will commence engagement with senior managers, clinicians and service users in the services participating in the study to raise awareness before recruitment commences and to ensure sign off from senior managers. The first Service User Reference Group (SURG) will take place before month zero to inform the development of study materials and pilot the full assessment pack.

The project duration is 34 months based on the need to recruit a total of 296 participants from 4 sites, following the planned Gantt chart (Table 3).

1) Set-up (M1-M3): finalising the trial protocol, study materials and KCTU databases; governance approvals, staff recruitment/training, site set-up and study promotion.
2) Review of internal progression criteria (M14): assessment of key study milestones as detailed in Table 1.
3) Recruitment (M4-M23): 296 participants, at an average of 3 per site per month for London, Newcastle, and Oxford and 5.8 per month for Manchester (60 and 116 per site over 20 months).
4) Treatment (M4-M31) and follow up (M13-31): an 8-month treatment window and 8-month (M13-M31) and 14-month (M18-M31) follow-ups for all participants.
5) Closure (M32-M34): data cleaning prior to database lock, analysis, site closure and report writing.

Table 3. Gantt chart

YEAR 1 **Calendar month**	**Pre-trial**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Trial governance													
Engage local NHS senior leaders													
Recruit trial staff													
SURG consultation (to be repeated as required)													
Convening TSC and iDMEC													
Ethics, HRA and local governance													
Finalise trial protocol and other study materials													
Randomisation/data platform, website, animation													
Staff training													
Site initiation meetings													
Recruitment and assessment													
Recruitment													
Baseline assessment													
Intervention delivery													

YEAR 2 **Calendar month**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24**
Recruitment and assessment												
Recruitment												
Baseline assessment												
8-month assessment												
14-month assessment												
Trial governance												
Progression criteria data review												
Intervention delivery												

YEAR 3 **Calendar month**	**M25**	**M26**	**M27**	**M28**	**M29**	**M30**	**M31**	**M32**	**M33**	**M34**	**M35**	**M36**
Recruitment and assessment												
8-month assessment												
14-month assessment												
Intervention delivery												
Trial governance												
Data cleaning/analysis, report, publications												

11. Research Expertise Within the Study Team

The Psychosis Research Unit (PRU) and Oxford Cognitive Approaches to Psychosis research group are world-leading research units with an extensive track record of successful multi-site NIHR-funded RCTs for developing/evaluating targeted psychological therapies in SMHP populations. In addition, both have established links with NICE and national training organisations/professional bodies, as well as NHS services with records of successful implementation of evidence-based practice for SMHP.

Collectively, the research team has 1) expertise in psychological models of VH, posttraumatic symptoms, psychosis, and the maintenance factors associated with them (Bowe, Branitsky, Corstens, Dudley, Freeman, Hardy, Longden, Morrison, Sheaves), 2) experience of chief and principal investigator roles, trial management, and/or training/supervising staff in the context of SMHP interventions (Bowe, Dudley, Freeman, Hardy, Longden, Morrison, Pyle, Sheaves), 3) expertise in trial methodology, analysis and CTU involvement (Emsley, Freeman, Morrison), 4) experience of training therapists, disseminating evidence-based therapies and/or ensuring adherence and competence in delivery of therapies (Bowe, Dudley, Hardy, Corstens, Freeman, Longden, Morrison, Sheaves), 5) experience of NHS management and implementation (Bowe, Dudley, Freeman, Hardy, Longden, Morrison, Pyle, Sheaves), 6) experience of promoting service-user involvement in service delivery and/or research (Branitsky, Corstens, Dudley, Freeman, Hardy, Jones, Longden, Morrison, Pyle, Sheaves), 7) experience of consulting with NICE Guideline Development Groups (Freeman, Morrison), and 8) have personal experience of VH and SMHP (Branitsky, Jones, Longden).

11.1. Applicant roles in the trial

Longden and Morrison will be joint Chief Investigators and Dudley, Hardy, and Sheaves will lead the sites. Emsley will be the Trial Statistician. Bowe and Corstens will be clinical co-leads with responsibility for monitoring fidelity/adherence to the treatment manual (Bowe) and providing training and supervision to trial therapists (both). Freeman and Pyle will provide consultancy and advice regarding trial management and oversight. Branitsky and Jones will provide lived experience expertise to the trial management structures and lead PPI activities.

12. Patient and Public Involvement

PPI work on the project will be led by Jones in collaboration with co-applicant Branitsky and joint lead applicant Longden, all of whom have lived experience of SMHP. Jones is a Service User Researcher based at the Manchester site with nearly five years' experience of conducting PPI activities with adults with SMHP, including organising PPI via the PRU SURG, and coordinating PPI on an existing NIHR-funded multi-site trial while providing ongoing consultation for a second.

Alongside clinically qualified colleagues, training of research staff/therapists will be co-delivered by Longden and Branitsky, with supervision of trial therapists likewise following the same model. All three lived experience applicants will contribute to trial management group meetings, with additional PPI scrutiny ensured for study procedures by inviting a representative with lived experience to be a member of the TSC. PPI activities will be monitored and recorded under relevant agenda items during trial management meetings, oversight committees and local site meetings, with PRU SURG providing additional consultation for relevant phases of study design and implementation. The results of PPI involvement will further be collated and used to contribute to the final report and other relevant dissemination activities.

13. Clinical Trials Unit Involvement

KCTU has internationally recognised expertise in the design, conduct, analysis and reporting of multicentre mental health trials. Professor Emsley will take responsibility for the conduct of the

trial processes and has been fully engaged with both CIs throughout the planning stage to ensure the optimal scientific design, with the best and most appropriate analysis and suitable methods of managing and conducting the trial. The statistician will take responsibility for all aspects of the statistical analysis; this will adequately support the trial's statistical needs (including specification of the randomisation system, liaison with database managers, preparation of the Statistical Analysis Plan, creation and delivery of progress reports to the TSC and IDMC, assist in enhancing the quality of the trial data by monitoring of accumulating data, and conducting all statistical analyses for the final data set).

Paper source data worksheets will be completed at sites and transferred to a web based electronic data capture system backed by an electronic data management system (InferMed MACRO version 4; KCTU) that will be hosted on a dedicated server within KCL. The system is compliant with Good Clinical Practice. The web- based system will be available for access 24 hours a day to authorised users. Roles will be assigned to users, giving the ability to enter data relating to participants or to view data and raise discrepancies. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system. No data will be entered onto the system unless a participant has signed a consent form to participate in the trial. The system is programmed to perform validation checks, such as range checks to prevent data entry errors. Missing data codes are routinely programmed into all fields, for ease of analysis. The system is also programmed to flag up when a missing data code is entered, to aid monitoring. A standard feature of InferMed MACRO data entry system is the built-in audit trail on all data fields, the automatic saving of data as you leave a form, and the ability to maintain a record of 'source data verification' checks. No data will be amended independently of the study site responsible for entering the data. Data entered from paper source worksheets completed at sites will be checked against the electronic data for accuracy. Accuracy will be checked for 100% of the primary outcome on the post-baseline timepoints across all sites. If the error rate is greater than 1% accuracy checks for all data will be triggered.

13.1. MACRO EDC

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system.

13.1.1. Data entry

The EDC will be created in collaboration with the trial analyst/s and the CIs and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. Source data will be entered by recruiting site staff, typically within 7 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

13.1.2. Security

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participants PIN numbers (allocated when registering on the EDC) and their age at consent will be entered on the EDC. Whereas NHS number, email addresses, participant names and addresses, and full postcodes will not be entered into the EDC system. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial.

13.1.3. Data quality processes
The CIs' team will undertake appropriate reviews of the entered data, in consultation with the project analyst, for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

The KCTU will provide the study team with Data management plan for Elsevier InferMed MACRO EDC once the system is made live and ready for use.

13.1.4. Database lock
At the end of the trial, the site PI will review all the data for each participant to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

13.2. KTCU Randomisation
A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Randomisation will be at the level of the individual using the method of random permuted blocks stratified by site and diagnosis.

13.2.1. Data entry
Randomisation will be undertaken by recruiting site staff, by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

13.2.2. Security
The CIs or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CIs or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CIs or delegate (e.g., Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the randomisation system. Whereas NHS number, email addresses, participant names and addresses, and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial.

13.2.3. Data quality processes
The CIs' team will undertake appropriate reviews of the entered data, in consultation with the project analyst, for the purpose of data cleaning. No data can be amended in the system, however CIs or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

13.2.4. Database Lock
Upon request, KCTU will provide a copy of the final exported dataset to the CIs in .csv format and the CIs will onward distribute as appropriate.

14. Project Management

14.1. Governance and oversight

Greater Manchester Mental Health Foundation Trust will be the primary Sponsor. In accordance with high standards of research governance, we will ensure staff receive training in the International Conference on Harmonisation Guidelines: Good Clinical Practice before recruitment commences. We will also establish a TSC and iDMC prior to the start of the study. The TSC will comprise representatives from the research team, two independent clinicians (including the Chair), an independent statistician, and an independent PPI representative and will initially meet before the trial begins for approval of the protocol and SOPs, then proceed to monitor and supervise progress and consider reports and recommendations on a 6-monthly basis. An iDMC will also be established to monitor 1) recruitment of study participants, 2) ethical issues of consent, 3) quality of data (including missing data), 4) the incidence of adverse events, and 5) any other factors that might compromise the progress and satisfactory completion of the trial. This will also have an independent Chairperson and include an independent statistician and PPI representative. It will meet on an annual basis and before the trial commences.

14.2. Communication within and between sites

Each site will hold weekly meetings to ensure regular communication between PIs, therapists, and RAs (with appropriate measures for avoiding blind breaks). There will be monthly Trial Management Group meetings with all applicants via video conference, with 6 monthly extended face-to-face meetings. The trial manager will conduct weekly telephone supervision with all RAs that will focus on assessment protocols, recruitment, liaison with referrers, compliance to follow-ups, and specific scoring queries. In addition, they will chair a fortnightly teleconference that focuses on recruitment and engagement to share best practice. The therapists will receive fortnightly peer-supervision coordinated centrally by clinically qualified co-applicants (Corstens/Bowe) and those with lived experience of VH (Branitsky/Longden). These sessions will focus on fidelity/adherence to the protocol and will be further supplemented by individual weekly supervision from site leads, focussed on problem-solving, personal wellbeing, risk management, and any local issues. Quarterly triadic site supervision involving supervisee, central supervisor and PIs will be used to ensure these arrangements operate smoothly. We have used these processes successfully in several previous multisite RCTs of psychosocial interventions.

15. Data Management

Each study participant will be assigned a unique trial identification number at the start of the assessment process. This number will be written on all clinical assessment forms, datasheets and databases used to record information on study participants. A registration record linking patient identity, contact details and trial identification number will be kept electronically at site. It will be kept securely with a password only provided to authorised users as per the study delegation log, and it will be stored on a secure NHS drive.

In accordance with GMMH's Information Governance procedures, the retention periods are as follows:

- Informed consent form will be retained for 5 years after the end of study.
- Research data will be retained for 5 years after the primary publication.
- Research management documents for 5 years after the end of the study.

16. Ethics

Necessary approvals with be sought from the HRA and NRES prior to commencing data collection. Only participants providing written informed consent will be included in the trial, with all potential participants receiving a PIS that meets requirements set out by NRES (58). Before providing

consent, all potential participants will additionally be apprised of the latent risks and benefits of trial involvement. All participants will also be reminded that they are free to withdraw from the study procedures at any point without affecting their statutory care.

16.1. Peer review

As an NIHR funded study the scientific quality of the research has been assessed throughout the funding review process through both peer review of experts in the field and through the NIHR Evaluation Mechanism Programme funding panel. The protocol has been reviewed by the study Sponsor, and the Ethics Committee.

16.2. Risks and anticipated benefits for trial participants

The trial will add to the evidence base for the range of psychosocial interventions that should be provided to improve outcomes for people with SMHPs, who remain among the most socially excluded groups in society. If the intervention is found to be significantly superior to TAU in reducing the negative impact of voices and promoting recovery without an adverse effect burden, this could have implications for the future evidence-based management of patients with similar difficulties within mental health services.

A potential risk is that some participants might find the research assessment process distressing. Participants' will be offered choice regarding the timing, modality (remote or face-to-face) and length of the assessments, including the option of breaks and assessments spread across multiple occasions (to minimise burden at any one time). We have a standardised protocol for managing distress, which has been developed with service users; this includes offering telephone contact within 48 hours of assessments in order to check on participant wellbeing. The RAs will gain advice from their supervisor and take any appropriate action to minimise the participant's distress. The participant will be able to freely withdraw from the study at any point, which will not affect their statutory care.

A further risk is that participants may find therapy to be aversive or distressing. The intervention will be delivered by therapists experienced in supporting clients with SMHPs who will liaise with existing healthcare teams as appropriate to ensure client wellbeing. Participants will likewise be reminded that they are free to withdraw from therapy at any point with no negative consequences.

Any concerns about participants noted by therapists and/or assessors will be reported to the responsible clinical team as appropriate (for full discussion of safety assessment, please see section 16.3).

16.3. Assessment of safety

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject to whom a medicinal product/device/intervention has been administered, including occurrences which are not necessarily caused by or related to the latter. An adverse event can therefore be any unfavourable and unintended sign (including abnormal lab results, traffic accident), symptom or disease temporally associated with the use of the medicinal product/medical device/intervention, whether or not considered to be related to the medicinal product/medical device/intervention. This may include incidents of self-harm.

A Serious Adverse Event (SAE), will be defined as an 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
- other important medical event if determined to be serious based on medical judgement

NB: Planned hospitalisation for a pre-existing condition, or a procedure required by the Protocol, without a serious deterioration in health, is not considered a serious adverse event.

NB: Life threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Clinical judgement should be exercised in deciding whether an SAE is serious in other situations. AEs that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed, should be considered serious.

NB: Foreseeable adverse events include psychiatric hospital admissions, self-injury and/or suicidal ideation with a behavioural component. Analysis of the feasibility and acceptability trial indicate these were commonly occurring adverse events within the study population (43).

Adverse events (including death) and intervention related adverse effects will be monitored. We plan to scrutinise any instances of participants being admitted to psychiatric hospital in the period of the trial. These events are likely to come to the attention of the therapists or assessors; however, we will also check medical records at trial exit. The responsible clinical team, the trial management group, the iDMEC, and the Sponsor will be informed of adverse events. The response to an adverse event will be determined on a case-by-case basis and in line with Health Research Authority (HRA) guidance.

SAEs will be reported to the main Research Ethics Committee (REC) when in the opinion of the CI(s) the event was: *related* (that is, it resulted from administration of any of the research procedures, and *unexpected* (that is, the type of event is not listed in the protocol as an expected occurrence). In order to ensure independent scrutiny of SAEs, the iDMC will monitor their occurrence for any patterns.

16.4. Obtaining informed consent

Written informed consent will be obtained from each participant prior to their inclusion in this study In line with the Information Sheets and Consent Forms, Guidance for Researchers and Reviewers, Version 3.2 May 2007 (NRES). Participants will be given least 24 hours to consider the information before providing written informed consent. We will prioritise recording informed consent in writing via a wet-ink signature from the participant and the researcher. However, in the event of it being unfeasible to seek written consent (e.g., where COVID-19 restrictions apply) consent will be taken remotely via telephone or MS Teams and audio recorded as evidence of the informed consent process. Audio recording will be carried out in line with the policy and procedures of the NHS site where the recording takes place.

16.5. Amendments to the protocol

Minor revisions shall be used to indicate where small changes have been made to the protocol (e.g., formatting, spelling, or grammar corrections), or where changes have been made that do not require further approval or acknowledgement. Minor revisions shall be indicated by making increments to the decimal place of the version number (e.g., V 1.2). Major revisions shall be used where changes to the protocol are significant and require re-approval. Major revisions shall be indicated by making increments to the whole number of the version (e.g., V 2.0). Amendments to the protocol will not be initiated until approval has been sought from the Sponsor and, where relevant, the REC and the HRA.

16.6. Access to the final trial dataset

The statistical support staff at KCTU, including Professor Emsley, will have access to the final trial dataset. After the main publication the Cis, co-investigators, and trial manager will have access to the final dataset.

17. Dissemination, Outputs, and Anticipated Impact

Data will be analysed on completion of the trial and a final trial report prepared for the NIHR.

All written and oral research outputs should acknowledge the NIHR funding, and support from the Clinical Research Network, iDMEC, TSC, and PPI groups.

The proposed study will provide evidence regarding clinical effectiveness of a novel, user-informed intervention that uses direct dialogue in reduce the impact of distressing VH in a transdiagnostic population within the NHS. This output will address a number of unmet needs, including improving the efficacy and accessibility of evidence-based psychosocial interventions for adults with SMHP, developing the workforce, and responding to the NHS's Long-Term Plan for implementing personalised, trauma-informed care as part of mental health provision. In addition to a number of high-quality peer-reviewed publications (including the trial protocol and analysis of primary and secondary measures), a core component of this project is the training and skilling-up of the workforce involved in the research. In this respect, intervention manuals will be made freely available via a web portal for clinicians to utilise which will facilitate effective uptake, sustainability, and implementation within the NHS. This will be supported through our existing links with the Innovation and IP Management Services within the host site, with no intellectual property barriers expected. We will further generate quantitative data that may be of interest to researchers examining the efficacy of psychosocial interventions (e.g., for systematic review, meta-analyses, and individual patient data analysis), including the impact of targeting key psychological processes to minimise distressing VH.

The fact that NHS clinicians will deliver the treatment should help to immediately disseminate the approach. In this regard, our pilot trial confirmed that CBTp therapists already experienced in working with voice-hearers were able to deliver the intervention without time-intensive training, which has positive implications for scalability. We will also utilise dissemination strategies applied during the pilot trial, which involved workshops and conference presentations delivered to a diverse range of audiences (i.e., service-users and their families, healthcare professionals, academics, and school children). We will continue to embed the perspectives of voice-hearers in sharing the results, including presentations delivered by team members with experience of SMHP, engaging with voluntary sector organisations like the Hearing Voices Network, and consulting with SURG where appropriate for feedback on our dissemination strategy (for details of how results will be shared with trial participants, please see p.16). In this regard, the current trial team has a strong track record of dissemination and implementation, which has been achieved through a systematic approach to delivering clinical workshops and training events. Collectively, we also have strong records of high impact peer-reviewed publications and in conducting research which has been directly translated into improvements in NHS service provision. Furthermore, we have an additional record of rapid impact on service delivery locally, nationally, and internationally.

Our focus on SMHP is clearly consistent with NHS priorities and needs, since it is associated with significant personal, social, and economic costs, and SMHP account for a large proportion of the national health and social care budget. If the intervention is found to be effective, this could have implications for the clinical commissioning of local mental health services, and for the development of national guidelines for the provision of care for patients with SMHP. Likewise, there is also potential for immediate impact on ~148 NHS patients who are allocated to receive TwV.

Authorship eligibility guidelines

Authorship will be reviewed on a publication-by-publication basis. We will follow the International Committee of Medical Journal Editors (ICJME) recommendations for authorship and review these for each individual publication. Prior to commencing a publication, the Chief Investigators and trial manager will review the list of research team members to consider who would meet the ICJME criteria.

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