

# BMJ Open RELATE – a randomised controlled feasibility trial of a Relating Therapy module for distressing auditory verbal hallucinations: a study protocol

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## ABSTRACT

**Introduction** Auditory verbal hallucinations (AVHs) are associated with distress and reduced functioning. Research suggests that distress is associated with the voice hearer's responding to AVH in a passive and subordinate manner. A novel approach focuses on relating to AVH and teaches assertive responses to AVH using experiential role-plays. A small pilot study found a large effect of this approach on AVH distress but an independent multicentre study is required to ascertain effectiveness across different settings. We aim to estimate the expected effect for a subsequent trial to demonstrate that adding a module of Relating Therapy (RT) to treatment as usual (TAU) is superior to TAU alone in reducing AVH distress. We also test the feasibility of patient recruitment, therapist training, and therapy monitoring in different psychological and psychiatric outpatient facilities in Germany.

**Methods and analysis** We will recruit 75 patients diagnosed with a schizophrenia spectrum disorder and persistent distressing AVH across four sites. Patients will be randomised to receive either 16 sessions of RT plus TAU or TAU alone within a 5-month period. Randomisation will be stratified by sites. Single-blind assessments will take place at baseline, at 5 months (T1) and at 9 months (T2). The primary outcome is the distress factor score of the AVH subscale of the Psychotic Symptoms Rating Scale at T2 adjusted for the baseline value. Secondary outcomes are change in depressive symptoms, quality of life, time spent in structured activities as well as negative relating to voices and to other people.

**Ethics and dissemination** The trial has received ethical approval from the German Psychological Society Ethics Committee. The trial results will be disseminated through conference presentations, peer-reviewed publications and social media.

**Trial registration number** ClinicalTrials.gov Registry (NCT04578314).

## INTRODUCTION

### Background and rationale

Despite its comparatively low prevalence, schizophrenia is listed as the eighth leading cause of disability-adjusted life years worldwide in the age group 15–44 years in the World Health Report 2001.<sup>1</sup> Thus, developing effective and enduring treatments

## Strengths and limitations of this study

- Prospective multicentre pilot study.
- Randomised controlled, single-blind study design.
- Patients cannot be blinded to the treatment allocation, which could introduce bias into the data.
- The two-armed study design lacks a third comparator that directly targets auditory verbal hallucination distress.
- Due to the lack of German-speaking therapists with experience in conducting Relating Therapy who could serve as independent experts, the adherence checks will be done by the supervisor (MH) based on translations of the recorded therapy sessions.

for schizophrenia spectrum disorders and facilitating recovery of patients are a crucial challenge. Many researchers suggest that treatments for severe mental disorders are most likely to be improved by focusing on clearly defined single symptoms.<sup>2,3</sup>

Auditory verbal hallucinations (AVHs) are a sensory experience in the absence of external stimulation of the sensory organ. AVHs typically involve hearing voices that vary in length, complexity and content (eg, benevolent or malevolent, critical, commenting or commanding). With a prevalence of about 60%–70%, AVHs are common in psychotic disorders<sup>4–6</sup> and are associated with high levels of distress,<sup>7,8</sup> reduced occupational and social functioning,<sup>8,9</sup> and an increased risk of suicidal behaviour.<sup>10</sup> In particular, the distress related to AVH is linked to functional impairment and harm to self and others.<sup>11,12</sup> It is therefore not surprising that patients with persistent AVH report the reduction of distress to be a priority for treatment.<sup>13</sup> In a survey by the International Consortium of Hallucinations Research, 93% of the participants rated AVH-related distress reduction among their top three most important

therapeutic outcomes over and above social and occupational recovery or general well-being.<sup>14</sup>

AVHs in the context of psychotic disorders are generally treated with antipsychotic medication as a first line of treatment (and in many cases the only line).<sup>15</sup> Clinical drug trials typically report small to moderate effects for psychotic symptoms in general and reanalyses of these trials indicate that these effects can be generalised to AVH.<sup>16</sup> Nevertheless, about one-third of the patients who take antipsychotics continue to have AVH.<sup>17</sup> Also, medication is often not taken as prescribed<sup>10</sup> and bears the risk of severe adverse effects, including metabolic and cardiovascular problems.<sup>18</sup> Finally, there is a growing concern over the cumulative effects of long-term use of antipsychotics on physical health and brain structure.<sup>19</sup> This underlines the necessity to develop safer treatments that are more readily accepted by patients.

Psychological interventions for AVH are mostly a form of cognitive-behavioural therapy for psychosis (CBTp) and typically include enhancing coping strategies and/or changing beliefs about AVH. Meta-analyses confirm a small effect of CBTp on psychotic symptoms in general.<sup>20</sup> There is also evidence of an effect of CBTp in terms of reducing AVH<sup>20,21</sup> as a secondary outcome, however these effects are small and diminish at follow-up assessments.<sup>20</sup> There have been several recent attempts to improve outcomes by taking a symptom-focused approach to AVH (ie, the COMMAND<sup>22</sup> and Avatar Therapy<sup>23</sup> trials), but these either do not show an effect on AVH distress,<sup>22</sup> the outcome prioritised by patients, or this effect was no longer superior to the control group at follow-up.<sup>23</sup>

Novel targeted interventions may be more successful in reducing AVH distress if they specifically target those mechanisms that are causing the distress. One likely mechanism causing AVH-related distress stems from the relationship people have with their AVH. Previous research shows patients to have subordinating and intrusive relationships with their AVH. These relationships share similarities with patients' relationships with people within their social environments<sup>24,25</sup> and empirical findings suggest that hearers have 'integrated, personally coherent relationships with their AVH<sup>26</sup> that are likely to be imbued with the complexity of social relationships. The intervention to be evaluated in this trial builds on these findings and on an interpersonal theory of relating by Birtchnell.<sup>27</sup> The application of this theory to the experience of AVH has suggested that AVH distress is associated with the hearer's perception that AVHs relate to them negatively in a dominant and intrusive manner, and with the hearer relating negatively in a distant and passive manner.<sup>24,25,28</sup> The Relating Therapy (RT) approach aims to reduce negative relating in order to reduce AVH distress. RT has been tested in a pilot randomised controlled trial (RCT) that compared RT+TAU (treatment as usual) with TAU and included 29 patients with distressing AVH in the UK.<sup>29</sup> This study established that it is possible to recruit and retain patients (87% remained in the trial by the 5-month follow-up). After 4 months, 50% in the RT+TAU

group and 13% in the TAU group had shown a clinically important decrease on the primary outcome; 5 months later these numbers were 43% and 13%, respectively (estimated effect size for follow-up of  $d=1.4$ ). If this effect can be confirmed in independent multicentre trials, RT could be incorporated into different healthcare formats and have a positive impact on the well-being and recovery of patients with AVH.

## Objectives

Although the UK pilot trial on the RT approach<sup>29</sup> produced a large effect on AVH distress, the trial was neither sufficiently powered nor set up to show that effects can be generalised across a variety of settings that will differ in terms of therapist training and in what constitutes TAU. Thus, an adequately powered multicentre trial is needed to demonstrate that the effects on distress are reliable and can be generalised across different settings. Prior to conducting a large-scale cost-intensive multicentre trial within the German healthcare setting, it is necessary to first establish in a feasibility study that:

1. the effect found in the small pilot trial can be replicated in German outpatient settings by training and supervising therapists. The question at issue here is whether the German translation of the therapy manual, the therapist training and the planned supervision are sufficient to deliver the RT module at a satisfactory standard and whether the patients are equally likely to complete and benefit from the intervention as they were in the UK setting, in which the initial pilot trial was conducted;
2. the trial infrastructure can be implemented, and a sufficient number of suitable patients can be recruited within German outpatient settings. Relevant settings for the future delivery of RT are practices of licensed psychologists and psychiatrists and outpatient wards of psychiatric clinics. For the purpose of the study, outpatient facilities situated at the university psychology departments and outpatient wards of university clinics that provide a research infrastructure for clinical trials will serve as proxies for these two types of settings.

The feasibility study will also inform our understanding of what constitutes TAU for this population within the selected settings, which will be used for a protocol of an optimised and more standardised TAU in a future definite RCT. The recruitment rates in the centres will provide a basis on which to establish the required number of centres. Moreover, we aim to establish a realistic estimate of trial and follow-up completion rates across all types of centres. Finally, the effect size from this feasibility trial will provide a more accurate basis for the power calculation.

## Trial design

This is a feasibility study for a subsequent fully powered single-blind, prospective, randomised, controlled, parallel-group, two-armed, multicentre, open trial to demonstrate that adding an RT module to TAU is superior to TAU alone in reducing AVH distress. The primary

efficacy aim is to show that the mean distress factor score of the PSYRATS-AVH<sup>30 31</sup> (Psychotic Symptoms Rating Scale–Auditory Hallucination Subscale) at 9 months (T2) adjusted for the baseline value is lower in the intervention than in the control group.

Feasibility questions will relate to patient recruitment, therapist training and therapy monitoring in different types of psychological and psychiatric outpatient facilities.

The results will be used to plan the design for a future trial within the German healthcare system.

## METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

### Patient and public involvement

The EmPeeRie (Empower Peers to Research) Network at the university clinic in Hamburg and the Psychosis Lived Experience Group (UK patient involvement group led by Mark Hayward) were involved in discussing the minimally relevant assumed treatment effect in the primary outcome measure. The EmPeeRie group also provided advice on how to recruit participants in patient networks.

The EmPeeRie group will consult on issues concerning informed consent, participant well-being, recruitment and retention, interpretation of findings and dissemination. This involvement will take place in the form of regular group meetings. An ‘involvement log’ will be kept to record and track the influence of the advice offered by EmPeeRie.

Finally, a person from this group with lived experience of AVH has consented to be a member of the Data Safety and Monitoring Board in a subsequent full clinical trial.

The EmPeeRie group consists of members with lived experience of mental illness, with multiple members having lived experience of psychosis and voice hearing. The EmPeeRie Project has been accumulating experience in initiating research projects based on the ideas of people with lived experience and in consulting researchers in clinical trials since its founding in 2017. Members of EmPeeRie receive continuing education as part of the group’s training programme for people with lived experience.

The current issues of the trial will be presented at the regular EmPeeRie group meetings on at least a yearly basis during the course of the study to consult on participant well-being, accessibility of study materials, recruitment and retention, and the interpretation of findings and dissemination. The ‘involvement log’ for each consultation will track the influence of the advice offered to the research team by EmPeeRie.

### Study setting

Participants will be recruited in four sites: (1) Psychotherapeutische Hochschulambulanz der Universität Hamburg (psychology outpatient clinic at Universität Hamburg), (2) Klinik und Poliklinik für Psychiatrie und Psychotherapie Universitätsklinikum Hamburg Eppendorf (Psychiatric Clinic of the university clinic in Hamburg), (3) Christoph-Dornier-Stiftung für Klinische Psychologie

Bremen (psychology outpatient clinic in Bremen in cooperation with Ameos Klinikum Bremen), (4) Psychotherapeutische Hochschulambulanz am Institut für Psychologie der Universität Leipzig (psychology outpatient clinic at Universität Leipzig).

### Eligibility criteria

Patients included in the trial will:

1. have a diagnosis of a schizophrenia spectrum disorder (International Classification of Diseases, 10th Revision, F2, confirmed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5));<sup>32</sup>
2. be reporting distressing AVH for at least 6 months (to be beyond the startle and adjustment phases) and score  $\geq 3$  on at least one item of the distress factor of the PSYRATS-AVH;<sup>30 31</sup>
3. be  $\geq 16$  and  $\leq 99$  years of age;
4. be able to understand the full implications of their decision by the responsible psychiatrist or clinical psychologist.

Patients are excluded from the trial, if they:

1. have AVH with a clear organic cause (eg, brain disease or injury);
2. have exclusively hypnagogic or hypnopompic AVH;
3. have a diagnosis of acute substance dependence (F1x.2).
4. have received CBT for psychotic symptoms during the past year within which distressing AVHs have been targeted;
5. are currently participating, or be confirmed to participate in another interventional study in which they are receiving an intervention which uses psychological therapy;
6. are non-German speaking to the degree that they are unable to fully understand and answer assessment questions or give informed consent;
7. are at immediate and serious risk to self or other

### Who will take informed consent?

Once a formal referral has been received by the research team, the potential participant will be contacted to discuss the study further and arrange a consent and eligibility meeting with a member of the research team. The potential participant will have a copy of the patient information sheet at least 24 hours before the consent and eligibility meeting takes place, so they will have time to read the information, discuss it with friends and family, and formulate any questions they may have.

### Interventions

#### Explanation for the choice of comparators

A two-arm RCT was chosen to enable: (1) any effect of RT to be differentiated from TAU; and (2) to test whether adding an RT module to the treatment of patients with psychosis and distressing AVHs is superior to TAU alone in reducing AVH-related distress.

## Intervention description

### Relating Therapy

RT for AVH is a symptom-specific behaviourally oriented intervention that targets interpersonal relating as a key mechanism associated with AVH distress.<sup>29</sup> The aim is that patients learn to relate more assertively within the difficult relationships they have with both the AVH and other people. The RT module will follow a treatment manual consisting of three phases:

**Phase 1:** Socialisation to RT and its implications for the inter-relating between the hearer and AVH. Guided discussions will explore relationships in terms of power and proximity, with reference to participant's experiences of relating to other people and AVH. Typical ways of responding to negative relating (giving in, fighting back and trying to escape) are considered and the possibility of relating differently to AVH is introduced.

**Phase 2:** Exploration of themes within the relational history of the participant and their experience of relationships with AVH, and interpersonal relating within the family and social environment (identifying any prominent themes, such as abuse, disempowerment or rivalry). Connections are developed across all forms of relating, generating a formulation that links past and present forms of relating.

**Phase 3:** Exploration and development of assertive approaches to relating to AVH and other people. A difficult relationship is chosen to be the initial focus of intervention and a specific conversation is explored with respect to the participant's response (identifying responses as passive or aggressive). Assertive responses are generated as an alternative and experiential role-plays are used extensively to practice relating in an assertive manner (including the taking of different roles and perspectives within the role-plays). Different relationships can be explored in response to need and between-session experiences.

Following the procedure in the pilot trial,<sup>29</sup> the treatment will take place in individual 50-minute sessions, weekly, within a maximum of 16 sessions over a 20-week period. This compares with the current National Institute for Health and Care Excellence<sup>20</sup> guideline recommendation to offer a minimum of 16 sessions of CBTp, and is supported by a process analysis of dose×outcome in CBTp within the German healthcare setting that found significant reduction of symptom-related distress to occur by session 15 and to remain stable thereafter.<sup>33</sup> Therapists will be clinical psychologists or psychiatrists enrolled in or with completed clinical training, trained and supervised by Dr. Hayward (MH).

Participants in the RT condition will continue to receive their usual treatment throughout their participation in the study.

### Treatment as usual

TAU will include medication management, supportive brief counselling sessions and various types of psychosocial support (eg, social work guided support, peer

support) and monitoring provided by mental health services, with individual and family psychological therapies offered occasionally. In recognition of the likelihood of TAU being heterogeneous across centres, the type and extent of any treatment received will be protocolled at 5 months (T1) and T2. TAU will be rated in terms of hours of therapist time spent with patient. Within a future definitive RCT, this will allow us to: (1) standardise TAU by providing all referrers with a manual for standard treatment which summarises good practice; and (2) factor the variation into the design and data analysis plan.

### Strategies to improve adherence to interventions

Therapeutic drift and contamination will be minimised by the use of highly detailed therapy protocols, intensive training of therapists and close supervision based on systematic adherence checks of the trial therapists. In addition, prior to the trial recruitment, therapists were encouraged to deliver RT to pilot cases. MH supervised these cases throughout the therapist training and invited the therapists to provide feedback on the acceptability of delivering RT from a practitioner's perspective. Feedback was generally indicative of high acceptance on the therapists' side. Emerging questions regarding RT techniques or special cases were resolved by discussion with MH. All therapy sessions will be audio-recorded (with the participant's permission) and two recordings per participant will be randomly drawn by the trial manager for subsequent adherence checks. Adherence of trial therapists' delivery of RT will be assessed by MH using an adapted version of the Cognitive Therapy Scale for Psychosis (CTS-psy).<sup>34</sup> Items F, G and H have been changed to reflect RT (eg, 'focus on the link between cognition and affect' was replaced with 'focus on the effects of the patient engaging in different patterns of relating'). The full CTS-psy with the adapted items can be found in the online supplemental file 1 of this article.

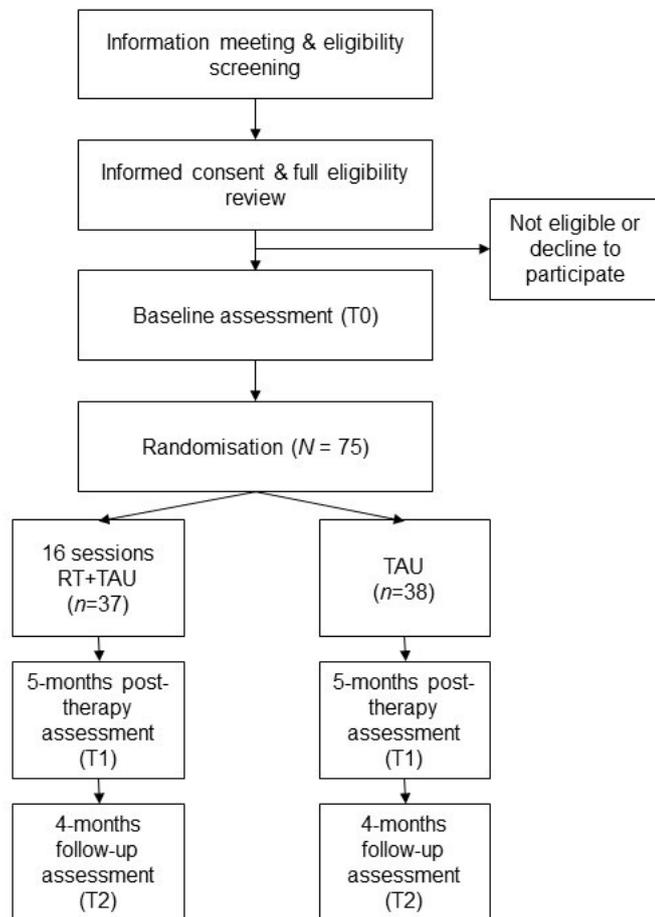
## Outcomes

### Primary outcome

The change in AVH distress is the primary outcome as distress has been prioritised by patients<sup>35</sup> and is relevant to functioning.<sup>11 12</sup> The change in the distress factor score of the PSYRATS-AVH<sup>30 31</sup> from baseline assessment (T0) to the follow-up assessment (T2) will be evaluated as candidate for the primary outcome to be used in a future definitive RCT.

### Secondary outcomes

Secondary outcomes will evaluate: (1) the change from baseline to T2 in time spent in social and goal-directed activities measured with the Time Budget Measure<sup>36</sup> (2) in health-related quality of life measured with the EuroQol Quality of Life Scale (EQ-5D-5L),<sup>37</sup> in negative relating to voices and social others measured with the Voice and You questionnaire (VAY)<sup>24</sup> and APPROVE questionnaires,<sup>38</sup> depressive symptoms (Patient



**Figure 1** Illustration of the participant flow through the study. RT, Relating Therapy; TAU, treatment as usual.

Health Questionnaire-9),<sup>39</sup> AVH frequency (PSYRATS-Frequency)<sup>30 31</sup> and the number of rehospitalisations as well as all outcomes at T1.

### Feasibility outcomes

The assessment of feasibility will include the calculation of: number of patients referred within each site, number of self-referrals within each site, number of referred patients within each site found to be eligible, number and proportion of consenting and eligible participants who attend 5-month (T1) and 9-month (T2) assessments within each site, number and proportion of consenting participants within the RT condition who reach the point of therapy ‘exposure’ (attended at least 8 of 16 therapy sessions), completeness of data collected, therapist adherence to therapy protocols and supervision protocols, and the number of adverse (AEs) and serious adverse events (SAEs).

### Participant timeline

Participant flow through the study is depicted in [figure 1](#) and will be reported in line with the Consolidated Standards of Reporting Trials<sup>40</sup> 2010 statement—extension to randomised pilot and feasibility trials.<sup>41</sup>

### Sample size

The sample size calculation is based on the primary endpoint, the distress factor score of the PSYRATS-AVH<sup>30 31</sup> at T2 adjusted for the baseline value, in the ITT (intent-to-treat) population including all randomised patients. The aim is to show that the intervention group is superior to the control meaning that the mean score at T2 adjusted for baseline is lower in the intervention group than in the control group. Sample size calculation is based on a two-sample t-test. Since the two-sample t-test ignores the influence of different baseline values, the baseline-adjusted analysis of covariance (ANCOVA) model will yield to an increase of statistical power. This strategy for sample size calculation defines a conservative procedure.

Hayward *et al*<sup>29</sup> reported observed mean values of 15.7 and 16.7 at baseline and values of 11.3 and 15.8 at 5-month follow-up for intervention and control, respectively, resulting in an estimated treatment effect of 15.7–11.3–(16.7–15.8)=3.5. For the purpose of this feasibility study, we assume that the treatment effect will be slightly larger at 4.0, which was confirmed as meaningful by people with lived experience. The reported SDs in Hayward *et al*<sup>29</sup> at 5-month follow-up were 5.7 for intervention and 4.9 for control, respectively. We therefore conservatively assume an SD of 7.0 resulting in a standardised treatment effect of  $4 / (5 \times \sqrt{2}) = 0.57$ . The required sample size to find a significant effect with a power of 0.7 at a two-sided significance level of 0.1 is given by 60 patients (30 per treatment arm) calculated with the software ADDPLAN, V.6.1. To account for approximately 20% drop-out (as motivated by the pilot study<sup>29</sup> and the COMMAND trial),<sup>22</sup> the total number of patients to be recruited is 75 ( $60 / 0.80$ ).

### Recruitment

Participants will be recruited through referrals from:

1. clinical practitioners (social workers, psychologists, nursing staff, doctors) with contact to patients with psychosis in the host cities (and sites).
2. clinical psychologists and psychiatrists in private practice.
3. practitioners in outpatient and inpatients settings (psychiatric clinics, outpatient counselling services) who will be provided with information about the study before the start of the recruiting period.

### Assignment of interventions: allocation sequence generation and concealment mechanism

Participants will be randomly allocated using the sealed envelope online service ‘simple+’ randomisation by <https://www.sealedenvelope.com/>.

The clinical trials unit statistician will set up and test the randomisation procedure using random block lengths. Participants will be randomly allocated based on a 1:1 allocation to receive either the study intervention and TAU (RT+TAU) or TAU. Treatment allocation will be stratified by site.

Following the set-up of the randomisation procedure, automated allocation will be performed remotely via a

website by the on-site contact as soon as inclusion criteria have been verified. The full list of participants (anonymous participant codes) and allocated treatment will be saved at <https://www.sealedenvelope.com/> for the duration of the trial. Direct access to the randomisation protocol and full participant randomisation list is limited to the trials unit statistician.

### Implementation

Trial therapists will be notified by the trial manager about the participants' allocation and will be asked to arrange a first appointment, if possible, within 1 week following the randomisation. A letter will be sent to all participants to confirm their allocation and details of their next appointment with the trial.

### Assignment of interventions: blinding

#### Who will be blinded?

Members of the research team and raters will not need to be blinded while collecting eligibility and baseline data as participants will be randomised after baseline data have been collected. Following the eligibility and baseline assessment, participants will be allocated to a group and raters will be blinded to the allocation and will remain blinded for all future assessments with the participants (5-month and 9-month assessments). The participant's therapist will be notified of the participant's group allocation and asked to not discuss this allocation with site raters. Participants will be reminded at the beginning of each assessment interview to not disclose the group to which they have been allocated. Raters will be shielded from discussion of participants in forums where the possibility of determining the allocation group of the participant could occur. The trial manager will manage an electronic system to ensure that raters will not access information in the database that would reveal the allocation group.

To further minimise the risks of unblinding, every attempt will be made to recruit the raters from within different settings so that they do not share offices and/or attend the same meetings as therapists, where unblinding may occur. If raters are from the same clinical setting as therapists, consideration will be given to office allocation of blinded versus unblinded members of the research team, and the research team must be conscientious when making phone calls to participants. 'Blinding' awareness and education will be promoted throughout the study, communicating to administrative staff and referrers the importance of the raters remaining blinded to minimise the occurrence of accidental blind breaks.

The blind assessor will be asked to record any breaks of blinding, even if the break is equivocal. In any of these cases, the assessor will be asked to guess the allocation group for the respective participant.

Reported breaks in blinding of raters will follow a standard operating procedure to maintain blind outcome assessments by reallocating 'blind' raters to collect and score study data, therefore not biasing results.

### Procedure for unblinding if needed

Reported breaks in blinding will be recorded. The audio files of the outcome assessments will be used for a second rating by another 'blind' rater.

As the therapists will be unblinded, no emergency unblinding procedures are required for this study.

### Data collection

#### Trial procedures and evaluations

See [table 1](#) for details of the assessment schedule.

### Description of instruments

#### Screening and eligibility measures

The assessment of eligibility in relation to the inclusion and exclusion criteria will be supported by the use of the Structured Clinical Interview for DSM-5,<sup>42</sup> the distress factor of PSYRATS-AVH<sup>30 31</sup> and the Columbia Suicide Severity Rating Scale.<sup>43</sup>

#### Clinical measures—primary

PSYRATS-AVH distress factor score.<sup>30</sup> The PSYRATS-AVH is a reliable and valid<sup>44</sup> 11-item rating scale designed to measure the severity of different dimensions of the voice hearing experience. Items are grouped together in four factors<sup>45</sup>: distress (five items on negative content, distress and control); frequency (two items: frequency, duration and disruption); attribution (two items: location and origin of voices); and loudness (loudness item only). The 'distress' subscale measures the impact that voices have on the individual.

#### Clinical measures—secondary

The Time Budget Measure<sup>36</sup> will be used as a highly individualised record of activity of the week. The measure consists of a week-long diary of activity, in four time periods for each day completed retrospectively during a structured interview with participants. Interviewers probe for activities, degree of independence in activities, and number or nature of social contacts. Each activity period is rated according to complexity and effort. The measure has demonstrated good inter-rater reliability and validity.

The EQ-5D-5L<sup>37</sup> will be used to assess health-related quality of life. The EQ-5D-5L<sup>37</sup> is a descriptive system and visual analogue scale with the endpoints labelled 'best imaginable health state' and 'worst imaginable health state'. The descriptive system comprises the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is used for estimating preference weight for that health status. By combining the weight with time, quality-adjusted life years (QALYs) can be computed. QALYs gained will then be used as an outcome in an additional cost-utility analysis in the subsequent full clinical trial. EQ-5D-5L<sup>37</sup> is one of the most commonly used generic health status measurements, and its good validity and reliability have been reported in various health conditions.

Negative relating between hearer and AVH will be assessed with the brief version of the VAY,<sup>24</sup> a 14-item measure of inter-relating between the hearer and their

**Table 1** Assessment schedule

	Eligibility screening	T0 baseline	T1	T2
Measure				
Eligibility assessments				
SCID-5-CV <sup>48</sup> affective disorders, psychotic disorders and substance section	x			
Sociodemographic questionnaire and clinical information (20 min)	x			
Distress factor of AVH subscale of PSYRATS <sup>30 31</sup> (5 items, 5 min)	x	x	x	x
C-SSRS <sup>43</sup> (10 items, 10 min)	x			
Functioning: Time Budget Measure <sup>36</sup> (20 min)		x	x	x
Quality of life: EQ-5D-5L <sup>37</sup> (self-report, 5 min)		x	x	x
PSYRATS-AVH <sup>30 31</sup> (6 items <sup>a</sup> , 6 min)		x	x	x
Depression: PHQ-9 <sup>39</sup> (self-report, 9 min)		x	x	x
Brief version of VAY <sup>24</sup> (self-report, 14 items) (5 min)		x	x	x
APPROVE <sup>38</sup> (self-report, 2×15 items) (10 min)		x	x	x
Post-therapy and follow-up interview standardised protocol to assess TAU interventions and rehospitalisation (20 min)			x	x
Cognitive Therapy Scale <sup>34</sup> —revised				Continuous monitoring and assessment
Adverse events (AEs); serious AEs; changes in medication				Continuous monitoring and assessment

AVH, auditory verbal hallucination; C-SSRS, Columbia Suicide Severity Rating Scale; EQ-5D-5L, EuroQol Quality of Life Scale; PHQ-9, Patient Health Questionnaire; PSYRATS, Psychotic Symptoms Rating Scale; PSYRATS-AVH, Psychotic Symptoms Rating Scale - Auditory Verbal Hallucinations subscale; SCID-5-CV, Structured Clinical Interview for DSM 5 - Clinician Version; TAU, treatment as usual; VAY, Voice and You questionnaire.

predominant AVH. Relating is measured across four scales: two concerning the hearer's perception of AVH dominance and AVH intrusiveness, and two concerning hearer distance and hearer dependence. The VAY<sup>24</sup> has good internal consistency and acceptable test-retest reliability. Sufficient fit for the brief 14-item version has been found in an English sample. The psychometric properties of the German version are currently being tested by the group of the coordinating investigator in collaboration with the authors of the original scale.

The APPROVE questionnaires<sup>38</sup> will be used to assess dysfunctional as well as functional relating. The APPROVE questionnaires<sup>38</sup> include two parallel 15-item versions to assess relating to AVH and to other people in difficult situations. Within each version, two subscales assess the putatively dysfunctional relating styles of passive relating and aggressive relating, whereas a third subscale assesses functional assertive relating. The APPROVE questionnaires<sup>38</sup> have been developed as a diagnostic tool for RT in a collaboration project by the group of the therapist supervisor and the group of the coordinating investigator. They have been found to be reliable and valid in both their English and German versions, with the German validation study currently in preparation for publication.

#### Additional assessments

A structured post-therapy and follow-up interview will also assess the types of intervention a participant has received in the period of interest (eg, during the intervention period, during the follow-up period) and time spent with a therapist in hours. It will also include an assessment of

frequency and duration of rehospitalisation (which is a secondary outcome). Furthermore, it will assess major events during the intervention and follow-up periods using the questions included in the Netherlands Mental Health Survey and Incidence Study.<sup>46</sup> Finally, it will assess any changes in medication during the intervention/TAU or follow-up periods.

Sociodemographic questionnaire and clinical information: this instrument includes sociodemographic questions, such as age, gender, living situation and marital status, as well as questions about the medical-psychiatric history of the participants.

#### Plans to promote participant retention and complete follow-up

Efforts will be made to engage all participants in follow-up assessments. Research assistants will support the raters to flexibly engage patients, offering appointments at times and locations which best suit the participants' schedule and offering shorter and split assessment sessions as needed. Participants will be offered reimbursement of €12 per hour of assessment and travel expenses will be made available. Retention rates will be monitored by the trial manager at least weekly and by the research team on a monthly basis throughout the trial.

#### Data management

The trial manager will manage the day-to-day data collection; the clinical trials unit statistician will have oversight of the process and provide guidance. All data will be collected by trained trial raters (or other appropriate

members of the research team) who will be supervised by the trial manager and the leads of the respective sites.

All of those involved in the collection and management of data will be given training on how to use and administer the clinical and health economic measures used in this study. A 5-hour training will be delivered by the trial manager and will include regular monitoring and supervision of the raters.

All members of the research team and any other individuals from collaborating sites involved in collecting, inputting, processing, using and sharing data have received information governance training. The management of the data will be a standing item on the agenda of the weekly meeting of the research team.

The feasibility data analysis will be carried out by the clinical trials unit statistician and quality checked by the trial statistician.

The quantitative data analysis of the clinical outcomes will be carried out by the trial statistician and quality checked by the clinical trials unit statistician.

### Confidentiality

All of the data collected within the research study will be kept confidential and identifiable information will not be released outside of the research team. Confidentiality will only be broken if participants disclose any information that would put themselves or another person at risk. The minimum amount of personal information needed to conduct the study will be obtained from participants. Personal and research data will be stored securely on study site premises. Physical data, such as consent forms, will be locked in filing cabinets on the study site's premises accessible only to members of the research team. Electronic data will be stored securely in password-protected or encrypted files on a computer accessible only to members of the research team at Universität Hamburg. All research data will be fully anonymised and will be stored separately to personal data. A link file will allow for participant research data to be identified. This link file will be a password-protected file accessible only by the chief investigator (CI) and the trial manager. This file will be securely destroyed following the end of the study. Quantitative and qualitative data will be appropriately aggregated in any publications arising from the trial to protect participant anonymity during and after the trial has ended.

### Statistical methods

#### Statistical methods for primary and secondary outcomes

All clinical outcomes will be summarised using descriptive statistics at pre-randomisation (T0), at 5 months (T1) and at 9 months (T2) for each arm (RT+TAU, TAU) of the study.

Confirmatory analysis will be conducted based on the ITT population, defined on the basis of the ITT principle. The aim is to show that the intervention group is superior to the control meaning that the mean score at 9 months (T2) adjusted for the baseline value (T0) is lower in the

intervention group (I) than in the control group (C). Let  $\mu$  denote the unknown true mean score values. Then the corresponding two-sided test hypotheses are formulated as follows:

$$H0: \mu_{36W, I} = \mu_{36W, C} \text{ vs } H1: \mu_{36W, I} \neq \mu_{36W, C}$$

An ANCOVA adjusted for baseline score values using group allocation and study centre as factors will be applied. The global two-sided significance level is 0.1. Missing values will be replaced using multiple imputation.<sup>4</sup>

### Secondary analyses

A sensitivity analysis to the primary efficacy ANCOVA model will be applied with additional covariates/factors given by age, gender and diagnosis. Descriptive methods will be used for the analysis of the secondary outcomes, including the calculation of appropriate summary measures of the empirical distribution as well as 90% CIs and calculation of descriptive two-sided p values. The safety analysis includes calculation of frequencies and rates of AEs and SAEs. Additionally, sensitivity analyses will be conducted for different populations (per-protocol population, patients with complete cases). Furthermore, statistical methods are used to assess the quality of data. All analyses will be conducted using validated statistical software.

Further details will be provided in a statistical analysis plan, which will be developed by the Institute of Biometry and Clinical Epidemiology, Charité Universitätsmedizin Berlin (director: Professor Dr Geraldine Rauch) who will be responsible for the data analysis.

## OVERSIGHT AND MONITORING

### Composition of the Trial Steering Committee

Medical Research Council Guidelines for Management of Global Health Trials<sup>47</sup> informed the constitution of the Trial Steering Committee (TSC), which includes an independent chair, independent experts, lay members and a person with lived experience, who will provide patient and public involvement oversight of the trial.

The scientific integrity including oversight of the safety and data integrity of the trial will be overseen by the TSC. During the study, the TSC will be asked to consider data on SAE and AE, discuss the interim safety analyses, and advise the research team on issues related to recruiting and on whether to continue, modify or stop the trial for reasons related to safety. Ethical considerations have been reviewed and approved by the ethics committee of the German Psychological Association and by the ethics committee of the Medical Board Hamburg.

### AE reporting and harms

Any unfavourable and unintended sign, symptom or illness that develops or worsens during the period of the study will be classified as an AE, whether or not it is considered to be related to the study treatment. AEs will include: an exacerbation of a pre-existing illness,

an increase in the frequency or intensity of a pre-existing episodic event or condition; a condition that is detected after trial intervention administration; and continuous persistent illness or a symptom present at baseline that worsens following administration of the trial treatment—and may be expected or unexpected. SAEs are those considered to be life-threatening, resulting in death, requiring inpatient hospitalisation or prolongation of existing hospitalisation, resulting in significant or persistent incapacity/disability or a birth defect or congenital abnormality.

AEs must be recorded by the trial team member notified of the AE in conjunction with the respective site lead, who will check the AE form at the earliest opportunity and inform the trial manager within 1 working day.

The trial manager will review the AE and disseminate to the CI within 72 hours of being informed to assess causality.

In any case of a SAE, the trial manager must be notified within 1 working day by a member of the trial team becoming aware of the event. The trial manager must notify the CI within 1 working day after becoming aware of the event. The CI (or a clinically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the site lead and the CI, both opinions and any justifications will be provided in subsequent reports. The CI will keep investigators informed of any safety issues that arise during the course of the trial. The CI is responsible for reporting fatal and life-threatening serious adverse reactions to the competent authorities within 7 days of the CI becoming aware of the event. The TSC will be informed of serious adverse reactions periodically.

### Data sharing

Data sharing will follow the guidelines set up by the German Research Foundation and taking into consideration the recommendations set up by the German Psychological Association (DGPs) in 2016 ([https://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/empfehlungen\\_forschungsdaten\\_psychologie.pdf](https://www.dfg.de/download/pdf/foerderung/antragstellung/forschungsdaten/empfehlungen_forschungsdaten_psychologie.pdf)). Only anonymised data will be shared outside of the research team. A data sharing agreement will be set up with individuals who are outside of the research team and who request to use the study data. It will be ensured that access to the data is still guaranteed when, through publication, the rights of use relating to research data are transferred to a third party.

The CI can give approval for data sharing requests. The possibility of data sharing will be made explicit to participants on the study consent form.

### DISCUSSION

Evidence for the effectiveness of available treatment options specifically for distressing voices in the context of psychosis is limited. RT is a promising and newly developed psychological therapy that has been developed from

the literature and explores the experience of hearing voices within interpersonal frameworks. RT aims to rebalance the hearer–voice relationship and other difficult relationships through the development of assertive responding and has been found to be safe, acceptable, and intuitively appealing to therapists and hearers within an initial pilot trial. This larger multicentre pilot RCT will generate a refined study protocol, an indication of recruitment and retention rates, and an estimate of the effect size, in order to inform the sample size calculation for a future definitive RCT within the German healthcare system. If evidence from a definitive RCT suggests that RT is effective, this will extend the range of evidence-based psychological therapies available to patients with psychosis who hear distressing voices.

### TRIAL STATUS

Recruitment to the trial commenced in October 2020 (study protocol—V.1.2, dated 24 September 2020) and is planned to finish in June 2022. Data collection is planned to continue until March 2023.

### ETHICS AND DISSEMINATION

The study received ethical approval by the ethics committee of the German Psychological Society (reference number: LincolnTania2020-03-19VADM). Participants will provide written informed consent prior to the completion of any study procedures. The sponsor played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Trial findings will be disseminated in open-access publication in high-impact scientific publications, including feasibility outcomes. Findings will be disseminated to participants' and patient organisations. Research team members will participate in dissemination including use of social media to disseminate findings, producing leaflets for wide distribution and submitting a summary of findings to a non-academic journal. Findings will be presented at patient events and at local, national and international conferences.

**Twitter** Mark Hayward @sussexvoices

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**Contributors** TML is the CI of the study and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MP and TML took responsibility for the main drafting of the manuscript. All authors made substantial contributions to conception and design. BS and MH have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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**Competing interests** There is a potential conflict of interest for one member of the research team. MH is an author on a self-help book on distressing voices that informs the RT approach. Therefore, the research team commits themselves to publishing the results of this feasibility trial irrespective of the findings.

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