Protocol title page

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

Full title:	MUSE ARMS Feasibility RCT: A feasibility trial employing a prospective randomised, open-label, observer blinded, endpoint design assessing a targeted, computer/web based guided self-help psycho-education toolkit for distressing hallucinations (MUSE) +treatment as usual (TAU) compared to a time matched TAU, offered by a multi-disciplinary team which includes emotional support, psychoeducation and stress management, aiming to reduce distress from hallucinations and improve functioning, in people with an At Risk Mental State (ARMS) for psychosis in UK secondary care mental health services.
Short title:	MUSE-ARMS Feasibility Trial
Protocol version:	Version 5
Chief investigator:	Dr Guy Dodgson
Sponsor:	Cumbria, Northumberland, Tyne & Wear NHS Foundation Trust

Research reference numbers

IRAS Number: 323903

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Sponsors Number: RES-22-038

Funders Number: NIHR204125

Protocol signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research and NIHR GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

For and on behalf of the Trial Sponsor:
Signature:

Date: 01/02/2024
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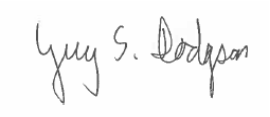
Position: Deputy Research & Development Manager

Chief Investigator:

Signature: .....  .....

Date: .05.../..02./.2024
Name: (please print):
.....Guy Stephen Dodgson.....

Principal Investigator for the research site:_____; I confirm receipt of this protocol and agree to work to this current version of the protocol in accordance with GCP and the UK Policy Framework for Health and Social Care Research.

Principal Investigator:
Signature: .....
Date: ...../...../.....
Name: (please print):
.....

Protocol amendments

Reference	Changes
NSA 01 13.03.2023	Incorrect submission redacted
Substantial Amendment 01 14.03.2023	Removed 'random permuted blocks method' from randomisation as this clashes with the minimisation method. Removed the Sine-Vocoded Speech computerised cognitive task and replaced it with the Jumbled Speech Task. Removed the Positive and Negative Affect Schedule questionnaire and replaced it with State-Trait Anxiety Inventory – Short Form. Inclusion of Verbal Consent forms to overcome literacy barriers. Inclusion of Therapist packs for data collection on content and adherence. Other wording changes to help clarify processes and correct typographical errors. Provision of missing measures already noted in protocol, and provide non-participant facing case report forms. Protocol version change to v2.0 12.03.2023
Substantial Amendment 02 03.04.2023	Removed the Dissociative Experiences Scale (II), and replaced it with the Severity of Dissociative Symptoms (Brief Dissociative Experiences Scale [DES-B]—Modified) Adult and Child versions.
NSA 02 03.04.2023	Minor changes to sociodemographic background questions to remove weekly income, add in a question to ascertain if the participant is still at school, add in a question to ask if the participant is estranged (cut off) from their family in the living situation items, and break down homeless but not roofless from homeless and roofless. Minor change to participant information sheets to allow NHS sites to use their preferred method of giving participant payment, e.g. Bank Transfer, Cash or Vouchers
NSA 03 28.04.2023	Minor changes to CAARMS-PA to remove collection of onset/offset date as this is not used in the trial. Minor changes to Withdrawal form. Correction of typographical errors.
NSA 04 17.07.2023	Change to protocol to reduce number of Cognitive Tasks during assessment visits to one task per subtype. Widening of scope of Verbal ICFs to also be used to take remote consent. Amendment to Topic Guide following piloting. Minor typographical amendments to PIS and Protocol (including removal of out-of-date URL links and update the description of the dissociative experiences scale used as per SA02).

	Protocol version change to v3.0 15.06.2023
NSA 05 26.09.2023	An additional page of Topic Guide inclusivity questions (Qualitative Interview: Additional trial inclusivity questions v1.0 25.09.2023) are added to ask: (i) What was your experience of coming into the ARMS service (where you were invited into this trial?) (ii) Do you think there were any cultural influences or factors related to your background or diversity that made it more difficult (or easier) to get help? (iii) Did you withdraw from any aspect of the trial (from therapy / the trial assessments), or leave the service for any reason? (if yes) Can you tell me about what happened and what this was like for you?. With related prompts for the interview.
Substantial Amendment 03 25.10.2023	(1) In our second Qualitative interview the participant wanted support from their family member. Their family member added to the qualitative discussion, which could influence the research. This had not been anticipated and yet it is likely it will happen again. We discussed with REC what is the best way to manage this, and were advised that if supporters influence the research then they should give consent. We have therefore added participant procedures to give family or friends participant information and take their informed consent if both parties wish for them to join the interview. The protocol has been updated to reflect this change Protocol v4.0 16.10.2023). (2) Further to this, there has been a minor change to add 'discharge information' to data collection at week 20 timepoint for any participants who have been discharged and the reason for this. (3) Finally we would like to give participants a study update with a newsletter following their participation, as well as at the study close. We believe the existing consent will cover this, which states, 'OPTIONAL: I would like to be contacted with end of study information on the trial', however, we have updated protocol wording to reflect and included an example of the newsletter, wording, which can be updated periodically, to send to participants completing in the next few months.
NSA 06 03.11.2023	We have amended the non-participant facing CRF document, 'Clinical Scales Assessment Totals Sheet MUSE ARMS v2.0 311023' in order for the MUSE Therapists to provide additional information on Subtypes. Changes are shown on page 2 and ask MUSE therapists to comment on: Were any of the other subtypes present? / Can you comment on the order that the subtypes emerged? / Any other comments, for example hallucinations in other modalities such as felt presence?

NSA 07 18.12.2023	Recruitment end date extended from 31.01.2024 to 23.02.2024
[Insert detail following Sponsor reference number]	The Service use: Discharge prior to end of trial CRF has been amended to capture completion of therapy data by the end of the trial at sites. This is in cases of CBT or other therapy lasting beyond the 20week assessment point. Data will be gathered from medical records and/or communication with therapists. The protocol has been updated to reflect this change Protocol v5.0 15.12.2023).

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ii. List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ARMS	At Risk Mental State (for Psychosis)
APR	Annual Progress Report
AVH	Auditory Verbal Hallucination
CI	Chief Investigator
CBT	Cognitive Behavioural Therapy
CBTp	Cognitive Behavioural Therapy for psychosis
CNTW	Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
DMC	Data Monitoring Committee
DPA	Data Protection Act 2018
EDI	Equality, Diversity and Inclusion
EIP	Early Intervention in Psychosis
ETCs	Excess Treatment Costs
EME	Efficacy and Mechanism Evaluation Funding Programme
FEP	First Episode of Psychosis
FT	Foundation Trust
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ICHOM	International Consortium for Health Outcomes Research
ISRCTN	International Standard Randomised Controlled Trials Number
LEAP	Lived Experience Advisory Panel
MUSE	Managing Unusual Sensory Experiences toolkit
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
RCT	Randomised Control Trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit Funding Programme
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment As Usual
TMF	Trial Master File
TMG	Trial Management Group

TSC Trial Steering Committee

iii. Trial Summary

Trial Title	MUSE ARMS Feasibility RCT: A feasibility trial employing a prospective randomised, open-label, observer blinded, endpoint design assessing a targeted, computer/web based guided self-help psycho-education toolkit for distressing hallucinations (MUSE) +treatment as usual (TAU) compared to a time matched TAU, which includes emotional support, psychoeducation and stress management, for managing hallucinations, improving functioning and reducing distress in people with an At Risk Mental State (ARMS) for psychosis in UK secondary care mental health services.	
Internal ref. no. (or short title)	MUSE ARMS Feasibility Trial	
Phase	Trial feasibility and mechanisms investigation	
Trial Design	A mixed-method feasibility trial employing a prospective, randomised, open-label, observer blinded endpoint design with MUSE+TAU compared to time matched TAU, with assessments at pre- and post-treatment and at five-month follow-up.	
Trial Participants	Patients aged 14-35 years with an At Risk Mental State (ARMS) for developing psychosis	
Planned Sample Size	88 participants recruited from At Risk Mental State NHS services and NHS Early Intervention in Psychosis serving ARMS patients in the UK	
Treatment duration	6-8 sessions (6 core sessions with an option of 2 extra)	
Follow up duration	20 weeks	
Planned Trial Period	1st January 2023 – 31st September 2024	
	Objectives	Outcome Measures
Primary	To conduct a randomised controlled feasibility trial to address key uncertainties of delivering MUSE in an ARMS population and identify preliminary effect of MUSE+TAU verses time matched TAU on	(i) Feasibility outcomes, including qualitative interviews (ii) Functioning (SOFAS) (iii) Hallucinations (PSYRATS hallucination total)

	general functioning and mental state in ARMS patients	(iv) Hallucinations target problem (PSYRATS distress & PSYRATS attribution) Post-treatment endpoint as primary endpoint
Secondary	1) to explore indicators of mental health treatment outcomes (and moderators) 2) to test the feasibility of investigating which psychological mechanisms are influenced by MUSE and contribute to its clinical effect 3) to collect routine data to enable later studies to examine which features of MUSE are most relevant to the prevention of development of psychosis	1) CAARMS-PA Subscale, GAD-7, PHQ-9, ReQoL-20, MMHS, ISI, ITQ/ITQ-CA 2) Self-report validated questionnaires and computerised cognitive tasks pertaining to participant experience subtype: Inner speech/Memory/ Hypervigilance/Visual 3) Clinical records documentation Qualitative interviews will also be undertaken with participants post-treatment to explore feasibility issues and understand subtypes/mechanisms
Novel Intervention	Managing Unusual Sensory Experiences (MUSE): A novel computer based guided self-help toolkit incorporating 8 modules for understanding and coping with hallucinations.	
Comparison Intervention	Treatment as usual: Primarily focusing on needs based emotional support, psychoeducation, normalisation, stress management and other multi-disciplinary support.	
Funding	This trial is funded by an NHS National Institute for Health Research (NIHR) Research for Patient Benefit scheme grant, NIHR 204125	

iv. Funding and support in kind

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
NIHR Research for Patient Benefit (RfPB)	Financial - Funding is provided to cover the research trial salary costs for the applicants and research staff. A small payment of £15 per assessment is provided to the participants as an acknowledgement of their time, and travel expenses are also covered.
NIHR CRN	Financial - Excess treatment costs are provided by the CRN to NHS research sites. The CRN also fund research delivery staff at NHS sites, who support research delivery. Non-financial - Research costing support is provided by the CRN.
CNTW	Non-financial - Research development support is provided by CNTW
CNTW and Durham University	Non-financial - Permission to use the MUSE toolkit in this trial, which is the shared intellectual property of these organisations
Wellcome Trust	Financial – Funding for publication Open Access is provided [180720/Z/15/Z]. Prior funding for the earlier development of the MUSE package also as part of the Hearing the Voice programme of work

v. Role of trial sponsor and funder

This research trial is sponsored by Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust. The Sponsor has oversight and responsibility for the conduct of the research. The Sponsor gives final approval to each trial process and all documentation prior to submission for research approvals.

The Sponsor will be responsible for sub-contracting to all other participating Trusts and HEIs. The Sponsor will be responsible for auditing the research trial for conduct in accordance with its ethically approved protocol and documentation and conduct in accordance with GCP and the UK Policy Framework for Health and Social Care Research.

This research is funded by NIHR through the Research for Patient Benefit programme (Funding ID NIHR 204125), and with additional NIHR resource support via the NIHR Clinical Research Network (CRN). The Funder reviewed and approved the content of the protocol, but does not have a role in data collection, management, analysis, or interpretation; nor in the writing of the final report or decision to submit the report.

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

vi. Roles and responsibilities of trial management committees /groups & individuals

The CI (Dodgson) will have overall responsibility for the project under the joint-applicant (Fernyhough)'s mentorship. The site PIs will be responsible for running the sites, under the CI's supervision. A Trial Coordinator, supervised by the CI, will oversee the running of the study and study teams.

Trial management group

The TMG will meet monthly. Its membership will include the Investigators, Trial Coordinator and site leads. It will be chaired by the CI and will manage the day-to-day running of the study. It will ensure good communication between trial sites, receiving monthly reports from each site on recruitment, therapy completion, adverse events, reviewing progress against milestones and finding solutions to problems as they arise. It will oversee the preparation of reports to the TSC, the funder and the REC. The CI and the co-applicants are highly experienced in working clinically with people with psychosis, and in carrying out research studies in this population.

Trial steering committee

The TSC will comprise three independent members: a chairperson, and senior clinicians and researchers, along with the study CI, Trial Coordinator and two patient representatives to provide oversight of the study. The frequency of TSC meetings will be agreed by the chair and the CI. The TSC will monitor: (1) recruitment of study participants; (2) ethical issues of consent; (3) quality of data (including missing data and unblindings); (4) the incidence of

Serious Adverse Events and Adverse Events; (5) Urgent Safety Measures (6) participation in the trial to ensure the study is inclusive of underserved groups; (7) any other factors that might compromise the progress and satisfactory completion of the trial.

The TSC will make recommendations on whether there are any ethical or safety reasons why the trial should not continue, with the safety, rights and well-being of participants being paramount. It will consider the need for any interim analyses, including potential requests from the Funder, and will advise the TMG regarding the release of data and/or information.

The TSC will consider the progression of the feasibility trial into an efficacy and mechanism trial and any requisites for research design learnt from this stage of the research.

There will be no Data Monitoring Committee owing to the small scale of the study. These tasks will be managed by the TSC.

vii. Protocol contributors

This protocol has been developed with contributions from the following individuals and PPI group as reported using a Contributor Roles Taxonomy (CRediT) author statement:

Guy Dodgson: Conceptualisation, Methodology, Investigation, Writing-Original Draft, Writing-Review & Editing, Supervision, Funding acquisition, Resources, PPI.

Charles Fernyhough: Conceptualisation, Methodology, Writing-Original Draft, Writing-Review & Editing, Supervision, Funding acquisition.

Rob Dudley: Conceptualisation, Methodology, Writing-Original Draft, Resources, Funding acquisition.

Jahnese Hamilton: Conceptualisation, Methodology, Writing-Review & Editing, Resources, PPI.

Jochan Einbeck: Statistical Conceptualisation, Methodology, Writing-Original Draft, Writing-Review & Editing.

Ehsan Kharatikoopaei: Statistical Conceptualisation, Methodology, Writing-Original Draft, Writing-Review & Editing.

Bronia Arnott: Qualitative Conceptualisation, Methodology, Writing-Original Draft, Funding acquisition.

Toby Brandon: Qualitative Conceptualisation, Methodology.

Chris Gibbs: PPI, Methodology, Resources, Writing-Original Draft.

Charlotte Aynesworth: Conceptualisation, Methodology, Resources.

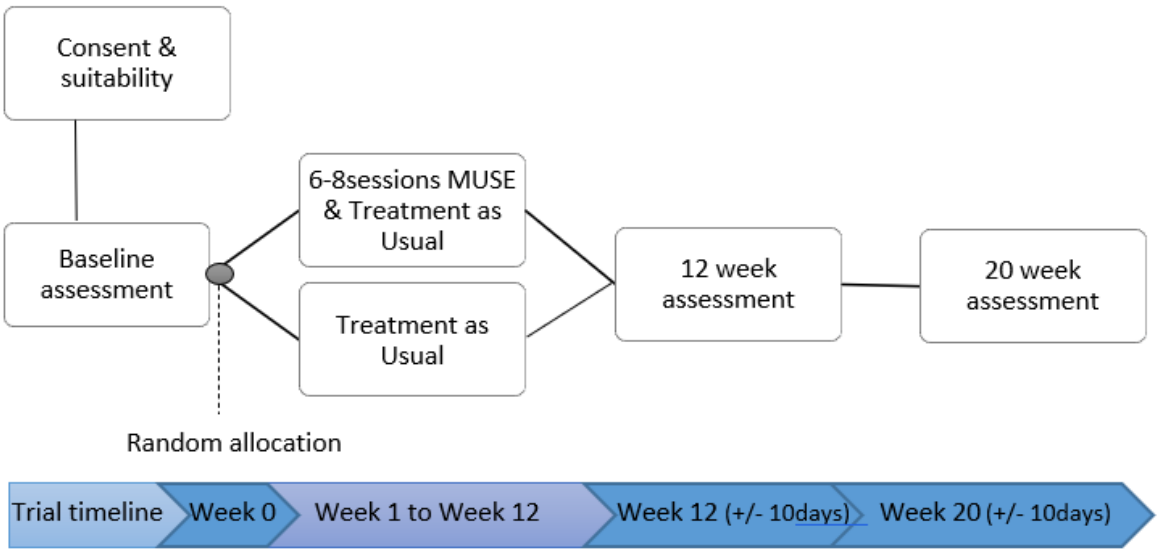
Stephanie Common: Conceptualisation, Funding acquisition.

Patients, service users, and carers involvement: Conceptualisation, Resources, Writing-Original Draft.

viii. Key words

Hallucinations; voices; visions; psychosis; At Risk Mental State; cognitive behavioural therapy/CBT, cognitive mechanisms; Managing unusual sensory experiences/MUSE

ix. Trial flow chart



1. Background

Psychotic disorders (such as schizophrenia) impose a huge public health burden, with hallucinations (hearing or seeing things that others do not) a significant and often highly distressing aspect of these disorders. Given the human costs of psychosis and the desirability of preventing its onset, therapeutic efforts have targeted groups considered at high risk, such as At Risk Mental State (ARMS) (Yung et al, 2021). Our novel psychological intervention, Managing Unusual Sensory Experiences (MUSE), uniquely focuses on the varied experience of hallucinations. In an accessible, intuitive digital format, MUSE provides information to patients about the psychological mechanisms underlying their experiences, along with coping techniques targeting these factors to reduce distress. Already proving its value in first-episode psychosis (FEP) (Dudley et al., 2022), our approach may be particularly impactful in treating unusual experiences in ARMS (when interpretations of unusual experiences are still highly changeable) thus reducing distress and potentially preventing transition to psychosis or other mental health conditions (Moritz et al., 2019). This work addresses Goal 1 of the recent shared goals for mental health research (Wykes et al., 2021) (namely to halve persistent mental health problems in children and young people). It could result in substantial benefits for patients and their families, the generation of new knowledge linking mechanism to hallucination phenomenology, reduction in pressure on services, and lessening of the societal cost of psychosis.

1.1 Why is this research important?

Unusual sensory experiences, such as hearing voices and seeing visions, are considered to occur on a continuum from benign, everyday experiences to more severe hallucinations that require treatment (Toh et al., 2022), often associated with psychotic disorders. 60–90% of individuals with schizophrenia experience auditory verbal hallucinations (AVH) (Bauer et al., 2011), and the significance of hallucinations in other modalities is increasingly also recognised (Fernyhough, 2019). Globally, schizophrenia contributes significantly to disease burden, disability and societal and health costs, including increased risk of early mortality and high suicide rates (Hjorthøj et al., 2017). In 2012, the total annual cost of schizophrenia to the public sector in England was estimated at over £7 billion (Andrew et al., 2012).

In comparison to FEP patients, who have already received a psychosis diagnosis and often have fixed delusional explanations for their hallucinations, ARMS patients present with complex and fluid interpretations of their experiences which lend themselves to alternative explanations (van der Gaag et al., 2019). ARMS is increasingly identified as a priority area for research and intervention (NICE, 2014), with active debate about how to refine the construct (Yung et al. 2021; Lång et al, 2021).

Current UK NICE (NICE, 2013, 2014, 2021) guidelines recommend that people meeting ARMS criteria should be referred for specialist assessment and offered CBT, and they should not be offered anti-psychotic medication to reduce risk of developing psychosis. While approaches involving CBT and CBT with supportive therapy show promise (Bosnjak Kuharic et al., 2019; Mei et al., 2021), the evidence for CBT for reducing progression to psychosis in patients with ARMS is inconclusive. No specific psychological intervention has been identified as having superior effectiveness in its treatment, there is no ‘Gold Standard’ treatment (Bosnjak Kuharic et al., 2019; Fusar-Poli et al., 2019; Fusar-Poli et al., 2017; van der Gaag et al., 2019). Recommendations for further research have also indicated a need to look further into the treatment mechanisms and efficacy for different age groups (Schmidt et al., 2015). Taking a staged, or stepped approach to psychological intervention has also been suggested, usually with CBT and needs based interventions prior to pharmacology (Addington et al., 2017; NICE, 2014; Schmidt et al., 2015). There is scope for research into briefer approaches requiring less expertise implemented prior to CBT in ARMS services, and emerging evidence from early intervention in psychosis research (Drake et al., 2014) that inclusion of briefer targeted evidence-based interventions prior to CBT may result in a reduction of need for more in-depth CBT as patients feel more insightful into their difficulties and less in need of interventions.

1.2 Why investigate the MUSE intervention for people with ARMS?

MUSE is unique in drawing on current, empirically supported psychological understandings to explain unusual experiences such as hallucinations. It exemplifies a novel approach to psychological therapy involving shorter, targeted treatments that use CBT-informed techniques to focus on specific symptoms. This has produced promising results for other psychosis symptoms such as paranoia (Freeman et al., 2016). MUSE is fully compatible with other important treatments such as CBT. This intervention also represents a significant technological innovation, potentially suited to a younger patient population who may be particularly open to material presented in a digital multimedia format, with potential for future adaptations for online administration. MUSE can easily be encompassed within current practice for future patient benefit.

Whereas existing research has tended to treat AVH as a uniform experience, it may be that therapy could be more effective when tailored to processes underlying specific subtypes of experience. AVH take different forms (Smailes et al., 2015) including inner speech (Fernyhough, 2004), memory-based (Varese et al., 2012) and hypervigilance (Dodgson & Gordon, 2009) hallucinations. Our preliminary review of CAARMS (Dudley et al., 2018) data suggests that hallucination subtypes are identifiable in ARMS, with all but one of a sample of 54 individuals identified as experiencing one or more subtype. High rates of visual hallucinations were also recorded; following feedback from patients and clinicians, MUSE now includes a module treating this experience.

Shaped by significant input from people with lived experience, MUSE uses insights into the underlying causes of hallucination subtypes to explain these experiences, with videos and tasks illustrating the concepts. These explanations then drive the selection of behavioural experiments and coping strategies to reduce distress and increase control. The manualised toolkit is loaded onto a tablet/laptop, standardising treatment, reducing training required and increasing staff confidence in delivery. MUSE's multimedia nature has proved popular with patients and therapists, with the embedded video-clips being particularly appreciated (Dodgson et al. 2021a). Although fully compatible with CBT, MUSE is a clear departure from traditional CBT in its focus on the lived experience of hallucinations, its brevity (6–8 sessions compared to 16–20 for CBT), targeting of underlying psychological mechanisms (rather than symptom appraisals), and tailoring to specific hallucination subtypes30. For individuals where hallucinations are the target problem, MUSE has potential to become an alternative to CBT, while other individuals may benefit from additional CBT for comorbidities, or from CBT after an initial MUSE intervention. We have conducted a preliminary feasibility study in FEP, with

promising results showing proof-of concept support for MUSE when delivered by psychological therapists, with high satisfaction ratings and promising therapeutic effects (Dodgson, et al. 2021a). Building on this work, MUSE-FEP was funded (from April 2021; RfPB award NIHR 201078) to trial feasibility of MUSE in FEP as delivered by community mental health practitioners, thereby increasing accessibility to interventions (Dudley et al., 2022).

A preliminary feasibility study (Dodgson et al. 2021b) in ARMS showed promise in reducing symptoms and distress, including high acceptability and no adverse reactions. This study however lacked a control group, data on acceptability of randomisation, and outcome data to inform a sample-size calculation. These previous studies have allowed us to improve MUSE by incorporating a wider range of information about hallucinations (including visions), more co-produced materials, and development of specialist training.

If MUSE works by targeting mechanisms underlying specific hallucination subtypes, it should be possible to investigate change in these mechanisms and their contribution to therapeutic efficacy. For example, hallucinations have been linked to internal experiences being erroneously attributed to events in the outside world (reality-monitoring) (Fernyhough et al., 2019). MUSE may help recipients to identify these confusions about the origins of their experiences, and the contributing roles of factors such as vividness of everyday inner experience, sleep and arousal (Dodgson et al. 2021b).

1.3 Comparison intervention

To control for risk of bias from an undefined comparative treatment, and potential bias from dose effects, a time matched TAU is included (Bosnjak Kuharic et al., 2019; Higgins & Green, 2011). In order to match the comparative brief intervention to practice within ARMS services, components of care were identified in an engagement meeting with ARMS service leads. These common core components could be described as Supportive Psychotherapy (needs based emotional support, psychoeducation, normalisation and stress management) were outlined as the interventions used by practitioners as part of their normal clinical toolkit, alongside routine multi-disciplinary care from the team. We will investigate how frequently and consistently these supportive psychotherapy interventions are offered to inform whether these interventions could act as a comparator intervention in future trials. CBT is a core intervention, recommended by NICE Guidance and offered across all services. However, in practice it is not always offered to all service users. It was therefore decided that CBT may form part of the care in both conditions, and that the number of

sessions received by participants would be measured to investigate whether MUSE impacts on the number of sessions required. .

2. Rationale

This study will gather essential feasibility data on the deliverability of a fully powered trial in the future to reduce distress associated with unusual sensory experiences and improve global functioning and in people with At Risk Mental State for psychosis through the delivery of brief targeted interventions. This research will also investigate the mechanisms assumed to be behind unusual sensory experiences, and the impact of the intervention, creating new scientific knowledge which can be used to refine the intervention and stratify treatment.

2.1 Patient population needs

ARMS includes three subgroups involving: 1) a brief (<7 days) episode of psychotic symptoms that remit without treatment; 2) attenuated symptoms not meeting thresholds for psychosis; and 3) deterioration in functioning and family history of psychosis (Yung et al., 2005). These groups can be reliably identified, with around 25% of ARMS individuals converting to psychosis within 36 months (Salazar de Pablo et al., 2021; Stafford et al., 2013). ARMS thus represents an important window for intervening to reduce distress and thus potentially to prevent the development of full psychosis (NHS England, 2019; Wykes et al., 2021) with implications for cost-effectiveness (McCrone et al., 2008; Shields et al., 2022).

Much attention has focused on hallucinations, the most common presenting problem in psychotic disorders (Waters et al., 2012) and implicated in driving development of delusions (Maher, 1974) and paranoia (Freeman, 2007). Increased frequency and intensity of hallucinations, alongside distress and a decline in functioning, are linked to transition to psychosis (Dudley et al., 2018; Yung et al., 2005) and are threshold criteria in scales recommended in ARMS services (Comprehensive Assessment of At Risk Mental States; CAARMS (Yung et al., 2005). Intervening to reduce the distress of hallucinations (or Perceptual Abnormalities, as they are described in CAARMS) may thus be key in preventing transition to psychosis (Yung et al. 2021).

It is also important to learn more about whether change relates to target mechanisms underlying hallucination subtypes. This could be important for further refinement of treatment.

2.2 MUSE intervention for ARMS population

MUSE endeavours to provide a scientific and normalising explanation that may provide an acceptable and helpful explanation for unusual sensory experiences and help to prevent more delusional explanations from developing. This difference between ARMS and EIP participants is evident from comparison of the PSYRATS hallucination scores from our preliminary MUSE-ARMS study (n=20) with the equivalent data from the ongoing MUSE-FEP study. Our ARMS participants had a mean hallucination score of 26.26 (sd 9.41), compared to participants from MUSE-FEP (n=45) having a hallucination score of 29.56 (sd 4.99), unsurprisingly showing more severe hallucinations in the FEP group. However, the contrast is far more marked for the PSYRATS delusions score, with the preliminary MUSE-ARMS group having a score of 3.42 (sd 6.06), compared to 13.96 (sd 7.18) for the MUSE-FEP group (Dodgson, Aynsworth, et al., 2021; Dudley et al., 2023). This evidence for lower delusional ideation in our previous ARMS sample supports our suggestion that MUSE could be ideally suited to targeting understanding of unusual sensory experiences before delusional explanations have developed.

2.3 Geographical setting

Psychosis has a high prevalence in the North-East (McDonald,et al. 2021), where the emotional wellbeing of young people is a regional priority (NHS England, 2019). Socioeconomic deprivation (Public Health England, 2022) and mortality rates in severe mental illness (Public Health England, 2016) are particularly high. The research will place in two large mental health trusts, Cumbria, Northumberland, Tyne and Wear NHS FT and Tees, Esk and Wear Valley NHS FT.

2.4 Potential future benefit

If proved effective in ARMS, our work could bring significant benefits to: help-seeking individuals (typically young people), who will become less distressed and isolated by their experience and thus less likely to transition to psychosis or other mental health conditions; staff for whom the caseload burden will be reduced; academic researchers acquiring new knowledge linking psychological mechanisms to hallucination phenomenology; and the general public, who will benefit from the reduced societal and financial costs of psychosis (Ologundudu et al., 2021).

2.5 Assessment and management of risks: Participants

Earlier development research into the MUSE intervention as delivered to people with psychosis has indicated that MUSE is safe and acceptable to participants (Dodgson, Alderson-Day, et al., 2021; Dodgson, Aynsworth, et al., 2021; Dudley et al., 2022). Therefore, we anticipate adverse reactions or events related to therapy would only be experienced by a small minority of participants, if any.

Regarding the qualitative component of the trial, a potential risk is that some participants may find topics discussed in the interviews distressing. However, it is anticipated that the qualitative interviews will provide participants with a supportive space in which to discuss any distress associated with trial participation, assisted by a lived-experience expert. During qualitative interviews, participants will be reminded at the start and throughout the interview that they are able to take breaks or stop at any point and that they do not have to answer any questions if they wish not to.

2.5.1 Assessment and management of risks: Staff

Researchers and trial therapists will assess risks prior to meeting with participants by liaising with referring clinicians. Lone working and safe working procedures will be followed in accordance with research site Policy and team procedures. Local safeguarding and incident reporting procedures shall be followed where appropriate, along with study safety reporting as required (see section 11 below).

3. Objectives

3.1 Primary objective

To conduct an ISRCTN-registered feasibility randomised controlled trial to resolve key feasibility uncertainties and inform the parameters of a future fully powered trial, to investigate the preliminary effect of MUSE+TAU verses time matched TAU on general functioning and mental state in ARMS patients post therapy and at five month follow-up.

3.2 Secondary objectives

To explore additional treatment effects on unusual sensory experiences, anxiety, depression, and quality of life, and whether there are indications of other factors (sleep disturbance and trauma) influencing treatment effects

To test feasibility of collecting measures of psychological mechanisms, including psychological and personal (phenotypical) factors implicated in the clinical course of hallucinations, in order to identify which psychological mechanisms are influenced by the treatment and contribute to its clinical effect, to inform a future investigation of whether any efficacy of MUSE is through impact on these mechanisms.

To collect routine data and participant consent for a future records investigation testing feasibility of tracking transition to psychosis through medical databases (hospital records/Mental Health Services Data Set (MHSDS)), to examine which features of MUSE (presenting, treatment response and mechanistic) are most relevant to psychosis prevention.

4. Outcomes

4.1 Primary endpoint

As the trial is running in clinical services, controlling for other treatments is a challenge. Accordingly the main outcome time-point of interest is at the post-intervention assessment. The secondary time-point of interest is at the follow-up assessment 20 weeks after randomisation.

4.2 Primary outcome (a): Trial Feasibility outcome

As this is a feasibility trial, feasibility outcomes for the delivery of a large scale randomised controlled trial are of key importance. The primary outcome of this feasibility trial is the ability of the trial to recruit 88 participants, who reflect the diversity within the region, and meet study inclusion criteria over the 10-month recruitment period, who complete assessment measures collected at baseline, post intervention (12 weeks post randomisation) and follow-up (20 weeks post randomisation), until all participants complete the follow-up assessment or withdraw.

This will enable us to address key uncertainties including: referral rate; recruitment rate; reasons for declining participation; allocation compliance rate and attrition rate; appropriateness and integrity of treatment protocols; completion rates of measures and

psychological tasks (see Table 1 &2); time needed to collect, clean and analyse data; robust estimates of effect size (primary/secondary outcomes, see Table 1&2) to inform sample-size calculations for future trials; and analysis of components of TAU at each site.

Qualitative data will inform our understanding of participants' subjective experiences of the intervention and its impact on their understanding of their voice-hearing experiences (e.g. changes in beliefs about origin), along with the acceptability of the intervention (including experiences of the quality of intervention and participant responsiveness) and trial procedures for participants and therapists.

4.3 Primary outcome (b): Treatment outcomes

The treatment delivered in this intervention aims to improve functioning and reduce distress associated with hallucinations. Accordingly, candidate primary outcomes measures that will be investigated for suitability for future trials are global functioning, as measured on the SOFAS (Goldman et al., 1992), and hallucinations measured using the PSYRATS (Haddock et al., 1999) hallucination scale, with attention to subscales of interest: distress and attribution (see Table 1). The effect of the interventions on outcomes will be estimated from the change from baseline as well as changes in the mean scores in each trial arm. The feasibility of measuring caseness and caseness change, or clinically meaningful levels of response will be explored.

Table 1. Main Outcome Measures

Outcomes	Focus	Measure
Primary Global State Outcome	Functioning	Social and Occupational Functional Assessment Scale (Goldman et al., 1992)*
Primary Mental State Outcome	Mental State	Psychotic Symptom Rating Scale hallucinations total* (Haddock et al., 1999)
	Hallucinations	Psychotic Symptom Rating Scale distress* (Haddock et al., 1999; Woodward et al., 2014)
	Attribution	Psychotic Symptom Rating Scale attribution* (Haddock et al., 1999; Woodward et al., 2014)

*clinician-administered semi-structured interview

4.4 Secondary outcome (a): Treatment effects

Additional treatment effects on perceptual abnormalities, anxiety, depression, and quality of life will be measured and explored in the secondary analysis; including whether other factors (sleep disturbance and trauma) indicate influence on treatment effects (see Table 2).

Table 2. Secondary Outcome Measures: Treatment effects and potential moderators

	Focus	Measure
Treatment effects	Perceptual Abnormalities	Comprehensive Assessment of At-Risk Mental State-Perceptual Abnormalities Subscale* (Yung et al., 2005)
	Depression	Patient Health Questionnaire-9** (Kroenke et al., 2001)
	Anxiety	General Anxiety Disorder-7** (Spitzer et al., 2006)
	Quality of life	Recovering Quality of Life-20** (Keetharuth et al., 2018)
	Multimodal hallucinations	Multi Modal Hallucinations Questionnaire** (Dudley et al., in prep.)
Moderators	Sleep	The Insomnia Severity Index** (Bastien et al., 2001)
	Trauma symptoms	International Trauma Questionnaire[**#] (Cloitre et al., 2018) [#]ITQ-Child and Adolescent Version for 14-17year olds

4.5 Secondary outcome (b): Cognitive mechanisms

To identify which psychological mechanisms (see Table 3) are influenced by the treatment and contribute to its clinical effect, thus informing a future investigation of whether any efficacy of MUSE is through impact on these mechanisms.

Table 3. Subtype Measures and Cognitive Tasks

Subtype (1-2 subtypes selected for assessment per participant)	Measure/Task	Delivery format
Inner speech	Varieties of Inner Speech Questionnaire-Revised** (Alderson-Day et al., 2018)	Self-report questionnaire
	Auditory signal detection (Moseley et al., 2021)	Computerised cognitive task
Memory	Dissociative Experiences Scale-Brief** (Dalenberg & Carlson, 2010a, 2010b)	Self-report questionnaire
	Inhibition of Currently Irrelevant Memories (Paulik et al., 2007)	Computerised cognitive task
Hypervigilance	State-Trait Anxiety Inventory – Short Form (Spielberger, 1983; Spielberger et al., 1970; Zsido et al., 2020)	Self-report questionnaire
	Jumbled Speech Task (Campbell & Morrison, 2007; Fernyhough et al., 2007)	Computerised cognitive task
Visual	Plymouth sensory imagery Questionnaire-SF** (Andrade et al., 2014)	Self-report questionnaire
	Visual signal detection (Smailes et al., 2020)	Computerised cognitive task
	Face pareidolia task (Smailes et al., 2020)	Computerised cognitive task

*Researcher selection criteria: Participants will only complete the above subtype-specific measures for a maximum of two subtypes, **self-report measure.*

4.6 Secondary outcome (c): Transition to psychosis

Transition to psychosis will be measured post-intervention and at follow-up time-points, as assessed by: Evidence of transition to psychosis from standard diagnostic classification systems or commonly used ARMS assessment schedule documented in clinical notes / Evidence of transfer to the Early Intervention in Psychosis pathway / Evidence of treated or untreated psychotic episode of one week's duration or longer / Evidence of initiation of treatment with antipsychotics.

A meaningful follow-up period for transition to psychosis would be three years. Therefore, we will seek participant consent to collect routine data for a the feasibility of tracking long-term transition to psychosis through the Mental Health Services Data Set (MHSDS)/medical records to answer additional questions about which features of MUSE (presentation, treatment response, mechanistic) are most relevant to psychosis prevention.

4.7 Secondary outcome (d): Adverse events

Adverse events relating to psychological wellbeing (see section 11) will be recorded and reported for the novel intervention and comparison treatment arms of the trial.

4.8 Secondary outcome (e): Impact of MUSE on Treatment as usual

A final outcome will be whether offering MUSE impacts on usual care: whether it reduces the length of CBT interventions needed, whether participants have been discharged (ie no longer in need of intervention) at the follow-up period; and other treatment use. Details of all treatment received in both groups will be recorded using the Client Service Receipt Inventory CSRI (mental health) questions 4 to 5, amended for this trial to add specific questions to measure receipt of relevant interventions in both arms for the duration of the study.

5. Trial design

A mixed-method feasibility trial employing a prospective, randomised, open-label, observer blinded endpoint design with MUSE+TAU compared to time matched TAU, with assessments at pre- and post-treatment and at five-month follow-up.

5.1 Equality, diversity and inclusion

This study seeks to serve the ARMS population aged 14–35years, who are of mixed ethnic and sociodemographic backgrounds. Prevalence and incidence rates of people who go on to have psychosis show rates to be proportionally higher in males, in people of ethnic minority, in inner city areas and in deprived areas, though these rates vary widely across England (Public Health England, 2016).

To match the sample of research participants to the general ARMS population, this study will recruit via ARMS service pathways in secondary care mental health. The inclusion and exclusion criteria seek to be as inclusive as possible, while ensuring inclusion of symptoms that the novel MUSE intervention intends to treat (distress relating to hallucinations). Clinical stability, ability to engage and capacity to consent are additional criteria in the study that

would also be anticipated requirements to engagement in a psychological treatment intervention.

As this feasibility study recruits only in the far North/North East of England, there will be some differences in population between the trial sample and the overall national population, as expected from research constrained to only a few geographical areas. It is anticipated that the trial sample will be similar to the ARMS population sample in these geographical areas. The proportion of individuals from ethnic minority backgrounds may be lower than is representative of some other locations due to the lower rates of ethnic diversity in the region (Office for National Statistics, 2022). The recruitment area includes urban, inner city and rural areas of mixed socioeconomic areas including areas of high deprivation.

In order to engage with and be inclusive of under-served groups, this study encourages and supports researchers to be adaptive to the needs of individuals who have literacy or language barriers. The preparatory work for this study included applying the INCLUDE Ethnicity Framework key questions (Witham et al., 2020), and identified transcribing of materials and access to translators as key barriers. To overcome these barriers, as well as other literacy challenges such as dyslexia or illiteracy, researchers will be guided to enable informed consent conversations and decisions by individuals who have additional needs but have capacity to consent. The study will also use a budget for interpreters to enable engagement with individuals who require this for different languages or sign language. The study will also use a budget for transcription where this is useful for individual participants. The Trial Steering Committee (TSC) will monitor participation and inclusivity of under-served groups.

Our therapists are experienced clinicians and will be culturally sensitive in their use of MUSE. Qualitative interviews will include questions to explore elements of inclusivity and diversity.

6. Trial setting

This is a multicentre trial taking place in NHS settings in the UK. The study will run through At Risk Mental State services and Early Intervention in Psychosis services that provide an ARMS service. Participating sites can be found listed on the Integrated Research Application System (IRAS) form.

7. Participant eligibility criteria

7.1 Inclusion criteria

- in contact with an ARMS service or accepted on an ARMS pathway by EIP services
- aged 14–35
- hallucinations / unusual sensory experiences scoring at least 3 on the Perceptual Abnormalities Subscale of the CAARMS
- hallucinations considered by the patient to be a key target problem
- judged to have been clinically stable for the preceding 2 weeks

7.2 Exclusion criteria

- intellectual disability or severe cognitive dysfunction affecting ability to engage with research materials
- lacking capacity to give informed consent

8. Trial procedures

Table 4: Trial Assessments and Key Participant Procedures Schedule

Assessments/ procedures	**Participant identification**	**Enrolment & baseline**	**Randomisation**	**Intervention Weeks 1-12**	**12 weeks post randomisation (+/-10days)**	**20 weeks post randomisation (+/-10days)**
Recruitment and eligibility discussions	X					
Informed consent		X				
CSRI Sociodemographic Q1-3.5		X				
Randomisation			X			
MUSE & TAU / TAU Intervention				← →		
Blinded assessments						
MUSE ARMS Primary Outcome Measures: SOFAS & PSYRATS		X			X	X
CSRI service use Q4.1-4.4		X				
CSRI Q4.5 criminal justice services and Q5 medication		X			X	X
MUSE ARMS Secondary Outcome Measures: CAARMS-PA, PHQ-9, GAD-7, ReQoL-20, ISI, ITQ/ITQ-CA, MMHQ		X			X	X
Subtype Measures & Cognitive Tasks*[1] (1-2 subtypes selected per participant): See Table 3		X			X	X
Treatment preference		X				
Unblinded assessments						
CSRI service use at follow-up Q4.1-4.4					X	X
Transition to Psychosis data					X	X
Adverse Event (AE) data					X	X
Therapeutic Alliance STTS-R					X	
Participants interviews (Withdrawals sub-sample)				← →		
Participants interviews (MUSE completers sub-sample)					← →	
Participants interviews (TAU sub-sample)					← →	

Therapists interviews (sub-sample)					⟷

8.1 CONSORT reporting

Patients who are referred will be considered as having entered the eligibility assessment process and will be reported upon using CONSORT. Here the number who are referred, who are ineligible, who decline, who meet for informed consent, who then decline or are ineligible, the number who give informed consent, the number who complete baseline assessments, the number that progress to randomisation, the number who complete post-intervention and follow-up assessments, and the number that do not, will be recorded.

Reasons for not progressing to randomisation will be (i) not meeting inclusion criteria (including those identified within the informed consent discussion leading to a decision not to take consent) (ii) declined, (iii) other.

Reasons for not completing post-intervention and follow-up assessments will be (i) withdrew (ii) unable to make contact/lost to follow-up, (iii) attended but participant was unable to complete all assessments, (iv) other.

8.1.1 Enrolment and consent criteria tracking

An enrolment log will be generated at site to record consenting participants (initials, hospital number, and participant ID only) consent and enrolment date and responses to optional consent points. Withdrawal information and degrees of withdrawal will also be recorded on the enrolment log. The log will be stored in the ISF and a copy sent to the TMF.

8.2 Recruitment

Recruitment will commence on the opening of the trial sites following Research Ethical Review, HRA approval and site confirmation of Capacity and Capability.

Recruitment will be via NHS secondary care mental health clinical teams providing services to patients with an At Risk Mental Health for psychosis supported by NIHR-funded portfolio delivery staff.

8.2.1 Participant identification

Clinical teams supported by their Trust's clinical research delivery team members, who work as an adjunct to clinical teams within participating NHS sites, will identify potential participants from caseloads, clinics and newly accepted referrals, who will have a Perceptual Abnormality

score of 3 or above in the last 4 weeks. Patients who potentially meet the eligibility criteria for the trial, and their parent/guardian where appropriate if under 18years, will be informed of the study by a member of their clinical team, or as appropriate by a Trust clinical research staff member who works into the clinical team for this purpose. Patients will be asked for their verbal consent to be contacted by a member of the research team and/or to receive further information on the study.

8.2.2. Eligibility

There is no post-consent eligibility testing. Participants will be checked for eligibility prior to informed consent via discussion with referring teams and in the participant-researcher discussion prior to giving informed consent.

8.2.3 Payment

Participants will be given £15 honorarium for each assessment time-point (baseline, post intervention and follow-up). Travel expenses will be provided if required (payments by BACS or NHS Trust approved process).

8.3 Informed consent

8.3.1 Information provision

The Participant Information Sheet (PIS) will be provided prior to the informed consent meeting[2]. The informed consent meeting for the trial will be scheduled at least three days after the potential participant has received the PIS. Informed consent will involve review and discussion of the participant information with an authorised member of the research team who is delegated this duty by the Principal Investigator, or is the Principal Investigator at site, and is trained in the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. Interpreters will be provided if required to support the informed consent discussion and participation in the trial.

Participants will be informed that participation is voluntary and they can withdraw at any time without giving reason and without their medical care or legal rights being affected. It will also be explained that if they withdraw from the study, or become too unwell to continue (lose capacity) the research team will keep the research data that they already have, and continue to track long term outcomes via the MHSDS/medical notes, unless the participant has withdrawn from this part of the study.

[2] Participant Information for the inclusion of family or friend supporters in the qualitative interviews can be provided on the day of the interview due to the nature of this visit and who may be asked to support.

The PIS and ICF will clearly outline what personal data is being used in the trial, how this is being protected, including any storage and transfer arrangements.

8.3.2 Inclusion of participants aged 14-15 years old

Potential participants aged 14-15 years old will be given an age appropriate brief summary of the research and what their involvement would be if they chose to take part. We are asking for parent or guardian informed consent in addition to child assent for all children/young people who are aged under 16years old, and on occasion for those who are aged under 18years old where they/ their parent or guardian or clinical care team think this would be helpful.

8.3.3 Documenting informed consent

Potential participants will provide consent using the ethically approved Informed Consent Form (ICF) or Young Person Assent Form with Parent/Guardian ICF, prior to any research assessments. Verbal ICFs are available for use if an individual has literacy or language needs. Verbal ICFs can also be used to take remote consent, which may be helpful e.g. for rural participants by reducing travel time and environmental footprint, or for conducting informed consent prior to baseline.

The Consent/Assent form will be stored in the ISF, the consent process will be documented in medical notes, and copies of the Participant Information Sheet and signed Informed Consent & Assent Forms saved in medical records at the participating NHS site. A copy of the Consent/Assent form will also be given to the participant (or consenting adult as appropriate). For participants who consent to long-term follow-up via the MHSDS/medical records, copies of ICFs will be transferred securely to the Central research team at CNTW for secure storage in the TMF at the end of participant procedures (see section 9.3).

8.3.4 Optional consent criteria

The ICF will include optional consent for participants who are interested in taking part in a qualitative interview. Details of this will be included in the PIS.

The ICF will include optional consent for participants' medical records being accessed to collect follow-up data as part of a longer-term study. Medical records include hospital records, and the Mental Health Services Data Set (MHSDS). Details of this will be included in the PIS and ICF.

8.3.5 Documenting consent of supporters in qualitative interviews

Where participants express preference for a family member or friend to support them in the interview, their supporter can also be included via informed consent if they wish to add points of view to the interview. This consent form will be stored in the ISF, and copies of the Participant Information Sheet and a copy of the signed Informed Consent Form will also be given to the participant.

8.4 Sociodemographic background data

Following Informed Consent and prior to Randomisation, sociodemographic background data to describe participant background diversity and age for randomisation is captured in the CSRI questions 1–3.5. Question 1.1 (referring to date of birth) will be amended to month and year of birth and age will be asked. This is to remove specific person identifiable information. Question 1.2 (referring to sex) will be amended to gender with three choices of male, female, other. This is for improved equality and diversity reasons. The sociodemographic subset (Questions 1–3.5) will be asked once after informed consent.

8.5 Randomisation

Eligible participants who have completed baseline assessments will be randomised. An independent web-based randomisation service (sealedenvelope.com) is used for the trial. Randomisation will be in the ratio 1:1 to the two groups: MUSE+TAU (intervention) or TAU (control). Randomisation will be stratified by site, gender (M/F/Other) and age (14–17years/18–35 years inclusive). Randomisation allocation will be independent and dynamically generated using a randomised modified minimisation method (Kuznetsova & Tymofyeyev, 2012) to assure allocation concealment along with preservation of allocation ratio.

The researcher who completes the baseline assessment will enroll participants for randomisation, and Sealed Envelope will assign participants to the two groups. Randomisation allocation is made known to the CI and site PIs, the Trial Coordinator(s) and the trial therapists only at the point of randomisation, by email. Research assessors for the trial will be blind to the allocation throughout the trial.

Authorised members of the research team will be assigned usernames and passwords to log into the system and randomise participants. Randomisation is confirmed via two sets of emails generated by the system. The first set contains the unblinded treatment allocation and is sent to relevant unblinded individuals in the team. The second set contains no allocation details but

is sent to relevant blinded researchers to confirm the participant is enrolled.

The unblinded trial coordinator or local site lead delegated to this role will inform participants of which group they been allocated to. The outcome of the randomisation will be written into the clinical care notes and a courtesy email sent to the referring clinician. A formal letter, using the REC approved template will be sent to the patient's lead professional with a copy of the PIS to inform their healthcare team of their participation in the trial.

8.6 Blinding

Research outcome assessors will be blind. Clinicians, therapists and participants will be unblind. Trial statisticians will be partially blind.

Maintaining blindness of research assessors is crucial, and care will be taken within the research team to avoid accidentally unblinding outcome assessors. Any cases of inadvertent unblinding will be discussed in a TMG, and TSC will monitor unblindings by each site regularly and implement corrective action if necessary. Participants and clinical teams will be reminded prior to each assessment timepoint by the research team that they must not inform the blinded researchers of their group allocation.

Where unblinding occurs during the assessment, no further assessments will be taken and another appointment will be made for a blinded member of the research team to complete the measures.

The Trial Coordinator will oversee the maintenance of blinding and will monitor any blinding breaches closely. Any unblinding of blinded assessors will be classed as a protocol deviation and reviewed by the site PI and Trial CI. The TSC will monitor any unblinding and implement corrective action if necessary.

8.6.1 Blinded assessments

The blinded assessments are the trial measures and cognitive tasks (see section 8.7), as assessed by a researcher who has no knowledge of the participant's allocation at the time of assessment, are completed at the three time-points: Baseline, Post-Intervention (defined as 12 weeks (+/- 10 days) post randomisation date), and Follow-up (defined as 20 weeks (+/- 10 days) post randomisation date).

8.6.2 Unblinded assessments/data collection

After randomisation, the CSRI service use (Q4-5) data (incorporating use of MUSE in either treatment arm), Transition to Psychosis data, and Adverse Event* data will be collected from medical records by an unblinded member of the research team. This is because it is not possible to access medical records data without becoming unblinded to the treatment allocation.

*Serious Adverse Events will be reported on immediately, within 24 hours of becoming aware of the event in accordance with section 11 of this protocol and all researchers including trial therapists will receive training and guidance on this.

8.6.1 Procedure for unblinding if needed

This circumstance is not applicable since participants and therapists are already unblinded.

8.7 Trial assessments

Assessments summary (See Table 4 for a visual overview):

- At each time point (Baseline, Post-Intervention and Follow-up) the Primary Outcome measures to be completed are the SOFAS and the PSYRATS. These measures are to be prioritised and are completed with the participant by a blinded assessor.
- At each time point (Baseline, Post-Intervention and Follow-up) the Secondary Outcome measures to be completed are the CAARMS-PA, GAD-7, PHQ-9, ICECAP-A, ReQoL, ISI, and ITQ. These are completed with the participant by a blinded assessor.
- The CSRI service use questions (Q4-5) (incorporating use of MUSE in either treatment arm), is completed at Baseline from self-report in the assessment meeting with the participant, supplemented by medical records as required.
- At each time point (Baseline, Post-Intervention and Follow-up) the participant Subtype measures and cognitive tasks will be completed. 1–2 Subtypes are permitted but no more than 2.
- At Post-Intervention and Follow-up, the CSRI service use questions (Q4.1-4.4) (incorporating use of MUSE in either treatment arm), Transition to Psychosis data and adverse event data will be collected by an unblinded researcher from medical records.

Details on each measure or task and its procedures are detailed below. The measures will take around 90 minutes to complete. Participants can choose to complete the measures over two sessions within the allocated time window, or not more than two weeks apart.

8.7.1 SOFAS*:* Social and Occupational Functional Assessment Scale (Goldman et al., 1992)

The SOFAS is a clinician/clinical researcher rated single-item scale to assess social and occupational functioning. The period of assessment for this trial is the last two weeks. Scoring is from 0 to 100; higher scores represent better functioning. Scoring is completed

independently of patient-reported psychological symptoms; however, impairment due to ill health (physical and mental) is scored, whereas impairment due to environmental factors or lack of opportunity is not scored. The SOFAS is used in UK ARMS services for this age population as part of the assessment of risk for psychosis. Clinically significant scores are: a 30% decline sustained for at least a month from normal functioning, which is considered significant decline; or a score of less than 50 for the last 12 months, which is considered chronic low functioning. For this trial, this assessment data can be obtained either from participant interview, or from medical notes where the measure has been completed by a qualified clinician within the last four weeks. Researcher assessors using this scale will be required to complete specific training including inter-rater reliability assessments.

8.7.2 PSYRATS: Psychotic Symptom Rating Scales (Haddock et al., 1999)

The PSYRATS is a clinician/clinical researcher administered semi-structured interview of hallucinations (11 items) and delusions (six items). Each item is rated by the interviewer on a 5-point nominal scale (0–4). The PSYRATS total score will be used to assess the severity of hallucinations and delusions. Scores for the hallucinations subscales (Woodward et al., 2014) of Distress (questions 6, 7, 8, 9 &11) and Attribution (questions 3 & 5), will be analysed with equal importance as key problem areas which MUSE is seeking to target. Researcher assessors using this scale will be required to complete specific training including inter-rater reliability assessments.

8.7.3 CSRI: Client Service Receipt Inventory CSRI (mental health) (Beecham & Knapp, 2001).

The CRSI (mental health) is a UK-specific tool to capture service use relevant to mental health. Additional questions ask about police contact and medication use.

CSRI questions 4–5 will be used to inform on TAU content received. Here details of all treatment received in both the intervention and comparison group will be recorded. Additional questions will be added, within the option labelled ‘other’, for question 4.3 to track receipt of (i) MUSE-based intervention, (ii) CBT and (iii) other psychological therapies. Similarly, for question 4.4, additional types of workers will be added into the ‘other categories’ to track contacts with psychological therapists, assistant psychologists, support workers, and other workers. Medication-use questions for this trial will be constrained to medications for mental health. To prevent double counting, questions pertaining to the last 3 months period will be amended to indicate ‘since last research assessment’.

Data to complete these questions can be obtained from self-report and medical records. Due to the risk of unblinding when completing questions 4.1-4.4 pertaining to service use, unblinded researchers will complete questions 4.1-4.4 at the post treatment and follow-up

assessment points from medical records. Training and guidance on recording for this measure will be given to ensure consistency.

If participants are discharged from their ARMS team during the period of the trial (up to and including 20 week visit) then this will be captured on an additional question at the end of the unblinded CSRI. Reasons for discharge will include: (i) Feeling better – no longer required the service, (ii) Disengaged (please specify why if indicated _____), (iii) A different treatment was indicated – onward referral, (iv) Other priorities meant this was not a good time to engage, (v) Not known. If participants have not been discharged an additional question will check if therapy has completed. In cases where therapy has not yet completed, unblinded researchers will gather end of therapy completion data from medical records and/or communication with therapists. The Service use: Discharge prior to end of trial CRF has been amended to capture completion of therapy data by the end of the trial at sites.

8.7.4 CAARMS: The Comprehensive Assessment of At-Risk Mental States (Yung et al., 2005)

The CAARMS is a clinician/clinical researcher administered semi-structured interview commonly used to assess patients referred to At Risk Mental State services. For this trial the CAARMS subscale of Perceptual Abnormalities only will be used to elicit further detail about the nature of unusual experiences. For this trial, this subscale data can be obtained either from participants interview, or from medical notes where the measure has been completed by a qualified clinician within the last four weeks. Researcher assessors using this scale will be required to complete specific training including inter-rater reliability assessments.

8.7.5 PHQ-9 and GAD-7: Patient Health Questionnaire and General Anxiety Disorder (Kroenke et al., 2001; Spitzer et al., 2006)

GAD-7 is a brief self-report questionnaire of 7 items, used as a screening tool for anxiety, which has good reliability and validity (Spitzer et al., 2006). PHQ-9 is a brief, self-report questionnaire of 9 items to measure depression symptom severity with good reliability and validity (Kroenke et al., 2001). Both questionnaires focus on symptoms over the last two weeks and answers can indicate if this has been the case on number of days labelled as: Not at all/Several days/More than half the days/Nearly every day.

8.7.6 ReQoL-20: Recovering Quality of Life (Keetharuth et al., 2018)

The ReQoL-20 is a brief self-report 20 item questionnaire and will be used to measure quality of life. Questions are rated using a 5-point nominal scale (0-4), with higher scores reflecting better quality of life, and an increase of 5 points denotes reliable improvement in quality of life, whereas a decrease of 10 points denotes a deterioration in quality of life. Keetharuth et al.

(2021) carried out an item response theory analysis of the measure and found that it has robust internal construct validity.

8.7.7 MMHS: Multi-Modal Hallucinations Scale (Dudley et al., in preparation)

The Multi-Modal Hallucinations Scale (MMHS) will be used to assess cross-modal sensory experiences. The MMHS is a brief self-report measure which assesses unusual sensory experiences in six modalities: auditory, visual, olfactory, gustatory, bodily sensations and sensed presence. The measure asks questions about the frequency and distress caused by these experiences and asks for a brief description. The MMHS is currently unvalidated, but has been included as it investigates whether the unusual sensory experiences are combined (for example seeing a vision which is the source of a voice).

8.7.8 ISI: The Insomnia Severity Index (Bastien et al., 2001)

The ISI is a brief self-report questionnaire of 7 items to assess sleep difficulties and severity of insomnia. Question answers are rated using a 5-point nominal scale (0–4) that asks users to answer questions relating to their quality of sleep and levels of insomnia over the past 2 weeks. Scores of 15 or above are indicative of clinical levels of insomnia, with scores between 8 and 14 being indicative of subthreshold insomnia. The ISI has excellent internal consistency (Cronbach's alpha= .92) (Gagnon et al., 2013), and has been successfully implemented to assess insomnia in patients with psychotic disorders in previous research (Miller et al. 2019).

8.7.9 ITQ: International Trauma Questionnaire (Cloitre et al., 2018)

The ITQ is a self-report 18 item questionnaire developed as a diagnostic measure for Post-Traumatic Stress Disorder (PTSD) and Complex-PTSD (CPTSD). Each question is rated using a 5-point nominal Likert scale (0–4). Questions are answered in relation to how much a specific traumatic event has caused difficulties in the past month. The measure assesses elements of both PTSD (Re-experiencing, Avoidance, Sense of threat), and disturbances in self-organisation (Affective dysregulation, Negative self-concept, Disturbances in relationships). The ITQ has been shown to be able to adequately distinguish between PTSD and CPTSD (Redican et al., 2021).

8.7.10 ITQ-CA: International Trauma Questionnaire - Child and Adolescent Version (Cloitre et al., 2018; Haselgruber et al., 2020)

The ITQ-CA is the child/adolescent validated version (Haselgruber et al., 2020) of the International Trauma Questionnaire (for adults; ITQ). The ITQ is a self-report 22-item questionnaire using a mixture of 5-point nominal Likert scale (0–4) responses and Yes/No

responses to consider how much problems have bothered the individual over the past month. This version of the International Trauma Questionnaire will be used for participants aged 14–17 in the trial for secondary outcome assessment on treatment mechanisms.

8.8 Subset assessments

Participants will only complete measures on relevant subtypes of unusual sensory experiences. The number of subtypes for which specific measures are collected will be a maximum of two. The research assessors will use the key questions from MUSE to identify subtypes. For example, a patient with inner speech voices, memory voices and visions would be asked which of these experiences is most significant to them (based on a combination of frequency and distress) and would only be asked to complete measures linked to the two they identify. A researcher standard operating procedure for selecting subtypes will be used in the trial, and specific training on this given to research assessors.

8.8.1 Inner speech subtype

VISQ-R

The Varieties of Inner Speech Questionnaire – Revised (VISQ-R) (Alderson-Day et al., 2018) is a 26-question measure, rated using a 4-point scale ranging from “strongly agree” to “strongly disagree”. The questionnaire is used to link everyday phenomenology of inner speech (such as inner dialogue) to different psychopathological traits. The VISQ-R measures both the phenomenological qualities of inner speech (dialogic, other people’s voice, condensed) as well as some of its functions (evaluative and motivational, and positive inner speech). The scale has been shown to have strong internal reliability (Cronbach’s alpha > .8) (Fernyhough et al., 2019).

Auditory signal detection (computerised cognitive task)

The auditory signal detection task is used to elicit hallucinatory phenomena under ambiguous conditions. This task works by delivering a combination of different types of white noise combined with snippets of an androgynous human voice over headphones. Participants are asked to respond with either ‘yes’ or ‘no’ when they believed that the white noise stopped, indicating the presence of a human voice. Past use of this measure has shown that individuals who are hallucination-prone are more likely to report false perceptions of voices when completing the task than those who are less hallucination-prone (Barkus et al., 2007; Bentall & Slade, 1985). These findings have been replicated a number of times, and the task has been successfully used on individuals as young as 15 years old (Barkus et al., 2011; Moseley et al., 2021).

8.8.2 Memory subtype

DES

Dissociative experiences will be assessed using the Brief Dissociative Experiences Scale — Modified (DES-B) (Dalenberg & Carlson, 2010a, 2010b) The Adult version will be used with participants aged 18+. The Child version is for participants Aged 11-17. The DES-B is an 8-question scale developed to measure severity of dissociative experiences. Participants answer on a scale of 0-4, from not at all, once or twice, almost every day, about once a day, or more than once a day. Scores are then calculated to result in a severity of sypmtoms score of none (0), mild (1), moderate (2), severe (3), or extreme (4). This brief measure will reduce participant burden during assessment sessions and is recommended for use by the American Psychiatric Association and is freely available.

ICIM (computerised cognitive task)

The Inhibition of Currently Irrelevant Memories (ICIM) task is a continuous recognition task originally developed by Schnider and Ptak (1999). The current version of the task was adapted by Alderson-Day et al. (2019). The ICIM consists of 3 runs, each containing a sequential presentation of black and white line drawings. For each drawing, participants are required to decide whether the drawing was previously presented within the current run, by either pressing number 1 (indicating this is the first time they have seen the drawing) or number 2 (indicating this is a repeated drawing). There is a 30-second break between runs one and two, and a 5-minute break between runs two and three. Across all three runs there are 35 opportunities to identify a repeated image, and 180 opportunities to report a false alarm by classifying an unseen image as a repeated image. Reporting more false alarms in this task is correlated with hallucination proneness (Alderson-Day et al., 2019; Paulik et al., 2007)(Alderson-Day et al., 2019).

8.8.3 Hypervigilance subtype

STAI-Short Form

State and Trait anxiety will be assessed using the Short version of the Spielberger state—trait anxiety inventory (STAI). The STAI was initially presented as a 40 item questionnaire (Spielberger, 1983; Spielberger et al., 1970) The Short Form version was developed from the original STAI and consists of five state anxiety questions and five trait anxiety questions, which show high item discrimination and good response difficulty parameters within a confirmatory factor analysis (Zsido et al., 2020). The STAI-Short Form demonstrated excellent reliability and internal consistency in this evaluation, and is therefore the preferred

version of the STAI as a sub-set questionnaire for this trial as it places less burden on participants, being shorter to complete.

Jumbled Speech Task (computerised cognitive task)

A jumbled speech task (JST), similar to the task employed in Fernyhough et al. (2007) and Campbell and Morrison (2007), will be used to assess individual differences in top-down processing. The task consists of twelve seven-second extracts of jumbled speech, plus one example extract presented at the start of the task. These extracts have been prepared from a 10-year-old girl reading a passage of prose. This recording was segmented at silence boundaries and these segments were reversed. These segments were then formed into a novel stream of reversed, continuous discourse. This discourse was randomly divided into a series of seven-second extracts that form the stimuli for the JST. Examples of the extracts of jumbled speech are available at this - tinyurl.com/34hxjwa2 - website. At the end of every extract, participants will be asked to report any English words they heard in the jumbled speech. Stimuli will be presented to participants via headphones and participants will be allowed to listen to each extract only once. The number of words 'heard' by each participant will be recorded, as will the total number of syllables 'heard' by each participant. Two versions of this task will be created, using 25 different extracts of jumbled speech (one example extract, which will be the same in both versions, plus 12 extracts per version), with one version being used for all baseline assessments and one version being used for all follow-up assessments.

8.8.4 Visual subtype

Psi-Q

A short form version of the Plymouth Sensory Imagery Questionnaire (Psi-Q) (Andrade et al., 2014) will be used to assess the individual's visual imagery. The Psi-Q is split into 7 sections, each section with 5 questions in. This study will use only the visual section. These questions ask participants to imagine the appearance of certain things, such as a sunset or a cat climbing a tree, and rate how vivid the image is from 0 to 10. A score of 0 indicates that there is no image at all, and a score of 10 indicates that the image is as clear and vivid as real life. The Psi-Q has been shown to have high internal consistency and be a valid instrument for measuring the vividness of mental imagery (Jungmann et al., 2022).

Visual Signal Detection Task (computerised cognitive task)

The Visual Signal Detection task (Smailes et al., 2020) consists of 60 trials. In each trial, participants are presented with visual noise (similar to the black and white pixels found on an un-tuned television) for 3.5 seconds. Halfway through each trial, a smaller image is presented

in the centre of the visual noise for 50 milliseconds. In 36 trials, this smaller image is a black and white face. In 12 of these 36 trials, the face is relatively easy to detect. In 24 of these 36 trials, the face is much more difficult to detect. The faces are two-tone, black and white photographs of three male and three female adults expressing a neutral emotion. Each photograph is used six times (twice as a stimulus that is easy to detect, and four times as a stimulus that is difficult to detect). In the remaining 24 trials no face is presented, and the smaller image consists only of more visual noise. After each trial, participants are asked to judge whether a face was presented in the visual noise (by pressing the 'P' key on a computer keyboard) or if a face was not presented in the visual noise (by pressing the 'A' key on a computer keyboard). Between the response screen and the subsequent trial, a blank white screen is presented for 1,000 milliseconds. Before beginning the task properly, participants will complete nine practice trials. In the first three practice trials a face is clearly present in the visual noise, in the middle three practice trials a degraded, difficult-to-detect face is presented, and in the final three practice trials no face is presented. After completing the practice task, it is explained to participants that in the first three trials a face had been present and should have been relatively easy to detect, that in the middle three trials a face had been present, but that it should have been difficult to detect, and that in the last three trials no face had been presented. If they confirm that they understand the task, participants begin the task properly. They are instructed that they will be presented with 60 trials of visual noise, and that in 12 trials a face should be easy to see, in 24 trials a face will be present but should be more difficult to detect, and in 24 trials no face will be presented. The task lasts around six to eight minutes. From the task, we will record the number of 'false alarms' made (i.e., the number of trials where participants incorrectly respond that a face has been presented) and the number of 'hits' made (i.e., the number of trials where participants correctly respond that a face has been presented).

Face Pareidolia Task (computerised cognitive task)

The Face Pareidolia task has been adapted from Smailes et al. (2020). Prior to beginning the task, participants will be given a written explanation of what a face pareidolia is and will be shown three examples of face pareidolia. The task consists of 36 trials, and in 24 of these trials participants will be presented with an image that contains a face pareidolia. In the remaining 12 trials, participants will be presented with an image that does not contain a face pareidolia. Each image will be presented for 750 milliseconds, with the images presented in a random order. Immediately after the image has been presented, participants will be asked to

decide whether or not a face pareidolia was present in the image. Responses will be made using a button press on a computer keyboard (with participants pressing 'P' to indicate that a face pareidolia was present and pressing 'A' to indicate that a face pareidolia was absent). The task takes around 4–6 minutes. The number of 'hits' made (i.e., how often participants respond that a face pareidolia was present in an image that did contain a face pareidolia) will be recorded, as well as the number of 'false alarms' made (i.e., how often a participant responds that a face pareidolia was present in an image that did not contain a face pareidolia).

8.*9* Assessing transition to psychosis

A study-specific Case Report Form (CRF) will measure transition to psychosis at the post-intervention and follow-up time points with data collected from medical records. The criteria for transition to psychosis are: Evidence of transition to psychosis from standard diagnostic classification systems or commonly used ARMS assessment schedule documented in clinical notes / Evidence of transfer to the Early Intervention in Psychosis pathway / Evidence of treated or untreated psychotic episode of one week's duration or longer / Evidence of initiation of treatment with antipsychotics.

8.10 Assessing adverse events

A study-specific CRF will collect data on adverse events and serious adverse events from interview with the participant and medical notes at the assessment time-points post-intervention and follow-up. Criteria will be as detailed in section 11 of this protocol.

Where Serious Adverse Events are identified outside of the scheduled research assessments these will be recorded and reported on using the same CRF and following the guidance in section 11 for reporting requirements.

8.11 Assessing therapy preference, satisfaction and acceptability

Early preferences for therapy: (i) number of sessions, (ii) target problem area ranking, and (iii) therapist approach preferences, will be obtained at baseline using a study specific set of questions. Then post therapy satisfaction with the therapist will be obtained using the Revised version of the Satisfaction with Therapy and Therapist Scale (STTS-R) (Oei & Shuttlewood, 1999; Oei & Green, 2008), a short scale assessing overall acceptability of the therapeutic interaction.

8.12 Qualitative assessments

Individual semi-structured interviews at study conclusion to explore participants', their supporters, and therapists' views of:

- recruitment and consent processes

- the assessment process
- the intervention for those who were allocated MUSE in the trial, including length/duration of sessions, usefulness of the MUSE format, relevance of MUSE content, utility of mechanistic explanations, and value and acceptability of treatment
- for those who were allocated MUSE in the trial, the subjective impact of treatment including for example implications for participants' daily lives and functioning, how the intervention influenced their views about the origin of their hallucinations and whether this was important to them
- therapists will also be asked about their experiences of supervision

Topic guides for all semi-structured interviews will be co-developed with LEAP, supplemented by input from the TMG and piloted in advance.

Interviews will be facilitated by dyads where possible, consisting of individuals experienced in working with service users, and members of the LEAP group who are previous service users or carers trained in introductory research methods and interviewing skills. The LEAP interviewers will also be given opportunity to engage in practice interviews, supported through peer-to-peer discussions, and receive ongoing guidance from the PPI and qualitative leads.

8.12.1 Qualitative sample recruitment

The approach to sampling is informed by guidance (O'Cathain et al., 2015) on maximising qualitative research in feasibility studies. A purposive sampling approach will be used to select a sub-set of trial individuals for interviews. Where participants express preference for a family member or friend to support them in the interview, their supporter can also be included via informed consent if they wish to add points of view to the interview[3]. Participants who *do not* want their family/friends contributing will have their wishes respected.

The sampling will be initially broad, maximising diversity of participants, experiences and subtypes, and potentially disconfirming cases, to ensure inclusivity and to address the key feasibility uncertainties. As data collection continues, concurrent analysis where possible will inform pragmatic sampling decisions. Our sampling framework will be informed by discussion with LEAP, but will initially include factors relating to study arm (intervention/control), recruiting site (CNTW/TEWV), subtypes (inner speech, memory-based, hypervigilance and visions), and participant in the trial / or therapist in the trial. Sample size will be informed by ongoing

[3] Alternatively, if the trial participant is happy for their family/supporter's views to be heard but wishes to be interviewed alone, then the family member/supporter can join the interview at the end to add comments, providing they give informed consent.

assessments of trustworthiness (Nowell et al., 2017), information power (Malterud et al., 2016), and data sufficiency (Vasileiou et al., 2018).

We will also sensitively approach two further groups to give feedback: i) those who consent but then decide they no longer want to complete the study (non-completion) and ii) those who do not consent to participate (non-consent)

i) The non-completion group will be sensitively asked about their reasons affecting their participation and will be invited to suggest how to make participation in future studies more appealing, utilising a barriers and facilitators approach.

ii) The non-consent group will be sensitively asked to share reasons for non-participation via the NIHR Participant Research Experience 'Okay to say No' (anonymous) questionnaire (https://myresearchexperience.com/), which asks an open question about the reasons for deciding not to take part, along with basic demographic information (age and ethnicity). Non-consenting participants will be asked if they wish to give feedback using this format which can be used by the research team to inform future studies. There will be no informed consent undertaken for the completion of this non-consent feedback and the completion of the 'Okay to say No' form will be classified as implicit consent to use the anonymous feedback for the qualitative analysis element of the study, as well as the basic demographic information for reporting of descriptive statistics on those who decline participation in the study.

8.13 Participant withdrawal

Participants will be withdrawn from the study if they withdraw their consent to continue. If participants wish to withdraw from the study, they may do so at any time, however in accordance with the trial informed consent and data integrity, data already provided during their involvement in the study will be retained. It is acceptable to withdraw from the MUSE intervention and remain in the study for continuing assessment, or to withdraw completely.

8.13.1 Withdrawal due to loss of capacity

If a participant loses capacity during their study involvement (prior to and including 20 week assessment), then no research procedures will be conducted and they will be withdrawn from the trial. Assessment of capacity after the final participant assessment is not feasible,

and therefore long-term outcomes via the MHSDS/medical records will be collected in accordance with the trial informed consent.

8.13.2 Documenting withdrawal

Withdrawal discussions will be documented in medical notes and on the REC approved withdrawal CRF, retained in the ISF and a copy stored in TMF.

8.14 End of trial

The study will finish at NHS research sites after the final assessment with the final participant is completed and the monitoring close-out visit has occurred at site.

8.14.1 Updating participants of the end of trial outcomes

Prior to the end of the trial, participants who have consented to be informed of study outcomes will be sent an end of study update in the form of a newsletter and/or video. A study update will be sent to participants after their trial participation at week 20 as well as after the study has completed data collection.

8.15 Long-term follow-up

Long-term outcomes (3 years post baseline) will be collected by the CI led central research team via the Mental Health Services Data Set (MHSDS) or medical records if the MHSDS is unavailable. This long-term follow-up activity takes place after research sites have closed and is limited to data collection via the MHSDS/medical records, meaning participants have no direct involvement with researchers at this stage. Sites will submit NHS numbers of consenting participants to the CI or delegate for this follow-up analysis. The CI or delegate will access personal data pertaining to the period from informed consent to 3 years after baseline assessment. The Assessing Transition to Psychosis study-specific CRF will measure transition to psychosis. The relevant data will be recorded and stored in a password protected computer file for the follow-up analysis under a participant code, no personal identifiable information will be recorded.

9.0 Data protection

9.1 Data controller and data processers

The Sponsor is the data controller for the trial. Data processers are NHS investigating sites, the electronic data capture software provider, and the contracted transcription service.

9.2 Personal identifiable information and anonymisation

Participants data provided for research will be pseudonymised and de-linked from their personal details such as name and address. Participant data will be stored under a unique participant ID number.

A participant recruitment sheet will record participant initials, hospital number and participant ID. It will thus serve as a code-breaker as required and enable researchers to access contact details to make appointments and to note entries onto medical records of contacts made for research, therapy sessions conducted, and any duty of care actions or concerns in accordance with local NHS record keeping standards.

9.3 Data storage and transfer

Collection, storage and transfer of participant data will abide by the Data Protection Act 2018, Good Clinical Practice (GCP) and local NHS policy. The DPA principles of transparency, data minimisation and storage limitation will be applied to the collection, use and retention of data. The data is processed under the legitimate basis of a task in the public interest for participants who have joined the study. The collection and use of the data will ensure appropriate safeguards are in place to protect individuals' confidentiality, and the quality of the data collected will be monitored to ensure accuracy and accountability.

Data collected as part of this research trial will be:

- Participant names on Informed Consent Forms (person identifiable). ICFs will be stored in the NHS Investigator Site File in a separate folder to any data case report forms or transcripts etc. ICFs will be transferred in a timely fashion from the location of consent to the ISF, stored in locked filing cabinets in locked offices on NHS premises and archived in the ISF at the investigating NHS site.
- For participants who consent to long-term follow-up via the MHSDS/medical records, NHS medical record numbers and copies of ICFs will be transferred securely to the Central research team at CNTW for secure storage in the TMF at CNTW and archive with the TMF. NHS medical record numbers and copies of ICFs will be sent separately. A long-term follow-up recruitment record with participant initials, consent date, and corresponding NHS medical record numbers will accompany the NHS medical record numbers. This transfer will occur after the last participant activity at sites to allow any potential withdrawals to be actioned prior to transfer.
- Assessment data (self-report) collected on paper or electronically (pseudonymised). This will be stored under a participant ID and transferred as an anonymous data set to the analysis team.

- Assessment data (researcher/clinician rated) collected on paper or electronically (pseudonymised). This will be stored under a participant ID and transferred as an anonymous data set to the analysis team.
- Audio recordings of therapy sessions (pseudonymised). Recordings will be made with the participant ID as the only identifier. Recordings will be taken using NHS Investigator Site IT approved encrypted password protected recording equipment* and stored securely at the investigating NHS site in a research folder on their server that is only accessible by authorised members of the research team. A sample of 10% of these recordings will be used for therapy adherence checks by an authorised member of the research team at the investigating NHS site. Following which the adherence checklist will be retained and the audio recordings destroyed.
- Audio recordings of qualitative interviews (pseudonymised). Recordings will be made with the participant ID as the only identifier. Recordings will be taken using NHS Investigator Site IT approved encrypted password protected recording equipment* and stored securely at the investigating NHS site in a research folder on their server that is only accessible by authorised members of the research team. These recordings will be securely transferred to the Sponsor NHS site as soon as possible for central storage, prior to batch transfer to the contracted transcription service. The contracted transcription service will be checked and authorised by the Sponsor to conduct this task in accordance with DPA. Confidential transcription and the review of the transcripts will involve an additional layer of anonymity checks and removal of any potentially identifiable information prior to analysis. Audio recordings will be destroyed (deleted) after receipt of transcripts.

*Where portable encrypted devices are used these will be password protected, stored in locked cabinets, and recordings will be downloaded onto the NHS server as soon as possible and deleted from the portable device.

9.4 Reporting data

Results reported in publications and other outputs will deal only with aggregated data, or de-linked qualitative illustrative quotes and will not include personally identifiable information.

9.5 Data incidents reporting

Any data related incidents will be reported to the Information Governance Team at the relevant NHS Trust using trust incident reporting procedures and to the research Sponsor.

10. Trial treatment interventions

10.1 MUSE Intervention

The MUSE intervention (as amended) is a novel targeted, computer/web based guided self-help psycho-education toolkit and psychological treatment manual for managing distressing hallucinations in mental health, developed and owned jointly by Durham University and CNTW. Patients work with experienced therapists, under expert supervision, who utilise the MUSE package within therapy sessions to develop a formulation explaining the development of hallucinations and foster new skills and strategies for their management.

The MUSE treatment is divided into the following Modules:

1) *What are Voices?* This module provides normalising information about the frequency of voices and the factors that tend to increase voice-hearing (for example substance misuse and sleep deprivation), along with testimonies from other voice-hearers.

2) *How the Mind Works*. This module outlines current understanding of key psychological processes such as threat detection, the importance of prediction (top-down processing) and how intrusive thoughts work.

3) *Assessment.* This module identifies the subtype of hallucination a service-user is experiencing. After the assessment the therapist should be able to identify whether the voice-hearing is an Inner Speech-Auditory verbal hallucination (AVH), a Memory Based AVH or a Hypervigilance AVH.

4) *Inner Speech.* This module provides psycho-education about the evidence that voice-hearing involves people not recognising their own inner speech. An individual understanding or formulation of voice-hearing experiences is co-produced and then targeted coping strategies and behavioural experiments are employed, such as means of interrupting and manipulating inner speech via singing or humming.

5) *Memory and Trauma.* This module provides psycho-education about how memories from trauma are more likely to be experienced as intrusive memories without contextual cues, and can therefore be experienced as belonging to the here and now. An individual formulation of how the memory may be experienced as a voice is followed by coping strategies and behavioural experiments that help people manage and reframe difficult memories.

6) *Hypervigilance.* This module provides psycho-education about how our brain uses prediction to interpret the world and manage the amount of sensory data received. If people are expecting threatening stimuli they may struggle to scrutinise poor quality sensory data and rely more heavily on predictions, whilst adopting a 'better safe than sorry' decision bias. These factors all make an individual more likely to hearing expected speech when it is absent. An individual formulation of how the hypervigilance hallucination occurred is developed and then targeted coping strategies and behavioural experiments are employed (such as reducing arousal and stress when under threat).

7) *Seeing Visions.* This module draws on these other modules, and explains how our visual perceptual system can lead to mistaken perceptions, for example how easily we see faces in clouds. An individual formulation and treatment plan is then developed that normalises the experience and addresses the key cause of distress and then targeted coping strategies and behavioural experiments are employed (such as training oneself to switch attention to and from visions).

8) *Sleep*. This module provides psycho-education and treatment strategies about sleep, which is often a key factor in all types of unusual sensory experiences.

The psychoeducation materials, behavioural experiments, and coping strategies included in the manual are refinements of existing psychoeducation, behavioural experiments, and coping strategies used in CBT for psychosis and related mental health problems (e.g., post-traumatic stress disorder, reducing arousal).

10.2 MUSE Treatment session measures

Treatment session measures will be used as part of the MUSE package to support therapists with participants to monitor any variations in hallucination frequency and distress. These sessional measures will be done at the beginning of the session and may then have a bearing on the selection of module used or revisited during the treatment session.

10.3 MUSE Intervention toolkit access

MUSE is loaded onto therapists smart tablet/NHS laptop (not reliant on Wi-Fi) and is available to patients via the CNTW website between sessions. No personal data are recorded or stored

on MUSE toolkit. Therapists are provided with step-by-step instructions for how to download MUSE onto an NHS laptop.

Clinicians open the desired module before the session (for example, 'How the Mind Works'), and then work through it with the participant, using the clinician's laptop. The only part of the MUSE package dependent on internet access is three videos that are copyrighted, but alternative videos that demonstrate the key learning have been included on MUSE, so progress is not dependent on internet access.

It is also possible to work through MUSE remotely (for service-users who request remote appointments), with the service-user and clinician working through the treatment together and discussing it using the phone or a video conferencing facility, such as Microsoft Teams. Alternatively, the clinician could use the share-screen function in Microsoft Teams.

10.4 Treatment as usual (TAU)

Both treatment groups will also receive regular monitoring, signposting to appropriate local services for unmet needs, social support and crisis management when required from the multi-disciplinary team. In an engagement meeting with the ARMS service leads, common core components of supportive psychotherapy were identified, which included needs based emotional support, psychoeducation, normalisation and stress management. These will be recorded in the TAU condition and used as a time matched intervention. However, variation across services precluded using this package of care as a comparison intervention

Participation in this trial will not lead to the withholding of any treatment based on clinical judgement and we will record the interventions received within TAU in both conditions.

10.5 Schedule of interventions

MUSE involves several weekly face to face sessions (~60min) of 6 core sessions with an option of two additional sessions. The number of sessions is based on previous work with other groups and feedback from ARMS therapists who currently employ MUSE in practice, but the clinician can choose to use the manual for more sessions, if they deem necessary. This design will ensure that participants receive adequate exposure to the manual in therapy sessions for us to determine its acceptability.

10.6 Therapists

The therapists will be either clinical psychologists or psychological therapists who are either accredited or working towards accreditation by the British Association of Behavioural and Cognitive Psychotherapists (BABCP) and be employed by the ARMS service. All therapists in the MUSE+TAU condition will have experience of MUSE through training and being part of previous studies.

10.7 Supervision

All therapists will receive usual clinical supervision. Additional fortnightly MUSE group supervision sessions will be offered whilst therapists deliver the intervention to support adherence to the model.

10.8 Treatment fidelity

Therapists will be asked to complete adherence checklists for each session. Adherence checklists will be specific to the intervention (MUSE / Supportive Psychotherapy).

Treatment fidelity will also be checked for participants in the MUSE arm of the study: With consent, each session will be audio-recorded to enable independent review of a random 10% sample to ensure fidelity to protocol within and across sites. Treatment fidelity will not be checked via audio recording for participants in the comparison arm of the study as this intervention is not constrained to one particular model.

Treatment fidelity will be assessed by the site PI or Co-Investigator/Clinical lead/Supervisor who is not a trial therapist.

11. Adverse Event (AE), Serious Adverse Event (SAE), and Urgent Safety Measures assessment and reporting

11.1 SAE assessment

A Serious Adverse Event (SAE) is defined by HRA Research Ethics Committee (REC) as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or,

(f) is otherwise considered medically significant by the investigator.

Sites shall inform the CI team within 24 hours of becoming aware of an SAE (see section 11.2: SAE reporting, below)

The Chief Investigator shall determine if an SAE is:
• "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.

For this protocol, we expect that there may be occasional untoward occurrence that are (b) life-threatening and (c) require hospitalisation.

11.2 SAE reporting
Sites will be provided with study safety reporting forms and guidance sheets for the reporting of SAEs.

Responsibilities of reporting are as follows:

- The site Principal Investigator (PI), or delegate shall report all SAEs within 24 hours of becoming aware of the event to the Chief Investigator (CI), or delegate via email to MUSE.ARMS@cntw.nhs.uk using the SAE reporting form.
- Local safeguarding and/or incident reporting procedures at sites shall also be followed.
- The CI, or delegate, shall report all SAEs to Sponsor within 24 hours following notification from site via email: CNTWsafetyreporting@cntw.nhs.uk
- Should the SAE be (i) Related and (ii) Unexpected then it must be reported to the REC within 15 days of the Chief Investigator becoming aware of the event. The report of the SAE shall be submitted by the CI or the Sponsor to REC and shall use the 'Non-CTIMP safety report to REC form' published on the HRA website: (See: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/)
- The CI, or delegate shall supply the Sponsor, REC and relevant NHS Trust R&Ds with any supplementary information they request.
- The Chief Investigator shall include SAE safety information within the annual progress report and within the final report to REC.
- The Trial Coordinator will track and record SAEs from each site and report on these monthly to the TMC.

- Urgent actions concerning participant and staff safety, communication with others, and clinical care will be immediately addressed by the Chief Investigator with the site Principal Investigators and reported to the TSC.

11.3 AE assessment

AEs will be defined as an untoward occurrence that does not meet the severity criteria to be counted as an SAE. This will be an untoward medical occurrence, unintended disease or injury, or untoward clinical signs in participants, whether or not related to the treatment.

AEs will be assessed during the research assessment timepoints of post intervention and follow-up to minimize bias between the reporting of each arm of the study. As this trial is investigating a psychological intervention, specific attention will be given to:

a) Clinically significant increases in distress and/or psychosis
b) Increased harm to self/harm to others
c) Increased suicidal ideation/attempts
d) Increased use of drugs/alcohol
e) Emergency room visits for mental health concerns
f) Access to crises services

AEs that meet any of the above criteria will be recorded and reported upon with additional information obtained on the following:

- Requirement of additional clinical care
- Impact on normal functioning
- Distress associated with completion of assessment measures
- Distress associated with therapy
- Distress associated with treatment as usual
- Severity in terms of mild/moderate/severe as detailed in the study guidance document

The Chief Investigator shall determine if an AE is:

• "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.

For this protocol, given the ARMS group consist of distressed young people, all of the above AEs would be expected in this study.

11.4 AE reporting

Sites will be provided with study safety reporting forms and guidance sheets for the recording and reporting of AEs.

Responsibilities of reporting are as follows:

- The site Principal Investigator (PI), or delegate shall record AEs and report these to the Trial Coordinator on a monthly basis using the study AE reporting form and submitted by email to MUSE.ARMS@cntw.nhs.uk.
- Local safeguarding and/or incident reporting procedures at sites shall also be followed.
- The CI shall assess the AE as per section 11.4 AE assessment guidelines above.
- The Trial Coordinator will track and record AEs from each site and report on these monthly to the TMC. The report will identify frequency, type, and severity of AE per trial arm.
- CI, or delegate shall provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety as specified in the protocol, via email to: CNTWsafetyreporting@cntw.nhs.uk.
- The Chief Investigator shall include AE information within the Final Report to REC. The Final Report will report numbers, types and severity of AEs by trial condition, as well as discontinuations, using descriptive statistics. AEs (from each site) will be pooled and reported quarterly to the TSC and monitored monthly at the TMG.
- The CI, or delegate shall supply the Sponsor, REC and relevant NHS Trust R&Ds with any supplementary information they request.

11.5 Urgent safety measures assessment

Should an investigator, or the research Sponsor have immediate concerns about a research participant or participants they may make appropriate changes to the conduct of a study in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. Urgent safety measures are defined in this protocol as actions by an investigator or Sponsor that meet the following criteria:

a) Early withdrawal of participant(s) due to safety concerns about the intervention or assessments
b) Changes to procedures due to concerns about staff or participant safety

11.6 Urgent safety measures reporting

Sites will be provided with study safety reporting forms and guidance sheets for the recording and reporting of Urgent safety measures.

Responsibilities of reporting are as follows:

- The site Principal Investigator (PI), or delegate, must inform the CI immediately by telephone (Tel. 01670844670 / alternatively Teams video/voice call for guy.dodgson@cntw.nhs.uk) of urgent safety measures defined above in section 11.5 (early withdrawal/changes to procedure due to safety concerns for staff or participants). This information shall be documented on the Urgent safety reporting form and submitted by email to MUSE.ARMS@cntw.nhs.uk.
- Local safeguarding and/or incident reporting procedures at sites shall also be followed.
- The Chief Investigator or Sponsor, or exceptionally the local Principal Investigator (PI) must inform the Research Ethics Committee (REC) who issued approval immediately by telephone and in writing by email within three days, that such measures have been taken and the reasons why.
- If the Urgent safety measure results in a non-anticipated change to research procedures then a substantial amendment shall be submitted within three days.
- Urgent safety measures will be reported monthly to the TMG by the Trial Coordinator and sent to the TSC chair by the CI.
- The Funder will immediately be notified on receipt of any information that raises material concerns about safety or efficacy, and of any recommendations from the TSC to end the trial.

12. Statistics and data analysis

12.1 Statistical analysis

Analyses will follow intention to treat principles, with data analysed according to randomisation irrespective of treatment received. A full statistical analysis plan (SAP) will be developed for the outcome measures and agreed with TSC before the end of data collection.

The effect of each arm (novel intervention MUSE+TAU versus TAU) on outcomes will be estimated as change from baseline as well as changes in the mean scores in each trial arm. All data will be summarised as appropriate using mean±standard deviation and median±interquartile range for continuous outcome data; frequency and percentages for binary or categorical data; and rate for count data. Analysis will be via the latest version of R.

The effects will be estimated using generalised linear mixed effect models with the appropriate distribution and link function. Normal distributions with identity link will be used for continuous outcomes, and negative-binomial distributions with log link for count data outcomes. All binary or categorical outcomes will be analysed using generalised estimating equations (GEE). The mixed-effects models and GEE account for the repeated measurements per participant over the follow-up time points. All models will be adjusted for treatment arms and stratification variables. The mixed model approach taken will allow identifying the individual effect of the two interventions w.r.t their baseline, as well as the difference in their effects through an interaction parameter of time and intervention. This can be considered as a model-based difference-in-difference analysis.

These models will be used mainly to estimate relevant parameters, since the trial is not powered for null hypothesis significance-testing. That is, while we are interested in identifying the magnitude of the signal of efficacy, we will not attempt to prove its significance.

In addition to estimating the difference between the intervention groups, structural equation models will be used to estimate the average causal mediation effects (ACME) and to examine how the different mechanism components mediate the estimated impact of the interventions on the primary outcomes. This will be carried out in further discussion with the research team to suggest possible candidates for the mediator variables. The mediation analysis may also inform candidate mechanisms for future trials.

A complier average causal effects (CACE) analysis will be carried out to determine the impact of the number of sessions on the MUSE effect. This analysis can be considered as a sensitivity analysis complementing the primary ITT analysis, which computes the effect that would have been obtained if all participants had fully adhered to the treatment that they were assigned to.

12.1.1 Dealing with missing data

If data are missing for a particular participant and outcome measure, this participant will be excluded from the analysis, for this outcome measure only, without further adjustment for missingness. However, the effect of missing data will be investigated additionally by sensitivity analysis using tabulation of rate of missing across trial arms and proper imputation methods. Sensitivity analysis for missing data will investigate the underlying missingness mechanism.

12.2 Qualitative interview analysis

Audio-recordings will be transcribed and analysed (in NVivo software). Interview transcripts will be analysed using thematic analysis(Braun & Clarke, 2006) allowing a transparent, replicable and robust process and demonstration of reflexivity and quality. Transcripts will be coded by two researchers until coding reliability is established; coding will then be conducted by one researcher, with reliability checks by the qualitative lead. Data will be extracted into a framework matrix, summarising data by category from individual transcripts, with quotations selected as illustrative exemplars. Initial findings from the qualitative analyses will be presented to LEAP for feedback on interpretation.

12.3 Health economic evaluation

As a feasibility study, we are not undertaking a formal economic evaluation. In consultation with RDS North-East, we will inform a health economic evaluation in a future definitive trial, piloting the ReQoL-UItility Index with the ReQoL-20 data for health economic analysis calculation.

12.4 Feasibility Trial success criteria

We will review the 14 ADePT (Bugge et al., 2013) items, and with input from LEAP and TMG develop a traffic-light system (above 80%: green; 60–79%: amber; below 60%: red) which will specifically focus on i) meeting recruitment/retention targets across sites; ii) acceptability of randomisation; iii) whether rated therapy tapes indicate acceptable adherence to treatment and therapy lasting ≥4 MUSE sessions; iv) completion of measures, including cognitive profile/process measures; v) reliable identification of subtypes.

Regarding signal of efficacy/proof of concept to inform a future trial, i) Go: primary outcome data suggest the intervention may show an effect indicating clinical value warranting further investigation; ii) Refine: primary outcome data indicate no measure of effect but one or more secondary outcomes indicates an effect; iii) Stop: no effect across any outcomes.

All Green outcomes: no/minor revisions prior to next development of the trial. One or more Amber (but not Red) outcomes: If feasible, substantial alterations to the trial protocol, assessments or intervention, supported by the qualitative work-stream and discussed with TMG and TSC prior to the next development of the trial. One or more Red outcomes: trial is unlikely to progress at that site or very substantial amendments are needed. We will also review the mechanism measures and tasks for sensitivity to change and reliability to inform the next development of the trial.

12.5 Long-term transition to psychosis analysis

Analysis of long-term transition to psychosis through the MHSDS/medical records is an exploratory feasibility analysis of about which features of MUSE (presentation, treatment response, mechanistic) are most relevant to psychosis prevention.

13. Data management

13.1 Monitoring

A monitoring plan will be used to check site procedures and data collection and reporting against study protocol, SOPs, and GCP. The monitoring plan will include review of:

- Participants enrolled, consent documentation, retention, and progress tracking
- Adverse events, reporting, and source documentation
- Site study records, the TMF, ISF, monitoring reports and responses
- Protocol & GCP deviations, recording, and corrective and preventative actions
- Data completeness and missing data
- Therapy adherence checks, feedback, and documentation of training, and corrective and preventative actions

Each NHS site will receive routine site monitoring according to the plan, and a monitoring close out visit. The plan will include data checks during and at the end of the trial after all data is collected, leading to a data lock prior to data analysis.

13.2 Audit

The Sponsor will include this trial within their annual audit plan. As an interventional trial, this study shall be subject to a 'first participant audit' following the first participant recruited to the study and an annual audit in accordance with the CNTW GCP Audits SOP. Additionally, study teams can request ad hoc audits where they feel this would be helpful.

13.3 Archiving

Archiving will occur at sites of ISFs and at Sponsor organisation of TMF. Essential documentation shall be archived until 3 years after the youngest subject reaches 18 years old, or 5 years after the conclusion of the study, whichever is longer.

14. Ethical and regulatory considerations

14.1 Ethical considerations

The main ethical issues in MUSE-ARMS arise from the patient population and the use of a new intervention. Patients may be engaging with mental health services for the first time, and will be experiencing potentially distressing pre-psychotic symptoms. The recruitment of patients to the study, including the timing and nature of the initial introduction to the study, have been carefully discussed with clinical teams and patients to ensure appropriateness. Patient representatives have also been consulted on the nature and timing of assessments, and agreed that they are suitable.

The novel MUSE intervention has already been tested in a non-randomised setting, with encouraging results indicating potential benefit (see appendix 3), and no related adverse events. All patients will continue to access treatment as usual, with half also receiving MUSE. MUSE is fully compatible with CBT, and thus does not undermine what we expect to be predominant TAU provision.

Patients will be free to choose not to attend sessions, and to withdraw from treatment and from the study, at any time and without their usual care being affected. Patients will continue to be under the care of the ARMS service, and treatment will be undertaken by trained practitioners, overseen by a senior member of the service. This would enable rapid review in the unlikely event that patients progress to psychosis within the timeframe of the study, or present with additional symptoms that require further clinical assessment and treatment.

MUSE-ARMS will be reviewed and approved by the Health Research Authority, and through this process by an NHS Research Ethics Committee prior to study inception. Additionally, Capacity and Capability assessment will be undertaken at individual centres, prior to a site initiation visit and the opening of the centre to recruitment.

Legislation and guidelines on storage and safeguarding of personal data will be observed throughout.

14.2 Regulatory considerations

14.2.1 Approvals

Before the start of the trial, approval will be sought from a REC and the HRA for the trial protocol, informed consent forms and other relevant documents, which shall be submitted through IRAS and approved by the Sponsor prior to submission.

14.2.2 Amendments

It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial. No amendments can be implemented prior to regulatory approval and Sponsor notification of amendments to sites, with the exception of Urgent Safety Measures, or non-notifiable non-substantial amendments as classified as such by the research Sponsor.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial and NHS R&D departments confirm they can be implemented in practice at sites.

14.2.3 Record keeping

Regulatory documentation and correspondence will be processed and filed as follows:

- All correspondence with the REC will be retained in the Trial Master File
- All approvals, amendments and confirmations to be retained in the Trial Master File and Investigator Site Files
- The notification of end of trial to the REC will be filed in the TMF and ISFs
- Final report to REC with the results, including any publications/abstracts, will be filed in the TMF

14.3 Patient and Public Involvement

To ensure a retained focus on patients, LEAP will include participants from the completed MUSE-FEP trial and ARMS service-users. Members will be recruited through advertisement via care coordinators in ARMS services. A focus will be made on recruiting people who have already received MUSE treatment, based on a recommendation of the MUSE-FEP LEAP. Their insight will enhance any feedback or advice provided by the group. Chaired by our PPI lead (Gibbs), LEAP will meet monthly in a mixture of online and face-to-face formats, with compensation of £20 an hour per attendee. LEAP will inform qualitative topic-guide development, shape trial procedures, including ensuring the study is inclusive, co-facilitate qualitative interviews, help disseminate study findings, and enable patient experience to inform design of future research and any revisions of the treatment.

Each member of the LEAP will be offered the opportunity to attend accredited training (co-facilitated by the PPI lead) offered through Northumbria University. This training comprises a 20-credit module at level 4. This training provides a foundation in knowledge in how research is designed and delivered. Skills in research delivery are also developed, including writing interview protocols, interviewing techniques and reviewing papers. This training should encourage a vibrant, assertive LEAP with the necessary skills to support the study in key tasks. We will ask graduates of this training to co-facilitate interviews alongside the researcher,

with support and supervision from our PPI lead and Qualitative Lead. We know that mental health difficulties are more prevalent in under-served groups(March et al., 2008) and recognise the importance of diverse LEAP membership to support our understanding of the study findings. All members of LEAP will also be offered the opportunity to join the TSC, and we will encourage at least two members of the LEAP to be permanent members of the TSC, with one taking a lead on trial procedures and the other on the inclusion of under-served groups. LEAP members of the TSC will be offered support before the meeting to encourage them to be active participants and a debrief after the TSC by the PPI lead and CI.

14.4 Indemnity

Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust has agreed to act as the sponsor for this research. Indemnity is, therefore, provided through NHS schemes. Dr Guy Dodgson, the CI, is an NHS employee, and the NHS indemnity scheme applies in his case. The study researchers are also employed by the NHS, and the NHS indemnity scheme applies in their cases.

Three of the co-applicants (Charles Fernyhough, Jochen Einbeck and Ehsan Kharatikoopaei) are employed by Durham University. Toby Brandon, is employed by Northumbria University. Both Northumbria and Durham University has in force a policy providing legal liability cover and the activities are included within that coverage for University's involvement in this study.

14.5 Competing interests

GD, RD, JS (PI TEWV), NB (PI CNTW) provide psychological therapies for individuals with psychosis in NHS settings. GD, RD, CF, NB, hold or have held grants to carry out trials of psychological therapy for individuals with psychosis.

15. Reporting and dissemination

15.1 Reporting to REC

It is the Chief Investigator's responsibility to produce the annual reports and end of study reports to REC, and shall be submitted as follows:

- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.
- An end of the trial report will be submitted to the REC within 90 days of the study ending using the appropriate form accessed on the HRA website. If the trial is ended

prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

- A final report will be submitted to the REC within one year after the end of the trial, with the results of the trial, including any publications/abstracts.

15.2 Reporting to the funders

- The First interim report is due within 6 months of the Commencement Date of the funding. This follows a format set out by the funders NIHR RfPB and shall include an outline of the Research Data, methods, an outline of any Foreground IP, Arising Know How results, Background IP and provisional conclusions together with management information and any other relevant information relating to the Research up to the relevant date.
- Subsequent interim reports are due every 6 months after the first interim report.
- A draft Final Report on the Research shall be submitted within FOURTEEN (14) CALENDAR DAYS of the Completion Date or date of termination the funders NIHR RfPB for comment and approval.
- A draft Final Report Summary of the findings for the Research in a form to be agreed with the funders NIHR RfPB shall also be submitted along with the draft Final Report for comment and approval.
- The Final Report and Final Report Summary shall be in a form to be agreed with the funders NIHR RfPB as amended from time to time or as otherwise required by the funders NIHR RfPB and shall include an outline of the Research Data, methods, an outline of any Foreground IP, Arising Know How, results, Background IP and the final conclusions of the Research together with management information and any other information relating to the Research up to the Completion Date.

15.3 Dissemination plan

15.3.1 Referencing and data standards:

Authors of publications for this trial shall ensure the following:

- An anonymised version of the main outcome quantitative data and mechanisms data will be available either in open access as encouraged by peer review publications or

from the trial team on reasonable request with publication of the trial outcomes paper and mechanisms paper.

- The MUSE toolkit is the joint intellectual property of Durham University and Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust. Studies using MUSE shall acknowledge this in all dissemination outputs.
- CNTW Sponsored studies are required to ensure the Sponsor, *Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust,* is named and acknowledged in all dissemination outputs.
- NIHR Grant holders are required to ensure that NIHR is named and acknowledged appropriately when submitting a paper or report for publication. Ensure that the following statement is included in any presentations, posters or papers: *This project is funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR204125). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.*

15.3.2 Peer review publication

The following papers shall be submitted for peer review publication from this trial:

a. Protocol paper

The protocol paper shall set out apriori the design, objectives, and outcomes measures investigated in the feasibility trial.

b. Trial outcomes paper

The feasibility trial outcomes paper will report on feasibility outcomes and the candidate primary outcome measures (SOFAS and PSYRATS).

Secondary reporting will detail the secondary treatment effects and influence of moderators.

Additional reporting will detail treatment integrity: data on treatment adherence to the model (sessions checklist data); exposure of participants to the interventions and additional treatments within usual care (CSRI data), the quality of treatment delivered and responsiveness of participants as reflected on by therapists and participants (STTS-R data, qualitative data), and the program differentiation between the novel intervention arm and the usual care arm (CSRI data).

c. Mechanisms Paper

The mechanisms paper will report on the analysis of secondary assessments for the purposes of informing which aspects of patient presentation the MUSE intervention works with, and informing the outcome measures in a future efficacy and mechanisms trial.

d. Long-term transition to psychosis

Long-term transition to psychosis through the MHSDS/medical records exploratory feasibility analysis will report which features of MUSE (presentation, treatment response, mechanistic) are indicated as most relevant to psychosis prevention.

15.3.3 Conference presentations

The research team, including the PPI team, will present the outcomes of the study in key forums. This will include the International Consortium on Hallucinations Research, the invitation only international CBTp Research leaders conference and the British Association of Behavioural and Cognitive Psychotherapists conference.

15.3.4 Public dissemination

This trial will benefit from the longstanding collaboration with the Hearing the Voice project. Public engagement has been at the heart of Hearing the Voice's activities since its inception in 2012. They have extensive experience of communicating research to the public, of co-creating research knowledge with non-academic partners, and of consulting and collaborating with individuals with lived experience. We will use our existing channels to communicate the findings of MUSE-ARMS, including our blog and Twitter feed (>5k followers) and our national and international media contacts.

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