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A randomized controlled trial comparing Avatar Therapy to Cognitive Behavioral Therapy in Schizophrenia with treatment refractory hallucinations

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SECTION 1 - THE NEED FOR A TRIAL

1.1 The problem: Treatment-resistant patients with schizophrenia Schizophrenia is associated with long-lasting health, social and financial burden, not only for patients, but also for families, caregivers and the wider society. The costs associated with hospitalization, lifelong treatment and loss of productivity lead to a great economic burden. In Canada, the total annual costs associated with schizophrenia are over $10 billion [1, 2]. The main reason for these heavy costs is that 25-30% of schizophrenia patients respond very poorly to antipsychotic medication [3]. For those who respond poorly to antipsychotics, the persistence of auditory verbal hallucinations (AVH) and their abusive utterances can take a major toll on patients. Unfortunately, psychotherapeutic treatment alternatives are very limited for this suffering population. ***This unmet clinical need requires innovation and action.*** Virtual reality (VR) opens exciting new avenues for the treatment of schizophrenia. As the patients' voices (hallucinations) are invisible entities, it is difficult to establish a direct relationship with them via traditional interventions such as *Cognitive Behavioral Therapy* (CBT). Using immersive VR, our laboratory recently tested a novel psychotherapeutic intervention, Avatar Therapy (AT), where the therapist engages in a dialogue with the patient through a virtual representation of the patient's distressing voice. This approach, being both dialogical and experiential, provides a unique opportunity to aid patients gain control over their voice by exposing them to the perceived threat and allowing them to experiment new strategies to respond to their voices. In a trial involving 15 schizophrenia patients with refractory AVH, we showed potent effects of AT on hallucinations (Cohen's d=1.0) [4]. Therapeutic effects were larger than those of traditional psychological interventions. Based on this success, we secured funding from Otsuka Pharmaceuticals to pursue a pilot Randomized-Controlled Trial (RCT) comparing AT to CBT. Preliminary results are already suggesting the superiority of AT in 39 patients on AVH, with therapeutic effects being of large magnitude. However, the main limitation of this pilot RCT was that the evaluators were not blinded to group allocation. Thus, we are now requesting funding from the CIHR to do a single-blind RCT seeking to demonstrate the superiority of AT over CBT. Such a demonstration would be a significant breakthrough in the field.

1.2 The research question: Does AT have a superior efficacy over CBT for the treatment of refractory auditory verbal hallucinations in schizophrenia?

Objectives: AT differs from CBT in that it is a *dialogical* and *experiential* approach which allows patients to enter in direct relation with their persecutory voice, and to experiment in vivo new strategies to respond to its threats. Based on the results of our pilot project, the ***primary objective*** of the proposed RCT is to verify if AT has a superior efficacy over CBT for the treatment of AVH in treatment-resistant patients with schizophrenia. The ***secondary objective*** will be to examine the effects of AT and CBT on the general symptomatology of schizophrenia, the quality of life, the beliefs and responses people have concerning their voice, the level of depression and the sense of presence in treatment-resistant schizophrenia patients with refractory AVH. The ***tertiary objective*** will be to explore if these superior improvements attributable to AT in comparison to CBT persist over time.

Hypotheses: Based on available evidence and our two pilot studies, the ***primary hypothesis*** is that AT will be superior to CBT in reducing the severity of AVH in treatment-resistant patients with schizophrenia at the end of the therapy sessions. The ***secondary hypothesis*** is that greater improvements will also be seen in positive psychotic symptoms and quality of life in the group receiving the AT, relative to the CBT group.

1.3 The need for this trial Schizophrenia is a severe psychiatric disorder, characterized by positive symptoms (delusions, hallucinations), negative symptoms (social withdrawal, amotivation), mood symptoms, and disorganized thinking [5]. For a majority of patients, the disorder follows a chronic evolution, with up to 80% of patients experiencing a psychotic relapse within 5 years [6]. The disorder severely impairs functioning, with 60-90% of patients being unemployed [7-9], and 60-75% being unable to sustain independent living [10]. Up to 10% of these patients die from committing suicide [11], and their life

expectancy is reduced by 20 years compared to the general population [12, 13]. According to the *World Health Organization*, schizophrenia is one of the top 10 causes of disability in developed countries.

Notwithstanding reliable evidence demonstrating the efficacy of antipsychotics for the treatment of schizophrenia [14], up to 1 patient out of 3 is treatment-resistant, and suffers from persistent psychotic symptoms, notably AVH [15]. A recent systematic review concluded that treatment-resistant schizophrenia is associated with substance use disorders, suicidal ideations, lower quality of life and functioning, and higher rates of hospitalization [16]. Based on 65 studies involving close to 5000 patients, it has been estimated that the annual costs are 3 to 11 times higher in schizophrenia patients with treatment resistance compared to those with adequate response [16]. This is mainly due to high numbers of hospitalization, causing **60%** to **80%** of the total economic burden of schizophrenia. Unfortunately, treatment options remain very limited for this complex population, apart from the antipsychotic 'clozapine', which provides modest benefits in this population [17].

AVH, or hearing "voices", are hallmark symptoms of schizophrenia [18], as their prevalence can reach up to 80% of these patients [19]. They are amid the most disturbing symptoms, and may cause significant anxiety and depression, and feed to suicidal and violent ideations [20]. To potentiate drug treatment, the most commonly used psychological intervention is CBT. Several studies have shown that CBT has modest clinical effects in schizophrenia, with low to moderate effect sizes [21]. However, only a minority of CBT studies have specifically targeted AVH. Moreover, most of these studies have tended to include patients with residual symptoms who do not meet proper criteria for treatment resistance [22].

Chadwick and Birchwood developed a comprehensive cognitive model of auditory hallucinations, which is the basis of CBT for voices [23]. According to this model, it is not the voice nor its contents that causes anxiety, but rather the way the patient interprets it. The stated aim of most CBT for psychosis (CBTp) is to improve tolerance towards the voice rather than directly change its frequency, mainly by modifying the appraisal of voices. Reducing the perceived power of voices and increasing the perceived control results in lowering distress [24]. The following components have been suggested as essential for CBTp: normalizing the psychotic experience, providing a range of meaningful alternative explanations, developing a shared understanding of the voices, changing the appraisal of the voices, testing unhelpful beliefs, reducing unhelpful coping strategies and increasing good coping strategies such as mindfulness. During this practice, patients ultimately learn how to better cope with their voice. The increased awareness of the cognitive processes underlying the patients' personal reactions to the voices enables them to develop an individualized formulation to make sense of their voices.

Although several trials have shown that CBT is effective in reducing the positive symptoms of schizophrenia, *up to 50% of patients do not respond* [25]. Even for those who have a response, *the effect size of the treatment is low to moderate* [26], as observed in our own pilot study. Thus, there is clearly a need to improve psychological therapies for schizophrenia patients with refractory AVH. One crucial explanation for the lack of efficacy of CBT for some patients is the fact that *patients are not in* ***direct relation*** *with their persecutory voices*. Typically, patients must imagine their persecutor and report the content of the voices to their therapist. Thus, CBT is not built to elicit strong emotions and to teach patients how to manage them during the therapy sessions.

The fundamental assumption of the current proposal is that treatment efficacy may be heightened by using a therapeutic approach with a strong ***experiential*** dimension in a secure environment. Compared to CBT, AT is an *experiential* intervention that permits the establishment of an intimate dialogue with the voice. Therefore, patients can learn how to *regulate* the strong negative emotions elicited by the persecutory voice, to be more *assertive* and to strengthen their sense of *self*.

Innovation in the treatment of auditory verbal hallucinations: The interpersonal dimension of AVH is increasingly acknowledged [27]. Based on this growing evidence, preliminary clinical work has shown that encouraging patients to enter in a dialogue with their voice(s) helps them develop a more constructive relationship with the voices and reduces their feelings of helplessness [28]. *Noteworthy, Dr O'Connor (co-investigator) was one of the first investigators at the international level to successfully use this approach for the treatment of disturbing inner voices* [29]. However, establishing communication with an invisible entity is difficult for both the patient and the therapist. To help overcome this clinical challenge, the group of Leff et al. [30] performed a ground-breaking proof-of-concept clinical trial where they used VR to recreate the face and the voice of the patient's persecutor. Their hypothesis was that engaging the patient in a dialogue with an external representation of their persecutor (e.g. avatar), with the support of the therapist, would aid the patient gain better control over their voice. Their randomized trial showed, in a small sample of 16 patients who had AVH for many years, that AT produced ***large*** improvements in hallucinations, whereas treatment-as-usual produced no effect. Recently, they extended their results in a randomized controlled trial comparing their computerized therapy to supportive counselling, which has doubtful efficacy for the treatment of AVH, as determined by meta-analysis [31-33]. Results showed the same large effect size of the therapy on AVH as their previous study [34, 35]. Given the important suffering associated with treatment-resistant schizophrenia, the promising results of their therapy deserve to be extended by an independent team. A direct comparison of AT to an evidence-based psychosocial intervention, such as CBT, recommended in international treatment guidelines [36-40] is currently critically lacking. ***The current trial is the first to propose to do so at the international level***.

1.4 Trial results AT may have implications for schizophrenia ***patients' health and quality of life that are potentially enormous***. Schizophrenia is an extremely complex disorder associated with significantly impaired social and occupational functioning. The current trial will contribute to the validation of a novel approach answering a *fundamental clinical need*. Although preliminary, the larger benefits reported by Leff et al. [30], Craig, Rus-Calafell [35] and by our own research team [4] are superior to the benefits of any other available psychological treatment at the moment for treatment-resistant schizophrenia.

Knowledge transfer plan: Our results will be diffused both locally and internationally at a variety of conferences and meetings; communications will be adapted for professional, academic and community audiences. Presentations in collaboration with patient-partners based on their testimonies will be delivered to voice hearing associations, support organizations, community groups and local clinics. Training based on the protocol will be offered at all levels, throughout the development of awareness of the protocols, as well as service delivery. Training will be systematized with the award of credits from professional orders for continuing medical education. The PI is active in voice hearers' associations and will publicize findings through this network. The PI and co-workers will act as consultants in the application of the protocol for mental health practitioners and service providers. They will also explore the commercial development of the protocol to benefit a wider population of Canadians.

Cost-benefit and implantation: The costs for VR systems are now low and easily accessible online and in stores (see **Annex I**), which make this technology simple to implement in clinical settings. The supplemental costs (i.e., VR material and application are around $10K) compared to CBT material are the costs necessary to offer a more effective therapy for some patients. The same material will be used for all VR therapy clients. Furthermore, with technological advancements (i.e., VR google), the therapy can take place in standard offices. Many psychiatric facilities have shown an interest to implement VR in their clinic (see letters of support). Further, the project will serve as a platform for a Trans-Canadian network on VR therapy for AVH, which will stimulate future patient-oriented research initiatives.

Study timeline: A detailed timeline has been included in the **Annex II** for this proposed 5-year study plan.

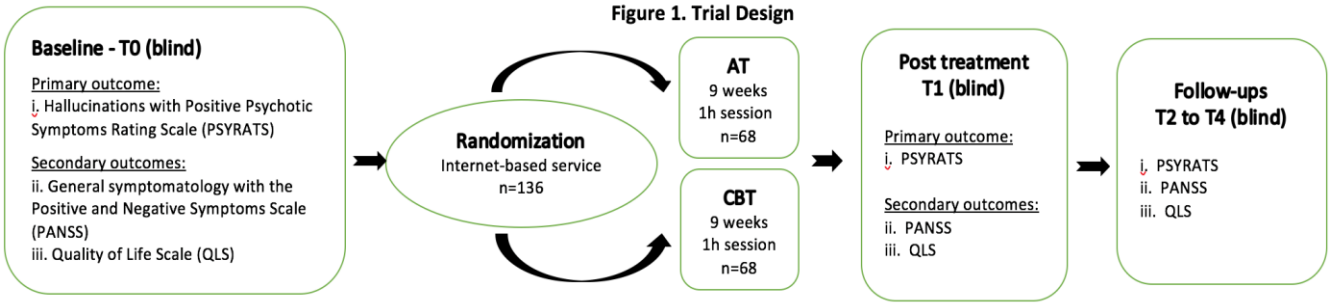
1.5 Risks to the safety of participants The main issue with the current trial is the tolerability of the first sessions of AT. Importantly, this issue has been fixed in our prior work [41]. As the first 2 AT sessions generate strong negative emotions in patients, this can lead them to consider quitting the therapy. In the trial

from Leff et al. [30], more than 30% of patients did not complete the trial. Being aware of this issue, we have integrated support provided by the therapist between sessions from the creation of avatar to session 3 or as needed by the patients. This support was also offered to CBT participants by the therapist. Additionally, we have upgraded our VR interface to make it more user-friendly reducing the time required to create the Avatar. Due to these improvements, we were able to lower the drop-out rate to 21.1%, which is very similar to the drop-out rate observed in CBT trials [42].

SECTION 2 - THE PROPOSED TRIAL

2.1 The trial design: Single-blinded randomized-controlled, single-site parallel study of AT versus CBTp developed in accordance with the CONSORT guidelines. Patients with schizophrenia or schizoaffective disorder will be randomized to receive either AT or CBTp. Conditions for treatment delivery, duration and monitoring will be equivalent across all allocations. Both groups will begin with a baseline clinical assessment before randomization (T0). Participants will receive 9 weekly sessions of 1 hour beginning within the next week after T0. After completion of the therapies, a post-treatment clinical assessment will be performed the week after the last session (T1). Follow-ups for treatment arms will be ensured 3 months (T2), 6 months (T3) and 12 months (T4) after the post-treatment clinical assessment (T1) during which patients will receive treatment-as-usual from their treating team. No further treatment from the research team will be offered after T1 apart from their regular appointments with their psychiatrist and other professionals.

Figure 1. Trial Design



2.2 The trial interventions: AT (experimental) and CBTp (control)

Avatar therapy (AT): As in our pilot projects, patients will undergo 9 weekly sessions. The first session of AT consists of the avatar creation/case formulation. Patients will create an avatar best resembling the most distressing person or entity believed to be the source of the malevolent voice, which will be designed to closely have both the face and the voice of the "persecutor". Patients hearing several voices will be requested to select the most distressing voice or the most dominant one for the creation of the avatar. Patients will create their avatar with the support of the therapist. The avatar's face will be created using the Morph3D character system and the *BehaVR* software and rendered with Unity game engine. The avatar's voice will be simulated by modifying in real-time the therapist's voice with the voice transformer Roland AIRA VT-3. Prosody lips synchronization will be performed via the SALSA with *RandomEyes* Unity asset. Patients will be immersed in VR through the Samsung GearVR head-mounted display and the Samsung Galaxy S6 smartphone. The virtual environment will consist of an avatar standing in the dark, seen from a first-person perspective. This VR environment has been developed and validated by the VR research team of the *Institut Philippe-Pinel de Montréal* [41, 43, 44], using major infrastructure funding from the Quebec government. It is the same environment that we successfully used in our initial trial on the AT [41]. The therapy will be provided by 2 licensed psychologists trained by Dr. Dumais. The therapist will talk to the patient through the voice of the avatar. The therapist's speech will be voice transformed in real time and played to the patient. The avatar will be animated with lip movement to increase the feeling of presence. Prior to the second session, the patient will have written down sentences used by their "persecutor" that are generally menacing (e.g. "you are stupid"). In sessions **2** and **3** ("*Exposition*" & "*Opening*"), patients will be confronted to the reproduced hallucinatory experience. The therapist will induce a dialogue between the patient and its avatar with the help of the sentences he/she provided. The patient will be encouraged to enter in a dialogue with

the avatar to improve emotional regulation and assertiveness. Self-esteem will be the therapeutic target in sessions **4** and **5** ("*Reconciliation*" & "*Self-esteem*"), which will be reinforced by enabling the patients to consider their personal qualities. At the 5th session, the therapist will include into the dialogue a list of qualities provided by the patient's close relatives (e.g. their mother). Over the course of sessions, the therapist will gradually modify the avatar's speech and tone to resonate with the patient's increased sense of empowerment. The avatar will thus change from being abusive to being more helpful and supportive. In the final consolidation sessions (**6 to 9**), patients will be encouraged to apply what they had previously learned in the experiential sessions.

Figure 2. Avatar Therapy (AT)

Session	Theme	Description
1	Avatar creation/ case formulation	Reproduction of the face and the voice of the "persecutor"
2 and 3	Exposition & Opening	Reproduction of the hallucinatory experience
4 and 5	Reconciliation & Self-esteem	Self-esteem, dialogue on the patient's qualities
6 to 9	Consolidation	Regulation of emotions and sense of empowerment

In the case that the patient becomes distressed or exceedingly anxious at any moment during the therapy, the session may be ended. At the end of each AT session, the feeling of presence will be evaluated with the *Igroup Presence Questionnaire,* a 14-item scale measuring the subjective sense of being in a virtual environment [45]. Importantly, in our pilot trial, the feeling of presence reported by patients was very strong (8.2 on a scale from 0 to 10), and this feeling of presence was maintained throughout the trial [41]. AT has been manualized (see **Annex III**), and all sessions have been audio-recorded. The verification of the recordings of 12 AT participants was performed by an independent rater with a grid developed to assess adherence to the manualised approach and to validate treatment integrity [46, 47]; moreover, our pilot data has shown large effects on AVH at the same level as available studies [4, 30, 35]. This confirms the content and convergent validity of our AT.

Cognitive Behavioral Therapy for psychosis (CBTp): Participants will be offered 9 weekly sessions of 1 hour, which will be administered in an individual format by 2 licensed psychologists trained in CBTp by Dr. O'Connor who has trained 35 psychologists throughout his career. The CBT program is derived and adapted from current evidence-based treatments for hallucinations [21, 48]. It has been manualized (see **Annex IV)**. The first session involves the voice history/case formulation. CBTp sessions will consist of a succession of learning modules and suggested task assignments (see **Figure 3**). Our adapted CBT has been developed by experienced researchers specialized in psychotherapies and has been overseen by Dr. O'Connor. All sessions have been audio-recorded. To ensure overall treatment integrity, an independent rater has verified, following an extensive evaluation grid, the recordings of 10 CBT participants. This permitted to establish that the sessions correspond to the contents and theme sequences covered in the manual. Moreover, our pilot data showed that the efficacy of our CBTp is in the same therapeutic range as other CBT interventions, as shown in a recent meta-analysis [26]. This confirms the content and convergent validity of our CBTp.

Figure 3. Cognitive Behavioral Therapy (CBT)

Session	Theme	Description
1	Voice's history/case formulation	History of the voice for goal setting
2	Psychoeducation and normalization of the hallucinatory experience	Assessment of hallucinations
3	Presentation of the cognitive model of hallucinations	Learn about hallucinations with voice journals
4	Metacognition 1- Attribution	Learn about diverse attributional mechanisms
5	Coping mechanisms	Interpretation of situations
6	Metacognition 2- Modification of beliefs and formulating alternative explanations	Final voice journal to detect the beliefs that are the cause of their ill-being
7-8	Mindfulness and Hallucinations 1 and 2	Practice mindfulness exercises, ask for feedback and learn to observe
9	Conclusion	End of the intervention and relapse prevention

2.3 Randomization method After completion of baseline assessment (T0), patients will be randomly assigned to a 1:1 ratio to either AT or CBTp. The sequence generation and allocation concealment will be ensured using an independent and secure Internet-based service (https://www.sealedenvelope.com) that conceals assignments by giving the allocation available one person at a time as the patients are enrolled. Treatment assignment will be determined by permuted block randomization with varying block sizes, which ensures that the researchers and research team members will not be able to predict the exact assignment sequence. Randomization will use cohort stratification to balance assignments according to potential confounding factors. Stratification will account for the potential confounding effects of gender and clozapine. Clozapine has a small-to-moderate superior efficacy for the treatment of refractory hallucinations in schizophrenia [20]. The inclusion of an equal ratio of men and women in each treatment arm will allow to perform exploratory analyses on potential gender differences. Importantly, 17 RCT conducted by our research team (Drs. Stip, O'Connor, Potvin and Dumais) on psychological, technological and pharmacological interventions, including 5 clinical trials funded by the CIHR [41, 49-64] and one recently funded trial by the CIHR (O'Connor 2018) have used the same methodology.

2.4 Blind assessments The study coordinator, the therapists and the participants will be aware of the interventions after the allocation randomization. The principal investigators and independent evaluators will be blind to the random allocation conditions. The participants will be reminded before each assessment to not disclose their allocation and all evaluation sessions will be audio-recorded. The same participant will be assigned to the same evaluator over time to lower the inter-rater reliability bias except for inadvertent nonblinding situations. In the event of unblinding, a new evaluator will be allocated to the participant and will assess the audio-recorded session (without the unblinding sequence) and take over the remaining follow-ups. Independent evaluators, will receive no information other than the participants' psychiatric history with the allocation sequence of randomization concealed. A research nurse will complete a short psychiatric history (diagnosis, age at the beginning of psychosis, medication during last 6 months, principal symptomatology and prior hospitalizations) before the randomization. The evaluators will be separated from the therapists by working at a separate location on the hospital grounds and will sign agreements not to discuss cases with any other team member. Management of evaluators will be delegated to a coordinator preventing any direct contact between the investigators and the independent evaluators. The same procedures have all been used successfully by Dr. O'Connor previously [65] and in a recently funded grant from the CIHR (O'Connor, 2018).

2.5 Inclusion and exclusion criteria The sample will include 136 eligible patients (68 per intervention group), men and women, of 18 years and older meeting the DSM-5 criteria for either schizophrenia or schizoaffective disorder. Diagnoses will be established with the Structured Interview for DSM-5 [66]. Patients will be recruited in the Montreal region from many psychiatric facilities highly interested to participate in the trial (see letters of support). Patients will be included if they have been hearing persecutor voices that did not respond to ≥2 antipsychotic trials, each lasting for more than 6 weeks with chlorpromazine equivalent daily doses of ≥ 600 mg and ≥80% of doses being taken (as determined by dispensing chart reviews and carer reports). This definition of treatment resistance is based on the recommendations from the *Working Group Consensus Guidelines on Diagnosis and Terminology* recently published in the *American Journal of Psychiatry* [67]. Adjuvant medications will be allowed. We will only recruit patients with stable doses of medication during the last 2 months prior to enrollment. Exclusion criteria will be as follows: (1) neurological disorders; (2) intellectual disability; (3) substance use disorders (in the last 6 months); (4) unstable and serious physical illnesses; (5) experiencing an acute psychotic episode; (6) having received CBT for the treatment of positive symptoms; and (7) requiring changes in medication during the clinical trial. The coordinator will validate the inclusion and exclusion criteria with the help of medical files and the clinical team. Inclusion and exclusion criteria are identical to those used in our successful pilot trial [41]. Psychiatrists will be requested to keep the medication type and dosage stable during the interventions (from T0 to T1). This procedure was successfully done through our pilot trials. During follow-ups post-therapies (from T2 to

T4), we will document medication dosages. All modifications will be controlled for in the final analysis. The trial will be registered on the clinicaltrials.gov website.

2.6 Duration of treatment period Both interventions consist of 9 consecutive weekly sessions of 1 hour.

2.7 Frequency and duration of follow up To verify if the improvements attributable to AT persist over time, the participants will be met after the post-treatment clinical assessment (T1), at 3 (T2), 6 (T3) and 12 (T4) months following T1 (3 follow-ups).

2.8 Primary and secondary outcome measures

Primary outcome will be evaluated with the auditory hallucination subscale of the *Psychotic Symptoms Rating Scale* (PSYRATS) [68], measured at baseline assessment (T0) and post-treatment assessment (T1). This subscale comprises of 11 items evaluated by interview, which provides a detailed measure of the frequency and the quality of the hallucinations (e.g., negative content, controllability, impact, distress, etc.). The PSYRATS is the instrument that was used to evaluate the primary outcome in the trials of Leff et al. [30], Craig, Rus-Calafell [35] and our research team [4], and the most frequently used scale in CBT trials on AVH. The PSYRATS has excellent psychometric properties (see **Annex V**). Importantly, the PSYRATS measures the multiple concerns expressed by patients during the 3 focus groups performed prior to this grant application. The choice of this primary outcome best captures the multi-component complaints of the 15 schizophrenia patients that were consulted during 3 different focus groups prior to the current grant application. Indeed, during these focus groups, patients expressed concerns not only about the frequency and intensity of the voice, but also about the negative content of the utterances and the distress caused by them.

Secondary outcomes: Positive psychotic symptoms will be measured with the *Positive and Negative Syndrome Scale* (PANSS) [69]. The PANSS is one the interview scale the most often used to measure positive symptoms in clinical trials on psychological interventions in schizophrenia, and is the scale that we successfully used in our two pilot studies [4]. Quality of life will be measured with *Quality of Life Scale* (QLS) [70], that we are successfully using in our ongoing pilot trial. Enjoyment and satisfaction will also be measured using the *Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form* (QLESQ-SF), a 16-item self-report scale measuring enjoyment and satisfaction experienced during the past week in various areas of daily functioning (score range from 16 to 80) [71]. Other general psychopathology measures will include measures of negative (e.g., social withdrawal) and affective symptoms, which will be assessed with the PANSS and the *Calgary Depression Sale for schizophrenia* (CDS), respectively. The CDS is a 9-item semi-structured scale to assess the level of depression in schizophrenia (score range from 0 to 27) [72]. Improvements in the beliefs about voices will be measured with the *Beliefs about Voices Questionnaire – Revised* (BAVQ-R), a 35-item self-report measure designed to assess key beliefs and responses people have concerning their voice. (score range from 0 to 105). This questionnaire includes 3 subscales: Malevolence (0-18); Omnipotence (0-18); and Benevolence (0-18) [73]. Changes in the sense of presence will be assessed using a 14-item scale, the *Change in Igroup Presence Questionnaire* (IPQ) [74]. As for ***safety measures***, treatment emergent Adverse Events will additionally be collected with the *Negative Effects Questionnaire* [75]. All these instruments are available in French and in English and have excellent psychometric properties (see **Annex V**).

2.9 Outcome measurements at follow up Primary and secondary outcomes will also be measured during the follow-up visits at T2, T3 and T4 **(Fig 1)**. The assessments will be identical for all time measurements.

2.10 Sample size justification In view of the large effects of AT on AVH observed by available studies [30, 35] and by our pilot data, in addition to the small to moderate effects of CBT [26] on these symptoms, we are expecting to observe a superior efficacy of AT over CBT (f, effect size for the difference on AVH is estimated at 0.25). We thus estimated with G-Power that the recruitment of 52 patients per intervention group will allow to detect superior effects (using pre- and post-therapy assessments) of AT over CBT on auditory hallucinations with a statistical power of 80% and an alpha of 0.05. To include the predicted attrition

of 20% (based on our ongoing trial) and 5 degrees of freedom to control for possible confounders, the total sample to recruit will be 68 per group (52x2=104; 104+5=109; 109/0,8=136 total; 136/2=68 per group).

2.11 Health service research issues: Our pilot data has been showing a greater improvement in the quality of life of patients after AT compared to CBT. We have thus included the QLS in the trial. The effect size for the difference on quality of life is estimated to be at least moderate (f, effect size of 0.25), which indicates that 68 patients per intervention group is enough to demonstrate the superiority of AT over CBT with a statistical power higher than 80% and an alpha of 0.05.

2.12 Recruitment We did presentations in various centers quarterly, resulting to the referral of at least one patient reference weekly. Since March 2017, we have been able to recruit at least 3 patients per month in the project. The recruitment of 136 schizophrenia patients with treatment resistance within 4 years is feasible (from April 2019 to January 2023) (see **Annex II** for a detailed Timeline).

2.13 Acceptability and adherence To estimate the acceptability of both interventions, we conducted a short survey on 10 patients. Patients reported that both therapies were helpful. As for AT, the initial sessions were more emotionally challenging, though as the sessions went on, they acquired more self-confidence. CBT participants, on the other hand, reported that the therapy did help to better understand their voices, however, they would lack the motivation to complete their homework (voice journal). Moreover, overall acceptability and adherence were measured based on our pilot data of 39 participants. We had an enrollment rate of 85% (i.e. patients assessed to be eligible and consented to participate) and a patient retention rate of 80% (i.e. completed the treatment), which is very similar to the rates observed in other CBT trials [42]. These observations confirm the strong acceptability of both treatments.

2.14 Follow-up rate Based on our current experience with the project, only 2 participants have not responded to their follow-up appointments. This results in a follow-up rate of 95%. In addition to scheduling assessments 2 weeks beforehand, as we are currently doing, the coordinator will give participants a courtesy-call the day before their appointment and the participants will receive a compensation at each assessment.

2.15 Centers Our research team has access to large cohorts of schizophrenia patients receiving treatment at the Mental Health University Institute of Montreal (1,500 patients) and the Philippe-Pinel Institute (300 patients). In the last 3 years, we have also established collaboration with many other clinical teams in the Montreal region (see letters of support).

2.16 Types of analyses To compare the effects of both interventions (AT and CBTp) on the primary outcome (e.g. AVH) from T0 (baseline) to T1 (end of both therapies), we will perform linear mixed-effects models (LMM) analyses [76-81]. Such analyses have been successfully used by Dr. O'Connor in CIHR-funded RCTs [82, 83]. The major capability of LMM is that it handles unequal variances and correlated data, which are very common in treatment trials. LMM also allows for an unequal number of repetitions. LMM procedure applies both fixed and random effects, which make it suitable for clinical trial data. LMM is based, furthermore, on maximum likelihood methods, versus the usual analysis of variance (ANOVA) methods, which require sphericity of data, and are not robust using small to moderate sample sizes. LMM thus presents a clear advantage over ANOVA methods in modeling real data. There will be a per-protocol analysis and an intention-to-treat analysis with the inclusion of withdrawals to yield a more conservative effect of treatments. Potential differences in socio-demographic variables at baseline will be considered as co-variates. The effects of both interventions on secondary outcomes from T0 to T1, as well as the effects on both interventions on primary and secondary outcomes *during the follow-up* (T2, T3 and T4) will also be assessed using linear mixed models.

2.17 Frequency of analyses A statistician will perform analyses on recruitment rates, retention rates, compliance rates and adverse events every 6 months for the safety data committee. The analysis of primary and secondary outcomes will be performed at the end of the trial.

2.18 Subgroup analyses Due to stratification, an equal number of men and women will be assigned to both treatment arms to examine the gender differences in both interventions. Our primary goal is to show the superior efficacy of AT on AVH. In our pilot data, we did not see any sex nor gender differences in this regard. We will nonetheless ensure this by completing an exploratory analysis on gender at the end of the study.

2.19 Pilot study Inspired by the study of Leff et al. [30], which used a simple laptop, we made the necessary technological improvements to offer patients a therapy with an enhanced feeling of presence and immersion. We first built a 3D therapy for a specific population of schizophrenia patients with well-defined treatment resistance and conducted a partial cross-over trial comparing AT to treatment-as-usual. In a sample of 15 patients, we showed that AT produced a large improvement in AVH, while treatment-as-usual showed no therapeutic effects. Notably, *clinical improvements remained significant at the end of the 3-month follow-up*. These results suggest that AT is a highly promising intervention for refractory AVH in schizophrenia. These findings have been published on line in *Schizophrenia Research* [4]. In addition to gathering this very promising data, we also adapted the well-known CBT developed by Birchwood and Chadwick [32] to ease future comparisons with AT. CBT was chosen as it is the best evidence-based psychological treatment for psychosis, while benefits are small to moderate [26]. Our research team secured a funding from *Otsuka Pharmaceuticals* allowing us to perform the pilot RCT comparing AT to CBT for the treatment of refractory AVH in schizophrenia. This 9-week modified CBT was administered to 16 schizophrenia patients and the intervention showed small to moderate effects on AVH that are in the *same therapeutic range* as a recent meta-analysis [26]. Preliminary results of this new trial comparing CBT (16 patients) and AT (23 patients) showed a trend toward the superiority of AT over CBT on AVH, positive symptoms of schizophrenia and quality of life. For the 3 outcomes, the difference between treatments was in the moderate range. The superior improvements attributable to AT were also present at the end of the 3-month follow-up. Recent evidence from other studies [30, 35] and our own phase-II clinical trial [4] justifies the importance of moving forward to now compare AT with another evidence-based psychotherapy (CBT) by using a more rigorous methodology. Thus, we are now requesting funding from the CIHR to do a single-blind RCT seeking to show that AT is superior to CBT for the treatment of refractory AVH in schizophrenia.

SECTION 3 – TRIAL MANAGEMENT

3.1 Day to day trial management

The study coordinator will be responsible of assessing patients' eligibility, obtaining informed consents and enrolling participants in the trial. The coordinator will ascertain intervention assignment by means of an external centralized website for randomization that will be independent of the recruitment process. After the randomization process, the coordinator will contact the corresponding therapist to provide participant information. The coordinator will manage the assessments to evaluators and participants for all time-measures, the inter-rater reliability simulations, and the data handling. He or she will also document medication dosages during follow-up assessments.

The therapists will conduct the 9 weekly sessions and offer support between sessions if needed. Independent counselling psychologists will conduct treatment-integrity evaluations twice yearly based on audio-recorded sessions and grids developed to assess adherence to manualised approaches and skills in delivery.

The independent evaluators having clinical experience with psychotic patients will be masked from objectives, hypotheses and intervention allocations. Inter-rater reliability simulations will be completed every 4 months with the coordinator.

The statistician will be masked from intervention allocations. He will produce outcome analysis at the end of the study and will produce a report to the data safety committee biannually or upon request. Statistical analyses will be performed by CE Giguère, a full-time biostatistician at the Mental Health University Institute

of Montreal. He has more than 15 years of experience and he is currently involved with more than 20 researchers at the Centre for different ongoing clinical trials on psychosocial interventions.

Data handling Data will be stored and processed anonymously, and codes will be allocated to each patient. We will use coded software designed to store and retrieve research data, which will be converted into SPSS or EXCEL files. Data flow will be monitored on a patient-by-patient basis by the coordinator with a summary file to provide information on patients' current status.

The data safety committee and stopping algorithm The committee will include a researcher with experience on RCT studies, a psychologist or a psychiatrist with clinical experience with this population, a biostatistician knowledgeable about statistical methods for clinical trials and a patient representative. The members will be external to the project. During biannual meetings, the statistician will present the statistics on recruitment rates, retention rates, compliance rates and analysis of adverse and major events, if any (e.g., psychiatric hospitalization). During the therapy, if there is a higher occurrence of a major adverse event in one group compared to the other ($p<0.1$) the committee will conduct a risk-benefit analysis. If the committee considers the risks to clearly surpass the benefits, the trial will be terminated immediately.

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