Chanen Andrew (Orcid ID: 0000-0003-4468-622X)
Cotton Sue (Orcid ID: 0000-0002-9386-8348)

Aripiprazole compared with placebo for auditory verbal hallucinations in youth with borderline personality disorder: Protocol for the VERBATIM randomised controlled trial

Authors:

Andrew Chanen, Email: andrew.chanen@orygen.org.au*

Jennifer Betts, Email:

Henry Jackson Email: henryjj@unimelb.edu.au

Patrick McGorry, Email: pat.mcgorry@orygen.org.au

Barnaby Nelson, Email: Barnaby.nelson@orygen.org.au

Sue M. Cotton, Email: sue.cotton@orygen.org

Cali Bartholomeusz, Email: cali.bartholomeusz@orygen.org.au

Martina Jovev, Email:

Aswin Ratheesh, Email:

Christopher Davey, Email: christopher.davey@orygen.org.au

Christos Pantelis, Email: cpant@unimelb.edu.au

Louise McCutcheon, Email: louise.mccutcheon@orygen.org.au

Shona Francey, Email: shona.francey@orygen.org.au

Amit Bhaduri, Email: amit.bhaduri@orygen.org.au

Danielle Lowe Email: danielle.lowe@orygen.org.au

Victoria Rayner, Email: victoria.rayner@orygen.org.au

Katherine Thompson, Email: katherine.thompson@orygen.org.au

Affiliations:

[1] Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne, Australia.

[2] Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia.

[3] Orygen Youth Health, Northwestern Mental Health, Melbourne, Australia.

[4] Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia.

[5] Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Melbourne, Australia.

***Corresponding author:** Professor Andrew Chanen

Orygen, the National Centre of Excellence in Youth Mental Health

35 Poplar Rd, (Locked Bag 10), Parkville VIC 3052, Australia

andrew.chanen@orygen.org.au

Phone: +61 3 9342 2800

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Abstract:

Background: Up to half of patients with borderline personality disorder report auditory verbal hallucinations that are phenomenologically indistinguishable from those in schizophrenia, occur early in the course of the disorder, and are enduring, distressing, and disabling. In clinical practice, this symptom is widely assumed to be unresponsive to treatment with antipsychotic medication and early intervention is rarely offered. The Verbal Experiences Response in Borderline personality disorder to Aripiprazole TrIal Medication (VERBATIM) study aims to be the first controlled trial to investigate the effectiveness of conventional pharmacotherapy for this symptom in this patient group.

Methods/design: VERBATIM is a 12-week, triple-blind, single-centre, parallel groups randomised controlled trial, with a 27-week follow-up period. Participants between the ages of 15 and 25 years receive either aripiprazole or placebo daily, commencing at 2 milligrams and increasing to 10 milligrams by day 15. Further dose escalations (up to 30 milligrams) may occur, as clinically indicated. The primary outcome is severity of auditory verbal hallucinations assessed using the Psychotic Symptom Rating Scale. Secondary outcomes include the severity of general psychopathology, borderline personality pathology, social

and occupational functioning, and change in brain resting state connectivity. The primary endpoint is week 12 and secondary endpoint is week 39.

Conclusions: The results will inform treatment decisions for individuals with borderline personality disorder who present with auditory verbal hallucinations.

Trial registration: Prospectively registered with the Australian and New Zealand Clinical Trials Registry ACTRN12616001192471 on 30/08/2016.

Keywords: aripiprazole, hallucinations, borderline personality disorder, controlled trial, psychosis.

Introduction

Borderline personality disorder (BPD) is a severe mental disorder that occurs in one in five adolescent or adult psychiatric outpatients (Chanen, Jovev, et al., 2008; Zimmerman, Chelminski, & Young, 2008). There is now strong scientific evidence that BPD has its clinical onset in adolescence and emerging adulthood (*young people*; age 12-25 years) and can be diagnosed in this age group (Chanen, 2015; Chanen, Sharp, Hoffman, & Global Alliance for Prevention and Early Intervention for Borderline Personality Disorder, 2017).

Although, BPD is commonly characterised by features such as emotion dysregulation, impulsivity, and relationship and identity instability, (Leichsenring, Leibing, Kruse, New, & Leweke, 2011), it also has distinctive cognitive and perceptual features. These include paranoia, suspiciousness, dissociation, along with impairments in episodic memory, negative personal schemas, and executive neurocognition (Fertuck & Stanley, 2006). Significantly, 22-50% of patients with BPD experience auditory verbal hallucinations (AVHs)(Kingdon et al., 2010; Pearse, Dibben, Ziauddeen, Denman, & McKenna, 2014).

Psychotic symptoms have been recognised in BPD since the 1940s (Hoch & Polatin, 1949). Diagnostic and Statistical Manual of Mental Disorders 3rd Edition (DSM-III (American Psychiatric Association, 1980)) era studies reported that

psychotic symptoms among people with BPD were common, of short duration, transient in nature, and did not significantly affect patients' lives (Chopra & Beatson, 1986; Gunderson, Carpenter, & Strauss, 1975; Miller, Abrams, Dulit, & Fyer, 1993; Zanarini, Gunderson, & Frankenburg, 1990). However, these studies were methodologically flawed because they excluded BPD patients who had co-occurring psychotic disorders and they did not directly compare BPD patients with other patient groups. A particular legacy of these studies is perpetuation of the term *pseudohallucination* to describe AVHs in BPD, despite the absence of empirical support for this construct (Berrios & Dening, 1996; Larøi et al., 2012; van der Zwaard & Polak, 2001).

More recent studies, using standardised instruments, have found that AVHs among individuals with BPD have a mean age of onset of 16 years (Slotema et al., 2012; Tschoeke, Steinert, Flammer, & Uhlmann, 2014; Yee et al., 2005)), are commonly enduring, and are phenomenologically indistinguishable from AVHs among individuals with schizophrenia (Hepworth, Ashcroft, & Kingdon, 2013; Kingdon et al., 2010; Pearse et al., 2014; Slotema et al., 2012; Tschoeke et al., 2014). Indeed, compared with patients with schizophrenia, patients with BPD find their AVHs significantly more distressing and negative (Kingdon et al., 2010). Comparing BPD patients with and without AVHs, the presence of AVHs is associated with greater suicidal ideation and more suicide attempts and hospitalisations (Slotema et al., 2017). To date, the neurobiological mechanisms

that underlie AVHs in BPD have not been studied.

In schizophrenia, AVHs are commonly treated with first or second generation antipsychotic (SGA) medication (Yow & Jayaram, 2017). Studies conducted in youth with first-episode psychosis have shown a greater tolerability and efficacy for SGA medications, but no difference in outcome according to medication type (Datta, Kumar, Wright, Furtado, & Russell, 2014; Kumar, Datta, Wright, Furtado, & Russell, 2013). The clinically significant side-effects from, and long-term complications associated with, antipsychotic medications suggest that they should be used only when there is a clear clinical indication for treatment, such as clinical distress, behavioural disturbance or functional impairment associated with positive psychotic symptoms (Pagsberg et al., 2017). Despite this, one third of patients with schizophrenia have treatment resistant hallucinations and delusions and 10-50% of patients are prescribed combination antipsychotics to address this lack of response to medication (Yow & Jayaram, 2017). Moreover, 49-67% of first-episode psychosis patients will relapse at least once due factors such as non-adherence (Di Capite, Upthegrove, & Mallikarjun, 2016; Pelayo-Terán et al., 2017). This has contributed to the emergence of other forms of non-pharmacological treatment for psychotic symptoms, such as AVH, including transcranial magnetic stimulation and cognitive behaviour therapy (Bohlken, Hugdahl, & Sommer, 2017).

Despite the above evidence supporting the clinical significance of AVHs in BPD and that their presence is associated with a poor outcome (Slotema, Blom, Niemantsverdriet, Deen, & Sommer, 2018), current clinical practice suggests that AVHs in BPD are widely assumed to be unresponsive to antipsychotic medications. This opinion is not evidence-based, as no RCT in BPD has measured AVHs as a primary outcome or used standardised outcome measures employed in RCTs for psychotic disorders (Hancock-Johnson, Griffiths, & Picchioni, 2017; Stoffers et al., 2010; Stoffers & Lieb, 2015). Some BPD studies do report secondary outcomes using proxy measures of psychotic symptoms. One study using aripiprazole found large and significant effects (SMD −1.05, 95 % CI −1.64 to −0.47) on the psychoticism scale of the Symptom Checklist-90-Revised (SCL-90-R; Nickel et al., 2006), although controversy has surrounded the consistency of findings from this research group (Stoffers & Lieb, 2015). Meta-analysis of olanzapine studies has also found small but significant effect on SCL-90-R psychotic symptoms (SMD −0.18, 95 % CI −0.34 to −0.03; Stoffers & Lieb, 2015). A placebo-controlled RCT found a significant effect for 150mg quetiapine on cognitive symptoms (mean change from baseline differences -0.63; Black et al., 2014).

Hence, it is unknown whether conventional pharmacotherapy for AVHs in disorders such as schizophrenia might be similarly effective for AVHs in BPD, or what might be the neurobiological mechanism of action of such treatments. This

is especially important in young people because both BPD and the traditional psychotic disorders have their onset during this developmental period (Chanen & McCutcheon, 2013; Jones, 2013) and because there is evidence that a co-occurring BPD diagnosis influences the treatment received by patients during the early stages of treatment for first-episode psychosis (Francey, Jovev, Phassouliotis, Cotton, & Chanen, 2017).

The aim of this study is to investigate whether aripiprazole, a second-generation antipsychotic (SGA) medication, can reduce the severity of AVHs in youth aged 15 to 25 presenting with BPD. The primary endpoint for the trial is at 12 weeks. The primary hypothesis is that participants who are treated with aripiprazole will show significantly greater reduction in severity of AVHs, compared with those treated with placebo. Secondary hypotheses are that participants receiving aripiprazole will have reduced severity of BPD symptoms, general psychopathology, and improved functioning. Further, reduction in AVHs will be associated with a significant change in resting state connectivity between regions related to auditory and speech processing.
Analyses will be repeated at the secondary endpoint at 39 weeks.

Methods

Study design

The study is a 12-week, triple-blind (prescriber, patient, research assessor),

single-centre, parallel-groups, randomised placebo-controlled trial of aripiprazole for youth with BPD and AVHs, with an additional 27-week follow-up period. The study has been developed in accordance with Good Clinical Practice Guidelines and Standard Protocol Items Recommendations for Interventional Trials (Chan et al., 2013). The trial is being conducted by Orygen, The National Centre of Excellence in Youth Mental Health (henceforth, referred to as Orygen), in accordance with the Declaration of Helsinki.

The trial is funded by a National Health and Medical Research Council Project Grant (GNT1102595) and has been approved by the Melbourne Health Human Research Ethics Committee (HREC2016.116) and has been prospectively registered (ACTRN12616001192471).

Study setting

The study is being conducted at the Helping Young People Early (HYPE) program at Orygen Youth Health (OYH), the government-funded specialist youth mental health service for residents of western metropolitan Melbourne, Australia. HYPE offers specialist early intervention for youth aged 15-25 years with severe personality disorder (Chanen, McCutcheon, & Kerr, 2014). All trial participants will receive HYPE treatment, which comprises clinical case management, individual Cognitive Analytic Therapy, and general psychiatric care.

Inclusion and exclusion criteria

The participants must:

- be aged 15-25 years (inclusive);
- be able to give informed consent and to adhere to study procedures;
- have sufficient fluency in English;
- have BPD, based on a Structured Clinical Interview for the DSM 5th Edition (SCID-5) – Personality Disorder (SCID-5-PD; First, Williams, Benjamin, & Spitzer, 2016) assessment; and
- have threshold AVHs (≥5 on severity, ≥4 on frequency and duration) for >1 week within the past 4 weeks using the Comprehensive Assessment of At Risk Mental State (CAARMS; Yung et al., 2005).

Potential participants will be excluded if they:

- meet a DSM-5 (American Psychiatric Association, 2013) diagnosis of schizophreniform disorder, schizophrenia, schizoaffective disorder, psychotic disorder due to another medical condition, catatonia, delusional disorder, bipolar I disorder, or substance- or medication-induced psychotic disorder;
- have prior sensitivity or allergy to aripiprazole or formulation;
- have received ≥ 200 mg equivalent of chlorpromazine treatment for ≥ 4 weeks within 8 weeks of study entry;
- are pregnant, lactating, or sexually active with no effective contraception;
- have clinically significant liver or thyroid dysfunction, or haematological findings that, in the opinion of the investigator, might present a safety

issue for the participant or confound the trial results;

- have an acute or unstable systemic medical disorder;
- have a psychiatric condition due to a medical condition;
- have severe disturbance, such that they are unable to comply with the requirements of informed consent or the treatment protocol;
- do not meet OYH's eligibility criteria.

For the neuroimaging component, participants will also be excluded if they have:

- a lifetime history of head injury;
- history of loss of consciousness for more than 10 minutes;
- significant medical illness that, in the opinion of the investigator, would preclude participation;
- or any other contraindication to magnetic resonance imaging (MRI) scanning (e.g., metal implants)

Discontinuation and withdrawal

Participants will be discontinued if:

- the participant requests discontinuation;
- participation in the intervention interferes with appropriate clinical management of risk to self or others;
- an adverse event leads to a request to discontinue a participant by an investigator;
- pregnancy occurs;

- the participant is diagnosed with DSM-5 schizophreniform disorder, schizophrenia, schizoaffective disorder, psychotic disorder due to another medical condition, catatonia, delusional disorder, bipolar I disorder, or substance- or medication-induced psychotic disorder.

Participants are withdrawn if their continued participation interferes with appropriate clinical management of risk to self or others or if consent is revoked.

Interventions

Participants will receive aripiprazole or placebo daily according to the following schedule: 2 milligrams (mg) in week 1; 5mg in week 2; 10mg in week 3; potential week 4 to week 12 increments to 15mg, 20mg, then 30mg for all participants who have persistent symptoms and can tolerate further dose escalation, with at least a one-week gap between increments. All capsules will be over-encapsulated to ensure that the placebo matches the aripiprazole in appearance, flavour and packaging. Participants will be asked to return all unused product, with medication adherence being assessed by capsule count and the self-rated Medication Adherence Rating Scale (Thompson, Kulkarni, & Sergejew, 2000). Prohibited medications during the treatment phase are fluoxetine and paroxetine, which can alter the blood levels of aripiprazole and its metabolites, along with other antipsychotic medications.

Aripiprazole was chosen for this trial because it has been associated with a

reduction in psychotic symptoms in youth and adults with psychotic disorders (Correll et al., 2013; Janicak et al., 2009) and with BPD (Nickel et al., 2006). Also, it has been associated with fewer side-effects than other SGAs, including less change in prolactin levels (i.e. less sexual and menstrual dysfunction), less sedation, and a lower risk of weight gain (Correll et al., 2009; Leucht et al., 2013).

Outcome measures

Table 1 presents the assessment measures and schedule. The primary outcome is severity of AVHs, measured using the auditory hallucination subscale of the Psychotic Symptom Rating Scales (PSYRATS; Haddock, McCarron, Tarrier, & Faragher, 1999).

The secondary outcomes include BPD severity (Borderline Symptom List (BSL-23); Bohus et al., 2009), general psychopathology (Depression Anxiety Stress Scales (DASS-21); Antony, Bieling, Cox, Enns, & Swinson, 1998), social and occupational functioning (Functional Remission of General Schizophrenia (FROGS); Llorca et al., 2009; Social and Occupational Functional Assessment Scale (SOFAS); Goldman, Skodol, & Lave, 1992), subjective experiences of psychotic symptoms (Subjective Experiences of Psychosis Scale (SEPS); Gillian Haddock et al., 2011) and resting state brain connectivity. In particular, the strength of connectivity between auditory and speech processing regions will be assessed using a 10-minute functional MRI (fMRI) resting state sequence run on

a 3.0T Siemens Skyra system with a 32-channel head coil.

Subsidiary measures include demographics, diagnosis (SCID-5 Research Version (SCID-5-RV); First, Williams, Karg, & Spitzer, 2015; SCID-5-PD; First et al., 2016), symptomatology (Positive and Negative Syndrome Scale (PANSS); Kay, Fiszbein, & Opler, 1987; Borderline Personality Disorder Severity Index (BPDSI); Arntz et al., 2003; Personality Inventory for DSM-5 brief form (PID-5-BF); Krueger, Derringer, Markon, Watson & Skodol, 2013; PSYRATS; Haddock et al, 1999); quality of life (Assessment of Quality of Life (AQoL-8D; Richardson, Iezzi, Khan, & Maxwell, 2014); and treatment.

Safety and adverse events

Both Orygen's Sponsor Operations team and an independent Data and Safety Monitoring Committee will monitor the trial. Adverse events (AEs) are collected after receipt of informed consent and are followed up until the event is resolved, the end of the week 39 assessment, or longer, as appropriate. Serious AEs are reported to the relevant regulatory authorities. Suicidality (Overall & Gorham, 1962), physical health (e.g., body mass index, blood pressure, heart rate, and fasting blood samples comprising: renal, liver and thyroid function tests, serum calcium and phosphate, Vitamin B12 and folate, prolactin, glucose, a lipid profile and a full blood examination) and potential side-effects (Barnes, 1989; Lingjaerde, Ahlfors, & Bech, 1987) will be monitored.

Enrolment

Routine screening for psychosis (using the CAARMS) and BPD (using the SCID-II Personality Questionnaire (SCID-II PQ; First, Gibbon, Spitzer, & Benjamin, 1997) occurs during OYH intake. A SCID-II PQ score >12 indicates the likely presence of BPD (Chanen, Jovev, et al., 2008). Clients who screen negative for BPD, or who are missed during screening but are identified by clinicians as meeting criteria for BPD, will be considered for eligibility if they are experiencing AVHs. Written informed consent will be obtained from the client (and a parent/legal guardian for minors). Baseline assessment will further confirm participant eligibility (see Figure 1).

Randomisation and blinding

Eligible participants will be assigned randomly and consecutively in a 1:1 ratio, using a password-protected computer program, with a randomisation sequence that is computer-generated by an independent statistician. Treatment allocation will use randomised permuted blocking, stratified by sex and age (cut-point <18 years old; 18 years is the mean age of HYPE clients).

During the treatment period, treatment allocation will be known only by the trial pharmacist and the unblinded trial monitor. Following the week 12 assessment, the participant and treating clinicians (including investigators with clinical roles)

will be routinely unblinded. The researchers, statisticians, blinded trial monitor, and other investigators will remain blinded for the duration of the study. In an emergency, early online unblinding can be performed by senior, medically-trained investigators. Where possible, treatment allocation information will not be shared with the treating clinicians, in order to facilitate the participant's continued involvement in the trial.

Data integrity

The research assessors are psychology or psychiatry graduates trained and supervised by the trial coordinator/Psychologist and the principal investigator/Consultant Psychiatrist. Assessment sessions will be audio recorded and inter-rater reliability checks of key psychosis and BPD interview measures will be conducted on 10% of randomly selected cases. Vignettes are used to test the assessors' reliability with functioning measures. Data entry verification is performed on a random sample of cases at each time point with an *a priori* acceptable error rate of 0.5%.

Statistical analysis

The main analysis will be based on the intent-to-treat population. To investigate group differences we will use a likelihood based mixed-effects model, repeated measures approach (MMRM; Gueorguieva & Krystal, 2004). The MMRM model includes the fixed, categorical effects of treatment, visit, and treatment-by-visit

interaction. Planned comparisons will be done with the MMRM models to determine between-group differences in change of symptoms measures from baseline to week 12, and repeated for baseline to week 39. Sensitivity analysis will also be undertaken to allow examination of the impact of various ways of scenarios (e.g., dealing with missing data) on the robustness of outcomes.

To analyse the resting state fMRI data, first-level connectivity maps for each participant will be carried forward to the group level using the summary statistics approach to random-effects analyses. We will adopt a 2 X 2 flexible factorial design (group x time) to impute the causal effect of aripiprazole on connectivity with the auditory cortex seeds. Statistical comparisons will proceed in two stages: (i) a small volume–corrected comparison of hypothesised regions-of-interest, and (ii) a whole brain exploration of connectivity differences.

Sample size determination

Adjusting for covariates, with the chance of detecting small to medium effects (effect size f = 0.20) at the 0.76 power level, and using a conservative attrition estimate of 20% (previous HYPE research attrition 14% (Chanen, Jackson, et al., 2008)), a total of n=154 (77 aripiprazole and 77 placebo) participants will be required.

For imaging, there is a consensus that groups of approximately n=22 are

appropriate for detecting small effects (Cohen's d=0.2) with 80% power (Desmond & Glover, 2002; Mumford & Nichols, 2008). As such, a subset of the sample will undergo an MRI scan.

Discussion

This will be the first RCT to specifically test the effectiveness of an SGA medication for treating AVHs in young people or adults with BPD. AVHs have their onset early in the course of BPD and they are common, distressing and disabling. Patients with BPD have been described as "dislikeable", "difficult" and "less deserving" of care and pejorative language is often used to describe AVHs in BPD (Adams & Sanders, 2011). In the absence of evidence, psychiatric opinion about whether to initiate antipsychotic medications for AVHs in BPD is simply conjecture. The evidence vacuum does not allow proper evaluation of the risk-benefit ratio associated with delaying or rejecting conventional pharmacotherapeutic treatment for AVHs, or exposing patients to metabolic and other adverse effects of antipsychotic medications.

This study will clarify whether AVHs in BPD respond to conventional treatment for first-episode psychosis. Should the trial find that aripiprazole is more effective than placebo, this will support the use of this antipsychotic medication, or antipsychotics in general, for treating AVHs in BPD. The trial also has the potential to provide evidence about the neurobiological mechanisms

underpinning these symptoms, which might be similar to other patient groups experiencing AVHs, such as people with schizophrenia.

Although aripiprazole is well tolerated in young people and has fewer side-effects than other antipsychotics, individuals taking aripiprazole are still at risk of physical and sexual side-effects. If there is no difference between the aripiprazole and placebo-treated groups at the primary endpoint, this will provide support for withholding the use of antipsychotics for AVHs and will limit the potential harm associated with unnecessary prescribing of SGAs.

There are some anticipated limitations. Clearly, there are known limitations to the effectiveness of SGAs in all psychotic disorders, including first-episode psychosis. Also, at the time of entry to the trial, participants might be experiencing the prodromal phase for a psychotic disorder, such as schizophrenia. Given the early onset and long-standing nature of AVHs among individuals with BPD, it is anticipated that transitions to schizophrenia-spectrum psychoses will be infrequent. However, this outcome will be monitored and transition to a DSM-5 psychotic disorder is one of the discontinuation criteria. Poor medication adherence has complicated the interpretation of pharmacological treatment for youth at ultrahigh risk of psychotic disorder (McGorry et al., 2017). To manage this, the VERBATIM protocol includes frequent, standardised assessment of side-effects, no limits on pharmacological

management of side-effects, and delivering investigational product in the community (e.g., delivery to participants at their homes). Given that intentional overdose using prescribed medications is a common risk among youth with BPD (Chanen, 2015), the trial's dosing schedule allows for weekly or fortnightly dispensing and the largest supply of investigational product will be 38% of the strength at which medically important signs and symptoms have been observed in adults who have overdosed (Otsuka Australia Pharmaceutical Co., n.d.).

RCTs in youth with BPD have typically suffered from low consent rates and high dropout rates (Chanen, 2015) and also, among youth, the presence and number of mental state and personality disorders at follow-up is associated with contact difficulty (Allott, Chanen, & Yuen, 2006). Therefore, recruitment and retention of participants might be particularly challenging in this trial. To address this, assessments can be conducted in the community and/or outside of business hours and participants might be contacted via a significant other (Allott et al., 2006).

The trial design has several strengths. It reflects 'real world' clinical practice, and has broad inclusion criteria and limited exclusion criteria, allowing both males and females with complex and challenging presentations who are receiving concomitant treatment to participate. The youth with BPD included in the study will be presenting for treatment early in the course of the disorder, and this

minimises duration of illness effects (such as cumulative traumatic events, recurrent mental state disorders, and pre-existing treatment (including polypharmacy)). A comprehensive assessment of both BPD and psychotic symptomatology will be undertaken with standardised measures routinely used in RCTs in both BPD and schizophrenia.

In conclusion, the findings from this trial have the potential to influence prescribing practices with regard to individuals presenting with both BPD and AVHs. Evidence of medication efficacy as well as our investigation of the neurobiological changes associated with AVHs in BPD could further legitimise the clinical occurrence of AVHs in patients with BPD, so that AVHs are recognised and treated appropriately.

Trial status

Trial recruitment commenced in September 2016 and is continuing. Twenty-five participants have been enrolled and enrolment was continuing at the time of manuscript submission.

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Figure 1: CONSORT flow diagram for VERBATIM trial

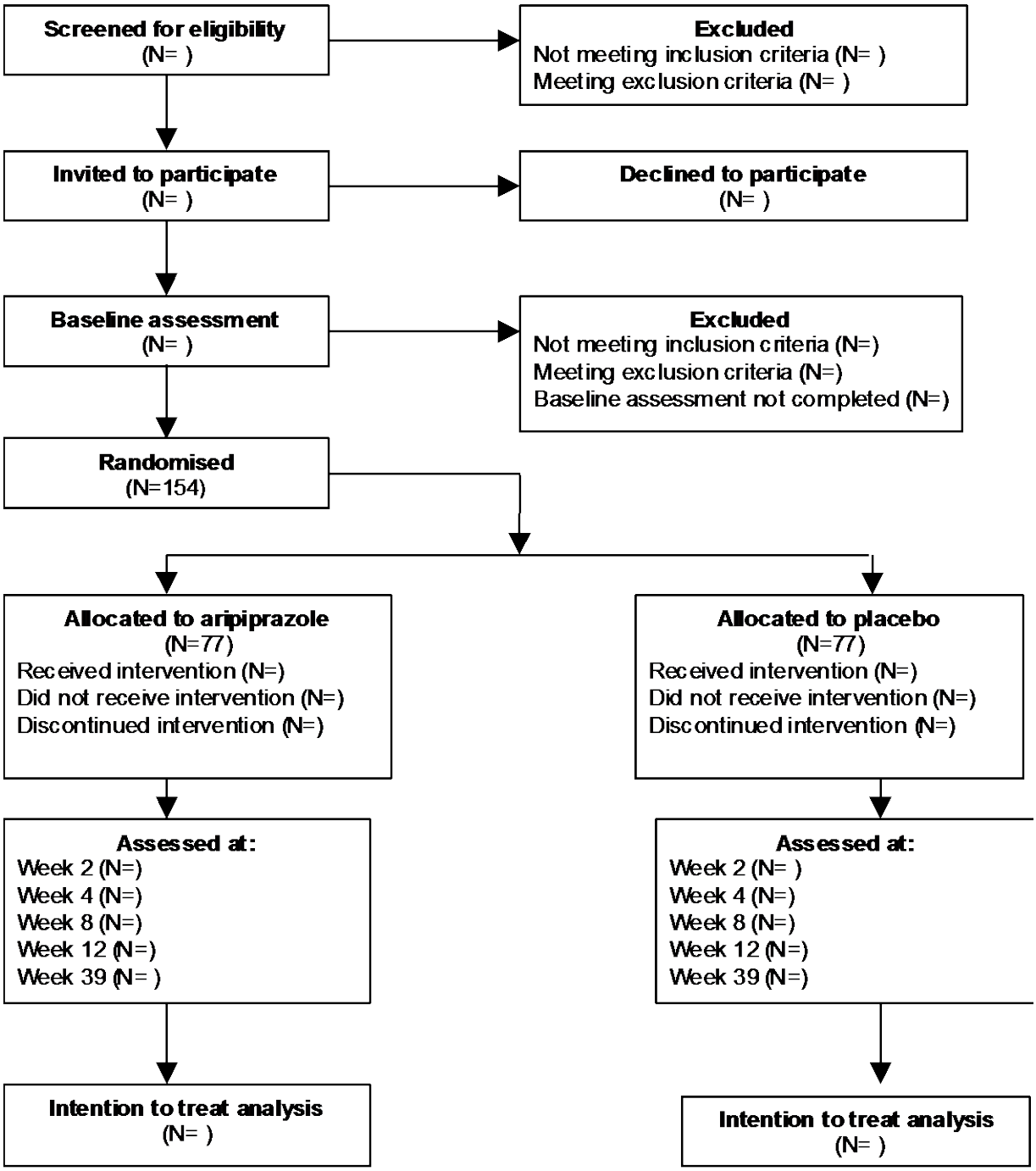

Table 1: Schedule of outcome measures

	Time point (weeks)					
Measure	**Baseline**	**2**	**4**	**8**	**12**	**39**
Primary Outcome						
Psychotic Symptom Rating Scales (PSYRATS)	✔		✔	✔	✔	✔
Secondary Outcomes						
Borderline Symptom List (BSL-23)	✔		✔	✔	✔	✔
Depression Anxiety Stress Scales (DASS-21)	✔		✔	✔	✔	✔
Functional Remission of General Schizophrenia (FROGS)	✔		✔	✔	✔	✔
Social and Occupational Functional Assessment Scale (SOFAS)	✔		✔	✔	✔	✔
Subjective Experiences of Psychosis Scale (SEPS)	✔		✔	✔	✔	✔
Resting state Magnetic Resonance Imaging (MRI)	✔				✔	
Subsidiary Measures						
Adverse Events record	✔	✔	✔	✔	✔	
Blood test	✔				✔	
Brief Psychiatric Rating Scale (BPRS) suicidality item	✔				✔	✔
Physical health examination	✔	✔	✔	✔	✔	
Barnes Akathisia Scale	✔	✔	✔	✔	✔	
UKU Side Effect Rating Scale			✔			
Medication Adherence Rating Scale (MARS)			✔	✔	✔	✔
Demographics	✔				✔	
History and concomitant pharmaceutical and psychosocial treatment information	✔	✔	✔	✔	✔	✔
Diagnosis DSM-5 SCID-5-RV	✔				✔	✔
Diagnosis DSM-5 SCID-5-PD	✔					
Positive and Negative Syndrome Scale (PANSS)	✔					
Borderline Personality Disorder Severity Index (BPDSI)	✔					✔
Personality Inventory for DSM-5 brief form (PID-5-BF)	✔					✔
Assessment of Quality of Life (AQoL-8D)	✔				✔	✔