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Staged treatment and acceptability guidelines in early psychosis study (STAGES): A randomized placebo controlled trial of intensive psychosocial treatment plus or minus antipsychotic medication for first-episode psychosis with low-risk of self-harm or aggression. Study protocol and baseline characteristics of participants

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The Staged Treatment and Acceptability Guidelines in Early Psychosis (STAGES) Study: A randomised placebo controlled trial of intensive psychosocial treatment plus or minus antipsychotic medication for first episode psychosis (FEP) with low-risk of self-harm or aggression. Study pr otocol and baseline characteristics of participants.

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ABSTRACT

Aims

It is now necessary to investigate whether recovery in psychosis is possible without the use of antipsychotic medication. This study will determine (i) whether a FEP group receiving intensive psychosocial interventions alone can achieve symptomatic remission and functional recovery; (ii) whether prolonging the DUP in a sub-group according to randomization will be associated with a poorer outcome and thereby establish whether the relationship between DUP and outcome is causative;and (iii) whether neurobiological changes observed in FEP are associated with the psychotic disorder or antipsychotic medication. Baseline characteristics of participants will be presented.

Methods

This study is a triple-blind randomised placebo-controlled non-inferiority trial. The primary outcome is the level of functioning measured by the Social and Occupational Functioning Assessment Scale at six months. This study is being conducted at the Early Psychosis Prevention and Intervention Centre(EPPIC), Melbourne and includes young people aged 15 to 24 years with a DSM-IV psychotic disorder, a DUP less than six months and not high risk for suicide or harm to others. Strict discontinuation criteria are being applied. Participants are also undergoing three 3-Tesla-MRI scans.

Results

90 participants have been recruited and baseline characteristics are presented.

Conclusions

STAGES will determine whether antipsychotic medications are indicated in all young people with a FEP and whether antipsychotic medication can be safely delayed. Furthermore, the relative contribution of psychotic illness and antipsychotic medication in terms of structural brain changes will also be elucidated. The findings will inform clinical practice guidelines.

INTRODUCTION

Early detection of psychotic disorders, which involves early access teams and educational campaigns, has been effective in reducing the known delays in the commencement of appropriate treatment for psychosis (Chan et al., 2016). Duration of Untreated Psychosis (DUP) has been identified as one of the main targets of intervention in FEP because of its inverse relationship with outcome (Marshall et al., 2005). Current early psychosis guidelines advocate for the use of antipsychotic treatment in conjunction with specialised psychosocial interventions (Galletly et al., 2016). However, existing guidelines do not differentiate treatment approaches based on the stage of the disorder.

The Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne reduced DUP to a median of less than nine weeks (Schimmelmann et al., 2008) and the Early Treatment and Intervention in Psychosis (TIPS) service in Norway reduced it to only five weeks (Joa et al., 2008). This has meant that the DUP can be now measured in units of weeks, as opposed to months and years, which was the case prior to the introduction of early intervention for psychosis services (Marshall et al., 2005). In accordance with the clinical staging model for

psychotic disorders, interventions should match the stage of disorder and as such, early in the course of a disorder, more acceptable and benign interventions should be trialled first (McGorry et al., 2007).

Antipsychotic medications are effective in reducing psychotic symptoms (S. Leucht et al., 2013), particularly positive symptoms, however there are multiple adverse effects associated with their use, including metabolic and cardiac effects (Correll et al., 2009), sedation (S Leucht et al., 2012), bone ill-health (Bulut et al., 2016) and sexual dysfunction (de Boer, Castelein, Wiersma, Schoevers, & Knegtering, 2015). Therefore, there is a potential cost associated with the benefit that can be derived from these medications (Alvarez-Jimenez et al., 2016). Antipsychotic medications are not recommended in those identified as being ultra-high risk for psychosis, as the cost of the adverse effects may out-weigh the potential benefit (Liu & Demjaha, 2013). Based on this potential risk, antipsychotic medications are also not indicated in young people experiencing full threshold psychotic symptoms for under one week, as they could be experiencing brief limiting intermittent psychosis (BLIPS). As already demonstrated, young people are entering early psychosis services with very short DUPs and the cost-benefit ratio of commencing antipsychotic medication in this group is unknown.

Antipsychotic medication is only one of the treatment modalities available, with psychological and psychosocial interventions such as cognitive-behavioural therapy (CBT) and family interventions demonstrating benefits in symptom reduction and relapse prevention (Alvarez-Jimenez, Parker, Hetrick, McGorry, & Gleeson, 2011; Bird et al., 2010; Gleeson et al., 2010; Gleeson et al., 2013). Typically these therapies are provided concurrently with antipsychotic medication. However, recently, a randomised controlled trial involving

individuals with an enduring psychotic disorder who had elected to not take antipsychotic medication, demonstrated that CBT alone could reduce the intensity of positive psychotic symptoms (Morrison et al., 2014). It is possible that CBT could be even more effective in the early stages of a psychotic disorder, as is the case for CBT in bipolar disorder (Scott et al., 2006). Therefore, the immediate introduction of antipsychotic medication may not be necessary for all cases of first episodes of psychosis (Francey et al., 2010). Despite this possibility, clinical practice guidelines provide little guidance for cases in which an individual with a FEP, who has decisional capacity, declines to take antipsychotic medication and expresses a preference for a different treatment modality.

Another potential contributor to the risk-benefit ratio regarding antipsychotic medication is the effect that it may have on the brain. Compared to controls, individuals with a diagnosis of schizophrenia show significant reductions in grey matter volumes and enlarged lateral ventricle volumes over time (Fusar-Poli et al., 2013). These reductions in grey matter volumes were found to be inversely correlated with cumulative exposure to antipsychotic medication (Fusar-Poli et al., 2013), and while it has been suggested that antipsychotic medications could be responsible for these observed changes, no study design to date has been able to establish causality.

A major aim of early intervention in psychosis services has been to reduce DUP due to its association with poorer outcomes, but direct causality has not been demonstrated. A true test of this association requires blind and random assignment to effective intervention or non-intervention which effectively increases DUP. Until recently it has been considered unethical to withhold effective treatment from patients with psychosis, however a number of factors

have led to a reconsideration of this view. First, there is now more concern about the potential medium to long-term risk of antipsychotic medication. Second, early intervention efforts have led to young people presenting for treatment much earlier in the course of psychotic illness when more benign treatments may be effective. Third, there is evidence that it is not harmful to withhold antipsychotic medication from patients with psychotic disorders (Bola, 2006; Johnstone, Owens, Crow, & Davis, 1999). at least in the short-term. Finally, criteria for the safe and ethical conduct of placebo trials in psychotic illness have been articulated (McNulty, 2006; William T. Carpenter, Paul S. Appelbaum, & Robert J. Levine, 2003) . Therefore, it is now ethical, feasible, timely and important to examine the risk-benefit equation for the use of antipsychotic medication in the initial phase of FEP. This will allow definitive testing of whether longer DUP causes poorer outcome in FEP.

The central aim of this study is to clarify a comprehensive range of risk-benefit issues with respect to the use of antipsychotic medication in FEP. The study will determine whether young people with a FEP with a short DUP who receive an intensive psychosocial treatment intervention (PIPT) and placebo will not have an inferior level of functioning at six month compared to those receiving intensive psychosocial treatment (MIPT) and antipsychotic medication. Functional recovery was chosen as the primary outcome due to the importance now placed on it by people affected by psychotic disorders, clinicians and caregivers. Additionally, the longer-term outcomes are of importance in this group and therefore functional outcomes after two years will also be reported. Strict inclusion/exclusion criteria are applied so that the study can be conducted safely and ethically. A parallel aim is to determine by magnetic resonance imaging (MRI) whether structural brain changes known to

occur in early psychosis are a result of the psychotic disorder process or antipsychotic medication.

The primary hypotheses of the study are: (i) levels of functioning in the PIPT group will be no worse, within a prior specified margin of clinical significance, than levels of functioning of the MIPT group at 6 month follow-up; (ii) it will be acceptable, feasible and safe to delay antipsychotic medication and thereby prolong the DUP according to randomization in a sub-group of young people with FEP who are receiving intensive psychosocial treatment from a specialized FEP service; (iii) changes in cortical grey matter and subcortical structure volumes and/ or thickness will be reduced in the MIPT group compared to the PIPT group. The secondary hypotheses of the study are: (iv) The PIPT group will have significantly less cardiovascular and metabolic risk compared with the MIPT group at 3 and 6 month follow-up; (v) the symptom levels of the PIPT group will be no worse than those of the MIPT group at the 6-month follow-up; (vi) the functioning and symptoms levels of the PIPT group will be no worse than those of the MIPT group over the longer term (i.e. at 12 months and 24 months follow-up); (vii) neurocognitive functioning of the PIPT group will be no worse, than that of the MIPT group at 6, 12 and 24 months follow-up.

METHODS/ DESIGN

Study design

The study is a triple-blind randomised placebo-controlled trial (RCT). There are two groups in the study: MIPT group and the PIPT group. This is a one-sided non-inferiority trial that aims to demonstrate that the experimental treatment (PIPT) is no less effective than an active

control treatment (MIPT). The primary outcome is the level of functioning, measured by the SOFAS.(Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000).

Setting

This study is being conducted at EPPIC, which is a specialist clinic for young people aged between 15 and 24 years of age with a first episode of psychosis. It is one of the clinics of Orygen Youth Health, a public youth mental health service that serves a catchment area of approximately 1 million in the inner, mid, north and south Western regions of Melbourne.

Participants

Young people, aged between 15 and 24 years, presenting with a first episode of psychosis, defined as fulfilling criteria for a DSM-IV psychotic disorder, including (but not limited to): schizophreniform disorder, delusional disorder, brief psychotic disorder, major depressive disorder with psychotic symptoms or psychosis not otherwise specified (NOS) are eligible to be included in the study. Potential participants must also fulfil the following inclusion criteria:

- Ability to provide informed consent
- Comprehension of the English language
- A duration of untreated psychosis of less than six months
- Living in stable accommodation

Participants must also not have met the following exclusion criteria:

- At high risk for suicide, defined as a score of 5 or greater on the Brief Psychiatric Rating Scale (BPRS) (Overall, 1962) Suicidality subscale in the two weeks prior to presentation. This level of suicidality corresponds to suicidal ideation with intent or plan or an impulsive suicide attempt using non-lethal methods or in full view of potential saviours.
- At high risk for aggression, defined as a score of 5 or greater on the BPRS Hostility subscale in the two weeks prior to presentation, which corresponds to making threats or having thrown things.
- Previous treatment with antipsychotic medication defined as having exceeded 7 days of antipsychotic treatment or a lifetime dose greater than 1750mg chlorpromazine equivalents.
- Previous treatment with lithium or anticonvulsant medication for a manic episode.
- Current pregnancy.

Procedure

Randomisation and treatment allocation

A stratified randomisation design is being used to allocate participants to either PIPT or MIPT treatment groups. As the DUP and gender are associated with outcomes in FEP, these are stratifying factors in the randomisation. DUP is included as a three-level factor (< 1 month, 1 – 3 months and 3 – 6 months). Along with gender, this results in six separate randomisation lists from which participants are drawn. Participants are allocated to a

treatment group using randomly permuted blocks within each stratum, to ensure that participant allocation to the treatment groups will be approximately equal.

Clinical trial registry

This trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org) in November 2007 and the trial ID is ACTRN12607000608460.

Side-effects and safety

In order to assess for adverse events and side-effects of the intervention, the UKU side effect rating scale (Lingjaerde, Ahlfors, Bech, Dencker, & Elgen, 1987) is being performed weekly by the treating doctor in the first month, at the 12 week assessment and at the 26 week assessment. Additionally, side-effects and adverse events will be assessed as part of the clinical care provided.

Intensive Psychosocial Intervention

All participants receive cognitive behavioural case management (CBCM), a comprehensive intervention developed specifically for early psychosis. CBCM provides formulation-driven cognitive behavioural treatment and psychoeducation delivered within a therapeutic case management framework (*Cognitive Behavioural Case Management in Early Psychosis: A Handbook*, 2010). This is enhanced by close monitoring of mental state and risks, family work and 24-hour crisis response.

Medication intervention and maintaining blinding

Participants allocated to the MIPT group received risperidone (1mg) or paliperidone (3mg), depending on when they were enrolled in the study and which antipsychotic and placebo was available to the study at that time. Dosages were increased by prescription of additional tablets as required. PIPT participants received placebo tablets that were identical in appearance, taste and packaging. Blinding will be maintained by ensuring that the packaging and appearance of the risperidone, paliperidone and placebo tablets are all identical. All tablets are over-encapsulated in order to appear and taste identical. In order to maintain blinding, research assistants would not be present at any clinical review meetings in which details about participants were being discussed that could lead to potential unblinding, such as discussion of side-effects.

Labelling, storage and accountability

The study medication is labelled, complies with local regulatory requirements and is stored securely at an appropriate temperature. Accountability records are maintained. Unblinding is only permitted in the case of a medical necessity when the appropriate management is dependent on the knowledge of the treatment allocation. All instances of unblinding will be reported.

Compliance assessment

In this study design, it is important to measure adherence to both the psychological intervention and the study medication. Following each appointment with the case-manager during the study intervention period, a checklist of the components of psychological intervention that were delivered is completed. The case-managers delivering the psychosocial

intervention receive at least monthly supervision with a senior psychologist. Adherence to study medication is measured by the counting of returned pills and assessment using the Medication Adherence Rating Scale (MARS) (Thompson, Kulkarni, & Sergejew, 2000). When the study medication is dispensed, participants are asked to return their previous pill containers and the remaining pills are counted to determine compliance. The MARS is also administered at monthly intervals throughout the duration of the study intervention.

Study medication discontinuation criteria

In order to ensure the safety of participants, strict study medication discontinuation criteria are applied in situations of failure to achieve satisfactory recovery, worsening mental state or for an increase in risks to self or others. These criteria are:

- an increase in suicidality or hostility, defined by a score of 5 or more on the corresponding BPRS subscale.
- a significant decrease in functioning, defined by a 20 point drop in Social and Occupational Functioning Assessment Scale (SOFAS) score from the baseline, that is sustained for at least a month
- failure to achieve an improvement in positive psychotic symptoms after 12 weeks as measured by the BPRS psychotic symptoms subscales
- pregnancy during the intervention period

In these circumstances, the study medication is discontinued and the participant is offered an alternative open-label antipsychotic medication (i.e. any second generation antipsychotic medication except risperidone or paliperidone). These participants continue to receive the

intensive psychosocial intervention and receives all of the scheduled assessments as per the study protocol.

Instruments and outcome measures

Diagnosis, symptomatology and functioning

The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II) is used to determine diagnoses (First, Spitzer, Gibbon, & Benjamin, 1997; First & Spitzer R.L, 1995). Co-morbid substance abuse disorders is determined using the World Health Organisation Alcohol, Smoking & Substance Involvement Screening Test (WHO ASSIST) (Newcombe, Humeniuk, & Ali, 2005).

Positive psychotic symptoms are assessed using the Expanded Brief Psychiatric Rating Scale (ExBPRS) version 4 and negative symptoms are assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984). The Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) are used to assess for depressive and anxiety symptoms respectively. The Duration of Untreated Psychosis (DUP) is defined as the interval between the onset of full threshold psychotic symptoms and entry to the study.

Functioning is assessed using the Social and Occupational Functioning Scale (SOFAS) (Morosini et al., 2000) and quality of life is determined using the Heinrich Quality of Life

Scale (QLS) (Heinrichs, Hanlon, & Carpenter, 1984) and the World Health Organisation Quality of Life Assessment (WHOQOL-BREF) (WHO, 1998).

Study assessments

Neuropsychological assessments

Baseline Only: The Wide Range Achievement Test-Fourth Edition (WRAT-4)-Reading subtest Scaled Score (Wilkinson & Robertson, 2006) is used to estimate premorbid IQ and a two-subtest short-form (Information and Picture Completion) of the WAIS-III (Wechsler, 1997) is used to estimate current full-scale IQ (Sattler & Ryan, 1999). The reliability and validity of the two-subtest full-scale IQ estimate for individuals aged 16-25 years is high (range r=.88-.91 and r=.72-.85, respectively) (Jeyakumar, Warriner, Raval, & Ahmad, 2004; Sattler & Ryan, 1999).

Baseline, 6, 12 and 24 months: Neuropsychological assessment is performed with a comprehensive battery designed to assess neuropsychological domains that have been shown to differ significantly between first-episode or early psychosis/schizophrenia patients and controls (Mesholam-Gately, Giuliano, Faraone, Goff, & Seidman, 2009). The instruments used to measure specific neuropsychological domains are presented in Table 1.

Physical health & biochemical assessments

The use of second generation antipsychotic medication is associated with an increased risk of obesity and metabolic syndrome (Tek et al., 2016), which are associated with increased risk of adverse cardiovascular health in the longer term. Therefore, the physical health of

participants is closely monitored. The following physical health measures are taken at baseline, 3, 6, 12 and 24 month timepoints: height, weight, blood pressure, waist circumference, fasting glucose, total cholesterol, low and high density lipoprotein and triglycerides. The results of the screening are monitored by the treating doctor and any abnormalities detected are treated as part of the standard clinical care provided.

Neuroimaging

Participants are undergoing 3 Tesla magnetic resonance imaging (MRI) using a Siemens Trio Tim located at the Royal Children's Hospital, Melbourne. Scans are conducted at baseline, 3 and 12 month follow-ups, allowing the short- and long-term effects of differences in treatment strategies on brain structure and function to be determined. Brain volumes are assessed using T1-weighted volumetric imaging, with the following parameters: time-to-echo (TE), 2.98 ms; time-to-repetition (TR), 2300 ms; flip angle, 9 degrees; voxel dimensions, 1 x 1 x 1.2 mm^3. Participants will also complete eyes-closed resting-state functional MRI at each session, consisting of 234 volumes, acquired using T2*-weighted echo-planar imaging with TE = 32 ms, TR = 2000 ms, flip angle = 90 degrees, voxel dimensions = 3.3 x 3.3 x 3.5 mm. At baseline only, participants also complete a diffusion-weighted sequence, consisting of 60 diffusion-weighted volumes with b = 3000 s/mm^2, TE = 112 ms, TR = 7750 ms, voxel dimensions = 2.3 mm^3, and ten volumes with b = 0 s/mm^2. The functional and diffusion-weighted imaging data will be used to compare treatment groups with respect to measures of functional and structural connectivity, respectively (Fornito, Zalesky, Pantelis, & Bullmore, 2012).

Statistical analyses

Non-inferiority trials are designed to show whether the experimental treatment is not inferior to the standard intervention (i.e. one-sided) (Greene, Morland, Durkalski, & Frueh, 2008). For this, a 'zone of indifference' or margin within which the interventions are considered non-inferior is defined. For the SOFAS, which is measured from 0 to 100, a non-inferiority margin of 10.5 was set. Any difference favouring the MIPT group in excess of this specified difference will be regarded as providing clinically important evidence of the inferiority of psychosocial-only (PIPT) treatment.

Primary analyses, Power and sample size calculation

The sample size calculation is powered on an analysis which compares the 6-month SOFAS scores of the PIPT and MIPT groups. It was determined that 30 participants per group are required for study to have 80% power to demonstrate that the treatment means are not-inferior and with alpha set at 0.05 (1-tailed test). Based on this calculation, a cohort of 60 participants is required. However, due to the strict discontinuation criteria, it is estimated that there will be a proportion of participants who will be required to discontinue the study medication, therefore a target sample size of 95 participants was set, which would allow for an attrition of 37.5%. This sample size will provide sufficient power to test the neuroimaging hypothesis, as sample sizes of 20- 30 per group in individual MRI studies demonstrate sufficient power to detect differences (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008).

Ethical Approval

Ethical approval was granted by the Melbourne Health Human Research Ethics Committee (HREC).

Results

Recruitment

By the December 2016, a total of 90 young people consented to participate in the study and baseline assessments were completed for 84 participants. Recruitment for the study ceased at this time and the final two year follow-up assessment will occur in December 2018. A flow diagram of those who were screened for eligibility is presented in Figure 1.

Baseline characteristics

A total of 54.8% (N=46) of participants are female, the mean age is 18.5 years (SD±2.8) and 90.5% (N=76) were born in Australia. The mean level of functioning according to the SOFAS was 54.3 (SD±11.9). A total of 21% (N=17) and 13.6% (N=11) had a diagnosis of schizophreniform disorder and schizophrenia respectively, 13.6% (N=11) had a diagnosis of substance-induced psychotic disorder and 22.2% (N=18) had a diagnosis of Psychosis disorder not otherwise specified (NOS). The demographic and clinical characteristics of participants are presented in Table 2.

DISCUSSION

This study is the first to investigate whether a sub-group of young people with a psychotic disorder, who have a short duration of untreated psychosis and are not high risk to themselves or others, can recover with intensive psychological and psychosocial interventions and without the use of antipsychotic medication. It will also investigate whether the brain changes observed in individuals with a treated psychotic disorder are associated with the psychotic disorder or antipsychotic medication. The findings of this RCT will inform clinical practice guidelines.

Strengths and Limitations

There are a number of practical challenges when conducting a trial of this kind. The wellbeing and safety of the participants is paramount and therefore there is very close monitoring and strict criteria for discontinuation. As a result, we may have a low rate for of completion of the six month study period. However, this in itself will be an important finding. Additionally, the use of two different antipsychotic medications during different periods of the study may initially be interpreted as a limitation however the aim of the study is to determine whether treatment with intensive psychological and psychosocial interventions are not inferior to treatment with these interventions plus antipsychotic medication, as opposed to one specific antipsychotic medication. Furthermore, an economic analysis was not incorporated into this study and this would form an essential component of any further studies that aimed to replicate the findings of this current study,

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Table 1: Outcome measures in the STAGES study and Assessment Schedule

	Domain	**Instrument**	**Schedule - week**						
			Base-line	4	6	12	26	52	104
Symptomatology	Positive psychotic symptoms	Expanded Brief Psychiatric Rating Scale (exBPRSvs.4)	X		X	X	X	X	X
	Negative symptoms	Scale for the Assessment of Negative Symptoms	X		X	X	X	X	X
	Depressive symptoms	Hamilton Rating Scale for Depression	X			X	X	X	X
	Anxiety symptoms	Hamilton Rating Scale for Anxiety	X			X	X	X	X
Functioning and quality of life	Functioning	Social and Occupational Functioning Scale	X	X		X	X	X	X
	Quality of life	World Health Organisation Quality of Life Assessment	X				X	X	X
		Heinrich Quality of Life Scale	X				X	X	X
	Treatment response	Clinical Global Impression Scale-Severity (CGI)	X		X	X	X	X	X
Neuropsychological	Speed of information	Golden Stroop Colour and Word	X				X	X	X

	processing	Test (Golden, 1978) words and colours subtests; and the Digit Symbol Coding subtest from the WAIS-III (Wechsler, 1997).							
	Immediate attention	Digit Span - digits forward from the WAIS-III (Wechsler, 1997)	X				X	X	X
	Working memory	Digit Span - digits backwards from the WAIS-III (Wechsler, 1997)	X				X	X	X
	Verbal learning and memory	Paired Associated Learning (PAL) Test (Savage, Saling, Davis, & Berkovic, 2002)	X				X	X	X
	Verbal fluency	Controlled Oral Word Association Test: COWAT and animal fluency (Strauss, Sherman, & Spreen, 2006)	X				X	X	X
	Executive functioning	Inhibition and cognitive control measured with the interference trial of the Golden Stroop Colour and Word Test (Golden, 1978)	X				X	X	X

Table 2: Demographic and clinical characteristics of participants			
	Mean (±SD)	**N**	**%**
Gender			
Male		38	45.2
Female		46	54.8
Age at baseline	18.5 (2.8)		
Country of birth			
Australia		76	90.5
Other		8	9.5
Level of functioning (SOFAS)	54.3 (11.9)		
Diagnosis			
Mood disorder with psychotic features		17	21
Schizophreniform disorder		17	21
Psychotic disorder NOS		18	22.2
Substance-induced psychotic disorder		11	13.6
Delusional disorder		6	7.4
Schizoaffective disorder		1	1.2
Schizophrenia		11	13.6
Duration of untreated psychosis*			
0 – 30 days		13	16
31 – 90 days		27	33.3
91 – 180 days		41	50.6
Physical health parameters			
Weight**	71.6 (17.4)		
Waist circumference***	83.3 (12.2)		
* Missing data for 3, ** Missing data for 12, *** Missing data for 44			

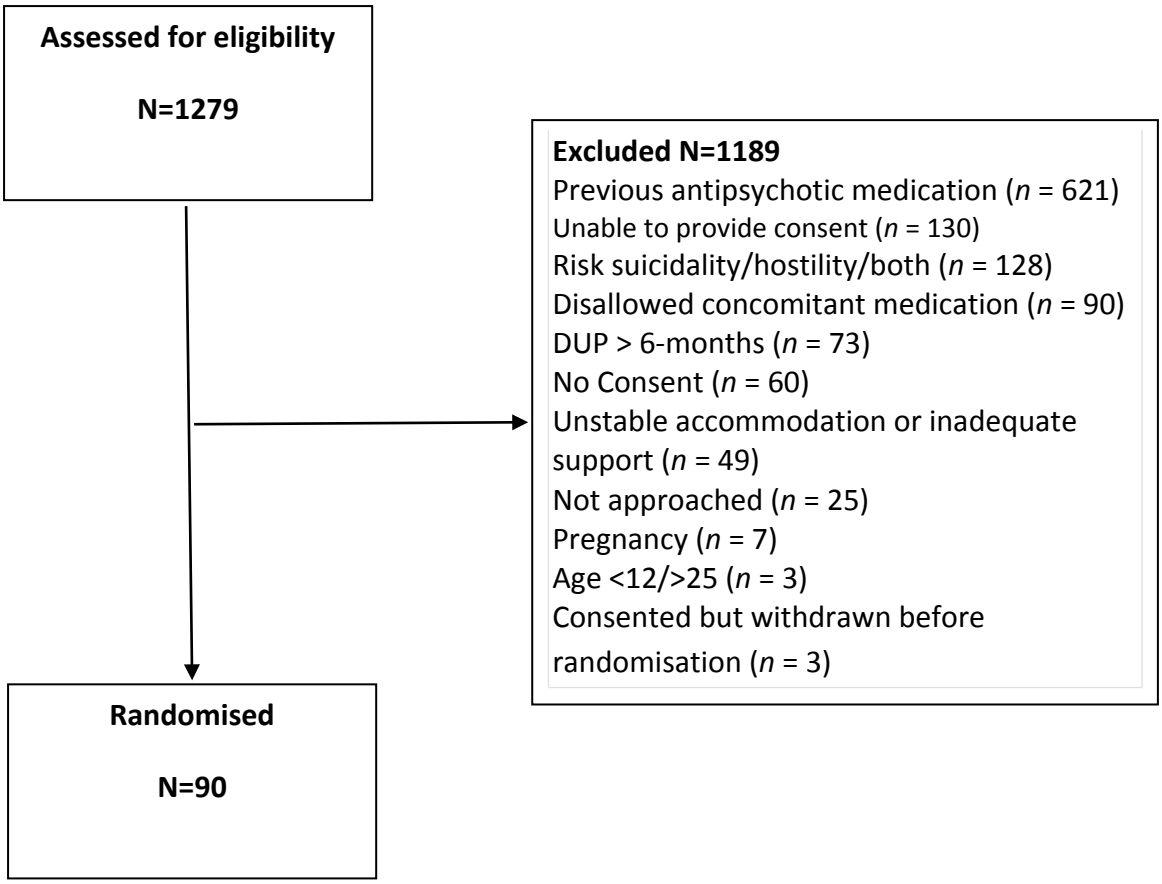

Figure 1: Outcome of screening and eligibility assessments