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Staged treatment in the ultra-high risk for psychosis clinical population: Baseline data of a sequential multiple assignment randomised trial (STEP Study)

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Abstract

Aim: Research has shown that preventative intervention in individuals at ultra-high risk of psychosis (UHR) improves symptomatic and functional outcomes. The STEP trial aims to determine the most effective type, timing and sequence of interventions in the UHR population by sequentially studying the effectiveness of (1) support and problem solving, (2) cognitive-behavioural case management, and (3) antidepressant medication with an embedded fast-fail option of (4) omega-3 fatty acids or low-dose antipsychotic medication. This paper presents the recruitment flow and baseline clinical characteristics of the sample.

Methods: STEP is a sequential multiple assignment randomised trial (SMART). We present the baseline demographics, clinical characteristics, and acceptability and feasibility of this treatment approach as indicated by the flow of participants from first contact up until enrolment into the trial. Recruitment took place between April 2016 and January 2019.

Results: Of 1343 help-seeking young people who were considered for participation, 402 participants were not eligible and 599 declined/disengaged, resulting in a total of 342 participants enrolled in the study. The most common reason for exclusion was an active prescription of

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7.Conflict of interest statement

PDM reported receiving grant funding from National Alliance for Research on Schizophrenia and Depression and unrestricted research funding from AstraZeneca, Eli Lilly, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational activities with AstraZeneca, Eli Lilly, Janssen-Cilag, Pfizer, Bristol-Myers Squibb, Roche, and the Lundbeck Institute. TN is co-founder and share holder in Safari Health, Inc. No other conflict of interests was reported.

antidepressant medication. Eighty-five percent of the enrolled sample had a non-psychotic DSM-5 diagnosis and symptomatic/functional measures showed a moderate level of clinical severity and functional impairment.

Discussion: The present study demonstrates the acceptability and participant's general positive appraisal of sequential treatment. It also shows, in line with other trials in UHR individuals, a significant level of psychiatric morbidity and impairment, demonstrating the clear need for care in this group and that treatment is appropriate.

Keywords

antidepressant medication; clinical trial; prodrome; psychosis; ultra-high risk

1. INTRODUCTION

The introduction of the at-risk mental state framework to prospectively identify young people at 'clinical' or 'ultra-high' risk (UHR) for psychosis resulted in a wide range of candidate early interventions being trialled, aiming to improve symptomatic and functional outcomes in this population. The results of these trials, ranging from (single and combined) psychological (Ising et al., 2016; Miklowitz et al., 2014; Morrison et al., 2012; Stain et al., 2016; van der Gaag et al., 2012), pharmacological (McGlashan et al., 2006; McGorry et al., 2013; Woods et al., 2017), and nutritional (Amminger et al., 2010; Kantrowitz et al., 2015; Nelson, Amminger, Yuen, Markulev, et al., 2018; Woods et al., 2013) interventions, showed that early treatment is associated with better outcomes (Preti & Cella, 2010; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013; van der Gaag, Smit, et al., 2013; McGorry, Mei, Hartmann, Yung, & Nelson, 2021; Mei et al., 2021). However, recent (network) meta-analytic studies failed to find evidence in support of any specific type of intervention over others (Davies, Cipriani, et al., 2018; Davies, Radua, et al., 2018; Devoe, Farris, Townes, & Addington, 2019). Given the now widely recognised heterogeneity of the UHR population (Fusar-Poli et al., 2016; Nelson & Yung, 2009; van Os & Guloksuz, 2017), the current lack of conclusive evidence for a single most effective form of intervention for the group as a whole is unsurprising. This indicates the need for more 'adaptive' intervention trials, i.e. trials which tailor the treatment type and intensity to an individual's needs and subsequently adapt this treatment according the individual's response and characteristics over time, in order to be able to determine the optimal type, timing and sequence of treatments in the UHR population (Murphy, 2005).

1.1 Clinical staging

The idea of adaptive intervention is inherent to the clinical staging framework. Clinical staging, a transdiagnostic heuristic approach adapted from other areas of medicine, blends a dimensional approach to mental illness classification with a categorical overlay of stepwise anchors for stage-specific treatment selection (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006; Scott et al., 2013; McGorry & Hickie, 2019). It also allows for understanding and testing neurobiological and psychosocial processes underlying the onset and progression of mental illness across the syndromal landscape of emerging mental illness. An individual's clinical presentation is mapped onto the spectrum of mental illness, facilitating treatment

selection and offering a prognosis of possible progression/remission trajectories (Mei, McGorry, & Hickie, 2019). Stages are defined using symptom severity, specificity, persistence and disability. An early stage is typified by mild symptom severity, a lack of specificity, and mild functional impairment; an advanced stage is associated with severe symptom burden, clearer syndromal specificity and stability, although comorbid syndromes accumulate too, significant functional impairment and persistent/recurrent patterns of illness (Cross et al., 2014; Hickie et al., 2013).

Clinical staging applied to UHR intervention proposes a *sequential approach to treatment*, with the safest, most benign, and least specialised interventions offered initially, and more targeted, more intensive interventions with increased risk of adverse effects, provided only to those who do not respond to initial steps in the intervention (Nelson, Amminger, Yuen, Wallis, et al., 2018). Intervention is, however, proactive, seeks to be pre-emptive, and identifies early failure to respond, rather than waiting for deterioration. This approach leads to a stepwise enrichment of the sample: non-responders to early simple interventions are likely to be enriched for higher transition rates and higher functional impairment. By sequentially enriching the UHR sample, the issues of 'false positives', low statistical power due to low transition rates, and ethical concerns (e.g. overtreatment) are addressed (van Os & Guloksuz, 2017; Ajnakina, David, & Murray, 2018; Fusar-Poli et al., 2018; Carpenter, 2018; Guloksuz & van Os, 2018; but see McGorry & Mei, 2020; McGorry & Nelson, 2020; Yung et al., 2021). Offering low risk, less specific and benign treatment as a first step may enable those with milder or self-limiting problems to remit, while those who do not respond to this first step - likely representing a subset of UHR at greater risk - can move quickly on to more specific and intensive treatment.

1.2 Adaptive trials

To be able to empirically test this staged treatment approach it is necessary to move away from traditional randomized controlled trials consisting of a single phase and type of treatment. A sequential multiple assignment randomized trial (SMART) design (Murphy, 2005) is perfectly suited for the purpose of evaluating multi-stage treatment trials and build the evidence-base to support adaptive clinical care (Bhatt & Mehta, 2016; Bothwell, Avorn, Khan, & Kesselheim, 2018). In a SMART, individuals are randomisedd to different treatments at each critical decision stage, where randomisation depends on the individual's response (e.g., responder vs non-responder) up to that stage. SMART trials have been increasingly implemented in a variety of fields, beginning in cancer research (Auyeung et al., 2009), and more recently, in the field of psychiatry, such as schizophrenia (Shortreed & Moodie, 2012), insomnia (Morin et al., 2020) and mood disorders (Kilbourne et al., 2014).

The STEP study aimed to determine the most effective type, timing and sequence of intervention in the UHR population. More specifically, it evaluated the short-term and long-term symptomatic and functional outcomes of a stepped treatment sequence: a general, benign psychosocial intervention strategy (Step 1: supportive problem solving therapy), a more intensive and specialised psychological intervention (Step 2: CBT), and finally a psychopharmacological intervention (Step 3: antidepressant medication) with an embedded rescue option consisting of a low-dose antipsychotic or omega-3 fatty acid ('fast fail'

option). These particular steps and order were chosen for their suggested benefit and safety (Nelson, Amminger, Yuen, Wallis, et al., 2018). Psychological interventions, specifically CBT, have been shown to be particularly beneficial and safe (Mei et al., 2021; van der Gaag, van den Berg, & Ising, 2019). Although not yet empirically tested, naturalistic evidence points to the benefit of antidepressant medication in UHR, possibly being more appropriate as first-line therapy compared to antipsychotic medication (Cornblatt et al., 2007; Fusar-Poli et al., 2015). An in-depth discussion of these issues is provided in the STEP protocol paper (Nelson, Amminger, Yuen, Wallis, et al., 2018). The STEP study also aimed to explore biological, psychological, and cognitive moderators and mediators of response in order to inform a more personalised approach to treatment, i.e., matching treatment to individual patients biological and psychological profile.

In this paper, we present the baseline demographic characteristics and diagnostic, symptomatic, and functional profile of the STEP study sample. Study recruitment flow and issues will be presented.

2. METHODS

2.1 Setting

This community study was conducted at the PACE clinic and four *headspace* centres (Sunshine, Werribee, Glenroy, Craigieburn) located in Metropolitan Melbourne. The Australian *headspace* system is a nationwide 'one stop shop' universal access model for young people with emerging mental health issues (McGorry et al., 2007; McGorry, 2007; McGorry, Trethowan, & Rickwood, 2019; McGorry, Goldstone, Parker, Rickwood, & Hickie, 2014). The study was approved by the Melbourne Health Human Research Ethics Committee and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616000098437) and clinicaltrials.gov (NCT02751632). Informed consent was obtained from participants prior to study commencement. For participants under the age of 18, consent was also obtained from their parent/guardian.

2.2 Participants

Young people seeking help at the recruitment clinics were eligible for participation if all the following criteria were met: (i) age between 12-25; (ii) ability to speak adequate English; (iii) ability to provide informed consent; and (iv) meeting UHR criteria[1]. Exclusion criteria were: (i) past history of a psychotic episode of one week or longer; (ii) attenuated psychotic symptoms only present during acute intoxication; (iii) organic brain disease known to cause psychotic symptoms; (iv) any metabolic, endocrine or other physical illness; (v) diagnosis of a serious developmental disorder; (vi) documented history of developmental delay or intellectual disability. Participants on current antidepressant or antipsychotic medication

[1]The UHR criteria are assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al., 2005). Young people at UHR are identified by one or more of the following characteristics: 1) Attenuated Psychotic Symptoms (APS) — young people who have experienced subthreshold, attenuated forms of positive psychotic symptoms during the past year, 2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) — young people who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated, and 3) Trait and State Risk Factor (Trait) — individuals who have a first-degree relative with a psychotic disorder or who have a schizotypal personality disorder in addition to a significant decrease in functioning, or chronic low functioning, during the previous year.

were assessed for rationale of prescription and excluded if needing ongoing prescription. Young people were screened using a standardized clinical assessment and the Prodromal Questionnaire-16 (PQ-16). Those who scored 6 and above on the PQ-16 or who had a family history of psychotic disorder were identified by a Research Assistant (RA). The RA would then approach and consent the young person (as well as parent or guardian if they were under 18). To ensure that the young person satisfactorily understood the consent form and what was expected of them, the RA would ask them to repeat important details back to them in their own words. They would then conduct a thorough clinical assessment to establish if study entry criteria were met. UHR status was determined using the Comprehensive Assessment of At-Risk Mental States (CAARMS), Social and Occupational Functioning Assessment Scale (SOFAS), SCID-II Schizotypal PD and Family History Index (FHI).

2.3 Measures

In addition to background demographic information and medical history, the following clinical measures were administered at baseline:

Structured Clinical Interview for the DSM-5 (SCID-5)(First, Williams, Karg, & Spitzer, 2015).—The SCID-5 is a semi structured interview guide for making the major DSM-5 diagnoses according to the classification and diagnostic criteria of the American Psychiatric Association (2013).

Comprehensive Assessment of At-Risk Mental States (CAARMS)(Yung et al., 2005).—The CAARMS is a semi-structured assessment tool to identify help-seeking young people who are at ultra high risk (UHR) of developing psychosis. CAARMS has subscales for disorders of thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech, which receive a global ‘severity’ rating and a frequency rating. The severity score ranges from 0 (‘never, absent’) to 6 (‘psychotic and severe); the frequency score ranges from 0 (absent) to 6 (continuous).

Brief Psychiatric Rating Scale (BPRS)(Overall & Gorham, 1962; Ventura et al., 1993).—The BPRS is a clinician-rated scale to measure psychiatric symptoms. It consists of 24 items rated on a continuum from not present (1) to extremely severe (7), with a maximum score of 168.

Scale for the Assessment of Negative Symptoms (SANS)(Andreasen, 1982).—The SANS is a clinician-rated 20-item scale which globally evaluates affective flattening, anhedonia-asociality, attention, alogia, and avolition-apathy. To enhance reliability, these symptoms feature a general description and each domain is divided into observable behaviours (e.g., lack of vocal inflections, physical anergia) and measured on a 6-point scale (from “none” to “severe”).

Montgomery–Åsberg Depression Rating Scale (MADRS)(Montgomery & Asberg, 1979).—The MADRS is a ten-item (scored 0 to 6) diagnostic questionnaire used to measure the severity of depressive episodes. A higher score indicates more severe depression, with a maximum score of 60. The following cut-off points have been

published: symptoms absent (0-6); mild depression (7-19); moderate depression (20-34); severe depression (> 34).

Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)(WHO ASSIST Working Group, 2002).—The ASSIST was designed to detect and manage substance use and related problems in primary and general medical care settings and consists of eight questions covering tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (including ecstasy) inhalants, sedatives, hallucinogens, opioids and 'other drugs'. A risk score is provided for each substance, and scores are grouped into 'low risk' (alcohol: 0-10; other substances: 0-3), 'moderate risk' (alcohol: 11-26; other substances 4-26) or 'high risk'(alcohol: >26; other substances: > 26).

Davos Assessment of Cognitive Biases Scale (DACOBS)(van der Gaag, Schutz, et al., 2013).—The DACOBS is a 42-item self-report instrument used to measure cognitive biases specific to positive symptoms of psychosis. In completing the DACOBS, the individual is required to indicate whether they agree or disagree with the statement presented considering the previous two weeks. Each item is scored on a 7-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. There are seven subscales: jumping to conclusions bias; cognitive inflexibility bias; attention to threat bias; external attribution bias; social cognition problems; subjective cognitive problems; and safety behaviours.

Childhood Trauma Questionnaire (CTQ)(Bernstein et al., 2003).—The CTQ is a 28-item retrospective, self-report measure of childhood abuse and neglect. It has five subscales: physical, sexual, and emotional abuse, and physical and emotional neglect. The total score for each subscale ranges from 5 to 25. The higher the score, the more maltreatment is being reported.

Social and Occupational Functioning Assessment Scale (SOFAS)(Goldman, Skodol, & Lave, 1992).—SOFAS is a numeric scale (1 through 100) used to rate subjectively the social, occupational, and psychological functioning. The SOFAS focuses exclusively on the individual's level of social and occupational functioning and is not directly influenced by the overall severity of the individual's clinical symptoms. A higher score indicates higher functioning.

2.4 Study Design

This was a sequential multiple assignment randomised trial (SMART) with three treatment stages plus a fast-fail option (detailed below and in Figure 1), totalling a 12-month intervention phase and a 24-month follow-up phase. Progression through the stages was determined by response versus non-response (Nelson, Amminger, Yuen, Wallis, et al., 2018). Recruitment commenced in April 2016, with all sites operational in September 2016, and ceased in January 2019. The majority of clinical assessments took place at the recruitment clinics, while in some cases the assessments took place at the participant’s choice of location (e.g., at their home) or via the phone/videocall.

Treatment stages—There were three treatment stages with one or two treatment arms, plus a fast-fail option: (1) Support and problem solving (SPS) alone, (2) SPS versus cognitive behavioural case management (CBCM[2]); (3) antidepressant versus placebo. Within the last step, there was a fast-fail option. These steps are outlined below. 'Response' was defined using the CAARMS (global rating and frequency score < 3 on all positive symptom scales over the past 2 weeks) and SOFAS (at least a 5-point improvement compared with baseline or at least a score of 70). Non-response was defined as not meeting the response criteria. The definition of response was set at a relatively high threshold, as the goal of treatment in our view should be substantial recovery or full remission (including both symptoms and functioning) not merely a modest response (Figure 1).

Step 1: Single-arm treatment consisting of SPS (6 weeks). All included participants went through this first stage of treatment which was not randomised and therefore not blinded. After this initial stage, *non-responders* were randomised to Step 2. *Responders* (during assessments at both week 4 & 6) were randomised to either SPS (monthly sessions) or monitoring only (3 monthly intervals) to assess response maintenance until the end of the intervention period.

Step 2: Double arm treatment consisting of CBCM vs SPS (20 weeks). This was a single-blind treatment stage, i.e., assessors were unaware of the participant's treatment allocation. At the end of stage 2, *non-responders* were randomized (stratified by depression as rated by the MADRS total score <21 or ≥21) to Step 3. *Responders* (week 12 & 24) were randomized to either SPS (monthly sessions) or monitoring only (at 3 monthly intervals) to assess response sustainment until the end of the intervention and follow up period.

Step 3: Double arm treatment consisting of antidepressant vs placebo in addition to CBCM (26 weeks). This was a double-blind treatment stage, i.e., both assessors and participants were blind to treatment allocation.

Fast fail: There was a 'fast fail' option within step 3 which facilitated a treatment intensification for participants not responding after 12 weeks. In this fast-fail option, participants were offered (a) an increase in dosage of antidepressant/placebo, (b) the addition of omega-3 fatty acids or (c) low-dose antipsychotic medication. The choice was made via a collaborative and shared-decision-making approach.

All participants were closely monitored for adverse events and concomitant medication use (medication for medical conditions and intermittent benzodiazepines) throughout the study. Over the follow-up period (year 2), treatment was not controlled – participants were referred on for further treatment on an 'as needs' basis.

For more information regarding the interventions, as well as definition of responders and non-responders, please see Nelson et al. (2018).

[2]Cognitive behavioural case management (CBCM) is cognitive behavioural therapy for UHR delivered within a case management framework, i.e. the same person delivers psychotherapeutic aspects of CBT, as developed for this clinical population, and provides practical case management support, such as liaisong with schools, family, accommodation support services.

2.5 Analysis

This paper reports descriptive statistics on the baseline clinical characteristics of the cohort in terms of demographics, diagnosis, symptomatic, functional, cognitive bias and exposure measures (mean, standard deviation, and frequencies) and participant recruitment flow.

3. RESULTS

3.1 Participants and participant recruitment flow

A flowchart detailing recruitment flow up until point of enrolment is presented in Figure 2. In total, 1343 help-seeking young people were considered for the study. Of these, 330 (25%) were deemed ineligible based on file notes and discussion with the treating team (for details please see below and the flowchart in Figure 2); 580 (43%) declined participation or the research assistants were unable to seek consent; and 432 (32%) were consented to the study. After the screening and baseline assessments, a total of 342 young people (25% of those considered) were formally enrolled into the STEP study (Figure 2). The most common reason for excluding an individual based on file notes and discussion with the treating team (N = 92) was medication-related: individuals were already prescribed antidepressant medication for a specific and recognised indication and, after review with the study psychiatrist, it was deemed unreasonable to stop the treatment in order to participate in the study. The second most common reason for excluding an individual based on file notes and discussion with the treating team (N = 81) was being over-threshold for UHR (e.g., meeting criteria for a first episode of psychosis currently or in the past) (Figure 2). Most young people who declined participation did so because they were not interested in taking part in this particular study or in participating in research studies generally (N = 111). The second most common reason for declining was medication-related (N = 52): the young person did not wish to participate in a trial involving medication or was already prescribed antidepressant medication and did not wish to discontinue if presented with the option.

Disengagement (N = 162) and referral out of service/seeking other service (N = 50) were the most common reasons that no consent could be sought from the young person.

3.2 Demographics, symptomatic/functional profile and other characteristics

The mean age of the 342 enrolled participants was 17.7 years (range 12 to 25) and 58% were female (sex assigned at birth). The majority of the sample was born in Australia (89%), living with their families (78%) and currently in education (72%). Further details regarding the baseline demographic characteristics are displayed in Table 1.

As detailed in Table 2, the majority (87%) of the enrolled sample was diagnosed with a non-psychotic DSM-5 diagnosis, mainly mood and anxiety disorders (>60%, see Table 2). The sample displayed symptoms comparable with a moderate illness as indicated by the global BPRS scores (Leucht et al., 2005) and moderate difficulty in social, occupational and school functioning as indicated by SOFAS scores (Table 2). The MADRS indicated a moderate level of depression. Negative symptoms, as measured by the SANS, were comparable to other UHR samples (McGorry et al., 2017; McHugh et al., 2018). The WHO ASSIST substance use score revealed a moderate level of tobacco and cannabis use, and low

level for alcohol. Further details are displayed in Table 2. As shown in Table 3, the sample reported a history of severe levels of emotional and physical abuse, moderate levels of sexual abuse, none or low levels of emotional neglect, and moderate levels of physical neglect, as measured by the CTQ. The DACOBS total score indicated cognitive problems and cognitive biases higher than what has previously been reported in a schizophrenia spectrum patient sample (van der Gaag, Schutz, et al., 2013). This seems to have been largely driven by the cognitive limitation subscales (social cognition problems: above average; subjective cognition problems: above average) and behaviour subscales (safety behaviour: above average) and less so by the cognitive bias subscales (jumping to conclusions: below average; belief inflexibility bias: average; attention for threat bias: average; external attribution bias: average).

With regard to UHR subgroups, the vast majority of participants (N = 292, 85.4%) met criteria for the attenuated positive psychotic symptoms (APS) group; N = 32 (9.4%) met criteria for both APS and trait vulnerability groups. Table 3 provides a full break down of UHR subgroups.

4. DISCUSSION

This is the first SMART in UHR individuals evaluating three steps of sequential treatment with increasingly intensive interventions. Different interventions were provided depending on the clinical response at each step, with the view to establishing a stepwise approach in the provision of care to UHR individuals.

Of the 1343 help-seeking young people considered for this study over the recruitment period, 342 (25%) were enrolled. One of the most frequent reasons for participants to decline participation or to be excluded was related to current medication use. Some young people were already prescribed antidepressant medication for a specific and recognised indication and, after the review with the study psychiatrist, it was deemed unreasonable to stop the treatment in order to participate in the study. Other participants did not want to stop their prescribed medication before enrolment or did not want to take the chance of being in the medication arm of the study. Only 22% of potential participants actively declined participation, which is lower than in RCT's involving antipsychotics in this population. For example, in an RCT in the UHR population involving risperidone, only one third of potential participants agreed to be involved in the study (Phillips et al., 2009). This result underlines the apparent patients' acceptability of – and openness to - sequential treatment trials. It is comparable to higher consent rates involving CBT or omega-3 fatty acids, which indicates that RCT's involving psychotherapy or nutraceuticals have higher consent rates than RCT's involving antipsychotics (Addington, Marshall, & French, 2012; McGorry et al., 2009).

In terms of baseline diagnostic and symptomatic characteristics, the enrolled STEP study participants are comparable to other UHR samples previously recruited from PACE and headspace centres. As in other studies, the vast majority of this sample had at least one DSM-5 diagnosis, mostly mood and anxiety disorders. Compared to the symptomatic and functional profile at baseline of the NEURAPRO sample (N=304 - a recent RCT in UHR testing the effectiveness of omega-3 polyunsaturated fatty acids) (Nelson, Amminger,

Yuen, Markulev, et al., 2018) the STEP sample shows slightly higher levels of general psychopathology, negative and depressive symptoms, but also slightly higher functioning. Moreover, in line with other UHR cohorts, they present with a significant symptomatic and functional impairment, and high level of childhood trauma. This supports the clear need for care in the UHR group and that treatment is appropriate and fully justified (Fusar-Poli et al., 2013). Furthermore, a high level of baseline general psychopathology seems to be an important predictor of poor outcomes broadly defined in the UHR population and therefore an important element to respond to in this population (Polari et al., 2020). Regarding cognitive problems and biases, the scores of the present UHR sample were comparable to those with later stage schizophrenia spectrum disorders. Future papers from this cohort will report on whether these subjective cognitive problems and cognitive biases correlated with symptom severity and functioning and whether they modulated treatment response.

Clinical implications

The results presented in this paper demonstrate that it is feasible to rapidly recruit a large sample of UHR individuals from a metropolitan catchment area. Furthermore, it became apparent that these individuals are significantly unwell and manifest high rates of anxiety/depression and prescription of antidepressants. A non-negligible portion of potential participants declined participation as they were already prescribed an antidepressant and did not want to titrate off when this was proposed by their clinician (if indicated), suggesting either that a) participants prioritised medication over psychological interventions or b) prioritised maintaining existing treatment over an experimental treatment, or both. This highlights the need for education of General Practioners and other health care providers about the value of effective psychological interventions, which should be offered to most individuals before antidepressants and other psychopharmacological agents are prescribed to young people (National Institute for Health and Care Excellence (NICE, 2014, 2016)). It also indicates the need for the provision of information about the UHR clinical phenotype to health care providers as well as health care consumers , especially since UHR status is a marker of clinical severity and risk for adverse transdiagnostic outcomes (Hazan et al., 2020) and poorer prognosis in young people with anxiety and depression (Kelleher et al., 2012).

Limitations

A substantial proportion of UHR participants declined or were excluded because they were already prescribed an antidepressant medication. This may raise questions about the wider applicability of this particular staged approach to treatment, i.e., is it feasible to titrate UHR individuals off medication prior to starting a stepped treatment approach? Notwithstanding this issue, it is necessary to empirically test the clinical efficacy and utility of antidepressants in this clinical group, particularly given that the present data and data from previous studies indicate the widespread prescription of these medications for the UHR group without a sufficient evidence base to date.

5. Conclusion

The relatively low rate of declining consent indicates the acceptability of the trial's sequential treatment approach in this clinical population, which models standard sequential

clinical practice of moving from benign psychosocial intervention to more specific and intensive treatment. It also demonstrates, in line with other studies in UHR individuals, a significant level of clinical morbidity and functional impairment, confirming the clear need for stepwise and expert treatment and care. Subsequent papers will report on participant flow through the staged treatment approach and clinical and functional outcomes in response to the trial treatments.

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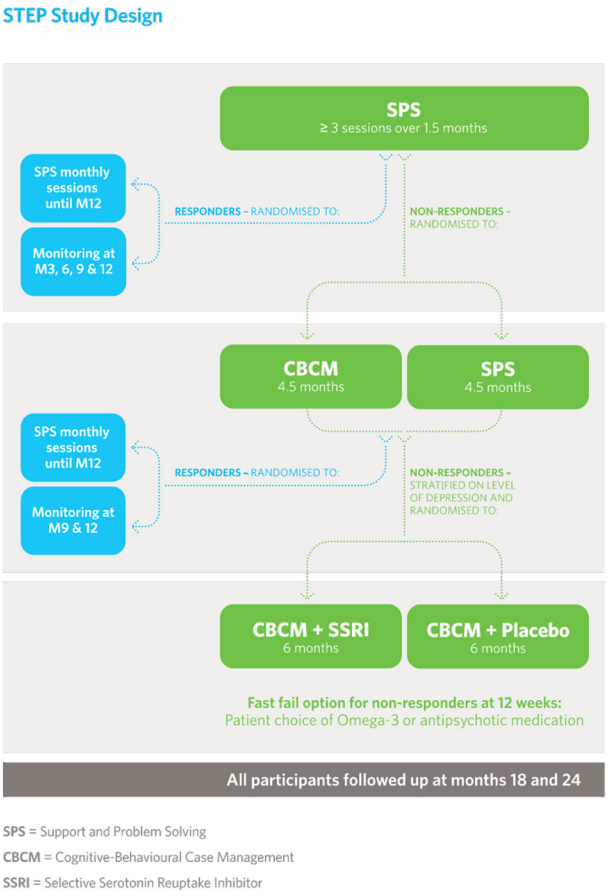

Figure 1.
Staged Treatment in Early Psychosis (STEP) study design.

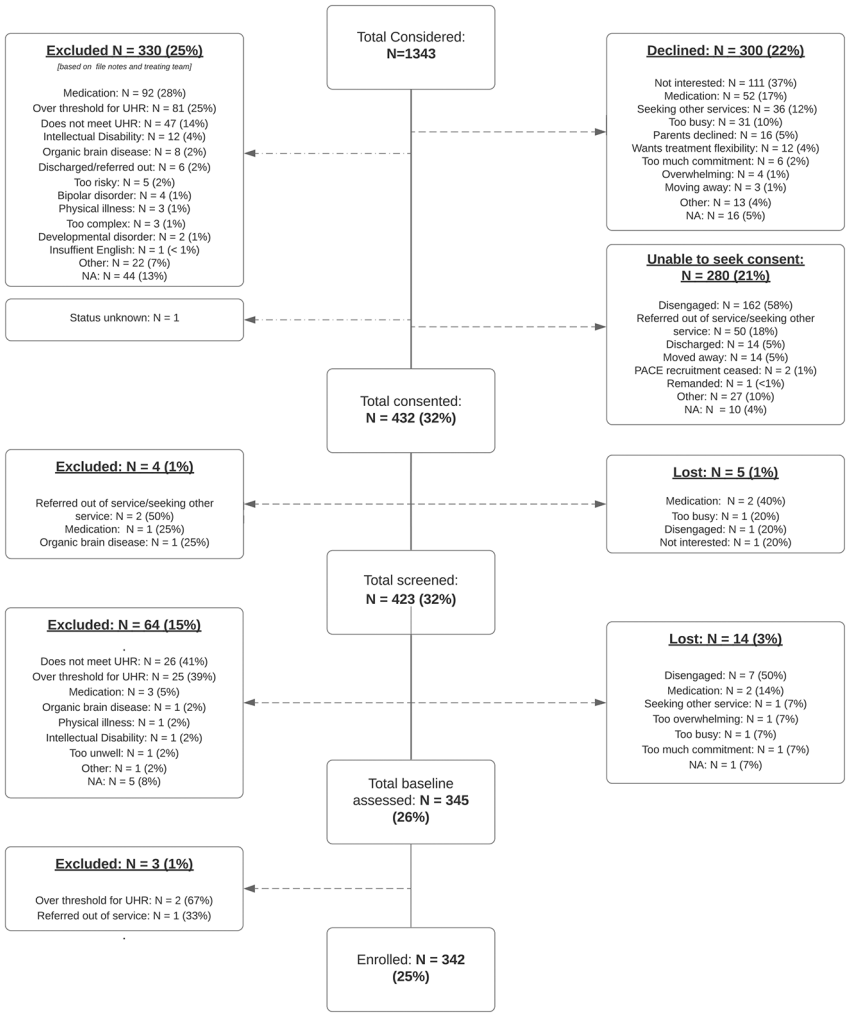

Figure 2.

STEP study recruitment flow up until enrolment. Please note, ‘exclusion due to medication’ refers to participants who were already prescribed antidepressant medication and, after review with the study psychiatrist, it was deemed unreasonable to discontinue the treatment. On the other hand, ‘declining due to medication’ refers to either (1) participants who were already prescribed an antidepressant and given the option to discontinue (if reasonable from a clinical point of view) but declined; or (2) the participant was not prescribed antidepressants but declined because they did not wish to participate in a trial involving antidepressant medication.

Table 1

Sample Demographics (N=342)

Category	Attribute	Mean/Count	±SD or %
Age		17.7 (12-25)	3.1
Gender	Female	198	57.9
	Male	144	42.1
Region of Birth	Australia	305	89.2
	Asia	15	4.4
	Europe	8	2.3
	New Zealand	5	1.5
	Other	9	2.6
Current Accommodation	House/flat with family of origin	268	78.4
	Rented room/flat/house	51	14.9
	Owned flat/house	4	1.2
	Other	17	5.0
	Missing	2	0.6
Current Relationship status	Single/never married	232	67.8
	Partnered (3 months to 2 years)	60	17.5
	Partnered (< 3months)	24	7.0
	Married/de facto	19	5.6
	Separated/divorced	2	0.6
	Other	5	1.5
Currently in education	No	95	27.8
	Yes	245	71.6
	Missing	2	0.6
Highest level of education [1]	Primary school	2	0.6
	Year 7-10	160	46.8
	Year 11-12	101	29.5
	TAFE	30	8.8
	University undergraduate	33	9.6
	University postgraduate	4	1.2
	Other	10	2.9
	Missing	2	0.6
Current Employment	Unemployed	218	63.7
	Casual paid employment	70	20.5
	Part-time paid employment	27	7.9
	Full-time paid employment	12	3.5
	Casual unpaid employment	8	2.3
	Part-time unpaid employment	2	0.6
	Missing	5	1.5

[1] Completed or currently enrolled

Table 2.

Diagnostic, symptomatic and functional characteristics

Category	N	Attribute	Mean/Count	±SD or %
Current diagnosis	342	No diagnosis	45	13.2
		Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	225	65.8
		Mood [affective] disorders	207	60.5
		Mental and behavioural disorders due to psychoactive substance use	54	15.8
		Behavioural syndromes associated with physiological disturbances and physical factors	30	8.8
		Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	26	7.6
		Borderline personality disorder	17	5.0
		Pervasive and specific developmental disorders	7	2.0
		Schizotypal disorder	6	1.8
		Obsessive-compulsive personality disorder	1	0.3
		Other	1	0.3
		Missing	15	4.4
CAARMS severity	342	Unusual thought content	2.6 (0-5)	1.8
		Non-bizarre ideas	2.9 (0-6)	1.7
		Perceptual abnormalities	3.1 (0-5)	1.5
		Disorganised speech	1.7 (0-5)	1.2
CAARMS frequency	339	Unusual thought content	2.4 (0-6)	1.7
	341	Non-bizarre ideas	3.0 (0-6)	1.7
	340	Perceptual abnormalities	2.6 (0-6)	1.4
	341	Disorganised speech	2.6 (0-6)	1.9
CAARMS Composite[†]	341	Attenutated positive psychotic severity score	34.6 (0-80)	16.8
Other symptoms	340	General psychopathology (BPRS)	44.6 (26-76)	8.7
	341	Negative symptoms (SANS)	18.4 (0-57)	11.2
	337	Depressive symptoms (MADRS)	23.5 (0-50)	9.9
Functioning	342	Social and Occupational Functioning (SOFAS)	56.7 (31-93)	11.6
Substance use (ASSIST)	332	Tobacco	7.0 (0-38)	9.6
	333	Alcohol	5.9 (0-35)	7.6
	334	Cannabis	6.3 (0-39)	10.6
	334	Amphetamine	1.9 (0-37)	5.6
	334	Sedatives	0.9 (0-29)	3.5
	333	Hallucinogens	0.9 (0-29)	3.2
	334	Inhalants	0.6 (0-27)	2.7
	333	Cocaine	0.5 (0-15)	1.8
	335	Opioids	0.3 (0-19)	1.6
	335	Other	0.2 (0-39)	2.4

CAARMS = Comprehensive Assessment of At-Risk Mental States; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; MADRS = Montgomery–Åsberg Depression Rating Scale; SOFAS = Social and Occupational Functioning Assessment Scale; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test

† Composite score according to Morrison et al. (2012)

Table 3

Other baseline characteristics

Category	N	Attribute	Mean/Count	±SD or %
Cognitive problems and bias (DACOBS)	314	Cognitive Bias Total	169.7 (85-251)	31.3
	327	Jumping to conclusions bias	23.1 (8-38)	5.5
	315	Belief inflexibility bias	20.6 (6-37)	6.2
	327	Attention to threat bias	27.4 (10-42)	6.4
	314	External attribution bias	23.4 (6-41)	6.8
	327	Social cognition problems	27.6 (9-42)	6.6
	315	Subjective cognitive problems	29.0 (9-42)	6.3
	315	Safety behaviour	18.2 (6-39)	6.9
Trauma (CTQ)	329	CTQ total	61.2 (43-111)	13.5
	330	Emotional Abuse	17.4 (10-25)	4.6
	330	Physical Abuse	12.9 (10-25)	3.8
	314	Sexual Abuse	11.7 (10-25)	3.7
	330	Emotional Neglect	8.8 (5-20)	3.5
	330	Physical Neglect	10.6 (8-22)	2.9
UHR subgroups	342	Trait vulnerability	9	2.6
	342	APS	292	85.4
	342	Trait + APS group	32	9.4
	342	BLIPS group	1	0.3
	342	APS + BLIPS	4	1.2
	342	Trait + APS + BLIPS group	4	1.2

DACOBS = Davos Assessment of Cognitive Biases Scale; CTQ = Childhood Trauma Questionnaire; APS = Attenuated Positive Psychotic Symptoms; BLIPS = Brief Limited Intermittent Psychotic symptoms