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Staged Treatment in Early Psychosis (STEP): A SMART Trial of Interventions for Ultra High Risk of Psychosis Patients

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Abstract

Aim: Previous research indicates that preventive intervention is likely to benefit patients 'at risk' of psychosis, in terms of functional improvement, symptom reduction and delay or prevention of onset of threshold psychotic disorder. The primary aim of the current study is to test outcomes of ultra high risk (UHR) patients, primarily functional outcome, in response to a sequential intervention strategy consisting of Support and Problem Solving, Cognitive-Behavioural Case Management, and antidepressant medication. A secondary aim is to test biological and psychological variables that moderate and mediate response to this sequential treatment strategy.

Methods: This is a sequential multiple assignment randomised trial (SMART) consisting of three steps: Step 1: Support and Problem Solving (1.5 months); Step 2: Support and Problem Solving versus Cognitive Behavioural Case Management (4.5 months); Step 3: Cognitive Behavioural Case Management + Antidepressant Medication versus Cognitive Behavioural Case Management + Placebo (6 months). The intervention is of 12 months duration in total and participants will be followed up at 18 months and 24 months post baseline.

Conclusion: This paper reports on the rationale and protocol of the Staged Treatment in Early Psychosis (STEP) study. With a large sample of 500 UHR participants this study will investigate the most effective type and sequence of treatments for improving functioning and

reducing the risk of developing psychotic disorder in this clinical population.

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Introduction

Since our first intervention trial in the ‘ultra high risk’ (UHR) for psychosis population in the late 1990s (1), eleven further RCTs have been conducted, testing a range of psychological, pharmacological, nutritional and multicomponent psychosocial interventions. A recent meta-analysis (2) found that the risk reduction of experimental interventions compared to control interventions was 54% over 12 months with a Number Needed to Treat (NNT) of 9. Cognitive-behaviour therapy (CBT) has been found to be of particular benefit and safety, with another meta-analysis indicating that it reduces the relative risk of developing psychosis by 50% at 6, 12 and 18-24 months (3). Integrated psychosocial interventions have also been shown to be of benefit (4, 5). Antipsychotic medication has also shown some efficacy, although a less favorable risk-benefit ratio means that it is not appropriate for first line therapy (6). Omega-3 fatty acids have shown a strong and sustained benefit in one double blind placebo controlled trial (4.9% versus 27.5% at 12 months, $p < .007$) (7), but we failed to replicate this finding in a subsequent larger-scale study(8).

Naturalistic data has been reported suggesting that antidepressant medication may be effective in reducing the risk of transition in UHR patients (9-11). For example, Fusar-Poli and colleagues (11) reported naturalistic data that antidepressant medication in conjunction with cognitive behaviour therapy was associated with greater benefits than antipsychotic medication in conjunction with cognitive behaviour therapy. The high rate of prescription of antidepressant medications (61% of the cohort) in our recent omega-3 intervention trial may have contributed to the low transition rate observed in that study (8). However, another study

failed to find support for antidepressant medications improving symptom progression in UHR patients (12). To date, the effect of antidepressant medications in this population has not been tested in a controlled trial. Antidepressants could reduce risk by improving mood and thereby indirectly reducing faulty appraisal of anomalous experiences linked to future psychosis. They may also modulate response to environmental stress and adversity, which has been found to increase risk for psychosis (10, 13). This effect may occur either directly via acting on the neurochemical pathways that mediate stress response (14) or indirectly by preventing depression, affective dysregulation and anxiety secondary to these stressors (15, 16) (17). Consistent with this, Cornblatt and colleagues (18) proposed that antidepressants may reduce some of the underlying core vulnerability factors (mood disturbance, social isolation, school failure) and thereby relieve the stress that might otherwise exacerbate attenuated psychotic symptoms. It also appears that antidepressants may possess some neuroprotective properties (19-21), which may halt a neurodegenerative process associated with the evolution of psychotic disorder.

Longer term follow up of the relatively brief interventions trialled to date reveals significant differences in transition rate tend to be lost over time (6, 22, 23). In the first intervention trial in this group, the benefits that were associated with a combined antipsychotic medication/CBT intervention over the 6 month treatment period were not maintained at 12 month (1) and medium term follow up (22). Similarly, trend benefits in favour olanzapine compared to placebo during the treatment year were not maintained over the follow-up year (6), nor were lower transition rates associated with CBT over a 6 month treatment period

maintained at medium term follow up (23). However, in contrast, Ising and colleagues (24) reported a benefit of CBT over treatment as usual at the 4-year follow up point. Overall, this suggests that the intervention for most patients may have merely delayed onset through reducing risk during the period of treatment. It also suggests different treatments, sequences and durations of therapy may be needed for sustained benefits, as seen with early psychosis services in general (25-29). The first generation of UHR trials have generally been modest single site studies testing one or two candidate therapies in single step, head-to-head designs. The next step is for further trials to determine the most effective type, sequence and duration of interventions, and how they might best be personalised or tailored to individual patients, based on clinical presentation, response profile and perhaps ultimately through the use of biomarkers or psychosocial variables.

Broadening the outcomes of interest: Functioning and non-psychotic outcomes

The UHR criteria have shown good predictive validity for progression of the psychosis phenotype, consistent with their original purpose. However, this special valence for psychosis outcomes has been shown to coexist with an increased risk of persistent subthreshold psychotic symptoms (41%), other non-psychotic syndromal outcomes (up to 40%) and a cross-diagnostic risk of poor functional outcome in a substantial minority (30-33). Even if UHR patients do not transition to psychosis, persistent subthreshold positive symptoms and/or mood and anxiety symptoms may seriously disable, and these syndromes are often not treated due to poor access to or engagement in subsequent care. Adopting a broader perspective for

UHR treatment is congruent with the general move to prioritise social and occupational recovery as a primary target for intervention in all mental disorders (34).

Declining transition rates and need for larger-scale, sequentially enriched studies

Another recent observation has been the declining transition rate in UHR cohorts worldwide. Early studies reported 12-month transition rates in the 30-40% range whereas more recent studies have reported rates of 10-20% (35, 36). The precise reasons for this are unclear, but may include a combination of lead-time bias (37), earlier intervention (38), a change in clinical characteristics of cohorts (39), referral pathways (40) and treatment changes. The fact that UHR patients are not only already symptomatic but functionally impaired underlines the need to clarify an evidence-based intervention sequence which may be translated directly into clinical practice. However, the declining transition rate does reduce power and highlight the need for larger sample sizes and sequential strategies to enrich risk.

The clinical staging model

The clinical staging model is a transdiagnostic heuristic approach aimed at understanding the neurobiological and psychosocial processes underpinning the onset and course of mental disorders. Clinical staging, through integrating stage and timing with evolution of clinical phenotype, also allows interventions to be tested from a preventive standpoint in reducing the risk of progression and persistence of illness, with less risk and greater potential benefit (41-44). Staging is a pragmatic blend of categorical and dimensional approaches which aims for

clinical and research utility, providing a heuristic framework to study the significance of biomarkers by stage and clinical phenotype, psychosocial risk factors and treatment response.

Applying the clinical staging model to UHR intervention means that a staged approach to treatment is offered, with the safest, most benign and least specialised interventions used initially, and “stronger”, more intensive interventions, with potentially more adverse effects, reserved for those who do not respond to the earlier stages of intervention. This adaptive strategy also addresses the lower transition rate through a stepwise enrichment of the sample such that non-responders to initial simpler interventions will be enriched for both higher transition rates to psychosis and for greater functional impairment. The staging model also hypothesizes that timing of intervention is critical in that therapeutic agents/strategies with neuroprotective and psychoprotective qualities will be most beneficial in this subthreshold stage of disorder in reducing the impact of the disease process. Finally, this staged approach to UHR intervention addresses ethical concerns regarding intervention in this group, namely the “false positive” issue, potential stigma, and a perceived relative lack of predictive power (45). Since there is a need for care for the presenting clinical problems, then providing safer, nonspecific and benign interventions as a first step will allow those with milder and responsive or self-limiting problems to remit, while those who fail to benefit can progress to more intensive or relatively more specific interventions. This ensures an “enriched” sample, with fewer false positives for both persistent and more severe illness (of any phenotype) and also for transition to psychosis, in which to test more specific intervention strategies.

Neuroprotection, inflammation and oxidative stress

Current biological treatment options for established psychoses have predominantly centered on the dopamine theory. However, it is unclear how central this theory is likely to be for UHR patients (46, 47). In addition, the side effects of dopamine antagonists (i.e., antipsychotic medications) significantly limit their preventive use. There is now a clear body of evidence to support a role for both inflammation and oxidative stress in the pathophysiology of psychotic disorders (48, 49). There is consistent evidence of increased blood concentrations of inflammatory cytokines (50). Inflammatory abnormalities are present in patients with first-episode, drug-naïve psychosis (FEP) compared with controls, suggesting an association independent of antipsychotic medication. Furthermore, the concentrations of some inflammatory molecules vary with the clinical status of patients, i.e., there appear to be separate groups of state and trait markers. State-related markers include interleukin (IL) 1-beta, IL-6, and transforming growth factor-beta. IL-12, interferon-gamma, and tumor necrosis factor-alpha (TNF-alpha) appear to be trait markers (51). Oxidative stress, a state where the levels of available antioxidants is reduced, or the levels of oxidative species is increased, is well documented in schizophrenia and related psychoses (48), with abnormal oxidative stress parameters reported in peripheral blood cells (i.e., erythrocytes, neutrophils, platelets), cerebrospinal fluid and postmortem brain. Inflammation and oxidative stress also reciprocally induce each other in a positive feedback manner (52). The incorporation of these factors into traditional monoamine neurotransmitter-system models facilitates a more comprehensive model of disease, potentially underpinning course of illness in psychotic disorders (53). This in turn has facilitated the identification of new therapeutic targets and neuroprotective

treatments that have the potential to interrupt the identified neurotoxic cascades (54). Although the current study will not test a pharmacological agent that targets these potential pathogenic mechanisms, relevant biological markers will be measured to assess their predictive value and whether they moderate outcome.

“Psychoprotection”

The cognitive model of psychosis posits that dysfunctional interpretations of anomalous experiences contribute, against a background of pre-existing biopsychosocial vulnerability, to the emergence and maintenance of psychotic symptoms (55, 56). These consist of cognitive biases (57) that emerge from underlying “core” beliefs or schemas about the self and world that have become entrenched during an individual’s developmental years. During the prodromal stage of psychosis, it is thought that such biases contribute to the evolution of attenuated into frank psychotic symptoms (58, 59). CBT for UHR individuals aims to identify, manage and correct these cognitive biases and dysfunctional interpretations of anomalous experiences through a variety of talking therapy and behavioural techniques and thereby diminish the risk of developing full-threshold psychotic disorder (59, 60). In this way, CBT may function as a form of “psychoprotection”(61) against cognitive vulnerabilities. In several trials to date, CBT has proven effective in UHR samples (NNT=13), although a link to the underlying mechanism of reducing cognitive biases and preventing the formation of delusional explanations of anomalous experiences, a focus of the present design, has not yet been clearly demonstrated.

Although CBT has been found to be more effective than monitoring it is not yet clear whether it is more effective than other, less intensive psychotherapies. In a trial comparing risperidone, CBT and supportive therapy, supportive therapy resulted in the same degree of symptomatic and functional improvement in UHR patients as CBT (62, 63). The current study will test cognitive-behavioural case management (CBCM), an intervention that delivers CBT in a case management format. It will therefore allow for further investigation of whether CBT provides additional advantages over supportive therapy for this patient group.

Neurocognitive and neurobiological predictors of psychosis

There is considerable literature showing that reduced neurocognitive performance predates the onset of frank psychotic symptoms and is evident in childhood (64) and adolescence (65) in people who go on to develop schizophrenia. UHR patients also show reduced neurocognitive performance compared to healthy controls across a range of domains (66). Within this group, those who transition to psychosis show even greater decrements. The precise pattern of neurocognitive deficits in those who transition is yet to be determined. However, the most consistent findings relate to reduced memory and executive function performance (67-77). Neurocognition will be assessed in the current study in order to probe the cognitive deficits that mark the pre-onset phase of psychotic disorder and whether neurocognitive profiles predict outcome and moderate/mediate response to treatment.

A key question in the aetiology of psychotic disorders is whether the brain changes seen in post-mortem and imaging studies of patients with long-standing illness arise during the

development of the illness and, if so, whether they represent a potential target for intervention. Significant reductions in grey matter in various brain regions have been observed across the transition to psychosis in UHR samples (78-83). White matter also shows changes around the time of transition to psychosis (84). MRI brain scans will be performed in the current study in order to further assess these changes and whether neuroimaging parameters predict outcome and moderate/mediate response to treatment.

Gene-environment interaction

An important current in psychosis research is understanding how genetic and environmental factors interact to contribute to the onset and evolution of psychotic disorders (85, 86). The current study will collect biological samples of blood and cerebral spinal fluid (87) for genetic analysis in order to investigate whether gene by environment interactions predict outcome and moderate/mediate response to treatment.

Internationally unique enhanced primary care platforms

The Australian *headspace* system is a nationwide platform of care for young people, which has already enabled access to clinical and social care to over 100,000 young Australians aged 12–25 years with emerging mental ill health. The system is essentially a “one stop shop”, universal access model for young people and families experiencing early stage mental and substance use disorders. Some early literature and data on the *headspace* model has been published (88-91). Research data gathered from these sites indicate that 38% of the patients meet the UHR criteria (92).

Study Rationale

The current study is a program of translational research with two linked elements. The first element is designed to create new knowledge and skills for intervening in the early clinical stages of psychotic disorders. The heterogeneity of the UHR stage of illness means that individualised “adaptive” treatment policies are required. Some patients will respond while others will not to the same intervention type, intensity or duration. Other reasons in support of adaptive and sequential approaches include the need for sample enrichment, changing responsiveness linked to stage of illness, presence of comorbidities and the high risk of relapse even when initial remission has been achieved (93). Creating an evidence base fit for implementation and for subsequent clinical translation requires a trial methodology which experimentally evaluates interventions via multistage designs, and which builds upon methods intended for the analysis of naturalistically observed strategies. A clinical trial design innovation, the Sequential Multiple Assignment Randomized Trial (“SMART”), used in several recent large scale studies in psychiatry to develop an evidence base to support adaptive clinical care, is a good fit with the clinical staging model, and is ideal for the current study (94). SMART designs involve multiple intervention stages that correspond to the critical decisions involved in adaptive interventions. Adaptive interventions are interventions in which the type or dosage of the intervention is individualised on the basis of patient characteristics or clinical presentation and then are repeatedly adjusted over time in response to patient progress (94, 95). Interventions can also be tailored at critical decision points

according to response or other patient characteristics such as specific biomarker changes or comorbidity, and also patient preference (96).

SMART trials have been implemented in a number of fields, beginning in cancer research (97-99). Recently concluded SMART trials include the CATIE trial of treatments for schizophrenia (100), Phase II trials at University of Texas MD for treating cancer (101), the ExTEND trial of treatments for alcohol dependence (102), and a SMART study of treatments for children with attention deficit/hyperactivity disorder (ADHD; see (95) for review). Trials currently in the field include a SMART for nonverbal children with autism (103), a SMART concerning behavioral interventions for drug-addicted pregnant women (104), and a SMART for the treatment of metastatic renal cell carcinoma (105). While adaptive trial designs add complexity to trial design and the statistical methods required, they will often provide greater statistical power and have more direct implications for real-world clinical decision making than RCTs due to the sequence of interventions based on patient response (94).

The second element involves the processing of this emerging new evidence and adapting and translating this to key parts of the United States (US) health care system (the study is funded through the National Institute of Health (NIH)). We will conduct a series of focus groups with key stakeholders recruited from across the U.S.: 1) consumers, 2) families, 3) mental health and primary care clinicians, 4) local and national public health leadership; 5) private payer leadership; 6) public and private program management. Each group will identify potential challenges and solutions to implementing the model in public and private healthcare settings,

focused on the following topics: diagnosis, assessment and eligibility, services reimbursement, prescribing issues and reimbursement, workforce training and sustainability, specialty services vs. integration, staged intervention algorithms, and cultural acceptability and adaptation. The resulting suggestions will be integrated and applied to the design of a feasibility study of open-label use of the staged treatment model in a university-based early psychosis specialty care clinic. Suggestions regarding adaptation might include guidelines for billing treatments in both public and private healthcare settings or adaptation of the model if all elements cannot be billed (e.g. case management vs. therapy for private insurance).

Study Aims

The main study aim is to test outcomes of UHR patients, primarily functional outcome, in response to a sequential intervention strategy consisting of Support and Problem Solving (SPS), Cognitive-Behavioural Case Management (CBCM), and antidepressant medication. A secondary aim is to test biological and psychological variables that moderate and mediate response to this sequential treatment strategy.

Hypotheses

Hypothesis 1: In Step 1 we hypothesize that 50% of participants (n=500) will respond to the open label SPS intervention. This prediction is based on modeling of response rate achieved over 6 weeks in a previous RCT we conducted in the UHR population (62).

Hypothesis 2a: In Step 2 (n=200), we hypothesize that there will be a significantly better response (on the primary outcome of functioning) to CBCM than to SPS. This prediction is based on the evidence to date for the efficacy of CBT in the UHR population.

Secondary hypotheses for Step 2 are as follows:

In the CBCM group, baseline cognitive biases and vulnerabilities will predict response and outcome (**H2b**), and those with better outcome and responders will show a significantly greater change on these variables than those with worse outcome (**H2c**) and non-responders (**H2d**). These predictions are based on the assumption that CBT engages and treats psychological mechanisms (cognitive biases and vulnerability to stress) that may drive the onset of psychosis in a subset of UHR patients.

Hypothesis 3: In Step 3 (estimated n=80), antidepressants will result in a significantly better outcome and greater response than placebo. This hypothesis is based on existing naturalistic evidence for the efficacy of antidepressants in the UHR population. The fast-fail subgroup (see below) is a naturalistic phase and no specific hypothesis is advanced.

Hypothesis 4: For the relapse prevention arm of the study extending over a period from 6 weeks after the start through to the end of the first year of the study, depending on the point of entry, we hypothesize that those receiving SPS will show a significantly reduced rate of relapse compared to the monitoring only group. This prediction is based on the assumption that regular supportive psychotherapy may result in better outcome than simple monitoring in a subset of UHR patients.

Study Objectives

Primary Objective

- To test the effect of a sequential treatment approach consisting of SPS/SPS and SPS/CBCM on functioning levels of UHR patients 6 months post baseline (end of Step 2).

Secondary Objectives

- To test the effect of a sequential treatment approach consisting of SPS, CBCM and antidepressant medication on functioning levels of UHR patients 12 months from baseline (end of Step 3).
- To test the effect of a sequential treatment approach consisting of SPS, CBCM and antidepressant medication on transition to psychotic disorder by 12 months and 24 months from baseline.
- To test the effect of a sequential treatment approach on UHR status (maintenance versus remission) 1.5 months, 6 months, 12 and 24 months from baseline.
- To test the effect of a sequential treatment approach in UHR patients on level of psychiatric symptomatology, including positive psychotic symptoms, negative psychotic symptoms and depressive symptoms 6 months, 12 months and 24 months from baseline.
- To test relapse rates (to UHR+ status) in the relapse prevention/responder arm of the trial (SPS v monitoring) during the first 12 months.

Exploratory Objectives

The study aims to also explore whether there is a relationship between treatment response and specific patient profiles. In the subset of responders to a specific intervention, such as CBCM

or antidepressants, the study will examine whether it is likely that the treatment was effective due to the proposed putative mechanisms (cognitive biases and neuroprotection). Psychological variables, inflammatory and oxidative stress, as well as related biomarkers will be measured at baseline, entry and exit from steps two and three and test whether these variables moderate or mediate response to treatment. The study will also investigate whether response to SPS or CBCM in Step 2 is mediated/moderated by degree of therapeutic alliance (quality of therapeutic relationship) between the participant and clinician. The study will also investigate whether SSRIs have any impact on inflammatory and/or oxidative stress biomarkers. Based on the background material reviewed above, we will also examine whether neurocognition, neuroimaging, CSF complement proteins and genetic variables predict outcome (persistent attenuated psychotic symptoms, transition to psychosis, poor functioning) and moderate/mediate response to treatment.

Study Design

This is a sequential multiple assignment randomized trial (SMART). Participants who are classified as non-responders at the end of a Step will graduate to the next stage of intervention, while responders are offered entry to a maintenance/relapse prevention arm in which modest psychosocial care is compared in a randomised design with monitoring alone throughout the first 12 months of the study. A “fast fail” feature is included in Step 3 if the participant deteriorates or fails to show improvement. This consists of dose enhancement and entry to a personal choice/shared decision-making treatment option.

Research Assistants (RAs) conducting the clinical assessments will be blind to treatment allocation (Step 2: single-blind). Step 3 of the study incorporates a randomised, double-blind, placebo-controlled stage of the study. The study design is represented in Figure 1.

Insert Figure 1 about here

The design consists of 3 steps:

Step 1: Open-label Support & Problem Solving (SPS): “Open-label” SPS will be provided to all participants. A minimum of 3 sessions will be provided within a 6-week period. We expect this initial step will produce resolution of the current clinical phenotype in around 50% of participants, and thereby enrich the remaining sample for psychosis risk and functional impairment for randomisation in subsequent steps (31, 32). We also expect this to help retention of participants as drop outs have tended to occur early in previous UHR trials (62). Participants who respond to Step 1 will be randomised to SPS monthly sessions v Monitoring at 3, 6, 9 and 12 months post entry to Step 1.

Monitoring will consist of the RA conducting a research assessment in addition to the clinician making contact with the participant in order to monitor mental state and risk and to assess whether there has been any mental health deterioration that would indicate a need for change in clinical management.

Step 2: CBCM vs SPS: Participants who do not respond (estimated at 50%) to Step 1 will be randomised to one of two treatment groups for 4.5 months: A more intensive psychosocial intervention (cognitive behavioural case management: CBCM) versus SPS. This design will test the potential benefit of a more intensive psychosocial intervention compared to extending the more basic intervention provided in Step 1 (SPS). It is possible that non-responders to Step 1 (6 weeks of SPS) have simply not received the SPS intervention for long enough (i.e., the “dose” of SPS has not been sufficient to achieve symptom response and functional improvement). Extending SPS to a total of 6 months duration in Step 2 will test this possibility, as well as the potential benefit of introducing a more intensive psychotherapy in the form of CBCM. This step will test an intervention that targets a key putative mechanism for psychosis vulnerability and risk: the psychological mechanism of dysfunctional cognitive biases.

Step 3 CBCM + SSRIs vs CBCM + Placebo: The estimated 50% who do not respond by the end of Step 2 (30, 37) will be randomised to antidepressant medication or placebo, in addition to CBCM, for a further 6-month period. Randomisation will be stratified based on depression scores (MADRS total score <21 or ≥21). This stage will test whether antidepressant medication in addition to CBCM contributes to improving the outcome of those who have failed to respond to previous interventions. It is appropriate to reserve antidepressants for this third step in view of their higher risk of adverse effects. By stratifying by depression at this stage of randomisation, we will be able to ascertain the impact of antidepressant medication on outcome in this population in relation to intensity of depressive symptoms, which will have

direct implications for clinical decision-making as well as shed light on the possible mechanisms underlying the benefit of antidepressant medication for this patient group.

“Fast fail” in Step 3: Step 3 will incorporate a “fast fail” feature such that if patients deteriorate or have not responded after 12 weeks of this third step of the study, they will be offered the option of:

1. Continuing as randomised
2. Increasing the dosage of antidepressant medication/placebo or
3. Continuing the antidepressant or placebo with the addition of Omega-3 fatty acids or low dose antipsychotic medication chosen via a shared decision making approach.

Responders: All responders during Steps 1 and 2 will be randomized at the end of each step to monthly SPS sessions or simple monitoring at 3 monthly intervals (Response to Step 1: 6, 9 and 12 months; Response to Step 2: 9 and 12 months) to assess whether such responses can be sustained. All relapsing participants at any stage and all non-responders at the 12 month point will be reassessed and offered “treatment as usual” via **headspace** and Orygen.

Rescue: A safety net or “rescue” strategy is built into the study design from Step 1 through to the end of Step 3 where participants whose psychotic symptoms worsen to the point of full threshold psychosis, or who develop acute mania, or sustained aggressive or suicidal risk as defined using the CAARMS are withdrawn entirely from the study and treated according to clinician’s choice, typically with antipsychotic or antidepressant medication, either as inpatients or with intensive community care and with full evidence-based psychosocial care.

Response: The definition of response is as follows:

- The Global Rating Scale or the Frequency score need to be less than 3 for all of the four positive symptoms (Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and Disorganised Speech) and
- There is an improvement of at least 5 points in Social and Occupational Functioning Assessment Scale (SOFAS) compared with baseline or the SOFAS score is at least 70.

The response status will be determined using the “current” ratings of CAARMS and will be determined at weeks 4, 6, 12, 24, 36, 52. These current ratings are based on the patients’ experience over the last fortnight and are for the four positive symptoms only.

The definitions for a responder at the different time points are as follows:

- A responder at the end of Step 1 is one who shows a response at both weeks 4 and 6.
- A responder at the end of Step 2 is one who shows a response at both weeks 12 and 24.
- A responder at week 36 is one who shows a response at week 36 (for the ‘fast fail’ option).

Non-response: All participants who do not meet the ‘response’ criteria (and who have not yet made a transition to psychosis).

All participants will be closely monitored for adverse events and concomitant medication use throughout the study.

Study Setting

The sites for this trial will be four youth mental health services (**headspace** centres) funded through the Commonwealth Government of Australia and the PACE clinic, a specialised UHR research clinic that has two decades of innovation, clinical and research experience with

this group of patients and their families (106-108). If recruitment rate is behind target, recruitment at additional **headspace** centres will be considered.

Study Duration

The controlled intervention component of the study is of 12 months duration. Participants will be followed up with research assessments up to 24 months post-baseline.

Inclusion Criteria

A participant will be considered eligible for inclusion in this study only if all of the following criteria apply:

1. Age 12 -25 years (inclusive) at entry
2. Ability to speak adequate English (for assessment purposes)
3. Ability to provide informed consent
4. Meeting one or more UHR for psychosis groups (see Table 1).

Young people seeking help via **headspace** centres will be screened using a standardised clinical assessment and the Prodromal Questionnaire-16 (PQ-16)(109). Those who score 6 or more positive symptoms on the PQ-16 will be assessed using the CAARMS(110) and SOFAS(111) to determine UHR status.

Insert Table 1 about here

Exclusion Criteria

The exclusion criteria are listed in Table 2.

Insert Table 2 about here

Potential participants who meet any of the following criteria will not be eligible for participation in this study:

Participant Discontinuation Criteria

A participant will be considered ‘discontinued’ from the study in cases where the study treatment is ceased. If appropriate, participants will be invited to continue in the study assessments in accordance with the study schedule, even though they are no longer receiving study treatment.

A participant will be discontinued from the study intervention in the following situations:

1. Serious adverse events at Investigator discretion.
2. Pregnancy during Step 3 (which involves antidepressant medication).
3. Severe non-compliance to protocol as judged by the Investigator.
4. At the Investigator’s discretion.

After consultation between the treating doctor and the study investigators, participant will also be discontinued from the study in the case of:

5. Transition to psychosis or mania. Transition is operationally defined via the CAARMS, as in previous studies (110), as positive psychotic symptoms occurring every day for one week or longer. A transition to full threshold mania will also mean that the participant is stopped since mood stabilisers will be administered.
6. Participants who have sustained risky levels of aggression or suicidality associated with their psychotic symptoms (or otherwise) at one of the follow up assessments. Sustained levels of aggression is defined as a CAARMS 5.4 scale score of 6 sustained over the past 2 weeks and sustained levels of suicidality as a CAARMS 7.3 scale score of 6 sustained over the past 2 weeks.

These cases may be offered antipsychotic or antidepressant medication as inpatients or via intensive community care, as per early psychosis guidelines (112, 113). This constitutes rescue treatment.

Visits and Assessments

The schedule of assessments are shown in Table 3.

Insert Table 3 about here

Study Interventions

Support and Problem Solving (SPS)

SPS consists of basic supportive counseling and problem solving strategies delivered within a positive psychology framework. This is a minimal-level ‘treatment as usual’ intervention for this group. Sessions will be weekly-fortnightly and of 30-50 minutes duration. Formal psychotherapy is not included in this intervention. SPS has proven safe, engaging and effective for the wider range of early diagnostic presentations in our primary care platform, **headspace** (114).

Cognitive-Behavioural Case Management (CBCM)

CBCM consists of CBT embedded within case management, as successfully developed and implemented in our previous studies (115). The CBT consists of four modules addressing attenuated psychotic symptoms, stress management, negative symptoms/depression, and other comorbidity. All modules consist of psychoeducation, behavioural strategies/experiments, and cognitive restructuring. There is preliminary evidence that yoga and mindfulness may be of value in early psychosis patients (116) and have therefore been incorporated into the current treatment package, delivered in a group setting. The treatment approach is modular and based on shared formulation with the individual client; it therefore does not prescribe which module should be delivered or for how long. The treatment components are provided within a case management framework addressing practical issues. The standard will be to deliver CBCM sessions weekly, but frequency of sessions will be flexible depending on the participant’s needs. Sessions will be 30-50 minutes in duration. A minimum of 6 sessions will be provided.

Medications

Antidepressants (SSRIs) in Step 3: Oral capsules of fluoxetine 20-40 mg or matched placebo daily for 6 months. Participants will commence on 1 capsule of fluoxetine 20 mg or 1 capsule of the placebo pill. The medication can be increased to fluoxetine 40 mg daily (or 2 placebo capsules) if there has been a poor clinical response after the first 6 weeks of Step 3.

Omega-3 fatty acids as “fast fail” option in Step 3 (12 weeks into Step 3): 2.8g/day of marine fish oil containing approximately 1.4g eicosapentaonic acid (EPA/DHA) in 4 X 0.700g capsules.

Antipsychotic medication as “fast fail” option in Step 3 (12 weeks into Step 3): Quetiapine 50-300mg/day or Aripiprazole 10-30mg/day.

Concomitant Medication and Therapies

All psychiatric treatments administered to 24 months will be recorded.

Procedures for Monitoring Compliance with Interventions

SSRIs: During Step 3 participants' compliance with study medication will be recorded via pill count. Compliance will also be monitored using a mobile application developed by our group ('Smartphone Ecological Momentary Assessment, SEMA'). This mobile phone application will consist of a system that prompts participants every evening to input their medication use (number of capsules taken) over the previous day.

SPS and CBCM: Sessions will be audiotaped and rated by blinded raters in order to assess fidelity to these psychological interventions. Fidelity will also be monitored by therapists

rating their own sessions on a checklist of therapeutic interventions. Any additional psychosocial interventions delivered will also be documented.

Statistical Analysis

The primary analysis will be to compare the two Step 2 treatments on the 6-month Global Functioning: Social and Role Scale score (117) using analysis of covariance with the baseline Global Functioning: Social and Role Scale score as the covariate. The treatment options in Steps 2 and 3 correspond to 4 treatment regimes for the non-responders. Comparing fluoxetine and placebo from Step 3 is equivalent to collapsing these regimes into two groups. A secondary analysis will be to compare these two groups using ANCOVA in terms of 12-month Global Functioning: Social and Role Scale score. Comparing the different treatment regimes will also be considered. Survival analysis will also be used for comparison of transition rates. Other secondary outcome measures at the various time points will be examined using appropriate techniques such as ANCOVA, chi-square tests and multi-level modelling. Potential confounders and predictors will also be taken into account. If the amount of missing values is non-trivial, then imputation techniques such as multiple imputation will be considered. Intention to Treat (ITT) analysis will be conducted.

Sample Size and Power

The study is powered on the primary aim of comparing six-month functional outcome between the two treatment groups in Step 2. Assuming a 50% non-response rate in Step 1, an entry sample size of 500, a drop-out rate of 20% and hence a step 2 sample size of 200, we will be able to detect a fairly small effect size (0.18 in a parallel cell design) with a power of 80% and significance level of .05 by the end of Step 2. Recent data indicates that

approximately 38% of young people seen at **headspace** meet UHR criteria, which means that approximately 2000 patients per annum will be eligible for the study. A two-year recruitment period means that 500 participants would need to be recruited from a pool of 4000 patients (12.5%). It is standard for SMART trials to be powered on a single stage or aspect of a multi-staged design (95). Nevertheless, a 50% non-response rate in Step 2 and 20% drop-out rate will result in n=80 in Step 3, which will be sufficient to detect a clinically important medium effect size (0.29) for comparing the two Step 3 interventions with a power of 80% and significance level of .05.

Summary

In summary, this study's sequential multi-stage design is intended to produce evidence to guide a stepwise clinical approach to treatment of UHR patients and reduction of risk for psychosis and other deleterious clinical and/or functional outcomes. The study will also collect data on key biomarkers and other mechanisms potentially underpinning risk, which may ultimately be used to adapt and personalise treatment. Major recent service reforms and expansions in Australia have enabled our research centre to access much larger clinical samples through which we can make a crucial contribution to assembling an evidence base that, with the assistance of the US investigators, will be translatable to US health care, and other settings worldwide with the goal of reducing the enormous human, social and economic costs of schizophrenia and other psychotic disorders.

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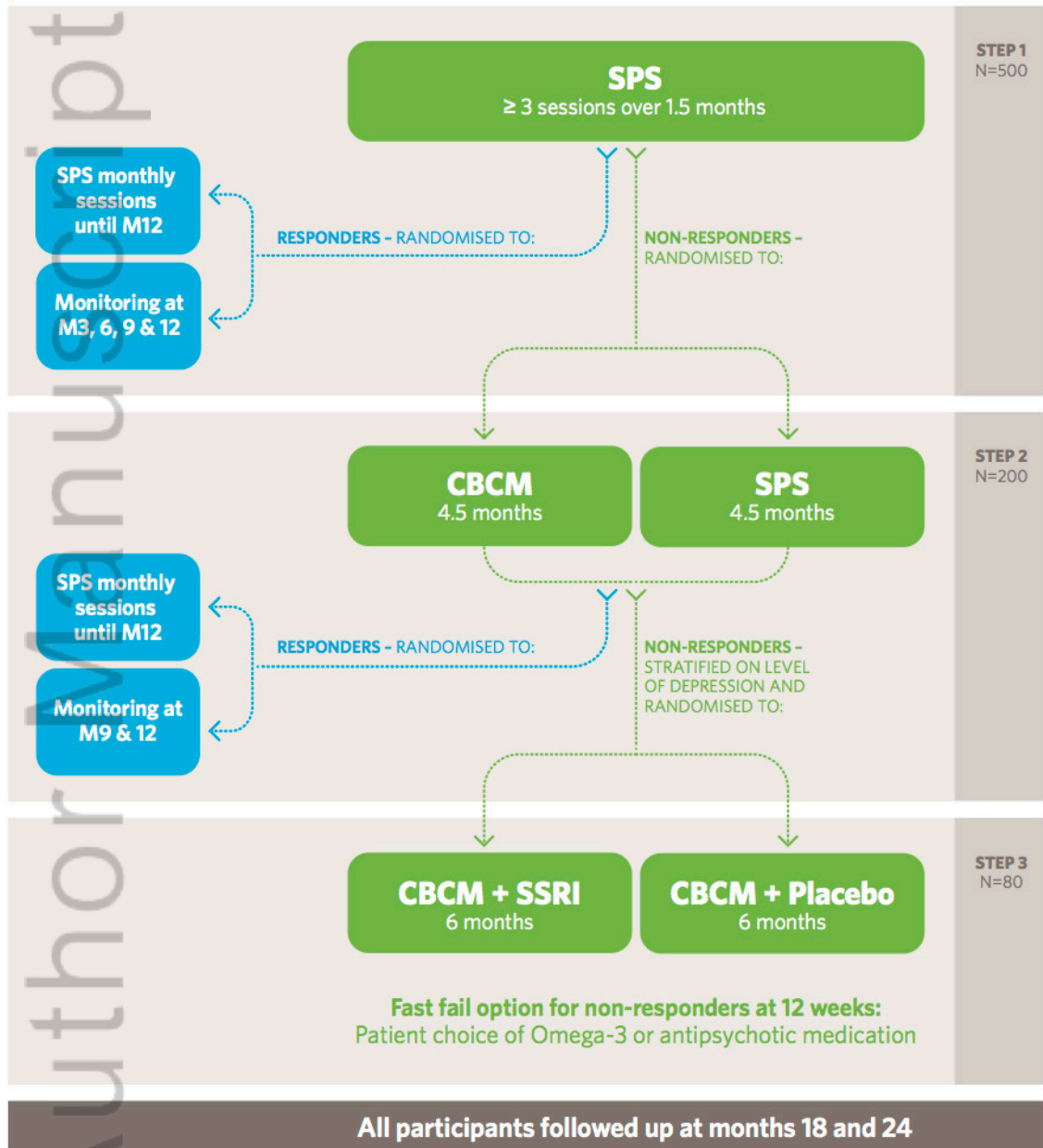
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STEP Study Design



SPS = Support and Problem Solving

CBCM = Cognitive-Behavioural Case Management

SSRI = Selective Serotonin Reuptake Inhibitor

Figure 1 Study Design.jpg