The NEURAPRO-E Study: A Multicenter RCT of Omega-3 Fatty Acids and Cognitive-Behavioural Case Management for Symptomatic Patients at Ultra-High Risk for Early Progression to Schizophrenia and Other Psychotic Disorders

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STUDY SPONSOR:

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Abbreviations

Abbreviation	Term in full
AA	Arachidonic acid
AE	Adverse event
APS	Attenuated Psychotic Symptoms
APTT	Activated Partial Thromboplastin Time
AQoL-8D	Assessment of Quality of Life – 8 Domains Instrument
ASSIST	Alcohol Smoking & Substance Involvement Screening Test
BACS	Brief Assessment of Cognition in Schizophrenia
BAR	Bipolar at-risk
BCSS	Brief Core Schema Scales
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At Risk Mental States
CBCM	Cognitive behavioural case management
CBT	Cognitive behavioural therapy
CGI	Clinical Global Impressions (CGI) Scale
COGDIS	Cognitive Basic Symptoms Group
CRP	C-reactive protein
DHA	Docosahexaenoic acid

Abbreviation	Term in full
eCRF	Electronic Case Report Form
EDIE	Early Detection and Intervention Evaluation
EFA	Essential fatty acid
EIPS	Early initial prodromal state
EPA	Eicosapentanoic acid
FBE	Full Blood Evaluation
FEM	First Episode Mania
FEP	First Episode Psychosis
FFQ	Food Frequency (Dietary) Questionnaire
FHI	Family History Index
FIGS	Family Interview for Genetic Studies
GRNS	German Research Network on Schizophrenia
HDL	High Density Lipoprotein
^{1}H-MRS	Proton magnetic resonance spectroscopy
IEC	Institutional Ethics Committee
IQ	Intelligence Quotient
INR	International Normalised Ratio
LDL	Low Density Lipoprotein
LSD	Lysergic Acid Diethylamide
LFTs	Liver Function Tests
LIPS	Late initial prodromal state

Abbreviation	Term in full
MADRS	Montgomery Asberg Depression Rating Scale
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
NIMH	National Institute for Mental Health
OTI	Opiate Treatment Index
P	Placebo
PACE	Personal Assessment and Crisis Evaluation
PAS	Premorbid Adjustment Scale
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SANS	Scale for the Assessment of Negative Symptoms
SCID I	Structured Clinical Interview for DSM-IV-Axis I
SCID II	Structured Clinical Interview for DSM-IV-Axis II
SDS	Severity of Dependence Scale
SOFAS	Social and Occupational Functional Scale
SSRI	Selective serotonin reuptake inhibitor
TFTs	Thyroid function tests
U&E	Urea & electrolytes
UHR	Ultra High Risk
UKU	Udvalg for Kliniske Undersøgelser Side Effect Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test

Abbreviation	Term in full
WAIS-III	Wechsler Adult Intelligence Scale-3rd Edition
WRAT4	Wide Range Achievement Test 4
YMRS	Young Mania Rating Scale

1 Introduction

1.1 Background

In recent years, clinicians have increasingly accepted the need to initiate treatment as soon as possible after the onset of sustained positive psychotic symptoms [1]. Long delays in treatment routinely occur and are associated with many damaging psychosocial consequences as well as risk of self-harm and aggression [2-4]. It has also been recognized that for most patients a prolonged period of attenuated symptoms and impaired functioning precedes the first psychotic episode [5,6]. Much of the disability associated with psychotic disorders, particularly schizophrenia, develops long before the onset of frank psychosis and is difficult to reverse even if the first psychotic episode is successfully treated [7]. This pre-onset period of illness has been termed the prodromal phase. Within the context of the early intervention paradigm, researchers have suspected that intervening during the prodromal phase may ameliorate, delay, or even prevent onset of fully-fledged disorder.

However, a major challenge has been to prospectively identify the prodromal phase, particularly given the non-specific nature of prodromal symptoms. Over the last decade, valid and reliable criteria have been introduced for the prospective identification of individuals at heightened risk of developing a first episode of psychosis (FEP) within a brief time period – that is, as possibly being in the prodromal phase of illness. These criteria are based on a combination of known trait and state risk factors for psychosis, including attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder. They have been termed the "ultra high-risk" (UHR) criteria. The first published

study using the UHR criteria found a transition rate of 40% to threshold psychotic disorder within one year [8], despite the provision of needs-based psychosocial intervention and antidepressant treatment where indicated. This finding has subsequently been replicated by several groups internationally. Using a combination of various studies, Ruhrmann et al [9] report an average one-year transition rate of 36.7% in UHR subjects who did not receive antipsychotic treatment.

A complementary early detection strategy drawing on a different clinical tradition and symptomatology was developed in Germany (the "basic symptoms" approach). This approach found that "basic symptoms", which refer to subtle, self-experienced disturbances in a range of domains, accurately predicted onset of schizophrenia over a long time frame [long-term (8-12 year) transition rate of 65% and 79%, respectively, depending on the basic symptom criterion applied] within a help-seeking clinical sample from possibly earlier in the course of the illness than the UHR criteria [10]. This led to a distinction between a late and early initial prodromal state (LIPS and EIPS, respectively) in the German Research Network on Schizophrenia, GRNS [11]. Further examination of the accuracy of predicting onset of psychosis within 12 months after index-assessment revealed that presenting with at least two out of nine symptoms of the "cognitive disturbances" cluster (COGDIS) resulted in a transition rate to psychosis of 23.9% within 12 months, an additional 22.4% within the second year and a further 14.9% within the third year. Thus the 12-month transition rate of the "cognitive disturbances" cluster of basic symptoms was comparable with individuals at-risk with attenuated positive symptoms (APS) from the UHR criteria (e.g., 12-month transition rate of 26.5% for APS alone [12]).

The successful identification of an 'at-risk' population justified the implementation of intervention trials to determine whether specific interventions are able to ameliorate, delay or prevent onset of fully-fledged psychotic disorder in this population. The first such trial, conducted in Melbourne, Australia, compared combined cognitive behaviour therapy and low dose atypical antipsychotic medication (risperidone) (n=31) with usual case management (n=28; [13]). Subjects were randomized, but neither patients nor investigators were blind to the intervention received. The rate of psychosis onset in the treatment group was significantly lower than in the control group after the 6-month treatment phase (9.7% v 35%, p=0.026). However, this finding was non-significant after a further 6 months of follow up, which was due to patients who were not fully adherent to the antipsychotic medication developing psychotic disorder in the second 6-month period. This study demonstrated that psychosis onset can at least be delayed by specific intervention, if not prevented. However, the active component of the treatment regime could not be identified as medication and cognitive psychotherapy were combined.

A more sophisticated randomized double-blind placebo controlled trial, PRIME, was then conducted in a UHR sample by a second group of researchers from Yale University, USA [14]. Low dose olanzapine (n=31) was compared to placebo (n=29) for 12 months followed by a 12-month monitoring period. Of the total sample of 60 participants, 16 (26.6%) developed psychotic disorder during the treatment period. Five of those who developed psychosis were in the olanzapine group and 11 were in the placebo group. Over the second 12-month period, an additional 3 from the olanzapine group and two from the placebo group developed psychosis. These results are similar to the first trial indicating that provision of a

specific antipsychotic medication could delay the onset of psychosis. However, this trial narrowly missed significance and the adverse effects were more serious leading to a more conservative interpretation of the findings [15].

A third treatment trial in a UHR sample was conducted in Manchester, UK. Subjects (n=58) were randomized to receive cognitive therapy for 6 months or monitoring of mental state only [16]. The group that received cognitive therapy had a significantly lower rate of transition to full threshold disorder (6% v 26%, $p<0.05$) and a significantly greater reduction in psychiatric symptoms ($p<0.02$) at 12 months.

Another critical finding from recent research in the UHR group is that the transition rate has been dropping in recent cohorts [17]. The reasons for this are unclear but it may be due to earlier detection of UHR samples, different sampling from referral sources, or more effective psychosocial interventions. The lower transition rates and consequently higher false positive rates (at least in short-term follow up) mean that safer interventions must be offered as the first line in treatment for people who nevertheless have a clear-cut need for care of some kind. Conceptually, this is supported by the clinical staging model [18,19], which proposes that the earlier in the course of illness that treatment is offered, the safer it should be and the more effective it may be in terms of remission and recovery rates. This approach is consistent with the early results of a recently completed study in Melbourne. 115 subjects were recruited to a 3 cell double-blind placebo controlled trial comparing combinations of risperidone (R), placebo (P), CBT, and supportive therapy (ST) (i.e., R+CBT v P+CBT v P+ST). The findings suggest that initial use of antipsychotics may not be necessary or advisable, with 6-month

transition rates being low in all 3 treatment groups. This suggests that UHR cases who are detected early are probably derived from less "enriched" samples in terms of true positive rate and that simple, supportive psychosocial interventions may be sufficient to reduce risk of transition, at least in the short term.

Finally, a recent key study (n=81) led by A/Prof. G. Paul Amminger and funded by the Stanley Medical Research Institute lends further support for this staged approach to intervention. This Vienna-based study found that 1.2g/day of omega-3 fatty acids (eicosapentaenoic acid, docosahexaenoic acid; EPA/DHA) ("fish oil"), provided for 12 weeks, were effective in reducing the transition rate to FEP in UHR adolescents [20]. 93.8% participants (76/81) completed the intervention. By study end (12 months), 4.9% (2/41) individuals in the omega-3 group and 27.5% (11/40) in the placebo group made a transition to psychosis (p=0.004). The difference between the groups in the cumulative risk of progression to psychosis was 22.6% (95% CI 4.8-40.4). Omega-3 fatty acids also significantly reduced positive symptoms (p=0.006), negative symptoms (p=0.019), global symptoms (p=0.01), and improved functioning (p=0.002) compared to placebo. Consistent with a preventive effect, group differences were sustained after cessation of interventions. The authors concluded that taking omega-3 supplements may offer a safe and efficacious treatment for subthreshold psychotic states. Interestingly, EPA/DHA showed only modest effects in FEP and no effect in chronic schizophrenia. The study by Amminger el al. [20] also found that clinical improvement was significantly associated with an increase of omega-3 fatty acids in red blood cells, and individuals in the placebo group who transitioned to psychosis were characterized by significantly lower arachidonic acid (AA) levels at baseline. These results suggest that fatty

acids deficits may predate onset of fully-fledged psychotic disorder and disturbed membrane fatty acid metabolism may contribute to the onset of sustained illness. It must be emphasized that in all omega-3 treatment studies, no treatment-related side effects or adverse biochemical or haematological effects have been observed. Across all RCTs, individuals with schizophrenia or other psychoses found omega-3 fatty acids highly tolerable. Also of note is the relatively high rate of acceptance amongst UHR patients to participate in an RCT involving substances that are normally found in the human body (76% in the Vienna cohort), compared to RCTs involving antipsychotics (35% in the most recent Melbourne cohort).

1.2 The Current Study

The research reviewed above indicates that intervention, both psychological and pharmacological, is likely to benefit 'at-risk' patients as defined by UHR criteria, both in terms of symptom reduction and delay or prevention of onset of threshold disorder. Non-significant findings (e.g., in the PRIME study and the 1 and 3 year follow up phases of the first Melbourne trial) may be due to low power from small sample sizes. Following the initial series of single site studies with relatively low numbers, research needs to progress to studies with substantially larger samples. The most effective way of achieving this is through a multi-center RCT. However, there are currently no multi-center intervention studies in 'at-risk' groups funded, and the centers with the capacity to do such research are spread across several countries. The US National Institute for Mental Health (NIMH) has favored funding "naturalistic studies", in which all forms of treatment are permitted including potent and potentially harmful options, notably antipsychotics and antidepressants. This means in these studies that a) there is widespread but uncontrolled exposure to antipsychotics (a key source of

the original ethical concern) and antidepressants (which have safety concerns in adolescents) and b) little can be concluded regarding prediction of transition or efficacy of any type of treatment. Beyond the NIMH orbit we believe that further RCTs are essential to guarantee ethical research in this field within which the key questions still remain in clinical equipoise [21-24]. A clear evidence base to guide clinical care of UHR patients is urgently needed. The risk is that they will be provided with ineffective and harmful treatments if this step is not taken.

The strong preliminary results for the effectiveness of EPA/DHA, coupled with the falling transition rate in UHR samples, mean that further study of such benign, potentially neuroprotective, interventions is clinically and ethically required. This does not mean eschewing the use of antipsychotic medication, but it does mean that the timing of such treatment must be studied, and that safer alternatives are to be preferred.

To this end, the next set of questions in UHR research are as follows:

- What is the optimal treatment for this phase of illness?
- For how long should treatment continue?
- How acceptable are the different treatment options to the patients themselves, their families and carers, health professionals and the wider community?
- What factors predict treatment response or non-response in this phase?

A multi-center trial, enabling a large number of subjects to be recruited within a short time period, is required to answer these critical questions. Our collaborative research group has created a unique opportunity for this to occur.

In view of recent data and after a careful review of other benign and potentially neuroprotective treatment options in early psychotic illness, we have decided to study EPA/DHA as a first line treatment for 'at-risk' patients. This will be provided on top of background clinical care of cognitive-behavioural case management (CBCM), in order to meet the case management requirements and treat the non-psychotic symptoms in this patient group. CBT is a treatment of proven safety and efficacy in 'at-risk' patients both according to UHR and basic symptom criteria, as reviewed above.

1.2.1 Aims

1. To investigate the effect of EPA/DHA, in addition to CBCM, on the incidence of FEP in an 'at-risk' cohort.
2. To investigate the effect of EPA/DHA on the level of symptoms and functioning in the 'at-risk' group.
3. To investigate if any candidate risk factors, such as negative symptoms, sociodemographic characteristics and neurobiological variables including metabolic parameters (such as erythrocyte membrane fatty acids, phospholipase A2 activity, oxidative stress markers and cytokines), neurocognitive deficits, genetic attributes and structural brain changes influence treatment response in the 'at-risk' group.

Several of these candidate risk factors (cytokines, genetic attributes and structural brain changes) will be evaluated as optional side studies. The details of these studies are included in separate protocols referred to as Side Study Modules. Sites participating in these studies will need to obtain ethics approval for the relevant side study module.

1.2.2 Research Questions

The main research questions are as follows:

1. *Is EPA/DHA, in addition* to CBCM, more effective than CBCM without EPA/DHA in reducing rate of transition to FEP in an 'at-risk' cohort over a 6 month period? [Primary outcome to be assessed at the end of the EPA/DHA intervention.]
2. Does the use of EPA/DHA result in a higher percentage of responders (i.e., symptomatic and functional improvement, see below) compared to placebo?
3. Do any candidate risk factors predict response to EPA/DHA treatment in the 'at-risk' group?

2 Methodology

2.1 Setting

The proposed study is an international multi-site study involving approximately 10 research centers across Australia (Melbourne, Sydney), the Netherlands (Amsterdam), Germany (Jena), Switzerland (Basel, Zurich), Austria (Vienna), Denmark (Copenhagen), Singapore, and Hong Kong (Pok Fu Lam). Each site has an established early psychosis center that conducts research in 'at-risk' subjects.

2.2 Sample

Individuals referred to the treatment service meeting standardized 'at-risk' criteria will be approached about participating in this clinical trial. Symptomatic inclusion criteria are based on those developed by the Melbourne group and consist of three subsets of subjects. Broadly, the intake criteria are as follows:

2.2.1 Inclusion criteria

A. General inclusion criteria:

i. Ability to give informed consent

Where participants are of legal childhood age, consent will also be obtained from one of the participant's parents. Both the parent and participant will be required to sign the consent form in such a case. It will be the investigator's responsibility to determine whether a participant of legal childhood age has the capacity to consent to the study.

ii. Age 13 - 40 yrs depending on site

B. Membership of one of the following 'at-risk' groups:

i. **Vulnerability (Trait and State Risk Factor) Group:** Individuals with a combination of a trait risk factor (schizotypal personality disorder or a family history of psychotic disorder in a first degree relative) and a significant deterioration in mental state and/or functioning or sustained low functioning during the past year.

ii. **Attenuated Psychotic Symptoms (APS) Group:** Individuals with subthreshold (intensity or frequency) positive psychotic symptoms. The symptoms must have been present during the past year and be associated with a significant reduction in or sustained low functioning.

iii. **Brief Limited Intermittent Psychotic Symptoms Group (BLIPS):** Individuals with a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week. The symptoms must have been present during the past year and be associated with a significant reduction in or sustained low functioning.

Full operationalized intake criteria are presented in Table 1.

Table 1: Operationalized intake criteria

Group 1: Vulnerability Group

Family history of psychosis in first degree relative OR Schizotypal Personality Disorder (as defined by DSM IV) in identified patient
AND
Drop in Functioning:
Recency: Change in functioning occurred within last year
Impact: SOFAS score at least 30% below previous level of functioning and sustained for at least one month.
OR
Sustained low functioning:
Recency: For the past 12 months or longer
Impact: SOFAS score of 50 or less.

Group 2: Attenuated Psychotic Symptoms Group

2a) Subthreshold intensity:
Intensity: Global Rating Scale Score of 3-5 on *Unusual Thought Content* subscale, 3-5 on *Non-Bizarre Ideas* subscale, 3-4 on *Perceptual Abnormalities* subscale and/or 4-5 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 3-6 on *Unusual Thought Content*, *Non-Bizarre Ideas, Perceptual Abnormalities* and/or *Disorganised Speech* subscales of the CAARMS
Duration: symptoms present for at least one week
Recency: symptoms present in past year
Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer.
2b) Subthreshold frequency:
Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5-6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 3 on *Unusual Thought Content*, *Non-Bizarre Ideas,*, *Perceptual Abnormalities* and/or *Disorganised Speech* subscales of the CAARMS
Recency: symptoms present in past year
Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer.

Table 1 continued . . .

Group 3: BLIPS Group

Intensity: Global Rating Scale Score of 6 on *Unusual Thought Content* subscale, 6 on *Non-Bizarre Ideas* subscale, 5 or 6 on *Perceptual Abnormalities* subscale and/or 6 on *Disorganised Speech* subscales of the CAARMS
Frequency: Frequency Scale Score of 4-6 on *Unusual Thought Content*, *Non-Bizarre Ideas, Perceptual Abnormalities* and/or *Disorganised Speech* subscales
Duration: Symptoms present for less than one week and spontaneously remit on every occasion.
Recency: symptoms present in past year
Impact: 30% drop in SOFAS score from previous level of functioning and sustained for a month within the past year OR SOFAS score of 50 or less for the past 12 months or longer.

2.2.2 Exclusion criteria

Exclusion criteria include:

i. Past history of a treated or untreated psychotic episode of one week's duration or longer
ii. Organic brain disease, e.g. epilepsy, inflammatory brain disease
iii. Abnormal coagulation profile parameters or thyroid function test results >10% above or below the limits of the normal range.
iv. Any physical illness with psychotropic effect, if not stabilized
v. Current treatment with any mood stabiliser, or recreational use of ketamine.
vi. Past neuroleptic exposure equivalent to a total lifetime haloperidol dose of >50 mg. [Refer to Appendix IV for a list of equivalent doses for other neuroleptic agents.]
vii. Diagnosis of a serious developmental disorder, e.g. Asperger's syndrome
viii. Premorbid IQ < 70 and a documented history of developmental delay or intellectual disability
ix. Current aggression/dangerous behaviour (CAARMS 5.4 severity score 6)

x. Current suicidality/self harm (CAARMS 7.3 severity score 6)

xi. Current pregnancy

xii. Current attenuated symptoms that are entirely explained by acute intoxication (e.g., current attenuated symptoms entirely explained by LSD use).

xiii. > than 4 weeks of regular omega-3 supplementation (≥2 capsules standard strength providing ≥600 mg combined EPA/DHA) within the last 6 months.

2.2.3 Discontinuation criteria

Participants may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from the study are:

i. Voluntary discontinuation by the patient who is at any time free to discontinue his or her participation in the study, without prejudice to further treatment

ii. Safety reasons as judged by the investigator

iii. Severe non-compliance to protocol as judged by the investigator

iv. Incorrect enrolment (i.e., the patient does not meet the required inclusion/exclusion criteria) of the patient

v. Patient lost to follow-up

vi. Patient meets exit criteria "transition to psychosis" or develops mania (first episode mania criteria 1: YMRS Mania met, per Appendix II)

vii. Development of exclusion criteria, e.g. pregnancy, etc.

2.3 Trial Design

The design is a randomized placebo controlled trial. Subjects will be randomized at entry to one of two treatment groups. The randomization will be stratified by site and the Montgomery Asberg Depression Rating Scale (MADRS) (total score <21 or ≥21), as both depression and antidepressants may impact on prodromal symptoms and illness progression. The treatment groups are listed in Table 2.

Table 2. Design for treatment allocation.

	Treatment group	6 months treatment
Subjects randomized at entry to 2 treatment groups	1	CBCM+P
	2	CBCM+EPA/DHA

P = Placebo; EPA/DHA = Eicosapentanoic acid; CBCM = Cognitive-behavioural case management.

Subjects will receive either EPA/DHA or P for 6 months. This will be provided on top of background clinical care of CBCM, involving 6 – 20 sessions within the first 6 months depending on the participant's needs (fortnightly sessions recommended where feasible), and then on an "as needs" basis for up to 12 months (from entry). Thereafter participants should receive standard clinical care according to local practices; however, the use of mood stabilizers and anti-psychotic medication is not allowable unless a participant is withdrawn from the study prior to 12 months. The randomization will be double-blind.

For the purposes of the study analyses, 'entry' will be considered to be the date the participant provides written informed consent for the study. However, participants will only be included

in the study after they have fulfilled the eligibility criteria and been randomized to one of the interventions described above. All eligible patients must be randomized and commence treatment within a week of the baseline assessment being completed.

For the purposes of the dates outlined in Table 4 and the calculation of visit dates, day 1 will be considered to be the day that the patient commences the oral intervention (i.e., starts taking the EPA/DHA or P capsules). The day prior to day 1 will be referred to as day -1. The week prior to day 1 will be referred to as the period from day -7 to day -1.

2.3.1 Sample Size and Power

We aim to recruit 320 subjects over a 2-year period. The study is powered on the primary outcome of difference in 6-month transition rate between the two treatment groups. Based on the conditions listed in Table 3, a sample size of 320 subjects is sufficient to detect a difference in transition rate between the two treatment groups of approximately 13%. This is a clinically important difference.

Table 3. Conditions for sample size and power determination.

The 6-month transition rate of the control treatment (CBCM + P) is expected to be approximately 15%.
The maximum recruitment time is two years, resulting in a total sample of 320 subjects (160 per year across approximately 10 sites).
A 10% dropout rate across the treatment and follow-up period of 12 months is assumed.
A level of significance of 5% and a power of 80% are used.
The logrank test (survival analysis) will be used to test for differences in transition rates.

2.3.2 Outcome Measures

2.3.2.1 Primary outcome measures

The main outcome measure is transition status to FEP at 6-months post study entry. Transition is operationally defined via rating scales, as in previous studies (see [27]), as one of:

1. Abnormal thoughts held with delusional intensity occurring every day for one week or longer
2. True hallucinations in any modality occurring every day for one week or longer
3. Formal thought disorder to the degree of incoherence and/or loose associations occurring every day for one week or longer

2.3.2.2 Secondary outcome measures

Include:

1. The incidence of FEP in each study arm at 12 and 24 months.
2. Level of symptomatology, including depression, positive, negative, and basic symptoms
3. Level of functioning across a range of domains including peer relations, family functioning, vocational, and occupational functioning

The following secondary outcome cut points will be applied: *Remission* will be defined as at least a 50% reduction in the CAARMS positive symptoms score. *Recovery* will be defined as at least a 50% reduction in key symptom measures (as above) plus improvement in functioning to premorbid level as evidenced by SOFAS recovery.

2.3.3 Exposure measures

Measures of risk factors for treatment response and non-response will consist of variables thought to influence treatment response and transition to psychotic disorder. These will include: demographics (age, gender, socioeconomic status, urbanicity, educational attainment); premorbid functioning level; psychiatric symptoms and syndromes; neurobiological variables (metabolic parameters, neurocognitive variables, brain structure and genetic attributes); dietary factors and family history of psychiatric disorder.

In addition, information on the following possible confounders will be collected: treatment compliance, number of CBCM sessions, content of CBCM sessions, concomitant medication, (especially antidepressant use), other psychiatric treatments and self-reported substance use.

2.3.4 Safety measures

2.3.4.1 Adverse Events

2.3.4.1.1 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In this study, any undesirable medical condition occurring from the time of signing consent (even if no study treatment or pharmaceutical product has been administered) will be considered to constitute an adverse event. Adverse events will be captured and recorded from the time of consent, until the 9 month follow up time point.

Adverse events will be recorded using the UKU side effect rating scale. Further information regarding adverse events recording and reporting is outlined in the *Study Procedures Manual*.

Serious adverse event

A serious adverse event is an AE that fulfils one or more of the following criteria:

• results in death

• is immediately life-threatening

• requires in-patient hospitalization or prolongation of existing hospitalization

• results in persistent or significant disability or incapacity

• is a congenital abnormality or birth defect

• is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

2.3.4.1.2 Reporting SAEs

SAEs will be reported to local regulatory authorities by the local principal investigator in accordance with local regulations. SAE's will be assessed and reported for the duration of the study period, from the time of signing consent, until the final 24 month visit has been completed. An SAE report will also be completed on the Sponsor specific template, and then sent to the sponsor (ORYGEN Youth Health Research Centre) at the time of reporting to the regulator. 'Transition to psychosis' is not considered to be a reportable SAE. Further information related to reporting SAEs will be provided in the NEURAPRO-E *Study Procedures Manual*.

2.3.4.2 Other safety measures

A full physical examination will be conducted at baseline. In addition, vital signs, weight and laboratory parameters (U&E, FBE, LFTs, TFTs, cholesterol and triglycerides; serum lipids

(HDL and LDL), High Sensitivity C-reactive protein (CRP) and coagulation profile tests: prothrombin time or INR, activated partial thromboplastin time and fibrinogen.) will be measured during the study. Furthermore, participants will be closely monitored by Investigators during critical periods before, during and after the trial when participants may be at increased risk of self-harm or harming others. Detailed information regarding the collection and recording of safety parameters and research blood collection is outlined in the NeuraproE *Pathology Manual*.

2.3.5 Instruments

- ***Inclusion criteria*** will be assessed using the CAARMS and SOFAS.
- ***Transition to psychosis*** will be assessed using the CAARMS.
- ***Diagnosis*** (including psychotic and non-psychotic diagnoses) will be assessed using the SCID (Axis I component and the schizotypal and borderline sections of Axis II).
- ***Symptomatology*** and ***functioning*** will be assessed using the CAARMS, BPRS, SANS (negative symptoms), SPI-A (basic symptoms), MADRS (depression), YMRS (mania symptoms), SOFAS and Global Functioning: Social and Role scales (functioning and disability).
- ***Exposures/Risk factors*** will be assessed as follows:
  - Premorbid functioning level, assessed using the PAS.
  - Psychiatric symptoms and syndromes, including schizotypal and borderline personality disorder, assessed using the SCID (full Axis I version and schizotypal and borderline sections of Axis II version).
  - Neurocognitive variables will be assessed using a premorbid IQ measure , WAIS-III 2-subtest short form and the BACS and UPSIT, as described in Appendix III.
  - Family history of psychiatric disorder, assessed using an abbreviated version of the FIGS [29], referred to as the Family History Index (FHI).
  - Substance use, assessed using the ASSIST instrument.
  - Dietary risk factors, assessed using the Food Frequency (Dietary) Questionnaire.
- Quality of Life will be assessed using the AQoL-8D (Mental Health) instrument.
- The clinician's impression of the client's illness severity, improvement and response to treatment, assessed using the CGI.

For time point of assessments, see Table 4.

2.3.6 Procedure

2.3.6.1 Baseline assessment and randomization

After subjects provide informed consent, a screening/baseline assessment of intake and exclusion criteria and exposure measures will be performed, as well as a full physical examination and blood tests for U&E, FBE, LFTs, TFTs, cholesterol and triglycerides; serum lipids (HDL and LDL), C-reactive protein (CRP) and coagulation profile tests: prothrombin time or INR, activated partial thromboplastin time and fibrinogen. Where pregnancy tests are required, it is acceptable for sites to use blood or urine as appropriate. Participants will also need to provide approximately 20 mL of blood for the analysis of metabolic parameters (such as erythrocyte membrane fatty acids, phospholipase A2 activity, oxidative stress markers and cytokines), including the compliance assessment described in section 3.1.1. Participants may also consent to additional tests from any side studies their hospital or clinic has approval to participate in.

The subject will then be randomized to one of the two treatment groups. Randomization will be stratified by site and MADRS score (total score <21 or ≥21), and there will be equal allocation to the two treatment groups. Computer generated random numbers will be used to carry out the randomization. The randomization will be double-blind. The subject must be randomized and commence treatment within a week of the baseline assessment being completed.

2.3.6.2 Frequency of Visits and Follow Up Period

The subject must be assessed in relation to the discontinuation criteria specified in section 2.2.3 at each visit. Subjects will be assessed monthly for psychopathology, functioning and adverse events/side effects for the first six months of the study, and then at 3-month intervals until the 12-month follow-up point, with one final psychopathology assessment at month 24 (see Table 4). During the first month, subjects will be assessed weekly for adverse events/side effects. Subjects will be followed up at 24 months and assessed for transition, symptomatology and functioning. In the case of subjects discontinuing the protocol early, assess the subject as per section 2.3.6.3 below.

2.3.6.3 Procedures for discontinuation

Following discontinuation, treatment will be offered on a "need for care-clinician's choice" basis according to existing clinical practice guidelines [28]. Wherever possible, subjects who discontinue the study prior to 24 months from entry will be followed with full regular assessments as per the subjects who continue with the protocol treatment (refer to Table 4 for the complete schedule of assessments). Ideally, such clients will also undergo a SCID-I (Axis I component) assessment at 6, 12 and 24 months post-entry, and also at 6 months post-transition if a subject discontinues the study for transition to psychosis (in order to assess the stability of their initial psychotic diagnosis). Psychiatric treatments delivered following early discontinuation will be captured. Should it not be possible to complete the full evaluation schedule outlined in Table 4, as a minimum, the assessments outlined in section 2.3.6.3.1 must be completed for subjects who discontinue the study early for transition to psychosis and those assessments outlined in section 2.3.6.3.2 must be completed for all other subjects who discontinue the study early.

2.3.6.3.1 Minimum assessments in the case of premature discontinuation because of "Transition to psychosis"

Participants who meet the "transition to psychosis" criteria during the course of the study will exit the RCT as completers and appropriate treatment will be recommended. Where it is not possible to continue to follow the participant per the schedule of assessments in Table 4, the following assessments must be performed as a minimum:

- At the "transition to psychosis" assessment the same assessments as the 12-month post entry assessment (see Table 4) will be performed. Neuropsychological assessments will also be performed at the time of early discontinuation (refer to Appendix III).
- At 6, 12 and 24 months after inclusion in the study, assess the participant using the CAARMS (transition criteria), SCID I (Axis I component), MADRS and AQoL-8D (Mental Health) instruments as a minimum. Psychiatric treatment received since discontinuation will also be captured at these time points.
- At a minimum, subjects who discontinue the study early for transition to psychosis and who do not follow the regular schedule of assessments, must undergo a SCID I assessment at the 12 month visit time point.

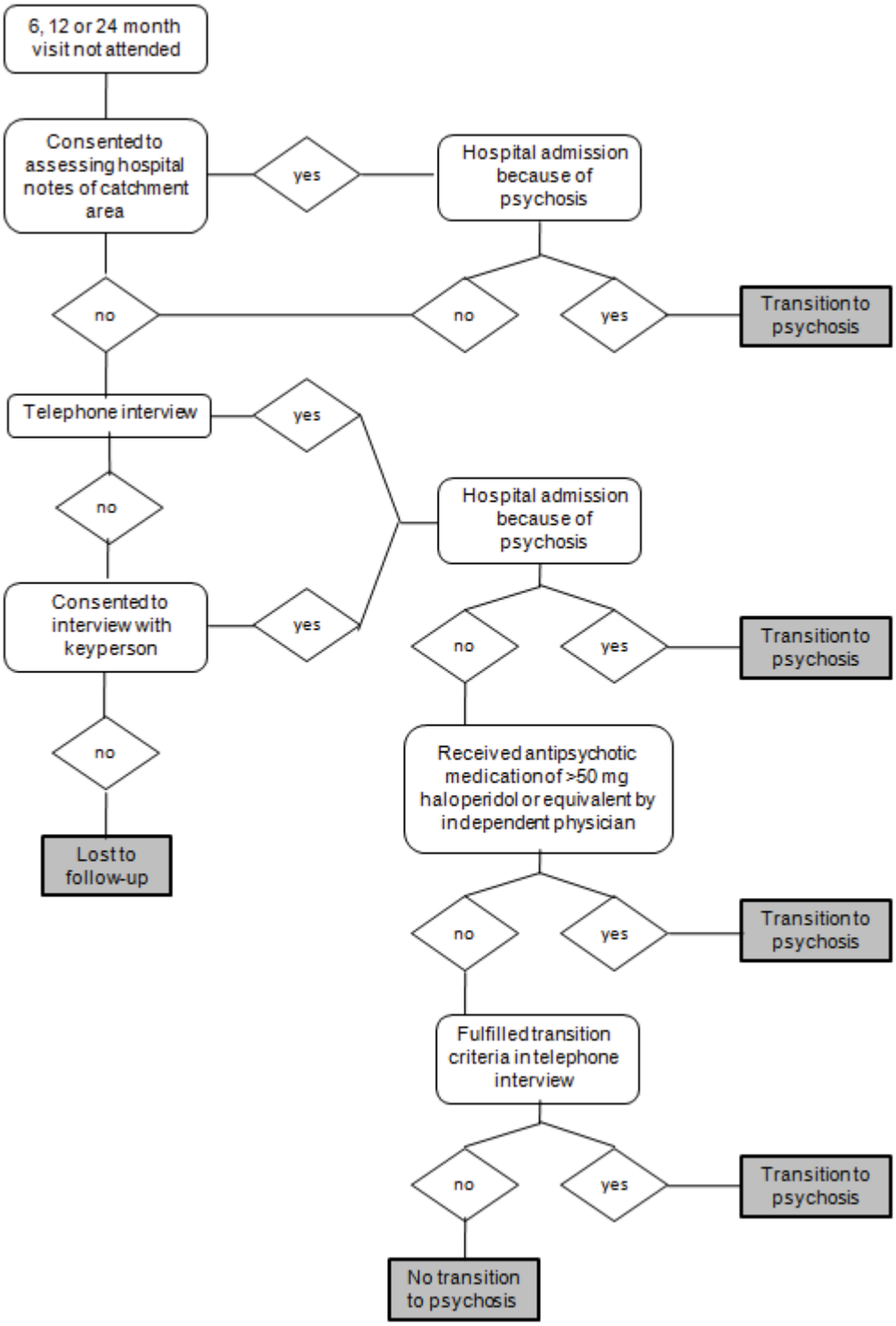
2.3.6.3.2 Minimum assessments in the case of premature discontinuation because of reasons other than "Transition to psychosis"

Where it is not possible to continue to follow the participant per the schedule of assessments in Table 4, the following assessments must be performed as a minimum:

- Participants who discontinue the study for reasons other than "transition to psychosis" will also be assessed at 6, 12 and 24 months after randomization using the CAARMS (transition criteria), SCID I (Axis I component), MADRS and AQoL-8D (Mental Health) instruments. In case of non-attendance, an operationalised step-by-step procedure will be applied (see Figure 1) to obtain outcome information. This

procedure will involve using telephone interviews and external validation criteria [(i) checking hospital records for admission due to psychosis, (ii) prescription of antipsychotic medication by independent physician, (iii) interview of key-person (i-iii only when informed consent is obtained)]. The telephone interviews will be conducted in a hierarchical manner. First, transition to psychosis will be assessed by checking transition criteria, hospital admission due to psychosis and the prescription of antipsychotic medication (see Figure 1). Second, the presence of prodromal symptoms will be assessed using the CAARMS instrument. Third, psychiatric diagnosis will be assessed by conducting a SCID-I interview. This procedure will not be followed for participants who withdraw consent from the study; however, attempts will be made to obtain their final diagnosis within the realms of their consent. Participants who discontinue will be asked the reason(s) for their discontinuation and the presence of any adverse events. If possible, the participant will be seen and assessed by an investigator(s). Serious and Unexpected Adverse events will be followed up clinically.

Figure 1: Follow-up of participants who discontinue study for reasons other than transition to psychosis and will not attend the 6, 12 or 24 - month follow-up visits



3 Treatment Modalities

3.1 Oral intervention

Eicosapentaoic acid (EPA/DHA): 2.8g/day of marine fish oil containing approximately 1.4g EPA/DHA in 4 X 0.700g capsules.
Placebo: Placebo will be matched with EPA/DHA capsules to ensure allocation concealment.

3.1.1 Compliance assessment

Patient compliance will be assessed by monthly pill counts over the first 6 months of the study, as well as through the measurement of the essential fatty acid content of red blood cells from blood samples collected at baseline and 6 months after study entry (or at the transition assessment if applicable). The blood samples will be stored frozen for batched analysis. The results of the fatty acid analysis will not be revealed to the investigator until the end of the study.

3.1.2 Labeling, storage and accountability

The study medication will be labeled in the local language and will comply with local regulatory requirements. The study medication will be stored securely at an appropriate temperature. Accountability records will be maintained. Storage and accountability details, as well as information on how to obtain the study medication, will be specified in the NEURAPRO-E *Pharmacy Manual*.

3.1.3 Blinding

The study medication will be identified by a code linked to the randomization chart. An independent person (typically a pharmacist) at each site will be provided with unblinding

envelopes to ensure that unblinding can occur if necessary. Unblinding will only be permitted in the case of a medical emergency when the appropriate management of the patient necessitates knowledge of the treatment randomization. All cases of unblinding will be documented.

If a participant experiences a severe adverse event deemed to be related to the study treatment, treatment should be withheld until it is safe for the patient to recommence treatment. If the event recurs once the participant recommences the study treatment, the investigator should consider whether the criteria for discontinuation per section 2.2.3 have been met. Unblinding should only be considered if knowledge of the participant's study treatment is deemed to be essential for managing the adverse event or unblinding is required by a regulatory authority.

3.2 Cognitive-behavioural case management (CBCM)

CBCM consists of cognitive-behavioural therapy (CBT) embedded within case management, as successfully developed in the Euro-CBCM study (Edwards et al, ongoing). The treating team will use a specifically developed manual that details the CBCM to be delivered in the trial, and which outlines the minimum standard of treatment to be delivered. The CBT will be based on the models developed at the PACE Clinic in Melbourne, in the EDIE trial, and in Cologne, as these have proven to be effective in RCTs. The number of sessions delivered will be captured for each client. In addition, fidelity will be monitored by therapists rating their own sessions on an established checklist of therapeutic interventions. Any additional psychosocial interventions delivered will also be documented. The case management component will consist of therapists addressing current interpersonal and social issues and providing practical help. 6 – 20 CBCM sessions will be provided within the first 6 months

depending on the participant's needs (weekly sessions recommended where feasible), and then further sessions will be provided on an "as needs" basis for up to 12 months (from entry). Thereafter participants should receive standard clinical care according to local practices. All psychiatric treatments administered to 24 months will be captured.

3.3 Concomitant medication

Within the first 12 months of the study, antidepressants (SSRIs only) will be permitted for moderate-severe major depression (defined as MADRS score ≥21 for at least two consecutive weeks).

The use of anti-psychotics or mood stabilizers is not permitted at any time during the trial unless a participant is withdrawn from the study prior to 12 months and these treatments are deemed necessary according to local clinical practice guidelines.

All psychiatric treatments administered to 24 months will be captured.

	Table 4 – Assessment schedule														
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Time of Premature Discontinuation**	
Day (d)	**-21 to -1**		**7**$^{+/-2d}$	**14**$^{+/-2d}$	**21**$^{+/-2d}$	**30**$^{+/-2d}$	**60**$^{+/-5d}$	**90**$^{+/-5d}$	**120**$^{+/-5d}$	**150**$^{+/-5d}$	**180**$^{+/-5d}$	**270**$^{+/-15d}$	**360**$^{+/-15d}$	**Transition**[10]	**Other Reasons**[11]
Month (end)		**0**				**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**		
Screening															
Informed consent	X														
Demographics	X														
Medical history[1]	X												X		
Inclusion/exclusion criteria[2]	X														
BAR subgroup criteria[3]	X														
Pregnancy test (females)[4]	X														
Treatment															
Randomisation[2]	X														
Capsule dispensing[5]		X				X	X	X	X	X					
CBCM intervention			*6 – 20 sessions in the first 6 months*									*Further sessions as required*			
Pill count						X	X	X	X	X	X				
Safety/physical examination															
Height	X														
Physical examination	X														
Vital signs & Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	
Blood collection for research tests[6]	X										X			X	
Clinical laboratory tests[7]	X										X				
Medication	X	X	X	X	X	X	X	X	X	X	X[9]		X[9]	X	X
UKU & Adverse events[8]		X	X	X	X	X	X	X	X	X	X	X			

Table 4 – Assessment schedule continued

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Time of Premature Discontinuation	
Day (d)	**-21to -1**		**7**[+/-2d]	**14**[+/-2d]	**21**[+/-2d]	**30**[+/-2d]	**60**[+/-5d]	**90**[+/-5d]	**120**[+/-5d]	**150**[+/-5d]	**180**[+/-5d]	**270**[+/-15d]	**360**[+/-15d]		**Transition**[10]	**Other Reasons**[11]
Month (end)		**0**				**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**24**[18]		
Ratings																
SCID-I		X									X[9]		X[9]	X	X	
SCID-II[12]		X											X		X	
CAARMS		X				X	X	X	X	X	X[9]	X	X[9]	X	X	
SPI-A[13]		X														
BPRS		X				X	X	X	X	X	X	X	X	X	X	
SANS		X				X	X	X	X	X	X	X	X	X	X	
YMRS[14]		X				X	X	X	X	X	X	X	X	X	X	
MADRS		X				X	X	X	X	X	X[9]	X	X[9]	X	X	
FIGS (FHI)[15]		X														
SOFAS		X						X			X	X	X	X	X	
PAS		X														
Global Functioning: Social & Role Scales		X						X	X	X	X		X	X	X	
ASSIST		X				X	X	X	X	X	X	X	X	X	X	
CGI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FFQ[16]		X														
AQoL-8D (Mental Health)		X									X[9]		X[9]	X	X	
Neuropsychology Assessments[17]		X									X		X		X	
	Optional Side Studies *A number of optional Side Studies will be run in association with this protocol. Sites that recruit participants to any of these side studies must obtain ethics approval for the relevant Side Study Module (separate document) and have access to the resources required for the side study. Refer to the relevant Side Study Module for further details about the assessments for these studies.*															

Table 4 Footnotes

[1] General medical history will be assessed.

[2] All eligible patients must commence treatment within a week of completing the baseline assessment. Procedures for randomization will be outlined in the NEURAPRO-E *Study Procedures Manual*. Day 1 is defined as the day on which the patient commences the oral intervention (i.e., first takes the active or placebo capsules). All visit dates subsequent to this event should be calculated based on the date of day 1. The eCRF database will automate this information once the date of the medication being dispensed has been entered into the database. Once the patient has commenced the study, the patient must be assessed in relation to the discontinuation criteria specified in section 2.2.3 at each visit. Procedures for discontinuation, including patient follow up, are outlined in section 2.3.6.3. Wherever possible, those patients who discontinue prior to 12 months should be followed according to visits 1 – 13 outlined above. Where such follow up is not possible, the minimum data required for patients who prematurely discontinue the study is outlined in the table above and also in section 2.3.6.3.

[3]The Bipolar at-risk (BAR) criteria are included in Appendix I. The criteria must be assessed for all participants who are randomized.

[4] As required locally. Blood or urine testing are acceptable as approved by each sites local HREC.

[5] EPA/DHA and placebo capsules will be dispensed monthly during the 6 month intervention period.

[6] The research blood samples will be used to measure the essential fatty acid content of red blood cells to assess patient compliance and the effectiveness of the EPA/DHA intervention, as well as to analyse other metabolic parameters, namely phospholipase A2 activity, oxidative stress markers and cytokines. Approximately 20 mL of blood must be collected at each time point in the morning before breakfast between 8 am and 10 am. The blood samples will be stored frozen locally for batched analysis. The samples for fatty acid analysis will be shipped to the laboratory of Prof Andrew Sinclair at Deakin University, Geelong, VIC, Australia. The results of the fatty acid analysis will not be revealed to the investigator until the end of the study. The samples for the oxidative stress analysis will be shipped to the University of British Colombia, Vancouver, Canada. Samples for phospholipase A2 testing will be shipped to the laboratory of Dr Stefan Smesny (Department of Psychiatry, Friedrich-Schiller-University Jena, Philosophenweg 3, D-07743 Jena, Germany). Samples for the cytokine study (optional component) will be sent to the laboratory of Professor Bernhard Baune (Department of Psychiatry and Psychiatric Neuroscience, School of Medicine and Dentistry, James Cook University, Queensland, Australia). Further specific procedural information related to collecting, processing & shipping the blood samples will be included in the NEURAPRO-E *Study Procedures Manual.*

[7] Baseline (visit 1) tests required: U&E, FBE, LFTs, TFTs, cholesterol and triglycerides; serum lipids (HDL and LDL), High Sensitivity CRP and coagulation profile tests: prothrombin time or INR, activated partial thromboplastin time and fibrinogen. Visit 11 tests: Total cholesterol, triglycerides; serum lipids (HDL and LDL) and High Sensitivity CRP. As well as Coagulation profile tests: prothrombin time or INR, activated partial thromboplastin time and fibrinogen and other tests that are clinically indicated. All tests performed at each time point will be captured in the NEURAPRO-E CRF. All of the clinical laboratory tests will be performed by a local accredited pathology service.

[8] In this study, any undesirable medical condition occurring from the time of signing consent (even if no study treatment or pharmaceutical product has been administered) will be considered to constitute an adverse event. Adverse events will predominantly be recorded using the UKU side effect rating scale.

[9] Minimum assessments for patients who have prematurely discontinued the study intervention when the full 6 or, 12- month assessment cannot be performed. The SCID-I assessment at 6 months is only required in those patients who have already discontinued the study intervention.

[10] A SCID-I assessment is required 6-months post transition. All of the other assessments required post-discontinuation for transition to psychosis are included in the table above (and are also outlined in section 2.3.6.3.1). Subjects who discontinue early for transition to psychosis should be followed per the original visit schedule (visits 1 – 13) wherever possible. Where full follow up is not possible, those assessments marked with footnote 9 must be completed.

[11] All of the assessments required post-discontinuation for reasons other than transition to psychosis are included in the table above (and are also outlined in section 2.3.6.3.2). Subjects who discontinue early for reasons other than transition to psychosis should be followed per the original visit schedule (visits 1 – 13) wherever possible. Where full follow up is not possible,

those assessments marked with footnote 9 must be completed. Should a client not attend either the minimum 6- and/or 12- month visits, the procedure outlined in section 2.3.6.3.2 and Figure 1 should be used to obtain outcome data for these patients.

[12] Only the schizotypal and borderline sections of Axis II.

[13] Only the 9 cognitive-perceptive Basic symptoms (inability to divide attention, thought interferences, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, disturbances in abstract thinking, unstable ideas of reference, captivation of attention by details of the visual field).

[14] Participants will also need to be rated according to the mania conversion criteria included in Appendix II.

[15] An abbreviated version of FIGS, referred to as the Family History Index will be used.

[16] Paper-based questionnaires that must be administered by the interviewer will be provided. The completed questionnaires must be posted to ORYGEN Youth Health Research Centre, as directed in the NEURAPRO-E *Study Procedures Manual*.

[17] Refer to Appendix III & Table 5 for further details about the neuropsychology assessments.

[18] Participants who have passed the Month 24 assessment time point will still be assessed, up to a maximum of 6 years post entry to the study. However it should be noted that all 24 month follow up assessments should be completed by the first quarter of 2016. Sites that wish to continue to follow up patients beyond 6 years post entry should discuss this with the Sponsor, OYHRC, and conduct assessments in accordance with local regulations and ethical approvals.

4 Multi-site Issues

As the trial will occur in multiple languages (English, Danish, German and Chinese), standardized instruments will be translated, if not already in existence, into the different languages with back translation. Standardized training in interviews and ratings (i.e., CAARMS, SANS, SOFAS) will be provided to all centers equally in English. Correspondingly, sites will initially be required to watch a *training and inter-rater* video prior to enrolment of the first study participant. Each rater (i.e. each staff member at each site responsible for conducting research interviews and screening assessments) must watch and then rate the following measures from the video: CAARMS, BPRS, SANS, MADRS, YMRS, SOFAS, and Global Functioning Scales (Role and Social). Any major deviations from the Sponsor's gold standard will be followed up and appropriate remedial training offered as necessary. As the main outcome is transition to FEP (based on the CAARMS criteria), the Sponsor has taken practical constraints into consideration and focused only on the inter-site reliability of intake group and transition criteria during the recruitment period for the NeuraproE study. Raters at each site will discuss each consented participant with a senior member of the Sponsor site who is experienced in the implementation of the CAARMS instrument. Each site will be assigned a dedicated Sponsor Representative who will assist with supervision of the study staff members' ratings of the UHR intake and transition criteria. Further to this, the investigators will ensure that CBCM will be similar across sites through the use of a manual, initial training, and regular meetings of coordinating personnel.

5 Data Analysis

Survival analysis and in particular, logrank test will be used to compare differences in transition rates between the treatment groups. Cox regression will be used to account for possible covariates. The primary analysis will be based on the intention-to-treat approach. For secondary outcome measures, general linear model analysis will be used for level of symptomatology and level of functioning, and logistic regression and survival analysis will be used to detect predictors of remission and recovery.

There will be a sub-group analysis performed regarding the bipolar at- risk (BAR) subgroup in the present UHR sample. In a recent pilot study 12.8 % of the UHR population at the same time fulfilled BAR criteria. In the same pilot study BAR have been found to present with a conversion rate of 22.7 % to first episode mania (FEM) within 280 days on average (Bechdolf et al., 2008). For a definition of the BAR subgroup and the conversion criteria to first episode mania (FEM) refer to appendix I and II. The primary aim of this sub-group study is to compare the conversion rate to FEM in BAR in the placebo group with the conversion rate to first episode mania in BAR in the EPA group at 6/12 months in order to generate estimates of effect sizes which could be used for the power calculation of intervention trials in BAR. Secondary aims are to confirm the conversion rate to FEM of the pilot trial and to characterize the BAR population as compared to non-BAR UHR.

In regard to this subgroup analysis, survival analysis (in particular Kaplan-Meier estimation) will again be used to estimate the 6 and 12-month rates of transition to mania. These rates will in turn enable the estimation of the effect sizes concerned. Also, the BAR and non-BAR subjects will be

compared using t-test (for continuous variables) and chi-square test (for categorical variables) in order to explore whether the two groups differ in terms of any characteristics.

6 Data Management

An appropriate electronic case report form (eCRF) will be used for this study. Data collected in the eCRF will be transmitted via a secure website. Access to the eCRF will be restricted to study personnel and the level of access will be set to maintain the privacy and confidentiality of participant information. A screening log will be maintained. Each site will be required to maintain source documentation (a 'Source File' including information that may be documented in the patient's medical record) that substantiates the information collected in the eCRF for at least 20 years and longer if required by local regulations (other study-related documentation as outlined in the Good Clinical Practice guideline will also need to be retained for the same period of time). The eCRF will be managed by staff at ORYGEN Youth Health Research Centre, who will also be responsible for data checking and verification.

7 Ethics & Research Standards

This study will not commence at any site until the final protocol, informed consent form and other associated documents are approved by the local institutional ethics committee (IEC). Any protocol amendments will also be managed in accordance with local ethical requirements. Sites will also be required to obtain ethics approval for any Side Studies conducted in conjunction with the NEURAPRO-E study.

This study will be conducted in accordance with Declaration of Helsinki and Good Clinical Practice guidelines as well as any local regulatory requirements.

8 Governance and Funding

ORYGEN Youth Health Research Centre is the sponsor of this study. The Stanley Medical Research Institute has provided funding for the study. The following investigators are coordinating the study:

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The study statistician and Clinical Trials Coordinator will reside at ORYGEN Youth Health Research Centre. The Clinical Trials Coordinator will be the primary contact for participating sites. A principal investigator will be appointed at each participating site. ORYGEN Youth Health Research Centre will enter into an agreement with each participating centre in relation to the conduct of the study. Each site must have access to the facilities and infrastructure to carry

out the trial protocol and to comply with the research standards stipulated in section 7. An agreement between ORYGEN Youth Health Research Centre and the participating centre will be in place before the study commences at each site.

9 Outcomes and Significance

The results of previous intervention trials with patients at high risk of psychotic disorder suggest the possibility of delaying, and perhaps even preventing, onset of psychosis in this population through specific pharmacological and/or psychological treatment. However, conclusions from these trials have been limited by relatively small sample sizes. Due to its large-scale design, positive NEURAPRO results will provide the strongest evidence to date that psychosis can be delayed or prevented and that symptomatic and functional improvement can be achieved in the 'at-risk' population through neuroprotective intervention with little or no side-effects. There is a clinical and ethical imperative to provide effective treatment with an acceptable risk-benefit balance for the 'at-risk' population. Preliminary findings suggest that EPA/DHA is a strong candidate for such intervention, and will therefore be the treatment used in this study. The study is an important step towards indicated prevention of schizophrenia and other psychotic disorders, which may be the strongest avenue for reducing the burden, stigmatization, disability, and economic consequences of these disorders.

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Appendix I - BAR subgroup criteria

INCLUSION CRITERIA for the bipolar at- risk sub group (BAR)

Fulfill criteria of at least one of three groups within the last 12 months:

☐ ***Group I: Sub-threshold mania***

For at least two consecutive days but less than 4 days:

☐ period of abnormally and persistently elevated, expansive or irritable mood + at least 2 criteria (3 in case of irritable mood) from the list:

- □ (1) inflated self esteem or grandiosity
- □ (2) decreased need for sleep (e.g. feels rested after only three hours sleep)
- □ (3) more talkative than usual or pressure to keep talking,
- □ (4) flight of ideas or subjective experience that thought are racing
- □ (5) distractibility
- □ (6) increase goal directed activity (either socially, at work, or sexually) or psychomotor agitation.

OR

☐ **YMRS -** score between 5 and 15 + elevated mood ≥ 2 + irritability ≥ 2 for at least 4 days.

☐ ***Group II: Depression + Cyclothymic features***:

D*epression*

☐ **For at least 1 week:** depressed mood, or loss of interest or pleasure + at least 2 criteria from the list:

- □ (1) significant weight loss
- □ (2) insomnia or hypersomnia nearly every day
- □ (3) psychomotor retardation or agitation
- □ (4) fatigue or loss of energy
- □ (5) feelings of worthlessness or excessive or inappropriate guilt
- □ (6) diminished ability to think or concentrate
- □ (7) recurrent thoughts of death, recurrent suicidal ideation

OR

☐ **BDI** total score above 10 **or MADRS** total score above 15 for at least 1 week.

AND

Cyclothymic features

Numerous episodes with sub-threshold manic symptoms not meeting group I criteria and numerous episodes with depressive symptoms e g. sub-threshold mania as defined in group I only for 4 hours within a 24-hour period and at least 4 cumulative lifetime days

☐ ***Group III: Depression + Genetic Risk***:

Depression

☐ **For at least 1 week:** depressed mood, or loss of interest or pleasure + at least 2 criteria from the list:

- □ (1) significant weight loss
- □ (2) insomnia or hypersomnia nearly every day
- □ (3) psychomotor retardation or agitation
- □ (4) fatigue or loss of energy
- □ (5) feelings of worthlessness or excessive or inappropriate guilt
- □ (6) diminished ability to think or concentrate
- □ (7) recurrent thoughts of death, recurrent suicidal ideation

OR

☐ **BDI** total score above 10 **or MADRS** total score above 15 for at least 1 week

AND

Genetic Risk

A first degree relative with bipolar disorder according to FIGS interview.

***EXCLUSION CRITERIA*:**

☐ (a) **Past history** of a treated or untreated manic episode for 4 days or longer

☐ (b) **YMRS** ≥ 15 for 4 consecutive days within the last 12 months

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Are criteria for bipolar at-risk sub-group fulfilled?

☐ **Yes,** criteria for at least one inclusion group and for no exclusion group are met.

☐ **No,** no criteria for any inclusion group or criteria for at least one exclusion group are met.

Appendix II - Conversion to FEM criteria

The conversion criteria are included on the next page.

Conversion criteria to first episode mania

☐ 1. YMRS Mania

Since the last assessment within the study has there been a period where the client scored ≥ 15 on the YMRS (+ elevated mood ≥ 3 + irritability ≥ 3) for 4 or more days?

□ ≥ 4 days < 7 days
□ ≥ 7days

☐ 2. DSM IV Mania

Since the last assessment within the study at least **four** consecutive days of abnormally and persistently elevated, expansive or irritable mood + at least 3 criteria (4 in case of irritable mood) from the list:

□ (1) inflated self esteem or grandiosity
□ (2) decreased need for sleep (e.g. feels rested after only three hours sleep)
□ (3) more talkative than usual or pressure to keep talking,
□ (4) flight of ideas or subjective experience that thought are racing
□ (5) distractibility
□ (6) increase goal directed activity (either socially, at work, or sexually) or psychomotor agitation.

□ ≥ 4 days < 7 days
□ ≥ 7days or hospitalization

☐ 3. Treatment for manic/hypomanic symptoms

Has the client's doctor or psychiatrist, suggested or prescribed medication because of manic/hypomanic symptoms since their last assessment within the study? What was prescribed?

specify

If the client is on existing medication has it ceased, been reduced or changed due to manic/hypomanic symptoms?

specify

☐ Not meeting conversion criteria

☐ Met conversion criteria 1. at ___.___.___

☐ Met conversion criteria 2. at ___.___.___

☐ Met conversion criteria 3. at ___.___.___

Appendix III – Neuropsychology Assessments

Neuropsychology Study Title: Premorbid Cognitive Moderators of Response to Benign Interventions (Short Title: Cognitive Moderators in UHR)

Aim(s)

General International Study:

(i) To evaluate the degree and nature of cognitive change over 6 months in UHR clients in response to EPA treatment;

(ii) To test the hypothesis that symptom response and cognitive functioning over 12 months in response to EPA treatment is related to baseline IQ in UHR clients;

Local Melbourne Study:

Optional for NEURAPRO-E Collaborators in English-speaking countries

(iii) To test the hypothesis that left olfactory identification deficits in UHR are related to poorer symptom outcome.

For the local olfactory study, it is expected that approximately 48 subjects will be recruited in the first 16 months. No reports have been made regarding lateralised olfactory identification deficits in UHR cohorts. Szsesko et al (2004) reported effects with 15 FEP patients, such that we are confident about being able to address the aims of this study with the available sample.

Rationale

Cognitive deficits are a core feature of established psychotic illnesses. Premorbid IQ is regarded as a risk factor for subsequent development of schizophrenia (Jones et al, 1994; David et al 1997; Fuller et al, 2002; Weickert et al, 2000). However the association between cognition and emerging psychosis in individuals found to be at ultra high-risk for psychosis (UHR) is less understood. In a recent review, Brewer et al (2006) found overall that general cognitive ability as assessed by standard batteries appears to remain relatively intact in UHR cohorts and is a poor predictor close to illness onset relative to other vulnerability factors. Further, decline may occur with illness progression, more consistent with state relative to trait factors. Hawkins et al (2008) found that neither the onset of frank psychosis or olanzapine treatment of the prodrome significantly altered neuropsychological course in a double-blind trial of 60 participants considered to be at high risk at their initial (pre-psychosis) assessment. However, this study is limited by small numbers in each treatment group, and the method of deriving functional cognitive domains as the dependent variable likely masked important individual differences in varying elements of cognitive processing. Moreover, no consideration was afforded to those clients with functional cognitive deficits at baseline who likely have poorer response to treatment due to poorer premorbid IQ as found in first episode cohorts (Carlsson et al 2006; Leeson et al, 2008; van Winkel et al, 2007). No study to date has addressed this issue in UHR cohorts.

Regarding more specific premorbid neuropsychological risk factors, olfactory identification deficits have been reported as a promising predictor of those UHR clients who later develop schizophrenia (Brewer et al, 2003). These likely implicate maturational compromise of prefrontal neural regions (Brewer et al, 2006). Greater olfactory deficits have been linked to poorer treatment outcome in chronic (Brewer et al, 1996) and first-episode cohorts (Brewer et al, 2001; 2003). However the degree of olfactory identification deficits prior to illness onset has not been considered as a likely risk factor for reduced treatment response in UHR cohorts.

Recent evidence also suggests olfactory deficits may be lateralised to the left hemisphere to a greater degree relative to the right in patients with schizophrenia (Good et al, 1998; 2002). Moreover, left nostril olfactory identification deficits have been associated with poorer outcome (Szsesko et al, 2004). In that study unirhinal olfactory identification assessments were conducted on 15 neuroleptic naïve patients experiencing a first-episode of schizophrenia and 17 healthy comparison subjects. Patients performed more poorly compared to healthy volunteers in their ability to identify odors across both nostrils, though there were no group differences in right and left nostril impairment. However, among patients, greater deficits in grooming and hygiene correlated significantly and more strongly with poorer ability in identifying odors presented to the left compared to the right nostril. The findings suggest that deficits in grooming and hygiene, including poor body odor, observed in patients experiencing a first-episode of schizophrenia are associated with an impairment in left nostril, and possibly left hemisphere, olfactory processing. These findings were consistent with Brewer et al (1996) who first reported an association between poor self care, negative symptoms and bilateral olfactory identification deficits in patients with chronic schizophrenia. Furthermore, olfactory identification deficits have been associated with negative symptoms at illness onset (Brewer et al, 2001). No study has reported unilateral olfactory function in UHR cohorts and linked the degree of deficit to prognosis.

It has been suggested that Ethyl-eicosapentaenoic acid (E-EPA) enhances symptom response over time in chronic schizophrenia (Vaddadi, 1989), first episode psychosis (Berger et al, 2007; 2008) and in UHR subjects (Amminger et al, 2007). However these finding are not reliable and have not been validated (e.g. see Fenton et al, 2001). The only study that has investigated change in cognition over time in response to EPA treatment in first episode psychosis found a non-significant advantage for E-EPA over standard therapy at the end of the trial, however, intermediate assessment points between baseline and follow-up were not incorporated into this design which was less sensitive to early response (Proffitt et al, 2004).

AIMS OF CURRENT STUDY

The current study aims to evaluate the degree and nature of cognitive change over 6 months in UHR clients in response to EPA treatment. Further, we seek to determine whether symptom response and cognitive functioning over 12 months in response to EPA treatment is related to baseline IQ in UHR clients. Finally, the hypothesis that unirhinal olfactory identification deficits lateralised to the left relative to right hemisphere in a UHR cohort will be tested with the expectation that left olfactory identification deficits will predict poorer symptom outcome.

Neuropsychological Measures

Sensitive measurement of change over time will be interpreted in the context of premorbid and baseline IQ (for review, see Brewer et al, 2006), along with a measure of olfactory identification, where deficits in this cohort have previously been reported and found to be a promising neuropsychological marker for schizophrenia (Brewer et al, 2003).

a. Premorbid IQ: The National Adult Reading Task (NART: Nelson & O'Connell, 1978), Wide Range Achievement Test 4 – Word Reading (WRAT4: Wilkinson & Robertson, 2006) or acceptable local language version will provide an estimate of premorbid intellectual ability, and will be utilised to ensure participants do not meet the exclusion criteria of IQ < 70.
b. Current IQ: A short-form (2 from 14: Vocabulary & Matrix Reasoning) of the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III; Wechsler, 1997) will provide a very reliable and brief estimate of current Full-Scale IQ.
c. Change over time: The Brief Assessment of Cognition in Schizophrenia (BACS: Keefe et al, 2004; 2008) provides a sensitive measure of change in cognition over time in individuals with psychosis, and includes measures of processing speed, verbal memory, working memory and reasoning & problem solving.
d. Olfaction: The University of Pennsylvania Smell Identification Test (UPSIT: Doty, et al., 1984) provides a measure of olfactory identification ability. The UPSIT is a standardised, self-administered multiple choice scratch-and-sniff test consisting of four booklets each containing 10 items. The 'suprathreshold' fragrances are microencapsulated and embedded in plastic capsules coated onto labels. For each odorant the subject is required to select the correct odour name from four possible choices, only one of which matches the odour. Ratio level scores are graded for a range of correct responses between zero and 40, with standardised cut-off scores indicating abnormal responses.

Measurement Intervals

Refer to Table 5 for the Schedule of Neuropsychology Assessments. All cognitive measures will be administered at baseline. At the 12 month assessment (or at the time of premature discontinuation due to transition), the BACS will be administered. The BACSwill also be administered at the intervening 6 month assessment.

Procedures

I. The standard order of test administration is 1) premorbid IQ measure, 2) WAIS-III, 3) BACS, 4) UPSIT (optional as negotiated with the English speaking sites).
II. Any participant with an estimated premorbid IQ < 70 and a documented history of developmental delay or intellectual disability meets exclusion criteria and should not be allowed to continue in the study.
III. All measures are to be administered in the local language. Where a local language version is not available provision may be made to administer an alternate measure which must be approved by the Lead Investigator. If the participant is fluent in English (second or additional language) the English versions may be administered.

IV. For those sites utilising the UPSIT: booklets 1 & 2 will be used to test left nostril only, and booklets 3 & 4 will be used to test the right nostril only.

V. If mental status is significantly compromised at the scheduled study visit, then re-assessment within no longer than 14 days of the scheduled study visit is recommended.

Table 5 – Schedule of Neuropsychology Assessments

NEURAPRO-E Study Visit		2	11	13	Time of transition	Comments
Day (d)[1]		-7 to -1	180	360		
Month (end)		0	6	12		
Instrument	**Sub-tests**					
Premorbid IQ measure[2]	All	X	-	-	-	
WAIS-III	• Vocabulary • Matrix Reasoning	X				
BACS	All	X	X	X	X	
UPSIT	All	X	-			English-speaking sites only. Participation of non-Melbourne sites is optional.

[1] All neuropsychology assessments to be performed within 14 days of the scheduled study visit.

[2] Acceptable local language version of a test that measures premorbid IQ and for which there are current local norms as determined by the Neuropsychology Study Lead Investigators; examples include the NART and WRAT4.

Data Management & QA

Training to administer the assessment protocol will be supplemented by manualised instructions. RA's will need to be either supervised by psychologists or be studying a psychology related post-graduate qualifications.

Lead Investigator(s)

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Questions relating to test administration, training & quality assurance should be directed to the lead investigator.

Co-investigators: Dr. Stephen Wood; Associate Professor Paul Amminger; Dr. Shona Francey; Dr. Tina-Marie Proffitt; others as assigned by the Lead Investigator.

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Appendix IV – Anti-psychotic dose equivalents

The doses provided in the table below are equivalent to a haloperidol dose of 50 mg.

Abbreviated Drug Name, Drug Name and Trade name		Dose in mg
AMS	Amisulpride (Solian)	1875
APP	Aripiprazole (Abilitat, Abilify)	187.5
CPZ	Chlorpromazine (Largactil)	2500
CLZ	Clozapine (Clozaril)	2500
DPL	Droperidol (Droleptan)	100
FLH	Fluphenazine HCL (Anatensol)	50
HPL	Haloperidol (Haldol)	50
OLZ	Olanzapine (Zyprexa)	125
PCZ	Pericyazine (Neulactil)	250
PIM	Pimozide (Orap)	50
PPH	Perphenazine (Trilafon)	200
QTP	Quetiapine Fumarate (Seroquel)	1875
RIS/RSP	Risperidone (Risperdal)	50
	Sulpride (Dolmatil, Sulpitil, Sulparex)	5000
THI	Thiothixine (Navane)	100
THZ	Thioridizine (Melleril, Aldazine)	2500
TPZ	Trifluoperazine (Stelazine)	125
ZPD	Ziprasidone (Geodon)	1500