The Taiora Trial: Protocol for a randomised placebo-controlled trial (RCT) investigating the efficacy and safety of micronutrients for improving dysregulated emotions in teenagers



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# Background

## Psychiatric Problems in Young People

*He Ara Oranga* discussed that there are growing number of adolescents in NZ struggling with mental health issues, with the suicide rate among young people being the worst in the OECD. In NZ, the estimated lifetime prevalence for experiencing a diagnosable mood or anxiety disorder ranges from 20-25% and is one of the costliest burdens on a primary health-care system.1-3 Based on the NZ Health Survey, rates of mental illness in children and adolescents increased three fold from 2006/2007 to 2015/2016,4 with studies of NZ youth showing rates of serious depressive symptoms range from 12.1-13.9% and suicide attempts range from 2.7-6.5%.5 There is a strong commitment from government to address the increasing burden that mental health difficulties place on society; this research intends to assist with achieving this delivery. This research will target the core underlying dysregulation believed to be at the heart of psychological distress in young people, that is, *emotional dysregulation* (ED).6

ED is a transdiagnostic dimension characterized by an excessive reactivity to negative emotional stimuli with an affective (anger/sadness/anxiety) and a behavioural component (aggression) and is present across anxiety, mood and behavioural disorders. Due to early onset, high prevalence and persistence, as well as developmental comorbidity, ED in childhood is one of the most psychosocially impairing and cost-intensive mental health conditions,6 with not enough people improving with conventional treatments.7 It is estimated 30-50% of emotionally dysregulated adolescents who receive any treatment will not respond.8 Further, even though *He Ara Oranga* recommended more talking therapies, even if they were successful, there are not enough psychological resources to meet the demand.9 Fresh approaches that are reachable, scalable and directly target this underlying dysregulation are necessary in order to have any opportunity to improve outcomes for our tamariki.

## Treatment of Emotional Dysregulation in Young People

Emotional dysregulation is considered trans-diagnostic, in that it is present across many psychiatric problems (including mood, anxiety, autism and behavioural disorders), it captures some of the core challenges that young people struggle with, but is also very difficult to treat with no clearly established guidelines or empirically validated treatments.10-13 The focus on a set of symptoms rather than a disorder per se resonates with the impetus to move away from research that targets diagnostic categories.14 Best evidence treatment for emotional dysregulation in children and adolescents advises psychological therapies, although effect sizes are generally modest.15 16 Even when psychotherapy is effective, it is difficult to access due to a small number of practitioners and long-waiting lists. Medications are often used despite poor efficacy data; nevertheless, prescription rates for children and adolescents have been increasing over the last decade.17 Fluoxetine is the only antidepressant that has shown superiority over placebo,18 but efficacy is modest and it also has side effects.19 20 There are also ongoing concerns about increased suicidality being associated with rising antidepressant use in young people.21 With youth in particular, increased suicidal ideation has been identified as a concerning challenge.22 Outside of procedural settings (e.g., dental procedures), anxiolytics have little evidence to support their use in young people.23 To contextualize the modest effect sizes of current treatments, it is estimated that between 30% to 50% of adolescents who receive any treatment will not respond.8 Despite billions of dollars being funnelled into such research, the outcomes have been largely disappointing. Fresh approaches, challenging conventional lines of treatment, are necessary to improve outcomes. We propose to study the efficacy and safety of nutrients on distressed tamariki in order to test whether we can improve outcomes with a simpler and more cost effective delivery.

## The role of nutrition in treating psychiatric problems

A promising new direction:

One option is to explore the effects of nutrient interventions on mental health given the growing association between poor diet and dysregulated mood and emotions across the lifespan, including adolescence.24 However, while dietary change is desirable, it is not always realistic to manipulate diet, particularly in teenagers, nor is it likely to be sufficient to address all nutrient deficiencies that may contribute to mental health issues.25 Research has identified that diet may be a significant risk factor for the development of mental health issues, in particular mood dysregulation, in adolescents.24 26 Long-term studies suggest that early malnutrition is an important risk factor for behavioural problems.27 However, given the challenges associated with changing diet in adolescents, another method to reduce psychological distress is through supplementation with micronutrients (minerals and vitamins). The advantage of such an approach is that it is a relatively simple intervention to swallow pills at a time when the motivation and ability to engage in major dietary changes is severely compromised. The concept underlying the primary use of multiple micronutrients for the amelioration of mental symptoms is that *mental illness may be a manifestation of suboptimal nutrition,* relative to genetically-determined needs for optimal brain metabolic activity. Such a concept, if shown to be relevant to mental health, could have far reaching implications across all ethnicities, particularly for Māori youth given that they disproportionally represent those with mental health challenges. Interestingly, in North America the concept of suboptimal nutrition as the cause of mental illness was the accepted wisdom until the mid-20th century. During pioneer times, when access to health care was extremely limited except in the largest urban areas, the People’s Home Library provided practical knowledge on everything from treatment of burns and colic to the management of tuberculosis. This 500-page tome explained that the primary cause of insanity was “imperfect nutrition” (p. 209).28 With the increasing use of medications, the role of nutrition as being relevant to mental health, became largely ignored. In NZ, we can see the significance of the rapid change in the food environment and the erosion of traditional healing practices as playing important roles in the deterioration in the health of Māori.

Research over a decade has demonstrated that using micronutrients (vitamins and minerals) in pill form can be effective in directly improving dysregulated mood across many conditions;25-29 however, the research on using micronutrients is poorly understood, is viewed as labour intensive and complicated and as such, the uptake into the community has been limited. This project intends to *disrupt* our current method of research delivery and couple this nutritional intervention along with the research identifying the use of digital technology as an effective mode of mental health care delivery for young people.30 31 This combination has never been researched before in youth. In so doing, we will foster new relationships in primary care and teach them a new way to conceptualize mental health problems in young people.

Rethinking the scientific paradigm: Providing nutrients *in combination* is not the usual approach in affecting change in psychiatric symptoms. Research on nutrients is typically done with individual nutrients. Perhaps the perpetuation of single-nutrient studies is because the study of single-nutrient treatments fits comfortably with traditional scientific methodology (in which only one independent variable is manipulated at a time), with the pharmaceutical paradigm (where drugs are usually single-ingredient), and with western thinking (in which the optimal solution to any problem is expected to be a single remedy); however, this approach is inconsistent with what is known about human physiology. The one-disease, one-nutrient solution to illness is outdated, and has been replaced by a model that is responsive to the broad spectrum of human nutritional needs. This model has become increasingly accepted by those doing research in physical health, but the work in the field of psychiatry is still lacking.32

Studies on physical illness provide some reassurance of good outcomes in that micronutrients improve recovery from infectious disease and stroke.33-36 However, shifting psychiatric research toward a consideration of broad spectrum formulations is going to require rethinking the scientific paradigm that has thus far shaped this field. One way to begin to possibly change the way we conceptualize mental illness is to design studies that can test whether nutrient intervention can be found to be efficacious in a population that to date has been challenging to study. If proven to be effective, this approach holds the advantage that implementation would be very straight forward and easy to execute through primary care.

Why might this approach work? Most scientific methodology alters a single variable at a time, so it is worth briefly considering the justification for multinutrient supplementation. There are a number of theories being proposed that fit comfortably in explaining the possible mechanisms. Every neurotransmitter goes through many metabolic steps to ensure its synthesis, uptake, and breakdown. Every one of those steps requires enzymes, and every enzyme is dependent upon multiple co-enzymes (cofactors). A variety of vitamins and minerals are required as cofactors in most if not all of those steps. Consequently, one possible mechanism underlying psychiatric symptoms is inborn metabolic dysfunction associated with slowed metabolic activity due to suboptimal availability of vitamin and mineral cofactors.37 38 Impaired brain metabolic activity associated with other disorders has already been shown to be correctable through nutrient supplementation.37 One can thus envision multinutrient supplementation as providing sufficient co-factor that even enzymes with drastically reduced activity become so supersaturated that near-normal function is restored.37 This implies that adequate diet *may not* be sufficient to correct these metabolic errors, only supplementation with more nutrients than one can typically get out of the diet will be able to adequately address the relative nutritional deficiencies relative to metabolic demand. We wonder whether those struggling with mental health issues may present with metabolic differences.

Biological plausibility**:** Research has already shown that nutrient dense food is critical to reduce the risk associated with the development of mental disorders.26 Micronutrients have been shown to effectively improve aggression and emotional dysregulation in children,39 as well as reduce self-harming,40 a behaviour that is particularly difficult to treat. Genetic variation leading to in-born errors of metabolism and slow metabolic activity due to suboptimal availability of vitamin and mineral cofactors,37 poor gut health and microbiome composition,41 42 presence of inflammation,43 and mitochondrial dysfunction that may result in decreased production of cellular energy in psychiatric disorders,44 all suggest a more complex nutritional intervention may be required.45 The presence of any or all of these factors could effectively reduce the availability of nutrients for optimal brain health. Publications on mechanism of action, that is, why do the micronutrients work, reveal that the effects of the nutrients are likely widespread, with small effects detected across genetics,46 microbiome,47 imaging,48 and nutrient serum levels.49 Short and long-term safety has also been well established.39 50-54

The evidence to date: Over the last decade, researchers have conducted clinical trials to establish efficacy of micronutrients in the treatment of psychiatric/psychological disorders. Studies assessing micronutrients for the treatment of behavioural problems in young people have reported positive benefits and large effect sizes with designs ranging from case reports55 to open-label,56-58 to retrospective database analyses,59 to patient preference studies,60 to randomized placebo-controlled trials.39 The role of micronutrients in the pathophysiology and management of other psychiatric disorders including bipolar disorder, anxiety states, and autism has also received considerable international attention because of large and beneficial effects,40 58 61-64 suggesting that this approach could prove meaningful although controlled trials, particularly in young people, are lacking. It is also important to note that trials that have not been shown to be effective have been ones that have chosen one or a few select ingredients. When a broad spectrum of nutrients is used, the findings appear more robust. Based on the overall findings, and the specific symptoms that appear to benefit, directly targeting emotional dysregulation in youth with a broad array of nutrients is logical but does require testing to determine whether this age group can adhere to the treatment with relatively little oversight. This proposal aims to address a substantial gap that remains in terms of whether this approach may be effective with adolescents as well as how to make the intervention simple for primary care to deliver.

Digital interventions: Over the last decade there has been a move towards developing online interventions as well as symptom monitoring via websites and this has necessarily accelerated with COVID19. What was once viewed as highly unlikely to be effective, has now been proven to be likely as effective as face-to-face therapy. “E-therapy” combines the advantages of structured self-help materials presented via the internet, with a clinician providing support and therapeutic advice via email as required. These therapies can vary from being entirely electronic to a mix of electronic intervention or assessment gathering alongside therapeutic or clinician input. E-interventions have been found to be a particularly important development for individuals who might be geographically isolated, have limited financial resources, experience stigma associated with their mental health problems, and difficulties with communicating directly with adults. Remarkably, some published studies reported equivalent or higher ratings for therapeutic alliance in e-therapy compared with face-to-face therapy.65 Two e-therapies (BRAVE, SPARX) have been trialled in NZ with children/adolescents demonstrating efficacy as a treatment for both anxiety and depression,30 31 providing evidence that assessments and interventions can successfully be delivered on-line. They also provide proof of concept that young people can be receptive to this mode of intervention delivery.

## Rationale and approach of study design

The RCT is viewed as the gold standard for testing treatment efficacy and is the appropriate starting point to test the theory that micronutrients provided in combination, yield a large impact on these debilitating psychiatric symptoms in adults. This proposed research will use RCT methodology and compare micronutrients with placebo in 150 adolescents struggling with emotional dysregulation in 1:1 ratio.

However, given the various aspects of this study and the previous research conducted using micronutrients, this study utilises both efficacy and effectiveness methodology and this must be reflected in the study design.66 67 Therefore, a mixed methodology will be used to implement this trial. Once control participants have completed the 8-week placebo arm, they will be offered the opportunity to receive micronutrient treatment, creating an open-label trial element.

Data will also be analysed using single-subject research methodology, to better capture any treatment effects of micronutrients at an individual as well as a group level.

To date, the research on micronutrients has been labour intensive, requires extensive assessments, constraining exclusion criteria, is always conducted in person with bimonthly face-to-face monitoring, and as such costly to research. It is also poorly understood by end users. We want to *disrupt* our current method of research delivery and couple this potentially useful intervention along with digital technology in order to determine whether we can establish these same effects observed in other populations but with no face-to-face contact. We will develop a website specific to this project that will be tailored to adolescents and their parents. This combination of nutrient intervention for youth with digital service delivery is a new methodology never researched before. We do not yet know if it is feasible for them to follow the routine of taking pills three times a day. Can we get them to regularly swallow the pills? Will on-line delivery of ongoing support effectively meet their psychological needs? Can this mode of delivery offer the flexibility that is required to work effectively with adolescents? Can we educate GPs on nutrient interventions by engaging them in the referral process?

The demand for services is too large to expect our society to be able to address the mental health crisis with extensive one to one approaches. We need to explore more innovative ways of service delivery. This research intends to accomplish this through working directly with primary services (GPs) as referral sources, and then deliver the intervention via online monitoring, mailing out the pills and having access to a clinical psychologist as required, but with a minimum of three phone calls or skype meetings to review consent and to then discuss the outcome of the intervention after the RCT and open label phases are completed. In between, we expect texting will suffice although if the need arises for more intensive intervention, our team will be available to respond.

We have some evidence that adults at least, like this type of service delivery. We also have evidence that nutritional approaches are deemed more acceptable to Māori given the high uptake of Māori participation in previous nutritional research.12 For the last two years, *Te Puna Toiora* at UC has been conducting an RCT exploring the feasibility of working directly through GP referrals via an online portal, connecting with potential participants via phone and email, mailing the product to participants and monitoring them via a website. We have made specific effort to develop relationships with Māori health providers. GP engagement has been high, with several referrals every week, and drop out remarkably low (5%). Our exclusion criteria have been minimal, moving away from diagnostic categories, trusting GPs to identify those people who are functionally impaired. This definition has successfully captured people from mild to severe. Participants have felt connected to the researchers and appreciated the flexibility of our approach. The research has enabled us to reach individuals who normally would not have easy access to a clinical psychologist, enrolling participants in rural parts of Canterbury. The nutritional approach has also been found to be acceptable to a variety of different ethnic and religious backgrounds, including Māori, Pacifika, and Muslim. Although youth live online, and there is research that shows that e-therapy has been a successful way to engage young people,31 we have no data to suggest that this combination approach will work for young people. However, the need to explore new avenues is imperative if we are going to effectively reduce the burden of mental illness in our tamariki.

There is an urgent need to explore treatments for at risk youth that have good reach, are scalable and affordable. Based on current resources, it is unrealistic to think that we can adequately address the growing mental health problem in this country with more 1:1 therapy.9 Although effective for some, there are simply not enough mental health practitioners to meet the needs of our communities. Our vision is to focus on testing efficacy of treatments that can more effectively address the treatment gap. Micronutrients alongside remote monitoring with a psychologist present as a testable intervention that, if successful, may provide an intervention that is easy and safe to implement within primary care.

# Aims and Objectives

This study will be the first double-blind (participant and investigators), parallel–group RCT designed to explore the efficacy and safety of a broad spectrum micronutrient formula compared with placebo in medication-free teenagers with dysregulated emotions in the community. It predicts that participants given DEN will have improved emotional regulation and better overall mental health functioning than participants given a placebo. Measures of effectiveness will include both standardised psychometrics and additional questions capturing general levels of anxiety, low mood and stress, alcohol intake, suicidality and other measures of safety such as adverse events. Cost effectiveness of micronutrient treatment will also be estimated through exploring rates of participants accessing medical treatment while participating in the study.

# Methodology

The design consists of five study periods:

1. Screening. Participants will be screened for eligibility. Those who are eligible and consent to the study will receive a baseline assessment (see below).

2. A 2-week baseline monitoring period.

3. An 8-week period of randomized, placebo-controlled, double-blind acute treatment.

4. An 8-week open-label extension period (OL).

5. A 12-month naturalistic follow-up (1 year following baseline)

## Inclusion criteria

1) between 12 and 17 years, 2) regular access to the internet/phone, 3) living in New Zealand, 4) considered reliable and compliant with protocol (including ingestion of as many as 12 capsules/day with food), 5) be presenting to their GP or school counsellor with functionally impairing emotional dysregulation which cannot be better accounted for by a medical condition or parental identified as showing disabling emotions that are interfering with their ability to function, 6) sufficient ability to read and write English in order to complete questionnaires, 7) be attending primary or high school, and 8) receive a CGI-S rating of at least 4 (moderately ill) on screening and a minimum score of 10 on the Emotion Dysregulation Inventory or 3 on the Affective Reactivity Index.

## Exclusion criteria

1) The main strict contraindications are metabolic conditions such as Wilson’s disease (copper), haemochromatosis (iron), phenylketonuira (phenylalanine) and trimethylaminuria (choline), 2) Known neurological disorders involving brain or other central function (e.g., previously diagnosed intellectual disability, autism spectrum disorder, epilepsy, MS, narcolepsy) or other major psychiatric condition requiring hospitalization (e.g. significant mood disorder with associated suicidality, substance dependence or psychosis), 3) pregnant or breastfeeding, 4) Any patient known to be allergic to the ingredients of the intervention or known or suspected allergy to any placebo excipient, and 5) Any medications with primarily central nervous system activity, including psychotropic medication (e.g. SSRIs, tricyclics, benzodiazepines). Participants must have been off these medications for a minimum of four weeks prior to the trial. Participants will not be encouraged to come off a medication in order to participate.

## Participant recruitment and referral process

The website will have two referral options with screening questions:

1. GP/counsellor referral: Participants can be offered the opportunity by the GP to participate in the trial once other treatment options have been discussed. **Dr Bagshaw**, an adolescent medical practitioner, will assist with GP liaison.
2. Parent/caregiver/self referral: the website will have an option for self referral.

Potential participants will either present to their GP or school counsellor with difficulties with emotional dysregulation (e.g., mood, anxiety, behavioural difficulties, irritability) or can self-refer or be referred by a parent. The Emotion Dysregulation Inventory (EDI) will be provided to GPs and counsellors (via the website) to guide them in identifying dysregulated youth. Parents or self will complete the EDI as part of screening.

## Screening phase

The online screening will ask for specific identifying information (contact details), questions assessing eligibility (ie age, taking medications or not) and will include the short form of the Emotion Dysregulation Inventory – Reactivity subscale in order to ensure the participant has a minimum threshold of symptoms (score ≥10) as well as the ARI in order to be eligible for the study. The screening questionnaire can be completed by the participant (>16 years) but must also be completed by the parent regardless of age. Involvement of a parent/caregiver is an essential component of the trial and a parent/caregiver will be required to give consent to participate in the trial. Once an electronic referral has been received, a monitoring psychologist will contact the participant/family to arrange a further phone screening. Each participant will be assigned to a monitoring psychologist. The same person will monitor that individual throughout the trial. In order to increase engagement with Māori youth, **Leona Manna** (a Kaupapa Māori clinical psychologist) will be available to work with those who identify as Māori.

During the screening, the psychologist will explain more about the study, ask further screening questions regarding risk and severity, answer any questions the individual and family have about the study, gain informed verbal consent, discuss contact with the individual/family during the study and explain the study website. This phone screening will include a brief functional assessment of their mental health, a review of the inclusion and exclusion criteria and collecting information regarding the participants’ General Practitioner (GP). Potential participants must be experiencing *functionally* impairing emotional dysregulation. The level of functional impairment will be assessed at screening by the monitoring psychologist and participants with no functionally impairing symptoms of emotion dysregulation will not be accepted into the study and will be provided with other appropriate treatment options.

This phone screening will also be used to assess severity of psychological symptoms from 1 (normal) to 7 (most severely ill). Only participants 3 and above (mildly ill) will be considered for the trial. Only participants with current GPs who consent to information sharing with their GP will be deemed eligible for the study.

At the conclusion of this phone screening, the psychologist will send an electronic consent form to participants/parents. For those who do not have access to a computer, a hard copy will be sent in the mail. These forms will need to be sent back before any product is received, either as a hard copy or electronically (photograph or submission via the website). If deemed clinical necessary, the psychologist will offer participants face-to-face interviews at the screening phase. In the case of self/parent referrals, GPs will be informed if potential participants are accepted or not accepted into the study and will be given two weeks (Baseline phase) to communicate with the principal investigator if they do not believe the participant is suitable for the study.

## Informed Consent

All invited participants and their family will receive oral and written information in plain language about the study, including its risks, benefits, and procedures, that the participation is voluntary, and that they may withdraw their participation at any time without any consequences to their treatment. Participants who agree to participate will be asked to sign an informed consent form, indicating that they fully understand the nature of the study and the consent form. For those participants younger than 16, we will have them complete an assent form and their parents will sign a consent form on their behalf. Regardless of the age of the participants, parents will need to be included in the consent process. Participants who turn 16 during the trial will be asked to provide consent at this time (having previously provided assent). Given that parents will also be providing information about themselves and their children, they will also be required to consent to participate in the study.

It is important to take into account issues that may compromise comprehension and cognitive capacity, and/or render the participant particularly vulnerable or compromise their capacity to provide consent. Such issues may include but are not limited to intellectual disability, mental illness, poor literacy and speaking English as a second language. Further, an unequal relationship will exist between participants and investigators.

We acknowledge that there is a possibility that, due to the unequal relationship between treating practitioners and their patients, patients may feel compelled to participate in the research.68 As such, the consent process in our study is designed to minimise the impact of this unequal relationship by ensuring they understand that there are other treatments available, that choosing not to participate will not affect their health care in any way.

Although a parent/caregiver will consent to participate in the study and provide information about their child, parent/caregivers will not have access to their child’s individual results neither will children have access to the data given by their parents.

## Baseline Assessment

After receiving written consent, participants and their families will be directed by the psychologist to access the website, create a unique log-in and complete baseline assessments. Both the participant and a parent will have their own login for the study. Eligible participants and a parent will complete a series of baseline questionnaires accessed through this the website. If any information in their baseline assessment documents or screening phone contact indicates they may be ineligible for participation, their cases will be reviewed with the principal investigator and the study physician. The participant may be contacted by the PI for further discussion. They may be permitted to continue with the trial, although their data may be separated from subsequent analyses. Participants will also be informed that their GP is able to withdraw their participation in the trial if they do not believe the participant fits the eligibility criteria. A second baseline will be repeated 2 weeks later. During this two week baseline phase, the first bottle of the intervention will be mailed out.

## Randomisation

The randomization scheme will be generated by the website, using a programme based on the Web site Randomization.c[om (http://www.randomization.com)](http://www.randomization.com) with the randomization sequence arranged in permuted blocks of size 4. Participants will be stratified by gender. Neither the participants nor the researchers involved in the study will have access to the randomization list, which will be double coded to protect randomisation. The pharmacist will be sent the randomisation list and will prepare individual participant kits in advance, which will contain all required study pills for the 8-week RCT. These kits will be sequentially numbered but identical. An administrator will mail the kits to individual participants based on the sequential numbering.

## RCT phase

Participants will begin taking their assigned intervention after the two-week baseline phase. Interventions will be mailed to participants in order to arrive within two days of finishing baseline data collection. There will be clear instructions both on the intervention and in the website directing participants to take the intervention only when the baseline data collection phase has completely finished. Participants will initially take one capsule, three times each day. Every second day, the dose will increase by three capsules until a maximum dose of four capsules taken three times a day is achieved: a total dose of twelve capsules per day. In some cases, participants may decide that two doses a day is all that they can manage, in which case they will start with 2 pills twice a day and increase by two every day until they reach 12 pills a day (six twice a day). Participants will initially be sent four weeks’ worth of intervention and will then be sent a further four weeks’ worth each month. Participants continue to take the study interventions for eight weeks. Participants will be required to send a photo through of their remaining pills at week eight and will also be asked to estimated missed doses every two weeks. This will be submitted through the website. Throughout the RCT phase, participants and their families will also be required to complete online questionnaires every week. At the conclusion of the RCT phase, participants will be required to complete the same questionnaires as completed during the baseline assessment phase. The monitoring psychologist will contact participants at the end of the RCT phase to discuss progress and offer the open label phase. The monitoring psychologist will also write to each GP informing them that their patient has completed the RCT and may be continuing to access micronutrients in the future.

## Open label phase

The open label phase, where participants in the placebo and the micronutrient condition are offered the micronutrient formula, will begin the week after participants have completed their eight-week intervention phase and assessments. Titration of capsules will follow the same procedure as done in the RCT phase. Participants will be required to complete online questionnaires throughout the open label phase and will be sent micronutrients in the same schedule as the RCT phase. At the end of the RCT and open label phase, study completers can independently access the product via a New Zealand distributor or via the internet. The monitoring psychologist will contact participants at the end of the open label phase to discuss progress and answer any questions the participants have regarding accessing micronutrients and confirm the one-year follow up.

## Follow up

At one year following the conclusion of the baseline monitoring period, participants will be contacted again to complete the same online questionnaires they completed during the screening phase.

## Study intervention

Both the micronutrient formula (DEN) and the placebo (see Appendix A for ingredients for

DEN and placebo) will be manufactured by Hardy Nutritionals, Canada; they will be

identical in appearance, presented in capsule form. The study intervention (DEN) and placebo will be provided in a bottle with only the participant number detailed on the bottle. The first bottle administered to participants will contain four weeks’ worth of either the study intervention or the placebo. The second bottle will also contain four weeks’ worth. DEN was chosen for this study as it (and its predecessor EMPowerplus) is the most studied multi-micronutrient formula (13 vitamins, 17 minerals, and 4 amino acids) for the treatment of psychiatric illnesses69 and has found medium to large beneficial outcomes for a range of psychological problems29 39 51 70 and may therefore be helpful for youth struggling with dysregulation emotions. The safety and tolerability of DEN is well documented in both adults and children.39 50-54 The placebo is an active placebo as it contains riboflavin which can change the colour of the urine. This ensures the blind is maintained throughout the trial. All bottles will have a vanilla sachet added to them to mask any potential differences in smell.

### Safety of the trial nutrients

Concerns about the long-term safety of nutrient-additive treatments have been raised; however, these studies typically use one nutrient at a time or in addition to selective-serotonin reuptake inhibitors.71 Less is known about whether nutrients given in combination hold the same risk as when given alone. However, large-scale safety reviews of all studies on children and adults using a broad spectrum of micronutrients have found no clinically meaningful negative outcomes and no serious adverse events linked to the consumption of micronutrients.72 73

Two RCTs explored the adverse effects of micronutrient treatment on children39 and adults51 with Attention Deficit Hyperactivity Disorder (ADHD). These studies reported only mild side effects (headaches, nausea, sleep disruption and dry mouth), and an equal number of adverse effects were also reported in the placebo groups. Three percent of the side effects reported were classified as moderate. These were biochemical changes including increased prolactin, glucose, alanine aminotransferase (ALT) and a single case of glossitis. Although these adverse events were rated as moderate, it was not clear these were related to the administration of the nutrients.51 Current data from the University of Canterbury and of other overseas studies have documented reassuring safety and toxicity information concerning the use of various micronutrient products including EMP and DEN, with children and adults at the dose to be used in this trial.73

Several ingredients in the DEN formula are higher than the specified upper level (UL) recommended by the New Zealand Ministry of Health.74 With regards to folate, this is for a practical reason, in that the UL for folate can be much higher if consumed with B12, as it is in DEN. With regards to copper, the UL is set to prevent a zinc deficiency; as such, given DEN also contains zinc, going above the UL is practical.

The five other ingredients in DEN that will be given at a dose higher than the UL are vitamin B6, magnesium, zinc, niacin, and manganese. The UL for vitamin B6 is between 60 mg (up to 13 years) and 80 mg (14-18 years). Long-term doses of vitamin B6 between 1-6g have been associated with severe and progressive sensory neuropathy.75 However, DEN provides a daily dose of 69.9 mg and as such, the daily dose in DEN is much lower than the doses identified as toxic and leading to negative effects. The American Food and Nutrition Board reviewed data on long-term vitamin B use up to 500 mg and found no evidence of neuropathy. They have increased the American UL to 100 mg, which is more than the daily dose of 69.9 mg found in DEN. Furthermore, the Institute of Medicine in the United States determined a no-observed adverse event level (NOAEL) of 200 mg and a lowest-observed adverse event level (LOAEL) of 500 mg for vitamin B6 based on their literature review.76 The Merck Manual reports toxicity effects at 2g (2000 mg) per day. Marks77 cautiously suggests a safety level of about 200 mg/day for chronic use. Thus, the amount of pyridoxine in this study is only 35% the amount that is safe to take chronically on a long-term basis and should pose no danger to the participants in this study.

The UL for magnesium is 350 mg for children and adolescents. This UL for magnesium has been set since excessive ingestion can cause or exacerbate diarrhoea. DEN provides a daily dose of magnesium at 600mg. A Cochrane Review of four trials concluded that magnesium doses of up to 1500 mg have not been associated with adverse outcomes in adults and although some noted gastrointestinal effects, none were deemed sufficient to withdraw treatment.78-80 It is rare for our participants to report diarrhoea, when it does occur, it is easily resolved through reducing the dose.

The UL for zinc is 23 mg for children (8-13 years) and 34 mg for children 14-18 years. DEN provides a daily dose of 48 mg. Toxic doses of zinc have been indicated for children at more than 6mg/kg and it has been suggested that regular doses of zinc greater than 100mg may be associated with prostate cancer in men.81 However, there is also evidence that DL and ULs for adults in regards to zinc may be lower than necessary, based on differences in diet and the quality of absorbed zinc.82 The World Health Organization report on trace elements in human health expresses the opinion that the primary issue of chronic exposure to high zinc levels is the resulting interference with copper utilization. Because DEN at the full dose provides 48 mg of zinc, it is worth quoting the WHO precisely on this topic:83 “The limited human data available indicate that clinically detectable changes or functional impairments can occur at an average zinc intake of 150 mg/day or more. Interactions with nutrients influencing their absorption and utilization have been detected biochemically at total zinc intakes as low as 60 mg/day when zinc was given in the form of a supplement to a diet that, it is reasonable to assume, already provided 10 mg zinc/day.” Further, the UL of zinc is partially set in order to prevent a copper deficiency. As the formula contains copper, this limit is less relevant.

There is no recommended daily UL set for niacin as niacinamide by the New Zealand Ministry of Health; however, a UL between 20 mg (age up to 13) and 30 mg (14-18 years) per day has been recommended for niacin as nicotinic acid. DEN provides a daily dose of niacin (as niacinamide and nicotinic acid) of 144 mg. The main concern is a niacin flush. The New Zealand and Australian Reference Values notes that the only reports of flushing associated with the ingestion of nicotinic acid with food occurred following the addition of free nicotinic acid to food prior to consumption and noted that previous research on the symptom of flushing indicated the symptom was transient.84 There have been no adverse liver or gastrointestinal effects of niacin measured in a study exploring niacin intake up to 1000 mg/d.85 Most importantly, we have never seen a case of flushing in our research with over a thousand participants.

The UL for manganese is 9 mg/day for 14-18 year olds and 6 mg per day for 9-13 year olds. The daily dose of manganese in DEN is 9.6 mg/day. The U.S. Food and Nutrition Board of the Institute of Medicine86 recommended the Tolerable Upper Intake Level for 70 kg adults as 11 mg of manganese/day, translating to an interim guidance value of 0.16 mg manganese/kg/day. The UL for children and adolescents were calculated by scaling the reference body weights for children and adolescents, noting there were no reports of manganese toxicity in children and adolescents (aside from water sources).

The Academy86 provided a risk assessment, concluding that, “The risk of an adverse effect resulting from excess intake of manganese from food and supplements appears to be low at the highest intakes noted above.” (It is noted that manganese in water is absorbed more readily and carries with it a higher risk.) Also, the Academy86 inserted its usual statement regarding the possibility of studying this ingredient at dosages that exceed the UL: “…intake above the UL may be appropriate for investigation within well controlled clinical trials.” The World Health Organization83 panel on trace elements and human health expressed little concern about toxicity. In fact, they stated that “Manganese is often considered to be among the least toxic of the trace elements when administered orally.” Industrial exposure seems to account for the only reported cases of human toxicity. All the evidence seems to indicate that manganese deficiency is a far greater problem than manganese toxicity. In our opinion, the level in the target study dose of DEN (9.6 mg/day) is below the (no-observed-adverse-effect level) NOAEL of 11 mg/day and far below the lowest-observed-adverse-effect level (LOAEL) of 15 mg/day to be of concern for possible neurotoxicity or liver damage.

## Website

Research indicates that the percentage of New Zealanders connected to the internet has increased substantively over the past decade. A 2012 report from Statistics New Zealand indicated that 4 out of 5 homes had access to the internet and one-third of households accessed the internet via a mobile phone (Household Use of Information and Communication: 2012, Statistics New Zealand). A more recent report generated by Research NZ indicated that 72% of all New Zealanders own a laptop and 70% own a phone with internet capabilities (46% increase from 2012). Given this information, this trial will be administered via the internet, with the development of a study website. The World Internet Project showed a self-reported access rate to the internet in NZ of between 91-93%; however, we are willing to visit with families who do not have access to internet or capacity to complete forms online to ensure that this study is accessible to as many whānau who need assistance. On the website information will be available regarding dosage, side effects, what to do in the case of adverse events and contact details for the PI. Participants will be offered the option of signing up for email/text reminders regarding taking their dose and completing the bimonthly progress monitoring scales. All website pages information appears in Appendix B.

### Managing risk using website

Both the intake questionnaires and the weekly progress monitoring questionnaires will

include a question monitoring risk.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | I don’t have any thoughts of killing myself | I have thoughts of killing myself, but I would not do it | I would like to kill myself | I would kill myself if I had the chance |
| In the past week which statement best describes your thoughts  | 0 | 1 | 2 | 3 |

Directly below this question, there is information for crisis support services available and an explicit instruction for participants to access these supports if they cannot keep themselves safe. Participant questionnaires, including this risk question, are reviewed by the monitoring psychologist within 24 hours of completion and further follow up with the participant will be completed if a participant scores a 2 or above on risk question. Information about crisis support services will be available at all times on the website. Should participants experience increased suicidality during the study, they will not be excluded from receiving the micronutrients if they would like to continue. This will be considered on a case- by-case basis in consultation with the study physician. A letter will also be written to the GP/counsellor if participants’ risk changes throughout the study.

## Measures

Participants will be monitored weekly via the website and will answer a range of questions about physical and mental functioning (see measures below). A parent will also be asked to complete questionnaires about their child. The schedule for completion of questionnaires is listed in Appendix C.

### Primary Outcome Measures

1. Clinical Global Impression: The CGI-I is widely and successfully used in clinical trials to measure subjective change and have been demonstrated to be clinical different and useful when compared to clinician ratings of change.87 88 At the conclusion of each phase, the monitoring clinician will review the participants’ outcome measures, talk to the families, and then make an estimation of improvement, on a 7-point scale from very much improved to very much worse. Responders will be identified as those with a rating of much to very much improved. Researchers rate change on a variety of area of function, including energy, mood, anxiety and general functioning.
2. To assist with the CGI-I rating, the Clinician-rated Temper and irritability Scale will be used (CL-ARI).89 This measure systematically evaluates the frequency, duration (ranging from mild to severe), and intensity of temper outbursts, irritable mood from mild to severe, and impairment associated with these behaviours and mood. The total sore ranges from 0-100. The measure will be administered at a minimum of baseline, end of RCT, end of OL.
3. The Emotion Dysregulation Inventory (EDI): The EDI90 will be used as a screening tool as well as for monitoring. It has two subscales: reactivity and dysphoria. Each item is rated from 0 (not at all) to 4 (very severe). A score greater or equal to 10 (on a scale 0-28) on the EDI Reactivity subscale will be used to identify mildly to severely dysregulated kids. The scale is typically completed by an observer (parent) but can be modified for self-referrals.

### Secondary Outcome Measures

*Participant-rated measures:*

The Affective Reactivity Index (ARI)

The ARI will be used as a baseline tool as well as for monitoring.91 92 A score above 2 (on a scale 0-12) on the self-report version is used to identify dysregulated kids or a score above 3 on the parent report. The scale contains 6 items related to feelings and behaviours specific to irritability and 1 item related to impairment. There is a parent and self- report version. They ask about presence of symptoms over the past week.

The Kessler psychological distress scale (K10)

The K10 comprises ten questions about psychological distress and has been successfully used with children and adolescents.93 94 It is designed to quantify the frequency and severity of anxiety- and depression-related symptoms experienced in the four weeks prior to screening. Each of the 10 questions is scored 1 (none of the time) to 5 (all of the time) and scores are summed to provide a total K10 score. The lowest possible score is 10 and the highest possible score is 50. A cutoff of 25 identifies moderate distress. It will be completed by the adolescent. Only those who score above 25 will be included as part of the POM analyses. Including the K10 will allow us to determine how representative the population is relative to the NZ population. It will be given only at switch points.

Generalised Anxiety Disorder 7-Question Scale (GAD-7)

The GAD-7 is a seven-item self-report questionnaire that measures the key diagnostic components of Generalised Anxiety Disorder and has been used in high school students to assess anxiety.95 96

Brief Resilience Scale: (BRS) The Brief-Resilience Scale intends to measure one’s ability to bounce back or recover from stress.97 These notions of ‘bouncing back’ and recovering from stress are closest to the original meaning of resilience. The Brief Resilience Scale is a 6-item scale that measures responses to the following statements:

* 1. I tend to bounce back quickly after hard times.
	2. I have a hard time making it through stressful events.
	3. It does not take me long to recover from a stressful event.
	4. It is hard for me to snap back when something wrong happens.
	5. I usually come through difficult times with little trouble.
	6. I tend to take a long time to get over setbacks in my life.

Scoring is measured on a 5-point scale, adding the responses on all six statements with possible ranges from 6-30. Item responses range from: strongly disagree (1) to strongly agree (5).

Modified Participant Global Impression (PGI-I)

Participants will be asked to rate how much they thought their mood, anxiety, stress, energy and overall functioning has changed since they started the trial. The PGI-I uses a 7-point scale from 1 (very much improved) to 7 (very much worse). Given the reduced face-to-face contact in this trial, this has been modified for participants to give a subjective rating of their own perceived change.

Strengths and Difficulties Questionnaire:

The SDQ has been developed for use for young people 11-17 years. The questionnaire assesses across a number of areas of functioning, including emotional, behaviours, peer problems, prosocial behaviours, hyperactivity and conduct problems.98

The paediatric quality of life enjoyment and satisfaction questionnaire

The PQ-LES-Q is a quality of life self-report measure designed specifically for use in children and adolescents 12-17, covering 15 areas (e.g., peer and family relationships, energy, getting things done) and ratings are made on a five point scale from “very poor” to “very good.”99

Children’s Revised Impact of Events Scale (CRIES)

The Children’s Revised Impact of Event Scale (CRIES-13) is a brief child-friendly measure designed to screen children at risk for Post-Traumatic Stress Disorder (PTSD), developed by the Children and War Foundation and based on adapting the adult scale Impact of Events Scale- Revised for children 8 to 17.100 Given the number of traumas adolescents face these days in NZ, it is an important construct to try to capture in this sample. It has good face and construct validity, a stable factor structure, correlates well with other indices of distress, and has been used to screen very large samples of at-risk-children following a wide range of traumatic events. It has been applied in a variety of cultures as post-traumatic stress symptoms in children are more similar than they are different from one culture to the other. There are 8 items that are scored on a four point scale: Not at all to Often. There are three sub-scales: Intrusion, avoidance, and arousal. A cutoff score of 30 on the CRIES-13 identifies those who likely have PTSD.

The Perceived Stress Scale (PSS): this self-report scale measures the degree to which one

experiences psychological stress.101 It has been used successfully to measure stress in adolescents.102 Items were designed to assess feelings of being overwhelmed and being unable to control or predict events in one’s life. This scale may be administered to high school students and adults who have at least a junior high school education. The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by circling how often you felt or thought a certain way. (Response range from never to very often).

Body mass index-BMI -height and weight will be asked for before and after RCT.

Pill adherence: this brief measure asks the child/parent to rate his/her adherence to taking the capsules since the last visit. Any problems with swallowing the capsules or remembering to take them are identified and discussed.

*Parent-rated measures:*

Strengths and Difficulties Questionnaire (SDQ)

The SDQ (above) has a parent form and assesses positive and negative psychological attributes measuring both problem behaviours and competencies.103

Modified Parent Global Impression (PGI-I)

Parents will be asked to rate how much they thought their child’s mood, anxiety, stress and energy changed since they started the trial from 1 (very much improved) to 7 (very much worse).

Parent Target Problem (PTP)

Nomination of one or two of child's biggest problems, and reports frequency, duration, impairment, and examples. Rated on:

1= problem resolved or extremely improved

2= much improved

3= definitely improved

4=minimally improved

5 = no change from BL

6=minimally worse

7=definitely worse

8 = much worse

9 =extremely worse

In addition, questions developed by Gabrielle Carlson about anger will be asked.

*Clinician-Rated measures:*

Columbia Impairment Scale: The Columbia Impairment Scale (CIS) is a 13-item scale that can be administered by a lay interviewer to provide a global measure of impairment.104 The 13 items tap 4 major areas of functioning: interpersonal relations, broad psychopathological domains, functioning in job or schoolwork, and use of leisure time. Items are scored on a spectrum ranging from 0 "no problem" to 4 "a very big problem." The CIS score obtained through parent interviews appears to provide a useful global measure of impairment. It has been validated for use with children and adolescents.105 There is a parent and youth version.

Children’s Global Assessment Scale (CGAS) The CGAS106 is used by the clinician to assess the overall severity of disturbance in children. It is a single numerical scale from 1 – 100.

Clinical Global Impressions Severity Scale (CGI-S)The CGI-S is a single-item rating of the clinician’s assessment of the severity of symptoms107. Its goal is to allow the clinician to rate the efficacy of treatment, change over time and the severity of illness.

ADHD Rating Scale IV – (ADHD –RS)– clinician version108 109. The ADHD Rating Scale-IV is an instrument for identifying ADHD symptoms in children and adolescents and for assessing treatment response. Containing 18 items, the scale is linked directly to DSM-IV diagnostic criteria for ADHD.

### Further Information

The Child and Adolescent Behavior Inventory

The CABI questionnaire consists of 75 questions to parents/caregivers.110 111 These explore a wide range of problem areas: somatic, anxiety, phobias, obsessive-compulsive, insecurity, depression, irritability, oppositional-defiant, conduct, impulsivity, hyperactivity, attention deficit, reality evaluation, social relationships, sphincter control, bulimia, anorexia, sex interest, smoking, alcohol and substance abuse, school performance and being bullied. In the CABI, some problems that can belong to two or more disorders are grouped separately: “sleep problems”, located among somatic symptoms, according to DSM-5 can be part of both depression and generalized anxiety; “irritability”, held as a separate subscale, can be part of depression, generalized anxiety and oppositional defiant disorder. This questionnaire can assist with classifying the sample.

Demographic information will be collected at baseline, including socio-economic status, socio-economic deprivation, ethnicity, level of education and psychiatric family history. The SES of each participant will be estimated using the New Zealand Socioeconomic Index of Occupational Status (NZSEI112) and deprivation will be assessed using the NZDep2013113. Food insecurity will also be assessed. Participants will also answer bimonthly questions on additional medication prescribed (e.g. antibiotics), visits to their GP, attendance at a hospital/afterhours clinic and reasons for their presentations (physical health, mental health), deliberate self-harm (frequency, intensity, duration and onset) any adverse events (physical symptoms which may be attributed to the capsules), and an estimate of substances consumed during the week, including alcohol and nicotine/e-cigarettes/illegal drugs/vaping.

Dietary Screening Tool (DST114): The DST is a 25 item self-report questionnaire that assesses dietary intake and identifies those at nutritional risk. The parent can complete on the child’s behalf.

Food Insecurity Assessment (New Zealand Health Survey, FIA): The FIA is an eight item self report measure that assesses various aspects of food insecurity such as access to food, variety of food purchased and budgeting regarding food. Parents will complete this on behalf of the child.

Acceptability: Parents and participants will rate the acceptability of the treatment after the completion of the study and at the 12 month follow-up.

Blinding question: To measure the integrity of the blind, at week 8, the monitoring psychologist will ask the parent/child whether they think their child received active or placebo treatment during RCT. The monitoring psychologist’s response will also be recorded.

Adverse event monitoring

The Side-Effect Checklist (ASEC115) and further questions to participants will assess side effects, safety & adverse events of the intervention. The ASEC has been adapted for the purposes of this study to remove references to anti-depressants. Side effects will be assessed weekly during the RCT and open label phase.

Questions about adverse events will be asked at each weekly monitoring. Should a participant indicate via the website/App that they are experiencing an adverse event, the monitoring psychologist who reviews the questionnaires will contact the participant within 24 hours. Any concerning adverse events will be discussed with the study physician and the co-investigators. Some participants may need to titrate their dose more slowly and this will be discussed with the participant, the study physician and the principal investigator. In the case of a serious adverse event, the investigators will consider whether termination of the study is necessary.

## Compliance

Compliance to the intervention will be assessed every two weeks whereby they will be asked to indicate how many doses they have missed over the last two weeks. The researchers will discuss strategies to overcome problems with adherence if needed. Compliance will also be determined by the number of unused or missed capsules reported via photo on the website or app at the end of the trial.

If a participant misses their weekly questionnaires, they will be sent a text reminder, asking them to complete their questionnaires in the next 24 hours. If they do not complete their questionnaires within this time frame, another text will be sent to them asking them to indicate via email reply or phone call to the principal investigator if they have chosen to stop participating in the study and why this might be. A variety of common reasons will be given e.g. Not able to take the pills, not wanting to take the pills, don’t think the intervention is working, started other medication. Participants will be asked to indicate which one applies. Should this include adverse events, the principal investigator will call and review the participant within 24 hours. If no contact can be made with the participant via email, the principal investigator will call the participant and/or caregiver to review their progress within 72 hours of sending the final email and assess their reasons for ending their participation in the study.

# Sample size and power calculations

Based on previous studies that examined the treatment of emotional dysregulation using broad-spectrum micronutrients compared with placebo in children with ADHD39 (*d*=0.66), an effect size of *d*=0.5 was chosen.116 As such, the total number of participants required would be 126 (63 in each group). Attrition rates in these types of studies can range between 3-19%.29 117 118 Allowing for a 20% attrition rate, the adjusted number-per-treatment condition would be 75 and total sample size required would be 150 randomized 1:1 to the two conditions.

# Data analysis Plan

### Datasets for Analysis

All data will be analysed on an intent-to-treat and per-protocol populations. All continuous measures will be analysed using generalised linear mixed-effect regression models and effect sizes will be reported using Cohen’s *d*. Clinically significant outcomes will be determined by calculating the Reliable Change Index.

The intention to treat (ITT) population for the primary analyses of outcomes will include all randomised participants. For the ITT population, if there is no exit effectiveness evaluation then the last evaluation will be carried forward, this may be the baseline assessment in some circumstances. This is also how missing data will be handled. For the ITT analyses, participants are analysed according to their randomly allocated treatment group irrespective of the actual treatment received.

The safety population, which will be used for all safety analyses, will include all participants who have taken at least one dose of study product. Treatment groups will be defined as the actual treatment received irrespective of randomised treatment.

The per-protocol (PP) population for each efficacy measure will include all participants who take at least 80% of the allocated pills, have no significant protocol deviations and have all appropriate assessments relevant to the outcome.

### Observation Period

The observation period for the efficacy endpoints from the double-blind phase will be from the baseline (pre-intervention) up to the 8 week assessment.

The observation period for the efficacy endpoints from the open-label extension will be from the 8 week (end of double blind phase) up to the 16 week assessment, end of open label phase.

### Demographic Data Analysis

Demographic characteristics will be compared across the treatment groups using independent samples *t*-tests in order to test for potential failures of randomization. For purposes of group statistical inference, data will be analysed first on an intention-to-treat basis using the last observation carried forward method and second on a per-protocol analysis that includes those who complied with and completed the protocol.

### Primary Outcome Measures

For the primary outcomes, the repeated measures of the outcome variables will be modelled using generalized linear mixed effects regression models. These models will permit the testing of differences between the micronutrient group and the placebo group over the course of the trial. Baseline scores on the primary outcome measures will be used as a covariate factors, as well as measures of demographic characteristics. The pooled mean scores (and standard deviations) over the course of the trial on each of the primary outcomes will be used to compute estimates of effect size (Cohen’s *d*). For the CGI-I, the groups will be compared at end of study treatment using t-tests. The CGI-I will also be reported as responder/non-responder by group using chi-square analyses/odds ratios. A score of 1 or 2 (very much improved and much improved) will be used to identify responders.

### Secondary Outcome Measures

For secondary outcomes, linear mixed effects models will also be used for those variables that were tracked over time. For data from randomized trials, this modelling procedure allows the researcher to fit individual-specific slopes and intercept terms, which can account for individual variability in treatment response more precisely than methods based on Analysis of Variance. The statistical test for differences between groups will be an F test. For secondary outcomes, linear mixed effects models will also be used, to explore the relationship between other psychiatric difficulties and the micronutrient intervention.

### Safety Outcomes

Treatment-emergent adverse events and risk events from the double-blind phase will be individually listed by randomized group, indicating the preferred term, date of onset, date resolved, severity, relatedness, frequency, action taken in relation to study medication and whether the adverse event is serious. The incidence of more common adverse events (greater than 5%) or adverse events of special interest may also be summarized for each randomized group.

Given the low risk associated with using micronutrients, the investigators will act as an internal data safety monitoring committee.

### Further Analyses

As a first step in determining the clinical significance of the outcomes on primary and secondary variables the Reliable Change Index119 will be determined for each measure using the best available psychometric norm data for the measure. Changes must exceed the relevant RCI before clinical significance of the outcome is addressed.

Patterns of change over time within and between groups will be further examined at the individual as well as the group level using modified Brinley Plots.119-121 These plots permit the simultaneous display of the extent of each individual’s change over time on each measure within the context of the RCI boundaries (making both improvement and deterioration available to inspection) supplemented by information about group means and the 95% Confidence Intervals (95%CI) of the means at each time point. The Concordance Correlation Coefficient122 will also be used to compare the extent of change produced by the treatment relative to the placebo on each measure.120

### Procedure for amendments to the Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that some scheduled analyses may not be performed. In addition, study observations or analysis results may suggest the need for additional statistical analyses of the collected study data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final study report.

# Anticipated costs

1. Pill organiser to help with compliance with taking doses: $15.00/participant

Courier bag for initial dose (size 3 bag $6.00- 255mm x 325mm)

Subsequent doses (per participant) (size 2 bag $4.50- 90mm x 280mm)

Four track and trace (3$ each): $12.00

Each participant receives one pill organizer, one size 3 bag and three size 2 bags throughout the trial plus 4 track and trace: $46.50/participant.

75 participants in first year ($3488), 75 in second year ($3488): total **$6976.00**

1. Web development and maintenance: **$10,000 over 2 years**
2. Advertising budget – social media, radio, GP liaison, printing brochures: **$10,000** over 2 years
3. Randomization: $8/per participant: $600 in first year, $600 in second year: total **$1200**
4. Clinical psychologists or child and family psychologists to monitor and oversee participants (these psychologists are also considered part of the researcher team): $300/participant: $22,500 for first year (75 participants), $22,500 for second year: total **$45,030** (plus salary related costs). Psychologists are required to monitor the participants because of the high risk associated with these youth. Estimated amount of time per participant is 4-6 hours. There is a high risk for self-harm and suicidal ideation that will need to be appropriately managed throughout the trial, possibly requiring referrals to other local services as necessary.
5. Clinical supervision and trial consultant: one hour per week for 48 weeks @ $130.00/hr: $**12,480** (plus salary related costs).
6. Research coordinator. We need to hire a coordinator to manage progression through the study, including sending out pills, sending reminders to complete questionnaires, etc. We estimate that this will require 0.2FTE, @40.00/hour, $17,000/year. **$34,000** (plus salary related costs).
7. Publication charges: **$3,000.** Open access journal costs can vary from $2000-4000/article.
8. Health economist to assist with statistics on cost savings: **$10,000** (plus salary related costs)
9. Top up credit for phones or vouchers: In order to participate, our participants will need phone credit: $20/month for text/calls/data. Given participation is about 4 months: $80/participant: first year ($6000), second year ($6000): $**12,000**
10. Koha to organizations to assist with recruitment (morning tea, food baskets): **$2000.00**

# Ethics

Participants may be discontinued from the study if they show adverse symptoms of either a physical or psychological nature, in response to the micronutrients. Adverse symptoms will be monitored on a bimonthly basis and the reporting of mental or physical adverse symptoms will be responded to within 24 hours of reporting. If a participant’s psychological state deteriorates to a clinically significant degree during the trial, the investigators will discuss with the participant the possibility of withdrawing from the study, or may decide that the participant should be withdrawn. Participants may request to be withdrawn from the study or withdraw consent at any time without penalty. If a participant, for any reason, requires treatment with certain therapeutic agents (i.e. antibiotics), it will be noted what they are taking and for how long. If a protocol exclusion violation has occurred (i.e. participant requires psychiatric medications), his or her involvement will be discontinued. If any patient is discontinued from the trial, we will carry out follow-ups to ensure participant well-being.

Safety information regarding micronutrients generally and DEN more specifically have been summarised previously. The most common adverse effects of micronutrient intervention include nausea and headaches. These difficulties can be avoided or reduced by taking the capsules on a full stomach, and it will be made clear to participants to always take their capsules with food. Additionally, slow titration can also prevent these side effects, hence participants will begin with three (3) capsules per day and increase gradually to the full dose. If ongoing nausea continues to be reported, participants will be advised to freeze the DEN product, which has been recommended by the manufacturer to also reduce nausea.

All participants will be required to provide informed consent prior to participation in the study. This will be completed via the website and will also be collected via the phone contact prior to participants entering the study. All information collected in this study will remain strictly confidential. Access to study information is strictly limited to the study administrator, investigators and designated laboratory staff. Confidentiality is treated very seriously by all staff involved – any information disclosed during any trial is kept in a confidential file, in a locked filing cabinet and/ or room. Data protection for the website has been carefully tested to prevent access and/or manipulation and this will be monitored throughout the duration of the study. Data collected by the website will be doubly encoded, to protect participant privacy. A professional wesbite development company has been retained to develop, test and manage the study website. All necessary legal and ethical steps will be taken to provide excellent security for data collected All data related to the study will be stored for 10 years after collection, in accordance with university regulations and the Privacy Act. With the permission of the participant, data from this study may be used in future related studies, which have received ethical approval from the Health and Disability Ethics Committee and the Human Ethics Committee at the University of Canterbury. However, all information will be kept as group data; forms will be coded and names removed so that no individual participant can be identified. Confidentiality will be respected and no material which could personally identify any participant will be used in any reports on this study. However, in cases where we are concerned about the safety of the participant, or of others, we may decide to breach confidentiality.

The Māori Research Advisory Group at the University of Canterbury has been consulted regarding this type of research and have given their approval to conduct nutritional research with Māori. A summary of this proposal was reviewed by the Māori Research Advisory Group as part of the HRC application. The group and other cultural support for investigators and participants is available for further consultation throughout the project. Furthermore, the primary investigator and co-principal investigator have been actively involved in developing cultural awareness including attending appropriate hui and cultural activities at their respective workplaces, attending Treaty of Waitangi workshops and maintaining on-going cultural competency as part of registration as clinical psychologists with the New Zealand Psychologists Board. Should any participants identify as Māori, they will be asked if they would like phone contact from a *Pukenga Atawhai* during their participation in the study.

# Responsiveness to Māori

Māori are consistently over-represented in many domains of poor mental health and as the mental health workforce moves towards addressing these imbalances, it is imperative research reflects Māori participation. Studies of NZ youth show rates of serious depressive symptoms are similar between Māori (13.9%), and NZ European (12.1%), but Māori youth report considerably higher prevalence of suicide attempts (Māori 6.5%, NZ European 2.7%) and poorer general wellbeing (Māori 10.5%, NZ European 6.8%).5 Although Māori currently make up 16% of the NZ population, the Māori population accounts for 23% of our target population. As a direct result of colonization, the traditional food environment for Māori has changed substantially with serious unstudied health implications.123 Food insecurity increases the risk of depression and anxiety, possibly through the effect poor quality food has on vulnerability to illness.123 It is essential that our interventions reach those in most need and target a risk factor contributing to poor health outcomes. Barriers that can impede access to services for Māori include stigma, finances, and transport, among others. This study is designed to break down barriers that can impair access to treatment through involving both Māori and non-Māori researchers to facilitate engagement across ethnicities. All members of the team are committed to broadening their cultural lens through supervision, workshops and acquisition of language skills. Having a kaupapa Māori clinical psychologist on the team involved in the design, delivery and transmission of the results ensures that we are cultural responsive to the community and engage directly with Māori health providers. Previous research has shown that this nutritional approach has been very appealing to Māori participants with percentage of Māori participants in our studies higher than NZ census figures. Micronutrient treatment delivered alongside online intervention presents as a novel, acceptable and cost-effective option to reduce the burden of mental illness

# Research Site

Although the participants can come from anywhere in NZ, the study will be primarily run through:

Mental Health Nutrition Laboratory, room 465

University of Canterbury

Private Bag 4800

Christchurch 8140, NZ

We may decide to have psychologists from other parts of NZ assist with data collection in order to make sure there is someone local for those participants. However, the study intervention will be mailed from Christchurch.

## **Investigators**

Prof. Julia Rucklidge: Principal Investigator (PI), Prof Rucklidge will provide support and supervision to researchers on the project, being available at all times, should any difficulties arise.

Meredith Blampied: Co-investigator and supervisor - Ms Blampied will oversee the running of the study and provide supervision to the monitoring psychologists.

Leona Manna: Ms Manna is a Māori clinical psychologist and will be involved in monitoring participants.

Dr Sue Bagshaw: Dr Bagshaw is a GP who specializes in the treatment of mental health problems in adolescents. She runs a Youth Hub and will partixipate in recruitment and liaison with GPs.

Prof Roger Mulder: Study physician/psychiatrist. Address clinical issues/adverse events as they arise.

Professor Joseph Boden: Professor Boden will provide statistical consultation and data analysis for the study. He has been consulted on the design of the study.

## Data Ownership

All data associated with the study, and all reports resulting from said data, will be owned by the authors.

# Risk Management

The responsibility for risk management (i.e. managing psychological symptoms) of the project will be undertaken by the monitoring psychologist along with Meredith Blampied (registered clinical psychologist) and Prof Rucklidge (registered clinical psychologist) in consultation with Dr Bagshaw and Dr Mulder. Any adverse effects will be discussed with Dr Bagshaw/Dr Mulder and whether further investigation is required, Dr Bagshaw/Dr Mulder may contact the participant as required. Prof Rucklidge will be consulted on all aspects of the project, and will therefore be aware of any foreseeable risks which can then be reviewed and cleared with the study physician. Any serious adverse effects will be reported to the ethics committees (HDEC and Human Ethics Committee at UC) and to the Data Monitoring Committee. The trial will be terminated if serious adverse effects known to be caused by the nutrients occur and/or if there is no evidence of any effect of the intervention.

# Time Table

|  |  |
| --- | --- |
| *August-December 2020* | Ethics and SCOTT applicationsDevelopment of the website |
| *February 2021-October 2023* | Collect data from 150 participants |
| *November 2023-December 2023* | Data analysis and writing up for publication |
| *January 2024-December 2024* | Collect one-year follow up data from all participants.  |

# Resources

Study formulas & capsules packaging will be donated by Hardy Nutritionals, Canada. Professor Julia Rucklidge has received an HRC Explorer Grant which covers the majority of the costs associated with this study. She also receives generous philanthropic donations to support her research and these funds can be used for pharmacy costs and participant reimbursement. Applications for external funding may also be required to cover any remaining costs.

# Appendices

## Appendix A: Ingredients: Daily Essential Nutrients and Placebo

|  |  |  |
| --- | --- | --- |
| **Ingredients:** | **1 capsule** | **12 capsules** |
| Vitamin A (as retinyl palmitate) | 144 mcg | 1728 mcg |
| Vitamin C (as ascorbic acid) | 50 mg | 600 mg |
| Vitamin D (as cholecalciferol) | 6 mcg | 72 mcg |
| Vitamin E (as d-alpha tocopheryl succinate & mixed tocopherols) | 16.2 mg | 194.4 mg |
| Vitamin K (75% as phylloquinone; 25% as menaquinone-7) | 10 mcg | 120 mcg |
| Thiamin (as thiamine hydrochloride) | 5 mg |  60 mg |
| Riboflavin | 1.5 mg | 18 mg |
| Niacin (as niacinamide & nicotinic acid) | 12 mg | 144 mg |
| Vitamin B6 (as pyridoxine hydrochloride & pyridoxal 5-phosphate) | 5 mg | 60 mg |
| Folate (as L5-methylfolate calcium & calcium folinate) | 75 mcg | 900 mcg |
| Vitamin B12 (as hydroxocobalamin acetate & methylcobalamin & adenosylcobalamin) | 75 mcg | 900 mcg |
| Biotin | 90 mcg | 1080 mcg |
| Pantothenic acid (as calcium D-pantothenate) | 2.5 mg | 30 mg |
| Choline | 16 mg | 192 mg |
| Calcium (as chelate) | 110 mg | 1,320 mg |
| Iron (as chelate) | 1.15 mg | 13.8 mg |
| Phosphorus (as chelate) | 70 mg | 840 mg |
| Iodine (as Atlantic Kelp) | 17 mcg | 204 mcg |
| Magnesium (as chelate) | 50 mg | 600 mg |
| Zinc (as chelate) | 4 mg | 48 mg |
| Selenium (as chelate) | 17 mcg | 204 mcg |
| Copper (as chelate) | 0.6 mg | 7.2 mg |
| Manganese (as chelate) | 0.8 mg | 9.6 mg |
| Chromium (as chelate) | 52 mcg | 624 mcg |
| Molybdenum (as chelate) | 12 mcg | 144 mcg |
| Potassium (as chelate) | 20 mg | 240 mg |
| **Proprietary blend ingredients: Great Salt Lake minerals, mixed tocopherols and mixed tocotrienols, Alpha-lipoic acid, Inositol, Acetylcarnitine (as acetyl-L-carnitine hydrochloride), Grape seed extract, Ginkgo biloba leaf extract, Methionine (as L-methionine hydrochloride), Cysteine (as N-acetyl-L-cysteine), Boron (as chelate), Vanadium (as chelate), Nickel (as chelate)****Other ingredients: vegetarian capsule (hypromellose, titanium dioxide), microcrystalline cellulose, magnesium stearate, silicon dioxide** |

**Ingredients: Placebo**

|  |  |  |
| --- | --- | --- |
| **Placebo Ingredients** | **Per capsule** | **12 capsules** |
| Yellow corn masa flour | 554.4 | mg | 6652.8 | mg |
| White rice flour | 45.25 | mg | 543 | mg |
| Caramel colour powder (Class 1) | 20.16 | mg | 241.92 | mg |
| Magnesium stearate | 4.25 | mg | 51 | mg |
| Microcrystalline cellulose | 4.25 | mg | 51 | mg |
| Silicon Dioxide | 1.58 | mg | 18.96 | mg |
| Riboflavin | 0.1 | mg | 1.2 | mg |
| Hypromellose capsule, size '00' white (contains HPMC & titanium dioxide) | 136 | mg | 1632 | mg |

## Appendix B: Information contained on the study website

The study webpage will have several different portals:

Trial Information Page: www.tairora.net

This will have general information about the study, as is contained in the information pamphlets available for potential participants.

It will contain a brief explanation of micronutrient intervention, links to relevant research and briefly outline the study.

It will also have the contact details for the principal investigator but will direct potential participants back to their GP to discuss any concerns they have about their mental health and any potential participation in the study.

Community Assistance Page:

This page will have information about the prevalence of mental health problems in young people in New Zealand and will contain links to other information sites including: <http://www.health.govt.nz/your-health/conditions-and-treatments/mental-health> <https://www.mentalhealth.org.nz/>

<https://depression.org.nz/>

<http://www.healthinfo.org.nz/>

It will also explain what to do if people are worried about themselves or someone that they love and provide the following information for support and crisis services:

Youthline: <https://www.youthline.co.nz/> 0800 376 633

Lifeline (Available 24/7) 0800 543 354

Depression Helpline (Available 24/7) 0800 111 757

Healthline (Available 24/7) 0800 611 116

Samaritins (Available 24/7) 0800 726 666

Suicide Crisis Helpline (Available 24/7) 0508 828 865 (0805 TAUTOKO) Crisis Resolution Services (Available 24/7), Canterbury 0800 920 092

This crisis support information will also appear if participants endorse increased risk while completing their psychometrics.

Information and Self-Referral Page:

This page will include information about the trial (taken from the Participant Information and Consent form), brief informational blurbs about the researchers, eligibility criteria and an electronic self-referral form. The electronic referral form will ask for contact details for the potential participant. It will ask the potential participant to confirm they are not taking anti-depressant medication and will ask them to list current medication. It will require the potential participant to confirm they have reviewed the exclusion and inclusion criteria they meets these criteria. A copy of the inclusion and exclusion criteria will be available. It will also ask for height and weight and contact information for the potential participant.

Information for General Practitioners and trial referral

This page will include information about the trial (taken from the Participant Information and Consent form), the ingredients of the products used in the trial and the inclusion and exclusion criteria. The trial referral form will ask for the GP name, prescriber number and contact details, the potential participant name, date of birth, height, weight and contact details. It will require the GP to confirm they have reviewed the criteria for referral and reviewed stepped care treatment options with the potential participant.

Participant Page:

This page will require participants to create a unique log-in after completing screening with the principal investigator. It will contain all information about the trial, risks associated with participation and who to contact during the trial (see Participant Information Sheet- Consent Form). It will collect all written consent from the participant. This portal will also include access (once consent has been given) to the demographic questions and study questionnaires. Participants will also access their weekly questionnaires through this participant portal and can sign up for weekly email reminders to complete their questionnaires.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Base-****line** | **Base-****Line 2** | Wk 1-7 | Wk8 – end of RCT | Wks 9-15 | Wk16 – end of OL | 1 Yr followup |
| **CLINICIAN** |  |  |  |  |  |  |  |
| CGI-S | X |  |  | X |  | X | X |
| CL-ARI | x |  |  | x |  | x | x |
| CGI-I |  |  |  | x |  |  | x |
| C-GAS | X |  |  | X |  | X | X |
| CIS | X |  |  | X |  | X | X |
| **PARENT** |  |  |  |  |  |  |  |
| EDI | X | X | X | X | X | X | X |
| ARI | X | X | X | X | X | X | X |
| PGI-I |  |  |  | X |  | X | X |
| CABI | X |  |  |  |  |  | X |
| SDQ | X | X |  | X |  | X | X |
| PTP | X |  | X | X | X | X | X |
| DST | X |  |  | X |  | X | X |
| Adverse Events | X | X | X | X | X | X | X |
| Compliance |  |  | X | X | X | X |  |
| **CHILD** |  |  |  |  |  |  |  |
| ARI | X | X | X | X | X | X | X |
| K-10 | X | X |  | X |  | X | X |
| GAD-7 | X | X | X | X | X | X | X |
| PQ-LES-Q | X | X |  | X |  | X | X |
| HSC | X | X |  | X |  | X | X |
| SDQ | X | X |  | X |  | X | X |
| CRIES-13 | X |  |  | X |  | X | X |
| PSS | X | X |  | X |  | X | X |
| PGI-I |  |  |  | X |  | X | X |
| BRS | X | X |  | X |  | X | X |
| BMI |  | X |  | X |  | X | X |
| Side Effects /adverse events |  | X | X | X | X | X |  |
| Compliance |  |  | X | X | X | X | X |

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