Study Title: *Diet and Coaching for the Management of Attention Deficit Hyperactivity Disorder and Related Depression Symptoms: A 16 Week Randomised Controlled Intervention Efficacy Study and Wider Mechanistic Analysis*

Internal Reference Number / Short title: FAD

Ethics Ref: MS IDREC 1090731

Date and Version No: 12/01/2026 v1.1

Chief Investigator:	Prof. Michael Browning, Dept. of Psychiatry, University of Oxford
Investigators:	Ewan Houston, Dept. of Psychiatry, University of Oxford Prof. Adrian Soto-Mota, ITESM Dr. Nicola Guess, University of Oxford Dr. Amedeo Minichino, University of Oxford Prof. Ana Andreazza, University of Toronto Dr. Georgia Ede Prof. Zoltan Sarnyai, James Cook University Prof. Leanne Hodson, University of Oxford
Sponsor:	University of Oxford
Funder:	Baszucki Family Foundation Public crowdfunding
Chief Investigator Signature:	
Statistician Signature:	
Conflict of Interest Statement:	Ewan Houston owns MetPsy. Prof. Adrian Soto-Mota is an advisor for MetPsy.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

TABLE OF CONTENTS

4. APPENDIX E: Randox Sample Handling Procedures Parts 1 and 2 41

1. KEY STUDY CONTACTS

Chief Investigator	Prof. Michael Browning, michael.browning@psych.ox.ac.uk, +44 (0)1865 618316
Sponsor	University of Oxford
Funder(s)	Baszucki Family Foundation, info@baszuckigroup.org Crowdfunding campaign
Statistician	Prof. Adrian Soto-Mota, adrian.sotom@incmnsz.mx

1. LAY SUMMARY

This study explores how diet influences ADHD symptoms, mood, and mental well-being. Many people with ADHD struggle with focus, energy levels, and emotional regulation, and research suggests that nutrition might play a role in these challenges.

The study aims to understand whether dietary coaching can improve ADHD symptoms and overall mental health by comparing two different dietary approaches.

Aims of the Research

The study aims to:

- Investigate whether dietary changes improve ADHD symptoms such as focus, impulsivity, and energy regulation.
- Explore whether a low-carbohydrate ketogenic diet (KD) affects mood, productivity, and mental clarity in adults with ADHD.
- Compare the ketogenic diet with a control diet (Hormesis Diet, HD) to determine if improvements are due to diet-specific effects or general lifestyle changes.
- Assess biological markers (e.g., blood ketones, glucose, lipids) to understand how metabolism relates to ADHD symptoms.

Study Design & Methods

The study lasts 16 weeks.

100 adults with ADHD will be randomly assigned to one of two diet groups:

- Ketogenic Diet (KD) Coaching Group (low-carb, high-fat diet).
- Hormesis Diet (HD) Coaching Group (control diet, used as a comparison).

Participants will receive weekly coaching sessions (group + individual) to help them follow their assigned diet.

Participants will complete self-reported mental health and productivity assessments. Metabolic health will be monitored through blood testing.

What Will Participants Be Asked to Do?
If chosen, participants will:

- Attend an online screening call to confirm eligibility.
- Be randomly assigned to one of two dietary coaching groups.
- Follow their assigned diet for 16 weeks, with weekly coaching support.
- Complete short daily and weekly surveys about mood, focus, energy, and productivity.
- Visit a Randox clinic for metabolic testing.
- Provide feedback about their experience at the end of the study.

Participation is entirely voluntary, and participants can withdraw at any time without giving a reason.

Study Objectives & Expected Outcomes
Primary Objective:

- Measure changes in ADHD symptoms (focus, impulsivity, organisation) using standardised questionnaires.

Secondary Objectives:

- Assess whether mood and anxiety improve.
- Evaluate how diet affects productivity and energy levels.
- Analyse blood biomarkers (ketones, glucose, lipid profile, mitochondria, etc.) to identify metabolic patterns linked to symptoms.
- Examine whether performance in specific cognitive function tests is related to symptom improvement.
- Analyse microbiome from poo to identify patterns linked to symptoms.
- Examine whether personality traits can change in relation to symptoms.

Expected Outcomes:

- The study will help to determine whether diet has a measurable impact on ADHD and mental well-being.
- Findings could support new dietary strategies for ADHD management.
- Participants may gain personal insights into how nutrition affects their health and cognition.

This research will help us to understand whether diet plays a role in ADHD symptom management. Participants will contribute to novel research that could shape future dietary recommendations for ADHD and mental health.

2. SYNOPSIS

Study Title	*Diet and Coaching for the Management of Attention Deficit Hyperactivity Disorder and Related Depression Symptoms: A 16 Week Randomised Controlled Intervention Efficacy Study and Wider Mechanistic Analysis*		
Internal ref. no. (or short title)	FAD (**F**ood for **A**DHD and **D**epression)		
Study registration	ISRCTN		
Sponsor	University of Oxford		
Funder	Baszucki Family Foundation, info@baszuckigroup.org Crowdfunding campaign		
Study Design	Randomised controlled study		
Study Participants	UK based, 18 years or over, previous ADHD diagnosis, scores 14 or more on ASRS Part A, and minimum score of 5 on PHQ-9		
Sample Size	100		
Planned Study Period	Four year project, 24 week participant period		
Planned Recruitment period	Twelve month period from February 2026 to February 2027		
	Objectives	Outcome Measures	Timepoint / Timepoints
Primary	To compare the effect of implementing ketogenic diet coaching with that of implementing "Hormesis Diet" coaching in ADHD symptoms	Adult ADHD Self-Report Scale (ASRS)	Baseline, end of week 16
Secondary	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in depression symptoms To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis	PHQ-9 Blood BHB, blood glucose, mitochondrial-driven metabolic dysfunction risk testing (MitoGENE),	Baseline, end of week 16 Daily capillary BHB and BG fasted first

	Diet coaching on metabolic wellness	advanced blood lipid panel, comprehensive metabolic panel	thing in the morning - finger lancet and measured by Keto Mojo device; Venous blood draw at baseline and end of week 16 for other testing
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on self-reported ecological momentary assessments (EMAs), and how they correlate with blood BHB and cognitive function tests	EMAs for mood, energy, and clarity of thought, marked by participants from 0 to 10, 0 meaning very low 10 meaning very high. EMAs for productivity, effectiveness, and procrastination.	Mood, energy, and clarity of thought daily. Productivity, effectiveness, and procrastination weekly basis
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in anxiety symptoms	GAD-7	Baseline, end of week 16
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis	WSAS	Baseline, end of week 16

	Diet coaching in work and day-to-day performance		
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in sleep quality	PSQI	Baseline, end of week 16
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in disordered eating symptoms	EDE-Q	Baseline, end of week 16
	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in ADHD symptoms	Adult ADHD Self-Report Scale (ASRS)	Baseline, end of week 6
	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in depression symptoms	PHQ-9	Baseline, end of week 6
	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in anxiety symptoms	GAD-7	Baseline, end of week 6

	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in work and day-to-day performance	WSAS	Baseline, end of week 6
	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in sleep quality	PSQI	Baseline, end of week 6
	To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in disordered eating symptoms	EDE-Q	Baseline, end of week 6
	Safety of the intervention	Adverse events	Continuous
Exploratory	To investigate the degree to which TSH level prior to commencing the intervention relates to adherence and outcome	Blood level of TSH	Baseline
	To investigate the degree to which vitamin B12 level prior to commencing the intervention acts as a covariate or moderator	Blood level of vitamin B12	Baseline, end of week 16
	To investigate the degree to which 25-OH vitamin D level prior to commencing	Blood level of 25-OH vitamin D	Baseline, end of week 16

	the intervention acts as a covariate or moderator		
	To investigate the degree of change in the Big Five Inventory (BFI) personality test results between intervention and control groups	The Big Five Inventory	Baseline, end of week 16
	To investigate the degree of change in the Big Five Inventory (BFI) personality test results between intervention and control groups early in the intervention	The Big Five Inventory	Baseline, end of week 6
	To quantify baseline ACEs and explore whether ACE burden is associated with (i) baseline symptom severity (ASRS-A, PHQ-9) and functioning, and (ii) the magnitude of change over 16 weeks and differential response to the two dietary interventions	Adverse Childhood Experiences Questionnaire	Baseline
Mechanistic	To investigate the degree to which symptom improvement is correlated with improvement in metabolic wellness	Blood BHB, blood glucose, mitochondrial-driven metabolic dysfunction risk testing (MitoGENE), advanced blood lipid panel, comprehensive metabolic panel	Daily capillary BHB and BG fasted first thing in the morning - finger lancet and measured by Keto Mojo device; Venous

			blood draw at baseline and end of week 16 for other testing
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on the microbiome	Stool samples (home test kits)	Baseline, end of week 16
	To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on cognitive function	CANTAB	Baseline, end of week 6, end of week 16
Intervention(s) ● IMP(s) ● nIMP(s) ● Other intervention(s)	None None Online one to one and group coaching on following a ketogenic diet.		
Comparator	Online one to one and group coaching on following The Hormesis Diet. Giving access to the online Hormesis Diet resources.		

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigators Brochure
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions

2. BACKGROUND AND RATIONALE

ADHD & Depression

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder worldwide in children[1]. Frequently persisting to adulthood[2], childhood-diagnosed ADHD affects an estimated 2.8% of the adult population worldwide, with symptomatic adult cases undiagnosed in childhood estimated to be 6.8%[3] of the adult population worldwide. Pharmacological and non-pharmacological interventions exist for ADHD with varying degrees of efficacy and risk[4,5]. Pharmacological treatment has the best proven efficacy, which is high in children and medium in adults[6]. With ADHD medication periodically and currently in short supply worldwide[7,8] there is a need for testing of novel interventions.

Major depressive disorder (MDD) has recognised pharmaceutical, somatic, and psychological treatments with a mixture of efficacies[9,10]. Most therapies for MDD are unsuitable for long term prevention, early intervention, and often for long term treatment, due to serious side effects or cost. MDD is accompanied by lower cognitive function, a set of symptoms also prevalent in ADHD, and the two disorders can be hard to distinguish clinically, from individual MDD or ADHD, when comorbid[11]. Up to 40% of patients with ADHD are comorbid with major depressive disorder (MDD), and the presence of both disorders is associated with a higher level of treatment resistant depression (TRD) when compared to MDD without ADHD[12]. An increased level of depressive symptoms, not reaching the diagnostic criteria for MDD, is higher still[13]. Standard pharmacological ADHD treatment may decrease the ADHD-related resistance to antidepressants[12], but work needs to be done to understand the underlying mechanisms of the relationship. In this study participants with a

diagnosis of ADHD and increased level of depressive symptoms (as defined by a score of five or higher on the PHQ-9) will be recruited.

Ketogenic Diet Intervention

Ketogenic diets have been studied for more than 100 years for neurological disease, particularly epilepsy, and have been shown to be effective, particularly in children, where they are most studied[14]. There are compelling reasons to suggest that a ketogenic diet may be effective in treating other neurological and psychiatric disorders[15], and some case studies and small studies showing early promise in this supposition, including for MDD[16]. These initial investigations suggest accruing benefit of the diet up to 16 weeks, which is why that duration has been selected in the current study. ADHD symptoms have not been studied in relation to ketogenic diet.

There are several proposed mechanisms for the efficacy of the ketogenic diet in neurological and psychiatric disorders. Several relevant pathological states e.g. cerebral glucose hypometabolism, insulin resistance, neurotransmitter imbalances, mitochondrial dysfunction, oxidative stress, and inflammation can be ameliorated by ketogenic diets, which are known to improve mitochondrial energy metabolism, inflammatory processes, oxidative stress, monoaminergic activity, and progression of neuro-degeneration[17]. Using a ketogenic diet has been shown to improve cognitive function, both working memory and speed of processing[18]. Beyond comorbid insulin resistance, MDD medications frequently negatively impact metabolism[19,20] (although on average accompany a slight improvement in cognitive functioning[21]). Carbohydrate restriction and ketosis have accompanied better metabolic health, including improved mitochondrial function, a halt or reversal of kidney disease, and sustained blood sugar control with less medication[22–24]. Conflicting evidence exists over the cardiovascular risk of eating a high fat low carbohydrate diet[25]. Both clinical long term carbohydrate restriction, and short term ketogenic diet in a pilot study for severe mental illness, have been observed to accompany a reduction in cardiovascular risk[26,27]. Elevated low-density lipoprotein (LDL) is sometimes raised on a ketogenic diet, which may imply greater cardiovascular risk in some people, though evidence on whether LDL levels go up on a ketogenic diet are conflicting[25]. A phenotype is emerging of leaner adherents to low carbohydrate and ketogenic diets who respond with higher LDL but lower overall cardiovascular risk, potentially inferring a non-pathological explanation for some instances of higher LDL in lean individuals on low carbohydrate or ketogenic diets[28].

This research proposes a novel intervention, combining a ketogenic diet and coaching support, online over Microsoft Teams, with a qualified health coach, to address ADHD and to understand ADHD's cognitive functioning with respect to standard depression testing. Ketogenic diet studies have previously shown low adherence without support, including a 94% dropout rate by the end of one study in depression[29], and up to 77% dropout rate for using the KD in adult drug-resistant epilepsy[14]. There is a call to furnish studies for the KD in mental health with both behaviour change support and specific KD domain knowledge in order to improve adherence[30]. In one study where this support was offered, adherence rate was high, with 91% of readings throughout the study showing

the presence of blood ketones[31]. This research aims to explore the impact of this integrated approach on symptomatology, daily functioning, and neurobiological markers.

Study Design & Participants

This 16 week study will recruit 100 people previously diagnosed with ADHD. They will be randomised into two equal-sized groups. Coaching will be provided to the intervention group on implementing a ketogenic diet (KD). Symptoms of depression will be a secondary outcome. The study will not specify a depression diagnosis, but will stratify randomisation for people with high/low depression scores.

In parallel, a control group will receive online coaching sessions with a dietitian providing healthy eating advice in the guise of a fictitious diet called the Hormesis Diet (HD). The invented scientific rationale of the HD is that what is unhealthy to eat in large quantities can provide health benefits in small quantities, and that evidence is emerging for ADHD and depression that a little bit of what's bad for you is actually good for you. Thus the HD diet will recommend some plant compounds like lectins, saponins, and phytochemicals, and also allow the inclusion of small amounts of sugar, flour, and modern oils. These compounds are common in the modern diet, and will likely already be being eaten. Therefore, only a small special emphasis has to be made on particular and common foods that contain these so-called "hormetic" properties. The control group will be given access to a website hosted by the University of Oxford detailing the fictitious "benefits" of the HD and how best to implement it, including dietary resources designed by our team. This control group aims to account for the influence of contact with the ketogenic diet coach while providing a believable rationale that controls for the placebo effect.

Symptom measurement of ADHD will be the primary outcome assessed from the Adult ADHD Self-Report Scale (ASRS). Mechanistic measures will include ketone measurements (including blood beta hydroxybutyrate (BHB) - we predict that better mood scores will correlate with higher blood BHB level), cognitive function measurements (computer based measures relevant to cognitive function in MDD and ADHD[32]), and mitochondrial function measurements. Secondary outcomes of interest include depression symptoms gauged by the Patient Health Questionnaire (PHQ-9), rates of adverse events, and effect on metabolic biomarkers.

This will be a tightly controlled experimental study investigating the initial efficacy and mechanisms of a ketogenic diet and coaching in ADHD with depression. If successful, the integrated approach could ultimately add a low risk and sustainable treatment intervention in an area where there is a dearth of such options.

3. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective		
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in ADHD symptoms	Adult ADHD Self-Report Scale (ASRS)	Baseline, end of week 16
Secondary Objectives		
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in depression symptoms	PHQ-9	Baseline, end of week 16
To compare the effect of implementing ketogenic diet coaching with that of Hormesis Diet coaching on metabolic wellness	Blood BHB, blood glucose, mitochondrial-driven metabolic dysfunction risk testing (MitoGENE), advanced blood lipid panel, comprehensive metabolic panel	Daily capillary BHB and BG fasted first thing in the morning - finger lancet and measured by Keto Mojo device; Venous blood draw at baseline and end of week 16 for other testing
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on self-reported ecological momentary assessments (EMAs), and how they correlate with blood BHB and cognitive function tests	EMAs for mood, energy, and clarity of thought, marked by participants from 0 to 10, 0 meaning very low 10 meaning very high. EMAs for productivity, effectiveness, and procrastination.	Mood, energy, and clarity of thought daily. Productivity, effectiveness, and procrastination weekly basis
To compare the effect of implementing ketogenic diet coaching with that of implementing	GAD-7	Baseline, end of week 16

Hormesis Diet coaching in anxiety symptoms		
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in work and day-to-day performance	WSAS	Baseline, end of week 16
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in sleep quality	PSQI	Baseline, end of week 16
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in disordered eating symptoms	EDE-Q	Baseline, end of week 16
To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in ADHD symptoms	Adult ADHD Self-Report Scale (ASRS)	Baseline, end of week 6
To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in depression symptoms	PHQ-9	Baseline, end of week 6
To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in anxiety symptoms	GAD-7	Baseline, end of week 6
To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in work performance	WSAS	Baseline, end of week 6
To compare the early effects of implementing ketogenic diet coaching with that of implementing	PSQI	Baseline, end of week 6

Hormesis Diet coaching in sleep quality		
To compare the early effects of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching in disordered eating symptoms	EDE-Q	Baseline, end of week 6
Safety of the intervention	Adverse events	Continuous
Exploratory Objectives		
To investigate the degree to which TSH level prior to commencing the intervention relates to adherence and outcome	Blood level of TSH	Baseline
To investigate the degree to which vitamin B12 level prior to commencing the intervention acts as a covariate or moderator	Blood level of vitamin B12	Baseline, end of week 16
To investigate the degree to which 25-OH vitamin D level prior to commencing the intervention acts as a covariate or moderator	Blood level of 25-OH vitamin D	Baseline, end of week 16
To investigate the degree to which the Big Five Inventory (BFI) personality test results change with blood BHB and cognitive function tests	The Big Five Inventory	Baseline, end of week 16
To investigate the degree to which the Big Five Inventory (BFI) personality test results change with blood BHB and cognitive function tests early in the intervention	The Big Five Inventory	Baseline, end of week 6
To quantify baseline ACEs and explore whether ACE burden is associated with (i) baseline symptom severity (ASRS-A, PHQ-9) and functioning, and (ii) the magnitude of change over 16 weeks and differential response to the two dietary interventions	Adverse Childhood Experiences Questionnaire	Baseline

Mechanistic Objectives		
To investigate the degree to which symptom improvement is correlated with metabolic wellness	Blood BHB, blood glucose, mitochondrial-driven metabolic dysfunction risk testing (MitoGENE), advanced blood lipid panel, comprehensive metabolic panel	Daily capillary BHB and BG fasted first thing in the morning - finger lancet and measured by Keto Mojo device; Venous blood draw at baseline and end of week 16 for other testing
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on microbiome	Stool samples (home test kits)	Baseline, end of week 16
To compare the effect of implementing ketogenic diet coaching with that of implementing Hormesis Diet coaching on cognitive function	CANTAB	Baseline, end of week 6, end of week 16

1. STUDY DESIGN

This study is a two-arm, parallel group, open labelled, superiority study with 1:1 allocation ratio and active treatment control.

Study data will be collected by the participants themselves, and in Randox clinics around the UK. Coaching will be provided online over video conferencing software.

Participants will be screened online shortly after application. When participants are recruited they will be required to agree to an appointment at a Randox clinic for measurements to be taken (the day that this takes place for them defines the start of week 1, the baseline). Prior to that appointment participants will be given a 45 minute introductory online group coaching session, in groups of no more than 10 participants, with the required basic information on starting the dietary strategy relevant to their assigned arm. They will also commit to completing the required self-report tests at baseline, and that they will start their dietary intervention at baseline. Every week participants in both arms will be coached online for 45 minutes, in groups of no more than 10, on implementing their

dietary strategy. This will take place at the same time each week. Participants will be encouraged to attend all of the sessions but will not be penalised if they are unable to attend one or more of these group sessions. They will have email access to their coach, and the coach will provision up to two hours per week for responding to any participant correspondence. Participants will have one to one sessions available to them every week with their practitioner, at a mutually agreed time. The first two weeks' one to one sessions will be up to 60 minutes long. From weeks 3 to 8, these sessions will be weekly and 30 minutes long. From weeks 9 to 16, these sessions will be fortnightly (i.e. at weeks 10, 12, 14, and 16), and will be 30 minutes long. Participants will be encouraged to attend all of the sessions but will not be penalised if they are unable to attend one or more of these one to one sessions. Participants will commit to completing their self-report tests at the ends of weeks 6 and 16 of the study. They will also commit to registering their daily and weekly ecological momentary assessments (EMAs). The coaching will last for 16 weeks.

Participants will agree to appointments at a Randox clinic at the end of week 16 of the study, or as close to that day as possible. Randox provides 23 testing sites across the UK allowing for wide geographical recruitment. Their protocols are uniform across all sites. Venous blood will be taken at each visit, as will various bodily measurements such as weight, and waist circumference, as per the Randox Discovery package. These provide a wide range of metabolic markers. Self-report questionnaires will be used to measure severity of ADHD and depression symptoms, as these are widely used and well understood both clinically and in research. Finger-prick ketone and blood glucose monitors will be used daily in both arms. They will provide good indication of adherence levels in the intervention arm. Justification will be made in the control arm for taking daily glucose and ketone measurements in order to mitigate the risk of unblinding control participants to the nature of the study. It will be explained that we do not aim for participants in the control arm to restrict their caloric intake, which if they did we would likely see as a positive ketone measurement. Therefore measuring is a way of monitoring this.

Baseline individual differences in gut microbiome might explain why some patients do not respond or do not tolerate the ketogenic diet. Furthermore, the gut microbiome can be modified by the diet, and this in turn can influence efficacy and tolerability outcomes. We will therefore collect microbiome samples at the start and end of the study.

At 16 weeks, participants will be asked to have a 1:1 discussion over the phone for about 30 minutes to talk about their experience in more detail. Consent will be taken to audio-record it. This is to aid understanding of what parts of the programme were helpful and how it could be improved in the future.

Sometimes people embarking on a ketogenic diet experience what is known as "keto flu", whose symptoms can include brain fog, cramping, diarrhoea or constipation, dizziness, food cravings, increased thirst, irritability, nausea, stomach ache, and trouble sleeping. Keto flu is generally mild and self limiting. Participants will be informed of the possibility of experiencing these symptoms and, where it occurs, will be encouraged to maintain adequate hydration.

1. PARTICIPANT IDENTIFICATION

1.1. Study Participants

Participants will be recruited online from social media ads, will score at least 14 on Part A of the ASRS, have a PHQ-9 score of at least 5, will be aged 18 years and over, and will live in the UK.

1.2. Inclusion Criteria

- Has a previous diagnosis of ADHD given by a UK psychiatrist.
- Scores 14 or more on Part A of the ASRS.
- Scores 5 or more on the PHQ-9 test, either with or without a previous depression diagnosis.
- Willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years and over.
- In the Investigator's opinion, is able and willing to comply with all study requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.
- English Language Requirement - Speak English to a level that allows people to understand the written information provided to them in the study.

1.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Participant who is pregnant, lactating or planning pregnancy during the course of the study.
- Significant known history of renal or hepatic impairment.
- Scheduled elective surgery or other procedures requiring general anaesthesia during the study.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
- Already on a ketogenic, low carbohydrate (under 100g per day), vegetarian, or vegan diet.
- Has been diagnosed with anorexia nervosa or bulimia.
- Low BMI (<18.5kg/m2).
- Has a bipolar disorder or schizophrenia diagnosis, or has experienced psychosis.
- Has type 1 diabetes.
- Acutely suicidal, and or has engaged in self-injurious behaviour, within the past two months.
- Active substance misuse or alcohol dependence - scoring two or more on the CAGE questionnaire, any use of class A drugs in the past three months, or any use of cannabis in the last month.
- Has serious food allergies (experiencing food hypersensitivity that leads to anaphylaxis or other severe symptoms, which may require hospitalisation or are life-threatening) or otherwise require a special diet that cannot be accommodated within a KD such as phenylketonuria.
- Treated with insulin, sulfonylureas, meglitinides, GLP-1 analogues, or SGLT2 inhibitors.
- Has gallstones, cholecystectomy, cachexia, porphyria, renal tubular acidosis, kidney stones, small bowel malabsorption or a history of pancreatitis.
- Has no access to cooking facilities or ingredients to make appropriate recipes.

2. STUDY PROCEDURES

2.1. Recruitment, Screening, & Eligibility Assessment

Participants will be recruited using social media advertising. The adverts will contain a link to the patient information sheet (PIS), and a link to apply to join the study. Nativve, a social media marketing

company which specialises in academic study recruitment, has designed and will administer the advertising campaign.

Interested potential participants will be shown an online consent form on the University of Oxford Department of Psychiatry Qualtrics platform which explains what will be asked in the screening, why it will be asked, and how the data will be used. This includes telling them that only certain people will be recruited and so providing the subsequent information will be the last thing they do in the study if they don't meet the initial criteria. Once the consent form is completed they will be initially screened for inclusion by taking Part A of the ASRS and the PHQ-8 on the same platform. If they score at least 14 on Part A of the ASRS and at least 5 on the PHQ-8, they will be screened for the inclusion and exclusion criteria on the same platform. If they don't score highly enough, or they don't meet the criteria, they will be told that they have not been selected for the study. The Qualtrics data will be stored on that system with only the study team having access. Those who pass this screening will be invited to talk with a study team member for further screening, including taking Part A of the ASRS and the PHQ-9.

2.2. Informed Consent

For this second screening and to take informed consent, participants will be contacted by phone and the study described to them. They will be sent a link to the online study consent form in advance and invited to sign and date it online during the call. The consent form will be hosted on the departmental Qualtrics system and will contain: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. Consent will include storing of blood samples for up to 10 years for potential further study, and for approach of the participant to take part in further study.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP, or other independent parties to decide whether they will participate in the study. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained on the Qualtrics system.

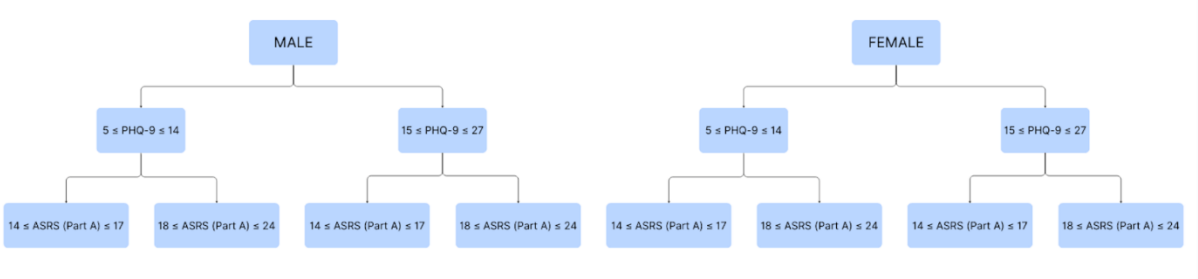
Prospective participants who have come this far will be registered then randomised. Their GP will be informed of their participation by email.

2.3. Randomisation

Eight groups will be created for stratified randomisation, see figure below. Randomisation will be stratified by biological sex, PHQ-9 score, and ASRS Part A score.

All codes will be randomised before the start of the study. 40 codes per stratum will be created to allow for some strata containing more participants due to uneven distribution in the population. Each

stratum's codes will be divided into blocks of four. These four codes will be randomised with each block containing two control group assignations, and two intervention group assignations. After a participant is recruited, their identifying number will be sent to a blinded randomiser who will fill the next slot in the appropriate stratum to which the participant belongs. The participant identifier will then be emailed to the assigned practitioner, whether that be in the intervention or control arm. In each arm there will be two practitioners, with each randomised group split evenly between the two practitioners, with each additional participant in each arm being assigned to an alternate practitioner. The assigned practitioner will then contact the participant to arrange when to begin.



2.4. Blinding and code-breaking

The central research team will be blinded to the allocation. The analysis of the study data will therefore be blinded. The central research team will receive study data exported from the Qualtrics, Randox, MyMojoHealth, and CANTAB platforms, which will all be blinded to the study allocation.

The participants and practitioners will be unblinded to the allocation.

2.5. Baseline Assessments

At home online:

- ASRS Parts A and B;
- PHQ-9;
- GAD-7;
- WSAS;
- PSQI
- EDE-Q
- CANTAB tests;
- EMAs for mood, energy, clarity of thought, productivity, effectiveness, and procrastination;
- The Big Five Inventory;
- Adverse Childhood Experiences;

- Demographic information, including age, sex, race/ethnicity, educational level, current employment status;
- Practitioners will note the level of caffeine consumption and ADHD medication level.

In a Randox clinic local to the participant:

- Randox Discovery Package measurements;
- Blood draw for MitoGENE and for further research projects

At home:

- capillary blood ketone and glucose measurements;
- stool samples

2.6. Subsequent Visits

One to one sessions: 60 minutes weekly in weeks 1–2, 30 minutes weekly in weeks 3–8, 30 minutes fortnightly in weeks 9–16. Weekly 45-minute group sessions with their practitioner and small group cohort. The practitioner will check whether participants have completed tests subsequent to baseline at the following allocated times.

At home online:

- ASRS Parts A and B - end of week 6, end of week 16;
- PHQ-9 - end of week 6, end of week 16;
- GAD-7 - end of week 6, end of week 16;
- WSAS - end of week 6, end of week 16;
- PSQI - end of week 6, end of week 16;
- EDE-Q - end of week 6, end of week 16;
- CANTAB tests - end of week 6, end of week 16;
- EMAs for mood, energy, clarity of thought - daily;
- EMAs for productivity, effectiveness, and procrastination - weekly;
- The Big Five Inventory - end of week 6, end of week 16;
- Practitioners will note the level of caffeine consumption and ADHD medication level - weekly.
- Practitioners in the control arm will ask about dietary adherence and note this - weekly.

In a Randox clinic local to the participant:

- Randox Discovery Package measurements - end of week 16;
- MitoGENE blood draw - end of week 16

At home:

- capillary blood ketone and glucose measurements - daily;
- stool samples - end of week 16

2.7. Sample Handling

Blood samples:
Randox Discovery blood draw will take place at baseline and the end of week 16. Testing and disposal of samples will take place within the Randox facilities. Some samples taken at the baseline and end of week 16 Randox visits will be used for mitochondrial testing at University of Toronto, and for further research in Oxford. Whole blood will be separated with the plasma and DNA kept. These will be stored onsite at the clinic where the blood was drawn until an internal courier ships to one of two Randox centres in England. These will be sent by courier to the University of Oxford storage facility. For Randox sample handling procedures see APPENDIX E. After being stored in Oxford some will be sent at the end of the study to Toronto for processing. The remaining aliquots of DNA and plasma will be kept in the neuroscience building in the department of psychiatry, University of Oxford, storage facility for use in further research, for up to 10 years.

Stool samples:
Microbiome data collection will be fully remote. Stool collection kits will be sent to participants at home via post. The kits contain two tubes for sample collection and a brief (5 mins) questionnaire to collect basic information about diet. Participants will collect their stool samples at home and mail the collection kit, which has a pre-paid shipping label, directly to the Oxford Centre for Microbiome Studies. We will provide participants with one stool collection kit at two time points (baseline and end-of-treatment at week 16). Each microbiome collection kit will have a unique identifier code (e.g., CMS_034_112), which will be recorded alongside the study ID. This will allow to match microbiome data with study outcomes. Once returned, stool samples will be stored in -80C freezer upon receipt. Stool samples will be analysed as soon as is practically possible with shotgun metagenomics and metabolomics analysis (MS-LC/NMR). Once analysed, samples will be destroyed according to OCMS procedure.

2.8. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

According to the design of the study, participants may have the following two options for withdrawal:

1) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

2) Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis. (Any limits to this type of withdrawal where, for example analysis of their data or samples has already been integrated into interim results or dose escalation decisions etc. should be explained in the participant information sheet).

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures

People who withdraw from treatment will be offered follow up and data collection as per the normal protocol for other participants. Their data will be analysed unless they request that all of their data be withdrawn. After three months after the end of the study we will delete the record of anonymisation

thereby limiting the time that participants can request for all of their anonymised data to be deleted. People who withdraw will not be replaced.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

If a participant is withdrawn from treatment due to pregnancy the pregnancy will be followed-up to outcome. See the Safety Reporting section below.

2.9. Definition of End of Study

The end of study is the point at which all the data has been entered and queries resolved.

3. STUDY INTERVENTIONS

3.1. Other Treatments (non-IMPS)

The intervention consists of online coaching on how to use and maintain a ketogenic diet for mental health. Compliance will be assessed by monitoring blood ketone levels. Participants in this arm will meet with their coach online using Microsoft Teams video conferencing software. They will be offered 45 minutes per week in an online group, and one to one online coaching sessions with their coach. In the first two weeks they will be offered 60 minutes. In weeks 3 to 8 they will be offered 30 minutes. In weeks 9 to 16 they will be offered 30 minutes every two weeks. Sessions will provide information about using ketogenic diet for mental health, and coaching to encourage participants to set and maintain goals. The ketogenic diet arm will have access to an Oxford university hosted webpage detailing the ketogenic diet.

The comparator arm will receive time-matched online coaching from a dietitian on how to use and maintain the Hormesis Diet for mental health. The comparator arm will have access to an Oxford university hosted webpage detailing the Hormesis Diet. Compliance for both arms will be assessed by monitoring daily fasted capillary blood beta-hydroxybutyrate (BHB) and glucose readings using a Keto-Mojo device, in addition to self-reported adherence discussed during weekly coaching sessions. Participants in this arm will meet with their dietitian online using Microsoft Teams video conferencing software. They will be offered 45 minutes per week in an online group, and one to one online coaching sessions with their coach. In the first two weeks they will be offered 60 minutes. In weeks 3 to 8 they will be offered 30 minutes. In weeks 9 to 16 they will be offered 30 minutes every two weeks. Sessions will provide information about using the Hormesis Diet for mental health, and coaching to encourage participants to set and maintain goals.

The aim is not to blind participants to the different names of the diet in their arm, but to foster equivalent enthusiasm in the prospect of their diet to improve their mental health.

4. SAFETY REPORTING

4.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life-threatening ● requires inpatient hospitalisation or prolongation of existing hospitalisation ● results in persistent or significant disability/incapacity ● consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: ● in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product ● in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the study in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

4.2. Assessment results outside of normal parameters as AEs and SAEs

Randox will provide follow up info for any test results outside of their normal ranges. Michael Browning will speak to affected participants and discuss if they want him to speak to their GP.

If suicidality is reported in the PHQ09 or to any member of the study team, the flowchart for assessing risk of suicide will be employed.

4.3. Assessment of Causality

The relationship of each adverse event to the study intervention will be determined by Michael Browning according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from study intervention administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

4.4. Procedures for Reporting Adverse Events

AEs occurring during the safety window for the study as defined above that are observed by the Investigator or reported by the participant, will be reported on the study CRF, whether or not attributed to study medication.

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to study intervention, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the study intervention as judged by a medically qualified investigator or the Sponsor will be followed up either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

Reporting Procedures for Serious Adverse Events

All SAEs must be reported on the SAE Reporting Form to the ethics committee immediately or within 24 hours of the Study Team becoming aware of the event being defined as serious.

11.5.2. Procedure for immediate reporting of Serious Adverse Events

- Site study team will complete an SAE report form for all reportable SAEs.
- Where the SAE requires immediate reporting, the SAE report form will be scanned and emailed to the BRC immediately i.e., within 24 hours of site study team becoming aware of the event.
- Site study team will provide additional, missing or follow up information in a timely fashion.

4.5. Expectedness

No SAEs expected.

4.6. SUSAR Reporting

All SUSARs will be reported by the sponsor delegate and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

4.7. Development Safety Update Reports

As the intervention is a commonly used diet a safety report will not be submitted. Any SAEs will be reported to the sponsor.

5. STATISTICS

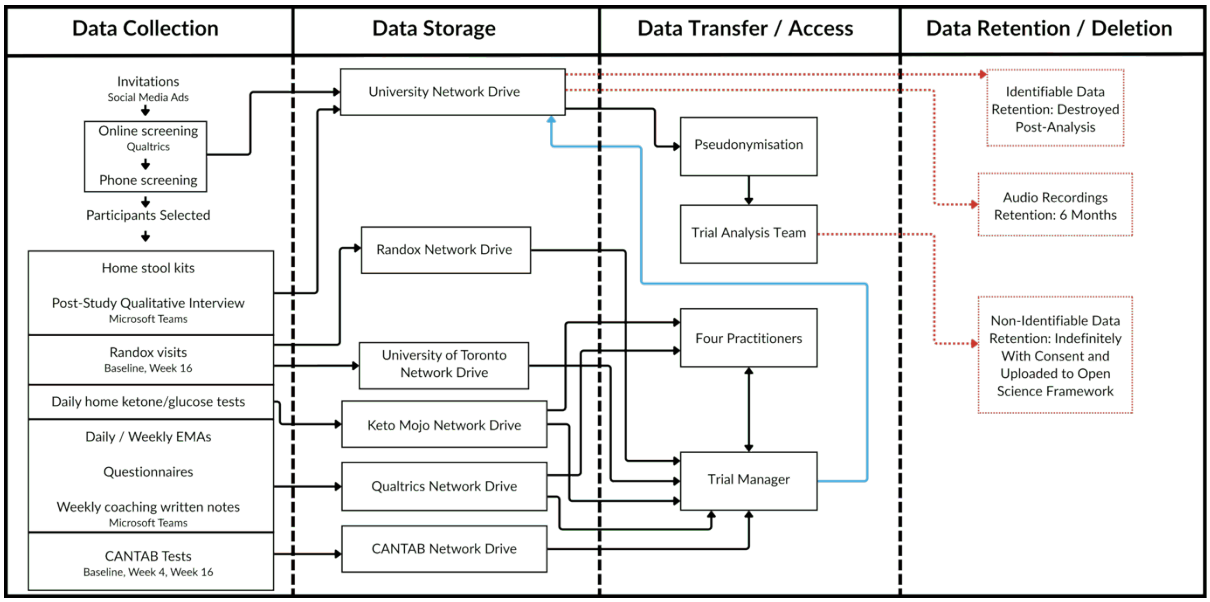
5.1. Statistical Analysis Plan (SAP)

This study aims to compare difference in outcome for the treatment and control groups to previous work using stimulant medication vs. placebo. Cohen's *d* of 0.7 is at the lower end of effect size in previous work investigating using stimulant medications for adult ADHD[33]. In order to achieve this value, the average participant in this study would have to score at least 5 points' difference between treatment and control groups on ASRS Part A, with a standard deviation of 7, based on control group mean outcome of 14, and treatment group mean outcome of 9. This standard deviation is justified from previous post-intervention outcome standard deviation[34]. For a 5% significance level and 90% power, 42 participants are required in each group. With 20% attrition conservatively projected for this dietary intervention we require 51 participants to be recruited into each group.

A full Statistical Analysis Plan (SAP) will be produced separately and will be available from the time that the first participant is recruited.

6. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study. A full Data Protection Impact Assessment (DPIA) and Transfer Risk Assessment (TRA) will be completed before the start of the study.



6.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

6.2. Data Recording and Record Keeping

Initial screening data will be taken using the University of Oxford Department of Psychiatry's Qualtrics platform. This will register and record the consent for protected data to be taken, and will record prospective participant responses to initial screening questions.

If prospective participants are suitable for further screening, they will be contacted by phone. Their information will be stored on a OneDrive folder assigned to a member of the study team's University of Oxford account. If unsuitable for the participation, their data will be removed at the end of the session. If suitable, their data will be kept in this OneDrive folder until the end of the study.

At home online:

- ASRS Parts A and B - baseline, end of week 6, end of week 16;
- PHQ-9 - baseline, end of week 6, end of week 16;
- GAD-7 - baseline, end of week 6, end of week 16;
- WSAS - baseline, end of week 6, end of week 16;
- PSQI - baseline, end of week 6, end of week 16;
- EDE-Q - baseline, end of week 6, end of week 16;
- CANTAB tests - baseline, end of week 6, end of week 16;
- Adverse Childhood Events - baseline
- EMAs for mood, energy, clarity of thought - daily;
- EMAs for productivity, effectiveness, and procrastination - weekly;
- The Big Five Inventory - baseline, end of week 6, end of week 16

In a Randox clinic local to the participant:

- Randox Discovery Package measurements - baseline, end of week 16;
- MitoGENE / further research blood draw - baseline, end of week 16

At home:

- capillary blood ketone and glucose measurements - daily;
- stool samples - baseline, end of week 16

Participants will enter the following data into the Qualtrics platform:

- ASRS Parts A and B - baseline, end of week 6, end of week 16;
- PHQ-9 - baseline, end of week 6, end of week 16;
- GAD-7 - baseline, end of week 6, end of week 16;

- WSAS - baseline, end of week 6, end of week 16;
- PSQI - baseline, end of week 6, end of week 16;
- EDE-Q - baseline, end of week 6, end of week 16;
- EMAs for mood, energy, clarity of thought - baseline, daily;
- EMAs for productivity, effectiveness, and procrastination - baseline, weekly;
- The Big Five Inventory - baseline, end of week 16

Participants will enter the following data into the CANTAB platform:

- CANTAB tests - baseline, end of week 6, end of week 16;

Participants will enter the following data into the Keto Mojo platform:

- capillary blood ketone and glucose measurements - daily;

The Qualtrics, CANTAB, Keto Mojo and Randox data will be exported to CSV file on the University of Oxford secure server by a study team member to be pseudo-anonymised to their study participant number.

Deidentified data will be stored indefinitely, identifiable data will be destroyed at the end of the study after completion of data collection and analysis.

7. QUALITY ASSURANCE PROCEDURES

7.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

7.2. Monitoring

The completeness and compliance of study documents will be assessed by the study team after 5 participants have completed the study and then 6 monthly until study completion. The assessments will report on the completeness of study records to the study oversight group.

7.3. Study committees

7.3.1. Study Steering Committee

Given the conflict of interest in Ewan Houston owning MetPsy, a study steering committee has been assembled to ensure proper oversight. The committee consists of an academic psychiatrist, a medical statistician, and an academic dietitian.

8. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

9. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the study protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the study; or

(b) the scientific value of the study".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, and regulatory authority within seven calendar days.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

10.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

10.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet, and any proposed advertising material, will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

10.4. Other Ethical Considerations

This study involves several sensitive topics, including mental health, ADHD, depression, metabolic health, and dietary behaviours. These topics are essential for assessing the impact of dietary coaching on ADHD symptoms, mood, and metabolic health.

There are several reasons to justify including sensitive topics. Clinical relevance – ADHD, depression, and anxiety often coexist, so tracking changes is essential. Dietary impact on mental health – The study explores whether metabolic interventions improve symptoms. Safety & risk monitoring – The suicidal ideation question is essential for participant safety.

Participants may find these topics uncomfortable but their inclusion is justified.

10.5. Reporting

The CI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the REC, host organisation, funder (where required) and Sponsor. In addition, an End of Study notification and final report will be submitted to the REC, host organisation and Sponsor.

10.6. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Study (EudraCT) Database within 12 months of the end of study declaration by the CI or their delegate.

Where the study has been registered on multiple public platforms, the study information will be kept up to date during the study, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the study declaration.

10.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic databases, with the exception of participants' name and email on the Keto Mojo Health platform and Randox clinic system. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

10.8. Expenses and Benefits

Participants will receive up to £50 in financial compensation via vouchers for the time spent in the study:

£10 for completion of assessments up to week 6

£10 for completion of assessments up to week 12

£20 for completion of week 16 assessments (end of diet programme)

£10 for completion of the qualitative interview after week 16

Reasonable public transport travel expenses to and from the Randox clinics will be reimbursed.

If a participant withdraws, financial compensation will be paid pro-rata.

11. FINANCE AND INSURANCE

11.1. Funding

Baszucki Family Foundation.
GoFundMe public crowdfunding campaign.

11.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

12. PUBLICATION POLICY

The results of the study will be written up as part of Ewan Houston's DPhil thesis and for publication in scientific journals. The study team will undertake to publish the results even if they are not positive.

13. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

14. ARCHIVING

All personally identifying information will be held on secure university servers until the end of the study - after all data analysis is completed - after which time it will be destroyed.

Consent forms will be stored for 10 years on a secure university server as per university policy.

Non identifiable information will be stored indefinitely. Consent will be gained for sharing of non-identifiable data after the study. This consent will be uploaded onto the Open Science Framework (OSF).

Non-identifiable digital data will be archived on university servers. Any pen and paper data will be archived as per the departmental policy that uses a secure offsite company.

4. REFERENCES

1. Francés L, Quintero J, Fernández A, et al. Current state of knowledge on the prevalence of neurodevelopmental disorders in childhood according to the DSM-5: a systematic review in accordance with the PRISMA criteria. *Child Adolesc Psychiatry Ment Health*. 2022;16:27. doi:10.1186/s13034-022-00462-1

2. Sibley MH, Mitchell JT, Becker SP. Method of adult diagnosis influences estimated persistence of childhood ADHD: a systematic review of longitudinal studies. *Lancet Psychiatry*. 2016;3(12):1157-1165. doi:10.1016/S2215-0366(16)30190-0

3. Song P, Zha M, Yang Q, Zhang Y, Li X, Rudan I. The prevalence of adult attention-deficit hyperactivity disorder: A global systematic review and meta-analysis. *J Glob Health*. 11:04009. doi:10.7189/jogh.11.04009

4. Veronesi GF, Gabellone A, Tomlinson A, Solmi M, Correll CU, Cortese S. Treatments in the pipeline for attention-deficit/hyperactivity disorder (ADHD) in adults. *Neurosci Biobehav Rev*. 2024;163:105774. doi:10.1016/j.neubiorev.2024.105774

5. Cortese S, Fava C. Long-Term Cardiovascular Effects of Medications for Attention-Deficit/Hyperactivity Disorder—Balancing Benefits and Risks of Treatment. *JAMA Psychiatry*. 2024;81(2):123-124. doi:10.1001/jamapsychiatry.2023.4126

6. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-738. doi:10.1016/S2215-0366(18)30269-4

7. Zubrzycki J. Effects of ADHD Drug Shortages Trickle Down Into Classrooms: Medication supplies can often be unpredictable. *Educ Week*. 2012;31(23):6.

8. Mahase E. ADHD: GPs are told to review some patients amid drug shortages. *BMJ*. 2023;382:p2250. doi:10.1136/bmj.p2250

9. Karrouri R, Hammani Z, Benjelloun R, Otheman Y. Major depressive disorder: Validated treatments and future challenges. *World J Clin Cases*. 2021;9(31):9350-9367. doi:10.12998/wjcc.v9.i31.9350

10. Hengartner MP, Plöderl M. Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. *BMJ Evid-Based Med*. 2022;27(2):69-73. doi:10.1136/bmjebm-2020-111600

11. van Hal R, Geurts D, van Eijndhoven P, et al. A transdiagnostic view on MDD and ADHD: shared cognitive characteristics? *J Psychiatr Res*. 2023;165:315-324. doi:10.1016/j.jpsychires.2023.07.028

12. Chen MH, Pan TL, Hsu JW, et al. Attention-deficit hyperactivity disorder comorbidity and antidepressant resistance among patients with major depression: A nationwide longitudinal study. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2016;26(11):1760-1767. doi:10.1016/j.euroneuro.2016.09.369

13. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;163(4):716-723. doi:10.1176/appi.ajp.163.4.716

14. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020;(6). doi:10.1002/14651858.CD001903.pub5

15. Kraeuter AK, Phillips R, Sarnyai Z. Ketogenic therapy in neurodegenerative and

psychiatric disorders: From mice to men. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;101:109913. doi:10.1016/j.pnpbp.2020.109913

16. Danan A, Westman EC, Saslow LR, Ede G. The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients. *Front Psychiatry*. 2022;13. Accessed November 23, 2023. https://www.frontiersin.org/articles/10.3389/fpsyt.2022.951376

17. Norwitz NG, Sethi S, Palmer CM. Ketogenic diet as a metabolic treatment for mental illness. *Curr Opin Endocrinol Diabetes Obes*. 2020;27(5):269-274. doi:10.1097/MED.0000000000000564

18. Mohorko N, Černelič-Bizjak M, Poklar-Vatovec T, et al. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. *Nutr Res N Y N*. 2019;62:64-77. doi:10.1016/j.nutres.2018.11.007

19. Gramaglia C, Gambaro E, Bartolomei G, et al. Increased Risk of Metabolic Syndrome in Antidepressants Users: A Mini Review. *Front Psychiatry*. 2018;9:621. doi:10.3389/fpsyt.2018.00621

20. Chokka P, Tancer M, Yeragani VK. Metabolic syndrome: relevance to antidepressant treatment. *J Psychiatry Neurosci*. 2006;31(6):414.

21. Prado CE, Watt S, Crowe SF. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychol Rev*. 2018;28(1):32-72. doi:10.1007/s11065-018-9369-5

22. Miller VJ, Villamena FA, Volek JS. Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health. *J Nutr Metab*. 2018;2018:5157645. doi:10.1155/2018/5157645

23. Virta Health clinical study patients showed lasting type 2 diabetes reversal and remission at 5 years. Accessed November 23, 2023. https://www.virtahealth.com/press/virta-sustainable-health-improvements-5-year-diabetes-reversal-study

24. Bhanpuri NH, Hallberg SJ, Williams PT, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study. *Cardiovasc Diabetol*. 2018;17(1):56. doi:10.1186/s12933-018-0698-8

25. Popiolek-Kalisz J. Ketogenic diet and cardiovascular risk – state of the art review. *Curr Probl Cardiol*. 2024;49(3):102402. doi:10.1016/j.cpcardiol.2024.102402

26. Unwin D, Delon C, Unwin J, Tobin S, Taylor R. What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss. *BMJ Nutr Prev Health*. 2023;6(1). doi:10.1136/bmjnph-2022-000544

27. Sethi S, Wakeham D, Ketter T, et al. Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Study. *Psychiatry Res*. 2024;335:115866. doi:10.1016/j.psychres.2024.115866

28. Budoff M, Manubolu VS, Kinninger A, et al. Carbohydrate restriction-induced elevations in LDL-cholesterol and atherosclerosis: The KETO Study. *Metabolism*. 2024;153:155854. doi:10.1016/j.metabol.2024.155854

29. Bellamy E. *The Impact of the Ketogenic Diet on Depression and Psychological Wellbeing: A Randomised Controlled Study with Integrated Qualitative Analysis*. phd. University of East London; 2024. Accessed August 28, 2024. https://repository.uel.ac.uk/item/8x2x3

30. Sarnyai Z, Kraeuter AK, Palmer CM. The Ketogenic Diet in the Treatment of Schizophrenia. In: Masino SA, Boison D, D'Agostino DP, Kossoff EH, Rho JM, Masino SA, eds. *Ketogenic Diet and Metabolic Therapies: Expanded Roles in Health and Disease*. Oxford University Press; 2022:0. doi:10.1093/med/9780197501207.003.0020

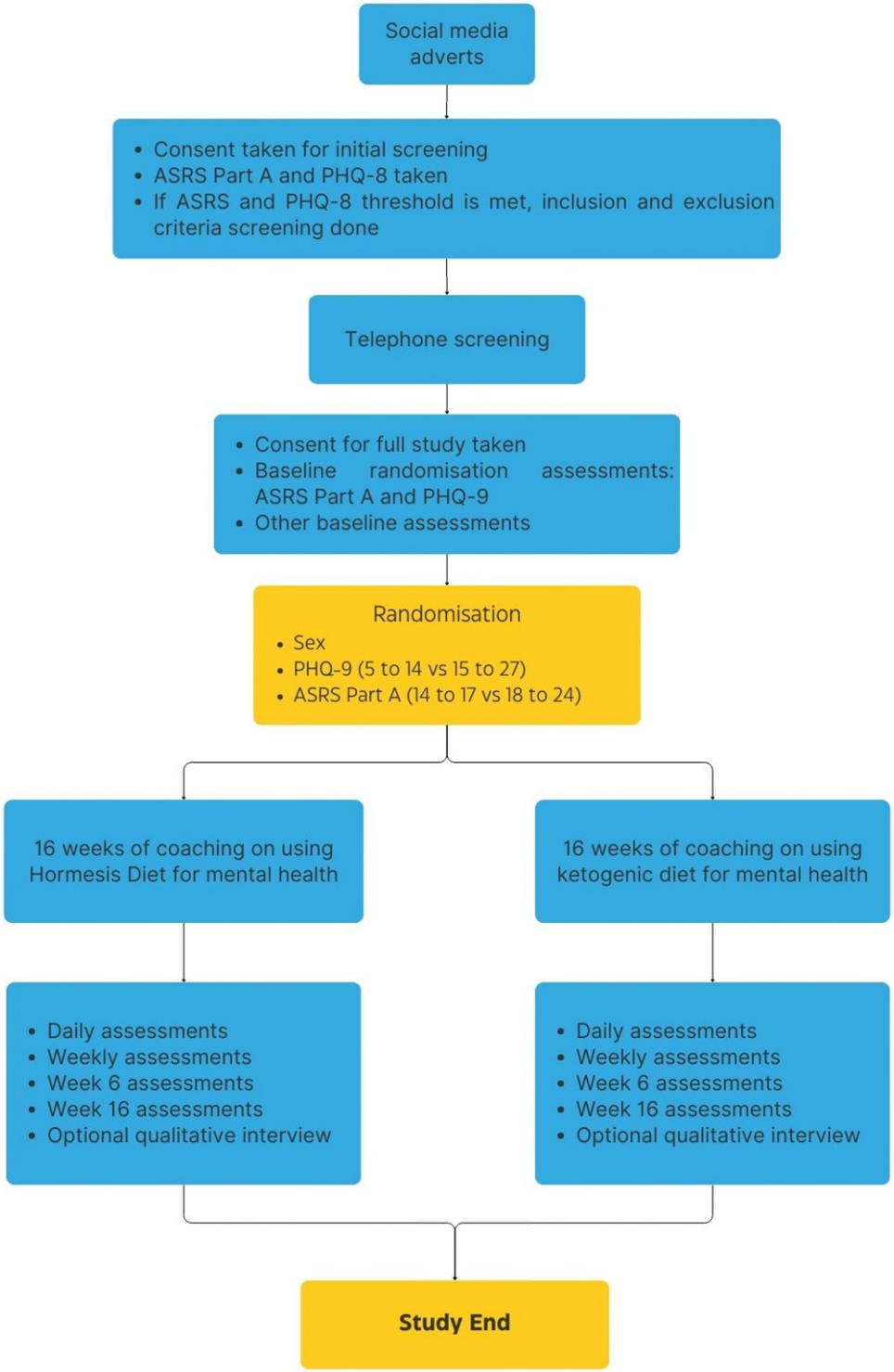
31. Needham N, Campbell IH, Grossi H, et al. Pilot study of a ketogenic diet in bipolar disorder. *BJPsych Open*. 2023;9(6). doi:10.1192/bjo.2023.568

32. Halahakoon DC, Kaltenboeck A, Martens M, et al. Pramipexole Enhances Reward Learning by Preserving Value Estimates. *Biol Psychiatry*. 2023;0(0). doi:10.1016/j.biopsych.2023.05.023

33. Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD—a systematic review of available meta-analyses. *CNS Spectr*. 2013;18(6):296-306. doi:10.1017/S109285291300031X

34. Spencer T, Biederman J, Wilens T, et al. Efficacy of a Mixed Amphetamine Salts Compound in Adults With Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiatry*. 2001;58(8):775-782. doi:10.1001/archpsyc.58.8.775

5. APPENDIX A: STUDY FLOW CHART



1. APPENDIX B: SCHEDULE OF PROCEDURES

SCHEDULE OF PROCEDURES					
Procedure	Screening / Pre-Baseline	Baseline (Week 0)	Weekly (Weeks 1–16)	Week 6	End of Week 16
Informed Consent	X	–	–	–	–
Eligibility (Inclusion/Exclusion)	X	–	–	–	–
Randomisation	–	X	–	–	–
Demographic Information	–	X	–	–	–
ASRS (Parts A & B)	–	X	–	X	X
PHQ-9	–	X	–	X	X
GAD-7	–	X	–	X	X
WSAS	–	X	–	X	X
PSQI	–	X	–	X	X
EDE-Q	–	X	–	X	X
Big Five Inventory (BFI)	–	X	–	X	X
Adverse Childhood Events	–	X	–	–	–
CANTAB (cognitive tests)	–	X	–	X	X
Randox Discovery Blood Draw	–	X	–	–	X
MitoGENE Blood Draw	–	X	–	–	X

Stool Sample (microbiome)	–	X (home kit)	–	–	X (home kit)
Daily EMAs: Mood, Energy, Clarity	–	–	Daily	–	–
Weekly EMAs: Productivity, Effectiveness, Procrastination	–	–	Weekly	–	–
Capillary Blood Ketones & Glucose	–	–	Daily	–	–
One-to-One Coaching (30 mins)	–	–	Weekly / Fortnightly	–	–
Group Coaching (45 minutes)	–	–	Weekly	–	–
Adverse Events Monitoring	–	–	Continuous	–	–
Qualitative Interview	–	–	–	–	X (post–Week 16)

2. APPENDIX C: SAE REPORTING FLOW CHART