StudySetGo

Accelerating Human Research

Research Protocol

Full Study Title	An investigation into the effect of a daily magnesium and melatonin based multi-ingredient dietary supplement on sleep quality in individuals with self-reported nighttime leg cramps.
Sponsor	StudySetGo Ltd.
Funder	Imagine Biolabs, LLC (DBA SaltWrap)
SSG Study Reference	SSG-26-001-001
Protocol Version	v1.0
Version Date	26May2026
Principal Investigator	Dr David Church, Dave_Church@alumni.baylor.edu
Coordinating Investigator	Dr Tom Jameson, tom.jameson@studysetgo.com

Authorisation

Principal Investigator	**Coordinating Investigator**
Name: Dr David Church	**Name:** Dr Tom Jameson
Signature: D Church	**Signature:** T Jameson
Date: 26 May 2026	**Date:** 26 May 2026

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1. Introduction

1.1 Background & Rationale

Adequate sleep quality and quantity are essential for maintaining physical and mental health, cognitive function, and overall quality of life. Sleep disturbances are increasingly prevalent with advancing age. Nocturnal leg cramps affect approximately 50% of adults over 60 years of age[1] and are independently associated with increased sleep fragmentation, reduced sleep adequacy, and shorter sleep duration[2]. Despite their prevalence and impact, evidence-based non-pharmacological interventions targeting sleep disruption specifically in individuals who experience nocturnal leg cramps remain limited.

Melatonin is an endogenous regulator of the circadian system, with secretion suppressed during daylight hours and rising in response to darkness to facilitate sleep onset. Exogenous melatonin supplementation has demonstrated beneficial effects on sleep quality in both healthy individuals and those with recognised sleep disorders[3]. Magnesium has similarly attracted growing interest for its role in sleep regulation, likely through modulatory effects on GABA receptors and the hypothalamic-pituitary-adrenal axis[4]. Additionally, magnesium supplementation has been shown to reduce nocturnal leg cramp frequency and severity, and to improve sleep quality in adults experiencing night-time leg cramps[5,6], though evidence for its efficacy as a standalone intervention for improving sleep quality in individuals with nighttime leg cramps remains inconsistent[7].

Combined melatonin and magnesium supplementation has demonstrated promise as an approach to improving sleep quality. A recent study demonstrated that in adults with self-reported poor sleep quality (PSQI score >5), four weeks of daily supplementation with 200 mg elemental magnesium combined with 1.9 mg melatonin produced significant improvements in PSQI scores compared with placebo[8]. Objective assessment via wrist-based accelerometry confirmed improvements across all measured sleep parameters, including sleep latency, efficiency, total sleep time, number of nocturnal awakenings, mean awakening duration, and movement index. Although the prevalence of nocturnal leg cramps was not reported in that study population, the findings provide robust evidence that combined melatonin and magnesium supplementation can improve both subjective and objective sleep quality in adults with disturbed sleep.

In addition to melatonin and magnesium, there are a number of other nutritional ingredients that have established or emerging roles in supporting sleep quality; including vitamin B6[9], KSM-66® Ashwagandha[10], Rhodiola rosea root extract[11], 5-HTP (5-Hydroxytryptophan)[12], GABA (gamma-aminobutyric acid)[13] and Passion Flower Extract (Passiflora incarnata)[14]. Given the disparate mechanisms by which these ingredients are proposed to support sleep quality, and the absence of studies targeting individuals with nighttime leg cramps specifically, there is a clear rationale for investigating a targeted multi-ingredient dietary supplement in this population.

The present study therefore aims to determine whether a multi-ingredient dietary supplement based on melatonin and magnesium, can improve subjective sleep quality (assessed via PSQI) and objective sleep parameters (assessed via Oura Ring wearable) in adults whose sleep is specifically disrupted by nocturnal leg cramps. Additionally, we will assess if the multi-ingredient dietary supplement impacts quality of life and self-reported nighttime leg cramp frequency and severity.

1.2 Hypothesis

The primary hypothesis is that 6 weeks of a daily magnesium and melatonin based multi-ingredient dietary supplement will be associated with a significant improvement in sleep quality determined by the Pittsburgh Sleep Quality Index (PSQI) compared to a placebo in adults who self-report poor sleep (>5 PSQI score) and ≥4 episodes of night-time leg cramps per fortnight.

1.3 Regulatory classification

This study does not require an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) for the following reasons.

The investigational product, MagR&R, is a commercially available multi-ingredient dietary supplement. It is legally marketed in the United States and is not classified as a drug under the Federal Food, Drug, and Cosmetic Act (FD&C Act). All active ingredients — including melatonin, magnesium bisglycinate chelate, ashwagandha, rhodiola rosea, 5-hydroxytryptophan, GABA, passion flower extract, and vitamin B6 — are sold freely as dietary supplement ingredients in the United States at the doses provided, have Generally Recognised as Safe (GRAS) status, and are not subject to FDA pre-market approval.

Under 21 CFR Part 312.2(b), an IND is not required for a clinical investigation of a lawfully marketed product where the investigation is not intended to support a new indication, a significant change in product labelling, or FDA marketing approval; does not involve a route of administration, dose level, or patient population that would materially increase risk above that associated with ordinary consumer use; and is conducted in compliance with IRB oversight and informed consent requirements. This study meets all of these conditions. The supplement is administered orally at its recommended consumer dose (up to 3 capsules per evening), in an adult population consistent with the product's intended and established consumer base, and the study is not designed to generate data in support of any FDA regulatory submission.

The study population comprises otherwise healthy adults with self-reported sleep disturbance and nocturnal leg cramps. No diagnosed medical condition is being treated, no prescription medication is under investigation, and no biological intervention beyond oral ingestion of a commercially available supplement is involved. The outcomes assessed — subjective sleep quality, leg cramp frequency and severity, and quality of life — are wellness endpoints, not clinical disease endpoints.

Accordingly, this study is classified as non-IND research and will be conducted under the oversight of an institutional review board (IRB) in accordance with the US Federal Policy for the Protection of Human Subjects (45 CFR 46, the Common Rule).

2. Objectives

2.1 Primary Objective

To evaluate the effect of 6 weeks daily magnesium and melatonin based multi-ingredient dietary supplementation on PSQI scores compared to a placebo in participants who self-report poor sleep (PSQI >5) and ≥4 episodes of night-time leg cramps per fortnight.

Primary endpoint:

Change in Pittsburgh Sleep Quality Index score from baseline to week 6 of supplementation.

2.2 Secondary Objectives

1. To assess the effect of supplementation on self-reported nighttime leg cramp frequency using a daily nighttime leg cramp diary.
2. To assess the effect of supplementation on self-reported nighttime leg cramp severity using a daily 10 point visual analogue scale.
3. To assess the effect of supplementation on quality of life using the validated 36-Item Short Form Survey (SF-36) questionnaire.
4. To assess the effect of supplementation on sleep metrics (e.g. total sleep time, sleep stages (deep, rem, light), sleep efficiency, latency, restfulness, and sleep timing) obtained using an Oura ring wearable device.
5. To assess the effect of supplementation on physical activity metrics (including steps) and autonomic metrics (including heart rate variability, resting heart rate, time in heart rate zone) obtained using an Oura ring wearable device.

2.3 Safety Objectives

1. To assess symptoms and adverse events associated with daily magnesium and melatonin based multi-ingredient dietary supplementation.

3. Study Design

3.1 Overview of Study Design

This study is a randomised, double-blind, 2-arm parallel group fully decentralised placebo controlled trial.

The total study duration is expected to be 7 months following IRB approval. Recruitment and enrollment will occur simultaneously until the required number of participants have been randomised. End of study is declared when the final participant completes the week 6 assessments.

Table 1. Anticipated study duration and key milestones

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
IRB approval							
Clinicaltrials.gov registration	Following IRB approval						
Recruitment and randomisation	Following IRB approval						
Data collection							
End of study							

3.2 Participant Interactions

This study is fully decentralised. E-consent and data will be collected using a data collection platform (Trialflare) and wearable Oura rings. Participants will not have to travel to a research centre or laboratory to participate in this trial. All contact between the participant and research team will be conducted remotely via video call, phone call, messaging or email.

3.3 Intervention

Active intervention: The active intervention is a commercially available multi-ingredient dietary supplement, supplied by Imagine Biolabs LLC (trading as SaltWrap) and sold under the brand name Mag R&R. The dose is up to 3 capsules per day taken 30 minutes before bedtime with water. The product is stored at room temperature. The product ingredients are listed below.

Table 2. Active intervention ingredients

Ingredient	Per capsule (mg)	Maximum daily dose (mg per 3 capsules)
Vitamin B6 (pyridoxine HCL)	0.6	1.7
Elemental Magnesium (as magnesium bisglycinate chelate buffered with magnesium oxide)	54	162
KSM-66® Ashwagandha (*Withania somnifera* root extract)	40	120
Rhodiola rosea (root) extract (standardized to 3% rosavins, 1% salidrosides)	40	120

5-HTP (5-Hydroxytryptophan) from *Griffonia simplicifolia* (seed)	33	100
GABA (gamma-aminobutyric acid)	33	100
Passion Flower Extract (*Passiflora incarnata*)	13	40
Melatonin	1	3
Other Ingredients: Gelatin capsule, silicon dioxide, microcrystalline cellulose, magnesium vegetable stearate **Allergens:** Contains Milk		

Placebo: The placebo is manufactured by the same manufacturer that produces the active product (Vitaquest International, New Jersey, USA). The placebo is visually similar to the active product and will be packaged in the same plain bottles as the active intervention to maintain the blind. The placebo dose is up to 3 capsules per day taken with water. Packaging is managed by Vitaquest International. The placebo ingredients are as follows:

Table 3. Placebo ingredients

Ingredient	Per capsule (mg)	Maximum daily dose (mg per 3 capsules)
Long grain white rice flour	660	1980
Hard vegetarian capsule (hypromellose) (100mg)	100	300

3.4 Intervention packaging and distribution

All active product will be sourced from a single batch, and all placebo product will likewise be sourced from a single batch. A certificate of analysis for active and placebo products will be obtained and filed in the trial master file prior to the initiation of participant enrollment.

Active and placebo products will be packaged in identical bottles, each containing the maximum dose required for a participant to complete the 6-week intervention period + 10% buffer. Each bottle will be labeled with a blinded product identifier that includes the study code (SSG-26-001-001), blinded group allocation code (Group A or Group B), and emergency contact information (PI and Sponsor Contact).

Product distribution is managed by Red Stag Fulfillment (Knoxville, TN). Upon randomization of a participant, a member of the research team provides the participant's shipping address to Red Stag. Red Stag will then dispatch the assigned product directly to the participant's residence. Red Stag will not store participant details beyond what is required to ship the product. A data processing agreement between StudySetGo and Red Stag will be completed prior to sharing any participant identifiable information.

4. Study Population

4.1 Inclusion Criteria

1. Adults aged 40-75 years
2. Self-reported poor sleep quality (PSQI >5) at screening
3. Self-reported nocturnal leg cramp averaging ≥4 episodes per fortnight at screening
4. Capacity to understand and provide electronic informed consent
5. Willing to wear an Oura Ring wearable device continuously throughout the study period
6. Access to a smartphone/tablet with iOS 15 or higher and Android 9 or higher and willing to install and use the Oura and Trialflare applications
7. Be a resident of and permanently living in Florida with no planned travel across more than one time zone for at least 1 night during the study period

4.2 Exclusion Criteria

1. Current or recent (within 4 weeks of randomisation) use of melatonin, magnesium, or other supplements specifically taken for sleep or leg cramps or listed as an ingredient of the intervention supplement.
2. Current use of any prescription medication
3. Diagnosed sleep disorder (e.g. obstructive sleep apnoea, restless legs syndrome, insomnia disorder)
4. Known or suspected secondary cause of nocturnal leg cramps (e.g. peripheral vascular disease, neurological condition, renal impairment, thyroid disorder)
5. Any current or prior diagnosis of:
    a. Cancer or malignancy of any kind (prior malignancy is not exclusionary if the participant is in confirmed remission and has completed all treatment)
    b. Cardiovascular disease (e.g. hypertension, coronary artery disease, heart failure, arrhythmia, stroke, peripheral vascular disease)
    c. Autoimmune disorder (e.g. rheumatoid arthritis, lupus, multiple sclerosis)
    d. Gastrointestinal disorder (e.g. IBS, malabsorption syndromes)
    e. Neurological disorder (e.g. epilepsy, Parkinson's disease, dementia)
    f. Hepatic or renal impairment
    g. Diabetes mellitus (type 1 or type 2)
    h. Severe psychiatric disorder (e.g. schizophrenia, bipolar disorder)
    i. Myasthenia Gravis
6. Known hypersensitivity or allergy to any ingredient in the active or placebo product
7. Rotating shift work or irregular sleep patterns
8. Current participation in another interventional clinical trial
9. Inability to comply with study procedures or remote visit schedule
10. Breastfeeding, pregnant, or planning to become pregnant during the study period

4.3 Recruitment

Participants will be recruited using digital social media advertisements. Individuals expressing interest in participating will be directed to a landing page where they will complete a brief pre-screening questionnaire on the eligibility criteria. Upon successful completion of eligibility criteria, participants will be provided a link to download the informed consent form. From the landing page, participants can either directly complete the e-consent (after being prompted to take appropriate time to review the informed consent form), book a call directly with one of the research team, or contact the research team via email. Participants will also be asked to provide an email address and phone number. Pre-screening data will not be stored or form part of the study dataset. Contact details provided at pre-screening will be securely deleted within 30 days for individuals who do not proceed to provide informed consent. Participants will be encouraged to raise any questions with the study team before providing consent. No research data will be collected until informed consent has been obtained.

Participants will be able to view StudySetGo’s Privacy Policy via a link on the landing page.

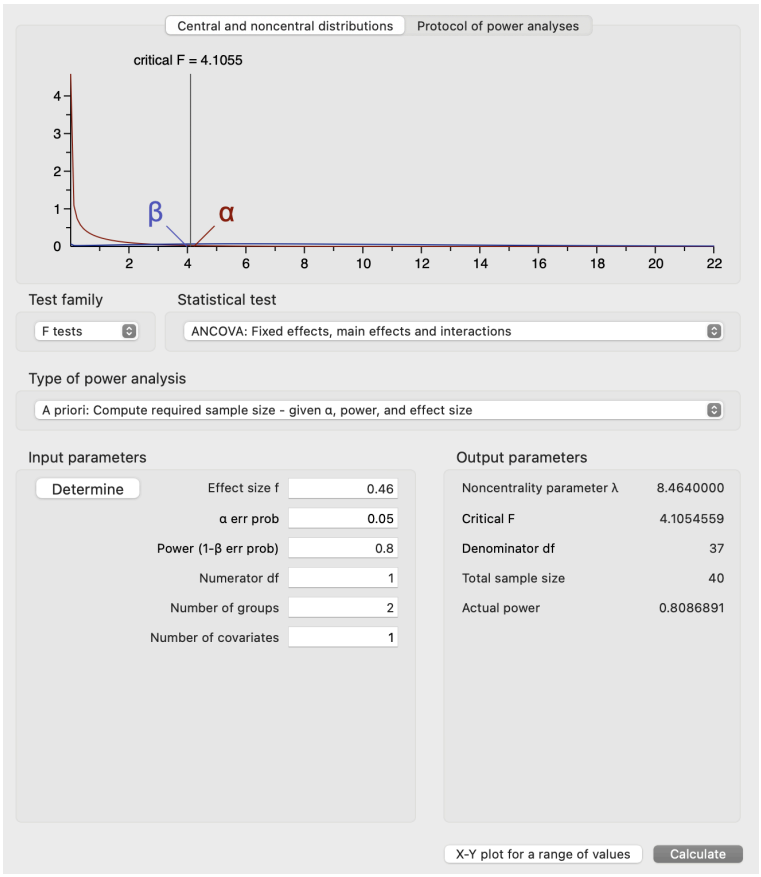
Link to study recruitment landing page: https://enrol.studysetgo.com/sleep-study/

4.4 Sample Size

Sample size was estimated based on the primary outcome of subjective sleep quality, assessed via the Pittsburgh Sleep Quality Index (PSQI). Effect size was derived from Carlos et al (2024)[8], which investigated the effects of combined melatonin (1.9 mg) and magnesium (200 mg) supplementation versus placebo on PSQI scores in adults with sleep disturbances. The intervention in the present study (MAG R&R) provides a greater dose of melatonin (3 mg v 1.9 mg) and comparable magnesium (162 mg vs 200 mg) to Carlos et al (2024), as well as additional ingredients which show independent effects on sleep quality (i.e. Vitamin B6, KSM-66® Ashwagandha, *Rhodiola rosea* [root] extract, 5-Hydroxytryptophan, gamma-aminobutyric acid, and Passion Flower Extract). Therefore the effect size calculated from Carlos et al (2024) is considered to be a conservative approach.

Sample size was calculated for an analysis of covariance (ANCOVA) with post-intervention PSQI score as the dependent variable, treatment group as the fixed factor, and baseline PSQI score as the covariate. The between-condition difference in PSQI scores in Carlos et al (2024) at endpoint was 1.7 points (MMPod: 5.3 ± 2.3; PPod: 7.0 ± 2.4). A baseline-endpoint correlation of r = 0.60 was assumed as a conservative estimate based on published data (i.e. r = 0.85)[10]. The Cohen's d of 0.72, derived from the between-condition difference and pooled endpoint standard deviation, was converted to a Cohen's f statistic of f = 0.36 using the formula f = d/2. Adjustment for the ANCOVA covariate yields an effective f = 0.46, calculated as $f_{adjusted} = f / \sqrt{(1 - r^2)}$.

Using G*Power (version 3.1.0.6; F-tests, ANCOVA, two groups, one covariate), with $\alpha = 0.05$ and 80% power ($1 - \beta = 0.80$), a sample size of ~20 participants per group (n = 40 total) is required. Assuming a conservative dropout rate of ~25%, a target enrollment of 25 participants per group (n = 50 total) is planned.


Central and noncentral distributions
Protocol of power analyses
critical F = 4.1055
β
α
Test family
F tests
Statistical test
ANCOVA: Fixed effects, main effects and interactions
Type of power analysis
A priori: Compute required sample size - given α, power, and effect size
Input parameters
Determine
Effect size f 0.46
α err prob 0.05
Power (1-β err prob) 0.8
Numerator df 1
Number of groups 2
Number of covariates 1
Output parameters
Noncentrality parameter λ 8.4640000
Critical F 4.1054559
Denominator df 37
Total sample size 40
Actual power 0.8086891
X-Y plot for a range of values
Calculate

5. Study Interventions & Activities

5.1 Description of Research Activities & Procedures

Total participation duration is expected to be 10 weeks. This includes a 2 week screening, consent and onboarding process, a 2 week baseline data collection period and a 6 week intervention period.

Screening
Following completion of informed e-consent, participants will complete the full screening process during a video call with a researcher. This will involve confirmation of all inclusion and exclusion criteria via self-report, collection of demographic information (name, date of birth, sex assigned at birth, ethnicity, self-reported body mass and height, and home address for shipment of study materials) and completion of the PSQI questionnaire.

Consented participants confirmed as eligible at screening will be randomised according to the randomisation schedule. Participants will be sent an Oura Ring sizing kit directly by Oura, and the blinded supplement bottle according to their randomised group allocation. Once Oura ring size is confirmed, an Oura Ring Generation 4 will be shipped to the participant's home address. Participants will be guided through device setup including charging, cell phone application download, and Bluetooth pairing via written instructions provided by Oura, with study team support available where required.

Baseline (Weeks 1–2)
For 14 days, participants will complete a daily nocturnal leg cramp diary via the Trialflare mobile application. An automated push notification will be sent each morning at approximately 09:00 to capture the number and severity (10-point Visual Analogue Scale) of nocturnal leg cramps experienced in the preceding night. Oura Ring data collected continuously throughout the baseline period will serve as the objective sleep baseline for wearable secondary and exploratory outcome analyses.On Day 14 ± 2 days, participants will additionally complete the PSQI and SF-36 questionnaire via the Trialflare application.

Prior to commencing the intervention, participants will submit a photograph of the received product via the Trialflare application to allow the research team to verify correct blinded group allocation. The interval between completion of baseline assessments and commencement of the intervention is expected to be 0-7 days. Participants will have a scheduled research remote contact before commencing the intervention.

Intervention (Weeks 3–8)
For 6 weeks, participants will take their assigned dose of intervention or placebo supplement approximately 30 minutes before bedtime. Each morning, participants will complete a daily questionnaire via the Trialflare application capturing the time and number of capsules taken the previous evening, nocturnal leg cramp frequency and severity, and any symptoms experienced (see Section 6.3 — Dose Titration and Adverse Event Monitoring).

On days 1-7, participants will complete an additional questionnaire in the Trialflare app on adverse events (see section 6.1).

At days 14 ± 2, 28 ± 2, and 42 ± 2 of the intervention period, participants will additionally complete the PSQI and SF-36 questionnaire via the Trialflare application. Oura Ring wear compliance will be monitored by a researcher via the Oura Enterprise Platform, and ad hoc participant reminders will be issued where necessary. Additional researcher-participant remote contacts will take place by messaging, email, or teleconference as per the schedule outlined in Table 4. Participants may contact the research team at any time via the Trial Flare application or by email.

On day 42 ± 2, participants will be asked to guess which group they were allocated to as part of a blinding integrity check.

End of Study (Day 42 ± 2 of Intervention Period)

Following completion of Day 42 ± 2 data collection, participants will be considered to have completed the study. This constitutes the end of participant contact and defines the end of the study for the purposes of ethics notification and trial registration. Participants will be instructed to safely dispose of any remaining study product.

Table 4: Participant schedule of activities

	Screening	Baseline		Intervention (supplementation period)					
Week (day)		**1 (7)**	**2 (14 ± 2)**	**1 (7)**	**2 (14 ± 2 days)**	**3**	**4 (28 ± 2 days)**	**5**	**6 (42 ± 2 days)**
Screening and e-consent	**X**								
Trialflare and Oura ring onboarding	**X**								
Randomisation and supplement shipment	**X**								
Daily supplementation				**X**	**X**	**X**	**X**	**X**	**X**
Wearable data collection		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PSQI and SF-36			**X**		**X**		**X**		**X**
Nighttime leg cramp frequency and severity (daily diary)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Supplement time and adherence (daily diary)				**X**	**X**	**X**	**X**	**X**	**X**
AE monitoring	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Scheduled researcher-participant contact	**X**	**X**	**X**		**X**		**X**		**X**

5.2 Study Arms / Groups

- **Arm 1 Intervention**: n=25 participants will orally consume up to 3 capsules of Mag R&R 30 minutes before bed every day for 6 weeks
- **Arm 2 Placebo**: n=25 participants will orally consume up to 3 placebo capsules 30 minutes before bed every day for 6 weeks

5.3 Randomisation & Blinding

This is a double-blind study. Participants will not be informed of their group allocation for the duration of the study. Researchers involved in participant contact, data collection, and outcome assessment will also be blinded to group allocation for the duration of the study.

Participants will be randomised 1:1 to active or placebo using a computer-generated random allocation sequence generated prior to the start of enrolment. Each position in the sequence is assigned a product code. The person responsible for allocation assigns the next sequential code to each eligible participant and is not aware of which code corresponds to active or placebo product. The code-to-treatment mapping is held securely by a nominated member of the StudySetGo research team not involved in conduct of the research and will not be accessed until formal unblinding following database lock. This approach ensures allocation concealment is maintained throughout the study.

The statistical analysis will be conducted whilst blinded to group allocation. The study will be formally unblinded following database lock and completion of the statistical analysis detailed in Section 7.

Participants who withdraw from the study or who are lost to follow up will not be replaced.

At the end of the study, participants will be asked to guess which group they were allocated to as part of a blinding integrity check. The proportion of correct guesses in each group will be reported alongside the primary analysis to allow assessment of whether blinding was successfully maintained throughout the study.

5.4 End of Study

The study will be considered complete upon the final enrolled participant completing their Week 6 remote assessment. This constitutes the end of participant contact and defines the end of the study for the purposes of ethics notification and trial registration.

5.5 Wearables Sampling

All participants will be provided, at no cost to them, an Oura ring generation 4 (Oura Health Oy, Finland). The Oura ring is used to collect sleep data, activity and heart rate data continuously throughout the study. The Oura ring is a consumer-grade wearable ring that has been independently validated for sleep measurement against polysomnography[15]. The Oura Ring measures sleep using a combination of sensors embedded in a non-allergenic titanium ring, including red and infrared LEDs for blood oxygen monitoring, green and infrared LEDs for heart rate and heart rate variability, a digital temperature sensor, and a 3-axis accelerometer for movement tracking. The device is water resistant to 100 m, weighs between 3.3 and 5.2 grams depending on ring size, and is designed for continuous 24/7 wear, with a battery life of up to 8 days.

Following screening and prior to the start of the baseline period, participants will be sent an Oura Ring sizing kit to self-measure their ring size. Following confirmation of correct size, an Oura Ring Generation 4 will be shipped directly to each participant. Each device shipment includes the Oura Ring, a USB-C charging cable, and a ring charger. Participants will be instructed to wear the device continuously on their non-dominant hand for the duration of the study, removing it only for charging, which typically takes 20–80 minutes. Participants must achieve a minimum of 5 valid nights of Oura Ring data per week to be included in the wearable secondary outcome analyses. A valid night is defined as a night where the ring was worn for at least 4 hours during the participant's reported sleep period.

Participants will be required to synchronise their Oura Ring with the Oura App daily to ensure completeness and accuracy of data capture. The Oura App is compatible with iOS 15 or higher and Android 9 or higher with Google Play services, and requires Bluetooth 4.0. Participants must confirm smartphone compatibility prior to enrolment, and this is specified as an inclusion criterion.

The Oura Enterprise Platform is used to collate data from all study participants where it can be monitored for adherence and subsequently exported in CSV format from the Oura Enterprise Platform for statistical analysis.

5.6 Participant Renumeration

As a gesture of appreciation for their participation, participants will be invited to retain their Oura Ring (retail value approximately $349 USD). Participants who wish to continue using the Oura ring following study completion will be required to purchase an Oura membership independently directly with Oura (approximately $5.99 USD per month). Participants who do not wish to retain the ring will be provided with a prepaid return

envelope to return the device to the StudySetGo research team, or may dispose of it appropriately. They will not be offered any alternative form of compensation.

6. Safety Management

6.1 Adverse events

Definitions

An adverse event is any untoward medical occurrence in a study participant administered a study product that does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavourable or unintended sign, symptom, or disease temporally associated with the use of the study product, whether or not considered related to the study product.

A serious adverse event is any adverse event that results in any of the following outcomes:

- Death
- A life-threatening event (i.e. the participant was at immediate risk of death at the time of the event)
- Hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Any other medically important event that, based on appropriate medical judgement, may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

Adverse Event Monitoring

Participants will be asked about adverse events at all scheduled researcher-participant contacts. Adverse events will be pseudonymously documented in an adverse event log in Trialflare and followed until resolution or until end of study, whichever occurs first. Participants will also be encouraged to report any adverse event to the research team via the provided email or phone number documented on the Informed Consent, or via the inbuilt messaging function in the Trialflare app. All AEs will be reported to the PI within 48h of the study team becoming aware. SAEs will be reported to the PI within 24h of the study team becoming aware.

A toll free 24 hour number will also be provided in the informed consent document and printed on the supplement bottle label for participants to report adverse events or seek further information.

Emergency Unblinding Plan

The blinding information is held securely by a member of the StudySetGo team who is independent of the study. The designated unblinded individual can be contacted by the PI or Sponsor Contact in the event of an emergency unblinding request.

Reporting of Adverse Events

All SAEs will be reported to the IRB within 5 working days of the PI or Coordinating Investigator becoming aware. Non-serious AEs will be reported in the end of study report submitted to the IRB.

6.2 Stopping rules

The study will be suspended and the IRB notified if any of the following thresholds are met at any point during the study:

- Two or more serious adverse events considered possibly or probably related to the study intervention
- Any single serious adverse event considered definitely related to the study intervention
- A pattern of non-serious adverse events judged by the PI to represent an unacceptable risk to continued participation

Any decision to suspend or terminate the study will be made by the PI in consultation with the Sponsor Contact and communicated to the IRB without delay.

6.3 Side effects

This study involves administration of a commercially available dietary supplement and a matched placebo. The active supplement contains a combination of ingredients that are generally recognised as safe at the doses provided. The anticipated risk profile of this study is considered low.

The ingredient most likely to be associated with adverse effects is melatonin (3 mg per dose). Melatonin is widely used and has a well-established safety profile at this dose[16]. Adverse effects associated with melatonin supplementation are generally mild, transient, and self-resolving, and may include drowsiness or grogginess upon waking, headache, dizziness, nausea, and vivid dreams or nightmares. Participants will be advised to take the supplement approximately 30 minutes before bedtime and to avoid driving or operating heavy machinery for 8 hours after taking the supplement. Participants will be advised that if they need to wake during the night, they should take care when getting up, move slowly, and ensure the room is adequately lit before standing, as the supplement may cause drowsiness or dizziness that could persist during the night.

Magnesium supplementation at the dose provided (162 mg elemental magnesium as magnesium bisglycinate chelate) is unlikely to cause adverse effects. The remaining active ingredients — Vitamin B6, KSM-66® Ashwagandha, Rhodiola rosea extract, 5-Hydroxytryptophan (5-HTP), GABA, and Passion Flower Extract — are used at doses consistent with commercially available dietary supplements and are not expected to cause adverse effects in otherwise healthy adults. Participants should be aware that 5-HTP may interact with certain medications, particularly serotonergic agents including selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Use of such medications is therefore an exclusion criterion for this study.

The product contains a gelatin capsule and milk-derived ingredients. Participants with known allergies or sensitivities to these ingredients will be excluded from participation.

Dose Titration Protocol

To minimise the risk of side effects, a standardised dose titration protocol will be implemented during the first week of the intervention period (days 0-7). All participants will commence at 3 capsules per evening. Each morning, participants will rate the severity of any of the following symptoms experienced (fatigue upon waking, grogginess, headache, dizziness, brain fog, nausea and vivid dreams[16]) on a 10-point Visual Analogue Scale (0 = not at all, 10 = worst imaginable). Dose adjustments will be made according to the following pre-specified decision rule:

- If symptoms are absent or rated <4 out of 10 → participant continues at current dose
- If the participant reports any symptom with a severity score of ≥4 out of 10 → dose reduced to 2 capsules per evening
- If symptoms persist at a severity score of ≥4 out of 10 on 2 capsules → dose reduced to 1 capsule per evening

Once a stable tolerated dose has been established, participants will continue at that dose for the remainder of the intervention period. Dose reductions will be recorded in the participant's case report form and accounted for in the adherence analysis. The dose titration period will last for a maximum of 7 days, after which the participant's dose will be fixed for the remainder of the study.

Compliance to study intervention and placebo will be monitored via a daily questionnaire completed by participants in Trialflare.

6.4 Risks

The overall risk to participants in this study is considered low. The study involves administration of a commercially available dietary supplement at its recommended consumer dose, with no invasive procedures, no blood sampling, and no in-person visits. The primary risks are mild and transient side effects associated with the active ingredients, particularly melatonin, as described above. These risks are mitigated through the pre-specified dose titration protocol, participant screening procedures, and ongoing adverse event monitoring throughout the study. The Oura Ring is a non-invasive consumer wearable device and does not constitute a medical device. Wearing the Oura ring wearable device poses no known health risks. Participants will be instructed not to wear the ring adjacent to other rings to avoid discomfort, and to contact the study team if they experience any skin irritation or discomfort at the wear site.

The anticipated benefits of improved sleep quality for individuals who experience nocturnal leg cramps are considered to outweigh the risks for the study population.

7. Statistical Analysis

7.1 Analysis Populations

The primary analysis will be conducted on an intention-to-treat (ITT) basis, including all randomised participants regardless of adherence or study completion. A per protocol analysis will also be conducted as a sensitivity analysis, including only participants who reported consuming at least 80% of the planned doses and completed all primary outcome assessments. Results of both analyses will be reported.

All analyses will be conducted following database lock prior to unblinding. A two-sided significance level of $\alpha = 0.05$ will be applied throughout. Results will be reported as mean difference with 95% confidence intervals (CI).

Baseline demographic characteristics will be summarised descriptively for each treatment group and presented as mean ± standard deviation. No formal statistical testing will be performed on baseline characteristics, consistent with CONSORT guidance. Baseline characteristics to be summarised include: age, sex assigned at birth, ethnicity, body mass index, PSQI global score, average nocturnal leg cramp frequency per fortnight and average nocturnal leg cramp severity (VAS).

7.2 Primary Analysis

The primary outcome is PSQI global score at Week 6. The primary analysis will use an Analysis of Covariance (ANCOVA) model with Week 6 PSQI global score as the dependent variable, treatment group (active vs placebo) as the fixed factor, and baseline PSQI global score as covariate. The treatment effect will be expressed as the mean difference between groups at Week 6 with 95% CI and associated p-value.

A linear mixed effects model will also be fitted including all post-baseline timepoints (Weeks 2, 4, and 6), with treatment group, time, and their interaction as fixed effects, and baseline PSQI global score as covariate. An unstructured covariance matrix will be used. Where a significant interaction is observed, pairwise between-group comparisons will be conducted at each individual timepoint (Weeks 2, 4, and 6) using estimated marginal means, with results expressed as mean differences with 95% CIs and p-values. Where no significant interaction is observed, the main effect of treatment will be reported.

Prior to conducting the primary analysis, the following assumptions will be checked: normality of residuals (Shapiro-Wilk test and Q-Q plots); homogeneity of variance (Levene's test); and linearity of the relationship between covariates and the outcome. Where assumptions are materially violated, a non-parametric alternative or appropriate transformation will be applied and documented.

7.3 Secondary Analyses

All secondary outcomes will be analysed using the ITT population. Unless otherwise specified, the same ANCOVA approach as the primary analysis will be applied at Week 6, with the respective baseline value as covariate. Results will be reported as mean difference with 95% CI and p-values. To characterise the trajectory of treatment response, a linear mixed effects model will additionally be fitted for all secondary outcomes across all post-baseline timepoints (Weeks 2, 4, and 6). Where outcomes are not measured at a single visit, the value at each timepoint will represent the average over the preceding two weeks. Each model will include treatment group, time, and their interaction as fixed effects, and the respective baseline value as covariate. An unstructured covariance matrix will be used as the primary covariance structure. The group × time interaction will be used to assess whether the treatment effect varies across the study period, with pairwise between-group differences at each timepoint expressed as estimated marginal means with 95% CIs.

The following secondary outcomes will be assessed:

- Sleep quality (PSQI sub-domains): Each of the seven PSQI sub-domain scores will be analysed individually: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

- Nocturnal leg cramps: Leg cramp frequency and severity will each be analysed using the two-week average value at each timepoint, with the corresponding baseline average as covariate.
- Health-related quality of life: SF-36 total and domain scores will be analysed with baseline as covariate.
- Objective sleep outcomes (Oura Ring): The following Oura Ring parameters will each be analysed using the two-week average value at each timepoint: total sleep time, sleep efficiency, sleep latency, REM sleep duration, deep sleep duration, light sleep duration, total time in bed, number of nocturnal awakenings, and awake time.
- Objective physical activity outcomes (Oura ring): The following Oura Ring parameters will each be analysed using the two-week average value at each timepoint: Steps per day, Time in sedentary behaviour (%), Time in light physical activity (%), Time in moderate to vigorous physical activity (%), Number of sedentary breaks per day.
- Objective heart rate outcomes (Oura ring): The following Oura Ring parameters will each be analysed using the two-week average value at each timepoint: Resting heart rate (bpm), heart rate variability average (milliseconds), respiratory rate average.

7.4 Safety Analysis

All adverse events will be reported descriptively, including frequency and percentage of participants affected by treatment group. Serious adverse events will be listed individually. No formal hypothesis testing will be conducted on safety outcomes.

7.5 Missing Data Handling

Missing outcome data will be handled using multiple imputation under the Missing At Random assumption. Imputation models will include baseline PSQI score, treatment allocation, baseline nocturnal leg cramp frequency, age, and sex as predictors. A minimum of 20 imputed datasets will be generated and results pooled using Rubin's rules. A complete case sensitivity analysis will also be conducted and results compared with the primary imputed analysis.

8. Consent Process

8.1 Traditional Consent (Paper & Wet Ink)

This is a decentralised study and will not use traditional paper and wet ink consent.

8.2 Alternate Consent Process

There are no alternate consent processes in this study.

8.3 Electronic Consent

The study will use Trialflare for electronic informed consent. Trialflare is compliant with 21 CFR Part 11 and incorporates the following features: end-to-end encryption; timestamping and immutable logging of all consent actions; two-factor verification at the point of study enrolment via email or WhatsApp; independent biometric and liveness identity verification using government-issued identification; and auto-generation of a signed PDF consent record which is automatically distributed to both the participant and the research team and stored in the Trial Master File.

Following confirmation of initial eligibility, participants will be provided with the Participant Information Sheet and link to complete the electronic Informed Consent. Participants may take as long as they require, and members of the research team will be available throughout to answer any questions with via Zoom call or email. Participants who wish to proceed will complete the eConsent process within the Trialflare platform, providing their consent via electronic signature. Participants will also complete an identification verification process integrated within Trialflare and provided by KYCAID. Participants will agree to the KYCAID privacy policy before proceeding with the ID verification A signed copy of the consent form will be automatically provided to the participant and a copy stored in the Trial Master File.

Should the protocol be amended in a manner that may affect participant willingness to continue, affected participants will be re-consented prior to continuing study participation, using the same electronic consent process described above.

8.4 Waivers

Informed consent is mandatory for all participants and there will be no waivers permitted.

9. Sponsor & Collaborators

9.1 Sponsor & Collaborators

Sponsor and CRO: The study is sponsored by StudySetGo Ltd., a UK-based contract research organisation. StudySetGo holds overall legal and operational responsibility for the study and will manage all aspects of conduct, including IRB submissions, participant recruitment, data collection, and data analysis, in collaboration with the Principal Investigator.

Funder: The study is funded by Imagine Biolabs, LLC (trading as SaltWrap), who are also responsible for supplying both the active and placebo investigational products via their manufacturer and distributor. A Master Services Agreement (MSA) governing the relationship between Imagine Biolabs and StudySetGo has been executed.

Principal Investigator: Dr David Church is serving as Principal Investigator for this study in an independent consultancy capacity, providing oversight of study conduct, safety monitoring and ensuring the research is carried out in accordance with the approved protocol and applicable regulations. An Investigator Agreement between Dr Church and StudySetGo will be executed prior to enrollment of the first participant.

9.2 Declarations of Conflicts of Interest

The Coordinating Investigator for this study, Dr Tom Jameson, declares the following conflicts of interest. Dr Jameson is currently engaged as an Advisor to StudySetGo Ltd., the Sponsor of this study, and has a confirmed intention to transition to a full-time salaried directorship at StudySetGo Ltd. during the conduct of this study. Dr Jameson additionally holds equity in StudySetGo Ltd.

These interests are declared in full transparency. The following measures have been implemented to mitigate the potential influence of these interests on study conduct and outcomes: independent Principal Investigator oversight is provided by Dr David Church, who has no financial interest in StudySetGo Ltd. or in the outcome of this study; data collection and management will be conducted through Trialflare, an independent platform with a full data audit trail; and statistical analysis will be conducted by the StudySetGo research team independently of the funder.

The study is funded by Imagine Biolabs LLC (trading as SaltWrap), who also supply the active and placebo study products and therefore have a commercial interest in the outcome of this study. The funder will have no role in study conduct, data management, or analysis, and will not have access to unblinded data during the study period. In accordance with the Master Services Agreement between Imagine Biolabs LLC and StudySetGo Ltd., the funder will receive anonymised participant data upon completion of the study.

10. Privacy & Confidentiality

10.1 Data Minimisation & Pseudonymisation

Only data directly relevant to the study objectives and delivery will be collected. The categories of data collected in this study are: contact details (telephone number and email address; demographic information (name, date of birth, sex assigned at birth, ethnicity, self-reported body mass and height); home address for shipment of study materials); study questionnaire responses (PSQI, SF-36, nocturnal leg cramp diary, daily symptom reports, and supplement adherence records, end-of-study blinding integrity assessment); informed consent records; and biometric sleep, activity, and cardiovascular data collected continuously via the Oura Ring wearable device.

At screening, each participant will be assigned a unique alphanumeric StudySetGo Study ID. All research data will be linked to this study ID rather than to personal identifiers wherever practicable. A list linking personal identifiers and study IDs will be stored separately from the research dataset in the trial master file, accessible only to authorised personnel for safety monitoring or audit purposes.

Participant contact details (name, email address, telephone number, and home address) will be shared with Red Stag Fulfilment solely for the purpose of supplement shipment, and with Oura Health solely for the purpose of Oura Ring delivery. These disclosures are made for logistical purposes only and do not constitute research data sharing.

Participant questionnaire data and informed consent records will be stored within Trialflare, a clinical research data management platform. Trialflare is a UK-based software company whose servers are located in the United Kingdom. Participant data collected from US-based participants will be transferred from the United States to the United Kingdom, where it will be held by StudySetGo Ltd. as UK data controller, the organization responsible for this research. Participant data is protected by UK data privacy protection law and the security measures described in this protocol.

10.2 Data Security

All research data will be protected by appropriate technical and organisational security measures throughout the study and retention period.

Participant questionnaire data and informed consent records will be entered by participants directly into Trialflare. Trialflare is a UK-based clinical research data management platform hosted on UK-based servers. Trialflare is compliant with 21 CFR Part 11 and employs end-to-end encryption, role-based access controls, immutable audit logging of all data actions, two-factor authentication, and automated backup procedures. Access to study data within Trialflare is restricted to authorised members of the research team. Access to participant data will be authorised on a study delegation log and via Trialflare's role-based permission access rules.

Participant biometric data collected via the Oura Ring will be processed and stored by Oura Health Oy and its affiliates, including Ouraring Inc. (collectively "Oura"), via the Oura Enterprise Platform hosted on servers in the United States, in accordance with Oura's Terms of Use (last updated 20 April 2026), under which StudySetGo Ltd. will execute an Order with Oura Health Oy (Finland) as its contractual counterparty prior to study commencement, consistent with Oura's standard terms applicable to non-US buyers. Participants will separately be required to accept Oura's Terms of Use and Privacy Policy during initial device registration via the Oura App prior to any data collection commencing. In the event of any conflict between those terms and this Informed Consent Form, the Informed Consent Form will control with respect to research data, as expressly provided in Oura's own Terms of Use and Privacy Policy.

Oura's platform employs industry-standard encryption, secure AWS hosting, strict access controls, network protections, and ongoing vulnerability testing. Data ownership and control remain with StudySetGo Ltd. throughout the study.

As a study-level data minimisation measure implemented by StudySetGo, participants will register their Oura Ring using a participant-specific pseudonymous email address (e.g. SSG-[ParticipantID]@[email domain])

rather than their personal email, such that biometric data within the Oura Platform is not directly linked to participant identity within the research dataset. Participant name and shipping address will be provided to Oura solely for ring distribution via Oura's OrderHub platform and will be held separately from the research dataset maintained by StudySetGo. Upon registering the Oura ring with the smartphone app, participants will be required to provide in-app consent before any data becomes accessible to the study team.

No study data will be stored on personal or unencrypted devices. Authorised personnel will access research data only via secure, individually password-protected accounts.

10.3 Participant Rights & Applicable Privacy Regulations

This study is conducted in accordance with the US Federal Policy for the Protection of Human Subjects (45 CFR 46, the Common Rule), under the oversight of the IRB. This is the primary regulatory framework governing participant privacy protections in this study.

This study is sponsored by StudySetGo Ltd., a UK-based research sponsor and contract research organisation. As neither StudySetGo Ltd., the Principal Investigator, nor the Funder are HIPAA covered entities or business associates as defined under 45 CFR 160.103, HIPAA and the HIPAA Privacy Rule do not directly apply to this study. Participant privacy is protected under the Common Rule framework, the ethical oversight of the IRB, applicable Florida state privacy law (Florida Information Protection Act, Fla. Stat. § 501.171 et seq., FIPA), and UK data protection law governing data stored on UK-based servers. Under FIPA, in the event of a data breach involving personal information of Florida-resident participants, StudySetGo Ltd. is required to notify affected individuals within 30 days of discovery.

Participants will be informed of the following rights in the Participant Information Sheet and Informed Consent Form: the right to access information about how their data is being used at any time during the study; the right to withdraw from the study at any time without penalty or loss of benefits to which they are otherwise entitled; and the right to ask questions about data handling and to receive a clear response from the research team. Participants who withdraw will not have data already collected deleted, as retention is necessary to maintain the integrity of the research record and to satisfy regulatory requirements. Participants will be informed of this at the point of consent.

Participant data will not be sold, licensed, or disclosed to any third party other than those described in this protocol and the informed consent form, except as required by law or necessary for participant safety.

10.4 Data Retention & Sharing

All study records, including participant questionnaire data, Oura ring data, informed consent records, adverse event logs, and trial master file documents, will be retained for a minimum of 10 years following the end of the study. All data and documents will be archived in an access-restricted StudySetGo organisational Google Drive folder for a minimum of 10 years following the end of the study. Access will be restricted to authorised personnel only. Following the retention period, all personally identifiable data will be securely deleted or destroyed. Anonymised research data may be retained beyond this period for scientific purposes.

Participant biometric data collected via the Oura Ring will be processed and stored by Oura Health via the Oura Enterprise Platform in accordance with Oura's Terms of Use (last updated 20 April 2026).

A fully anonymised study report will be provided to the study funder, Imagine Biolabs LLC (trading as SaltWrap), upon completion of the study. This report will include the outcomes of all statistical analyses and anonymised aggregate and individual data. The funder will not receive any individually identifiable participant data at any time, in accordance with the Master Services Agreement between Imagine Biolabs LLC and StudySetGo Ltd.

Study results may be submitted for publication in a peer-reviewed journal or presented at a scientific conference. Any publication or presentation will use only anonymised aggregate data. No individually identifiable participant information will be disclosed in any publication or presentation. Results will be reported regardless of the direction or magnitude of findings.

10.5 Breach Response

StudySetGo Ltd. is committed to the protection of all participant data. In the event of a suspected or confirmed breach involving participant personal information or research data, the following response procedures will be followed.

Upon identification of a potential breach, the Coordinating Investigator and Principal Investigator will be notified immediately and all reasonably practicable steps will be taken to contain the incident and prevent further unauthorised access, use, or disclosure. A formal internal investigation will be initiated within 24 hours of identification to determine the nature, scope, and likely impact of the breach.

The IRB will be notified of any data breach involving participant information in accordance with the IRB's applicable reporting requirements and timelines.

In the event of a breach involving data held by Trialflare, StudySetGo Ltd. will engage with Trialflare's incident response procedures and coordinate notifications to affected parties as required. In the event of a breach involving Oura Ring biometric data, StudySetGo Ltd. will engage with Oura Health Oy's incident response procedures and coordinate notifications to affected participants as required.

In the event of a breach that involves personal information of Florida-resident participants, StudySetGo Ltd. will notify affected individuals within 30 days of discovery, as required under the Florida Information Protection Act (Fla. Stat. § 501.171). In the event of a breach involving Oura Ring biometric data held on the Oura Enterprise Platform, StudySetGo Ltd. will engage with Oura Health Oy’s incident response procedures and coordinate notifications to affected participants as required. Should the number of affected Florida residents equal or exceed 500, StudySetGo Ltd. will additionally notify the Florida Department of Legal Affairs, as required under Florida law.

All breach incidents, whether confirmed or suspected, will be documented in a breach log retained in the trial master file, including the nature of the incident, the parties affected, the response actions taken, notifications made, and the outcome of the investigation.

11. Reporting & Dissemination

The study will be registered on clinicaltrials.gov prior to enrolment of the first participant, and will be updated with a summary of findings following completion of the study.

A full anonymised study report will be provided to the study funder. This will include the outcomes of all statistical analysis and all anonymised raw and mean data.

The results of this study may be submitted for publication in an appropriate peer reviewed journal or submitted as a conference abstract.

Participants will receive a summary of the anonymised main study findings and will be informed of their unblinded group allocation if requested (following final unblinding of the study).

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