Study Protocol

A Pilot Observational Study Examining the Outcomes of Sip2Sleep®, a supplement containing Montmorency tart cherry extract and Venetron® on Sleep Disturbance In Adults.

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Abbreviation	Meaning
AE	Adverse Event
App	Application
CAPA	Corrective and Preventive Action
CFR	Code of Federal Regulations
CHLOE	Consumer Health Learning and Organizing Ecosystem
DTC	Direct to Consumer
GAD-7	Generalized Anxiety Disorder-7 Scale
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ISI	Insomnia Severity Index
NIH	National Institutes of Health
OTC	Over the Counter
PHI	Protected Health Information
PI	Principal Investigator
VAS	Visual Analogue Scale

1.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints/ Measurements
Primary Objective	
1. To observe the effect of the Sip2Sleep® product on sleep quality for participants with self-reported sleep disturbance	1. Change in average sleep quality score by 1 point as measured by daily 10-point visual analogue rating scale (VAS) from baseline and 1 week of no product use
Secondary Objectives	
1. To assess the effect of Sip2Sleep® product on symptoms of sleep disturbance 2. To assess the effect of Sip2Sleep® product on anxiety 3. To assess the effect of Sip2Sleep® product on the level of alertness during the daytime	1. Change in Insomnia Sleep Index (ISI) by 4.5 points from baseline and 1 week of no product use 2. Change in Generalized Anxiety Disorder-7 (GAD-7) by 4.5 points from baseline and 1 week of no product use 3. Change in average level of alertness during the daytime score by 1 point as measured by daily 10-point visual analogue rating scale (VAS) from baseline and 1 week of no product use
Exploratory Objectives	
1. To observe the change in sleep duration via personal health tracking wearable device 2. To observe the change in sleep latency via personal health	1. Change in average nightly sleep duration as measured via personal health tracking wearable device from baseline and 1 week of no product use 2. Change in average nightly sleep

tracking wearable device 3. To identify improvements for future participant-centered study designs using feedback	latency as measured via personal health tracking wearable device from baseline and 1 week of no product use 3. Assessment of patient satisfaction survey of study experience including design and use of app-based data collection tools

2.0 INTRODUCTION: BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

2.1 Introduction/Rationale for Development

Insomnia occurs in up to 50% of adults in the U.S., while chronic insomnia disorder is estimated to impair 10-15%.[1] Lack of quality and quantity of sleep negatively affects every part of an individual's life, both personally and professionally. Poor sleep is associated with various comorbidities including depression, stroke, cardiovascular disease, obesity, dementia and Alzheimer's disease, and increased risk of developing type 2 diabetes.[2,3,4,5] Furthermore, there has been an increase in evidence of the long-term harm (i.e., increased risk of cognitive dysfunction and impairment such as Alzheimer's disease) of taking prescription sleep aids such as Ambien, Lunesta, benzodiazepines, and OTC sleep aids like Benadryl.[6]

Sip2Sleep® was developed in conjunction with a leading sleep physician who has focused efforts in assisting patients improve sleep problems and insomnia by identifying the root cause(s) of the issues. Sip2Sleep® uses a proprietary formula of Montmorency tart cherry extract and Venetron®.

Montmorency tart cherry is a special kind of cherry that is known to provide a natural source of melatonin. The ruby red pigments in this specific cherry are proanthocyanidins, natural compounds that help increase the brain availability of tryptophan—an essential amino acid and precursor to the natural sleep aid serotonin. Proanthocyanidins inhibit an enzyme (indoleamine 2,3 dioxygenase) that degrades tryptophan, a known predictor of insomnia. The minimization of tryptophan degradation may allow tryptophan to work more effectively in the body while increasing bioavailability for serotonin synthesis, leading to a positive effect on sleep while improving mood and decreasing inflammation.[7,8]

Researchers at Louisiana State University presented data in 2018 showing that drinking Montmorency tart cherry juice just twice a day for two weeks helped increase total sleep time by nearly 90 minutes among older adults with insomnia. Greater than 75% of participants reported a positive response to the cherry juice with a significantly reduced amount of time to initiate sleep and improved ability to maintain sleep.[7]

Venetron® is a patented, purified, powdered extract derived from the Rafuma leaf, *Apocynum venetum*, which is a safe botanical alternative to St. John's Wort. It helps insomnia by:[9,10,11]

- Not affecting the CYP3A pathway in the liver that many OTC natural substances (St. John's Wort) and medications can impact. This means it does not increase the risk of side effects and other drug interaction
- Containing bioactive flavonoids
- Supporting serotonin concentrations in clinical trials by reducing the degradation of serotonin in the blood and brain, thus helping sleep and improving mood
- Producing a calming effect by acting on the GABA-ergic system

Together, Montmorency tart cherry extract and Venetron® are a powerful, natural solution to insomnia. They work synergistically to increase the presence of serotonin in the brain to improve sleep. Additionally, together they improve mood because Venetron® exerts a calming effect on the mind and helps the overactive mind relax for quicker, longer-lasting sleep.

2.2 Overview of and Rationale for the Study Design

The rationale for this study is to determine the effect of a consumer-grade, unique formula called Sip2Sleep®, which is a combination of Montmorency tart cherry extract and Venetron®, a patented, purified, powdered extract derived from the Rafuma leaf, *Apocynum venetum,* on sleep disturbance in adults. Because this product is currently available in the OTC market across the United States, a consumer-driven, decentralized observational clinical research study is well-suited for examining the effect of this formulation on sleep.

Sleep disturbance is highly prevalent and impacted by many interdependent variables. We will examine self-reported sleep disturbance in a broad age-range of adults who have chosen to use this product. The study will incorporate participant reported outcome questionnaires, daily surveys, and the participants' personal health tracking wearable device (e.g. Apple Watch, Fitbit, Smartwatch, etc.) to engage the participant in their sleep health and explore objective digital outcome measures of sleep. An important feature of this consumer-driven study design is to help individual consumers observe the effects of this product on their own sleep patterns during the study itself. There is no "doctor-patient" relationship as part of this research since the participant as a consumer is making the informed choice to take the product and take part in the observational process with self-reported measures. Findings from this study will contribute knowledge toward the design of future sleep research studies, the improvement of the Sip2Sleep® product formulation, and may help inform clinical recommendations for adults interested in using alternative products for sleep.

The following self-reporting measures are used in order to evaluate the effect of Sip2Sleep® in adults with self-reported sleep disturbance:

Surveys to reflect sleep quality, sleep latency, total sleep duration and level of alertness during the day to be distributed daily. Sleep quality and level of alertness during the day will be evaluated with a single 10-point visual analogue scale (VAS) and objective sleep data reflecting sleep latency and total sleep duration will be collected from personal wearable devices.

Insomnia Sleep Index (ISI) is a brief self-report instrument measuring the patient's perception of both nocturnal and diurnal symptoms of insomnia during the past two weeks. The ISI comprises seven items assessing the perceived severity of difficulties initiating sleep, staying asleep, and early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. Each item is rated on a five-point scale and the total score indicates the severity of insomnia, with a range of possible scores from 0-28. A score higher than 14 has been indicated to be the optimal cut-off for insomnia as a disorder. The ISI has been widely used in clinical and research settings as it is brief and easy to administer, and can provide valuable information for diagnosis and treatment planning. Research has found that the ISI is sensitive in detecting changes in the patient's perception of treatment outcome, and a good degree of convergence exists between the patient and the clinician's evaluation of insomnia severity.[13,14]

Generalized Anxiety Disorder-7 (GAD-7) is a self-reported anxiety survey utilized in primary care consisting of a 7-item anxiety scale. The instrument is well supported to use in a general population and normative data can be used to compare a subject's GAD-7 score with those determined from a general population reference group, with evidence of significant reliability and validity with congruent agreement in self-reported and interviewer-administered versions of the

scale. GAD and Depression symptoms frequently occur together, but previous studies have supported via factor analysis that this measure can detect GAD and depression as distinct dimensions.[15] This measure will be used in combination with other scales to observe self-reported effects on sleep disturbances and insomnia, such as anxiety or other psychiatric disorders.

3.0 SAMPLE SIZE, COHORT CHARACTERISTICS, ELIGIBILITY AND INVOLVEMENT

3.1 Sample Size and Cohort Characteristics

The sample size for this study will be 47 volunteers who meet the participant eligibility.

3.2 Eligibility

Participants must meet all the following criteria on screening examination to be eligible to participate in the study:

Inclusion

1. Age ≥ 18 years old
2. Has self-reported sleep disturbance
3. Insomnia Severity Index (ISI) score of ≥ 15 at screening
4. Interested in understanding more about the quality of their sleep and chose to use the Sip2Sleep product for sleep
5. Willingness to do a minimum of 1 week wash out of current OTC or other products for sleep (e.g. melatonin, anticholinergics)
6. Willingness to do a minimum of 1 week wash out of any cannabis products
7. Able to receive shipment of the product at an address within the United States
8. If taking prescription hypnotics (e.g. zolpidem, zaleplon, benzodiazepines) or other class of medication for sleep, must be on a stable dose for at least 4 weeks.
9. Able to read and understand English
10. Able to use a personal smartphone
11. Has and is able to use a personal health tracking wearable device (e.g., Apple Watch, Fitbit Smartwatch, Oura Ring, etc.)
12. Able to understand and provide informed consent
13. Able to complete study assessments over 5 weeks

Exclusion

1. Research participants who have no computer, smartphone, and internet access and/or do not use a computer or smartphone
2. Concomitant Therapies:
    a. Participants taking daily prescription medication for sleep (for example, prescription hypnotics like zolpidem, zaleplon, benzodiazepines) not on a stable dose for at least 4 weeks
    b. Participants receiving Cognitive Behavioral Therapy for Insomnia (CBTi)

c. Participants receiving any investigational therapies or treatments

3. Other Illnesses or Conditions: Participants who have the following co-morbidities are excluded:

   a. Confirmed diagnoses of the following sleep disorders: Narcolepsy, Restless Leg Syndrome, Circadian Rhythm Disorders

   b. Confirmed diagnosis of Sleep Apnea that is untreated or not well controlled

   c. Current or prior psychotic disorder

   d. Current or prior Substance Abuse Disorder

   e. Current or prior cardiac dysrhythmias (for example, atrial fibrillation, supraventricular tachycardia)

   f. Currently pregnant, planning to become pregnant in the next 1 month, or breastfeeding

   g. Allergies or adverse reactions (for example, anxiety) to Montmorency tart cherry extract and/or Venetron®

3.3 Duration of Participation and Overview of What is Expected from Participants

Participants will complete a 5-week study consisting of screening assessments, baseline scales and surveys, objective digital measure, 2 weeks of product use (1 week on - 1 week off - 1 week on), scales and surveys, and end of study assessments and surveys. This is a remote observational study that will use the People Science app-based data collection platform Consumer Health Learning and Organizing Ecosystem (CHLOE) for study participants to report their assessments and collect objective sleep data from personal wearable devices. Participants will receive the study product during the baseline period. Demographic and medical history data will be collected for the study.

3.4 Participant Recruitment

Participants will be recruited through professional networks and email/social media channels. Advertisement will be in digital format and will link to a study landing page to enable sign up.

4.0 STUDY ACTIVITY CALENDAR

Table 4.1 Study Calendar

Protocol Activities	Screening[a]	Study Duration[b]				
		Baseline	Product Use[c]	No Product Use	Product Use[c]	End of Study
Week	Up to 1 Week	Week 1	Week 2	Week 3	Week 4	
Day	Day -7 to -1	Day 1	Day 8	Day 15	Day 22	Day 29
Informed Consent	X					
Demographics	X					
Medical History	X					
Insomnia Severity Index	X	X	X	X	X	X
Eligibility	X					

Daily Objective Data Collection and Surveys[d]		X	X	X	X	X
Use of Study Product			X		X	
Generalized Anxiety Disorder-7		X	X	X	X	X
Experience Survey						X

a. Screening to occur within 7 days prior to Baseline (Day 1)
b. Planned duration of study is 4 weeks
c. Participants to consume Sip2Sleep® product 30-60 minutes prior to lying down in bed.
d. Participants will complete daily surveys to review objective data from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.

5.0 RECRUITMENT, CONSENT AND ENROLLMENT

5.1 Recruitment

Participants will be recruited from several channels including outreach to sleep clinics, sleep physicians and providers, Sip2Sleep® customer base via the product website, People Science community base and social media. Social media channels may include Facebook, Reddit, Instagram, and Google.

Recruitment outreach will consist of IRB approved advertising by email, digital flyers/postcards, printed flyers and word of mouth to patients.

A study landing page will provide information about the study and criteria for qualification. The landing page will lead to an IRB approved pre-screening questionnaire to determine qualification and then collect first and last name, email, phone number, and zip code of qualified individuals. New leads will receive further instructions by email to continue the enrollment process.

5.2 Consent

Virtual electronic informed consent, including a study specific privacy authorization and the California subject's bill of rights (as applicable) will be conducted through a HIPAA compliant cloud-based platform to obtain electronic consent that will ensure that the consenting process follows all required elements (see Section 7.0). A digital copy of the signed consent will be stored with the participant's profile in the study data platform which is the same technology used for electronic consent. In addition, a copy of the signed consent document will be available to the participant within the CHLOE app.

5.3 Enrollment

Eligible participants who provide virtual electronic consent will be automatically registered into the study by CHLOE (see Section 12.6). Participants will be asked to complete a screening ISI assessment and 3 additional screening surveys to review demographics, medical history, and product shipment address if eligible.

After confirmation of eligibility, the participant will be enrolled in the study and receive an email with instructions to start study assessment in CHLOE and await Direct to Consumer (DTC) shipment of the Sip2Sleep® study product.

6.0 STUDY PROCEDURES

6.1 Study Overview

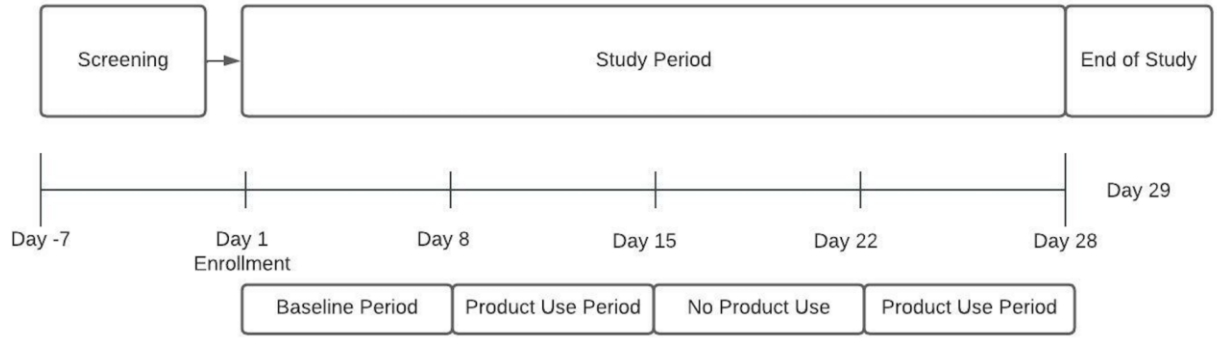

Figure 1. Study Design

Upon enrollment, the study assessments can be accessed via CHLOE mobile app available on Apple iOS and Android devices as well as any web browser. The participant's activities are as follows:

Screening (Day -7 to Day -1):

- Informed Consent
- Complete demographic and medical history data intake.
- Screening Insomnia Severity Index (ISI) assessment.
- Provide preferred shipment address for product shipment during Baseline.

Baseline Period (Day 1 to Day 7):

- Complete Insomnia Severity Index and Generalized Anxiety Disorder-7 (Day 1 only).
- Begin discontinuation of non-prescription products used for sleep.
- Begin nightly use of personal health tracking wearable device through Day 28.
- Complete daily survey to review objective data (sleep duration and sleep latency) from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.
- Receive shipment of study product and instructions for use.

Product Use Period (Day 8 to Day 14):

- Complete Insomnia Severity Index and Generalized Anxiety Disorder-7 (Day 8 only).
- Continue nightly use of personal health tracking wearable device through Day 28.
- Complete daily surveys to review objective data (sleep duration and sleep latency) from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.
- Administer nightly dose of study product 30-60 minutes prior to lying down in bed through Day 14.

No Product Use Period (Day 15 to Day 21):

- Complete Insomnia Severity Index and Generalized Anxiety Disorder-7 (Day 15 only).
- Continue nightly use of personal health tracking wearable device through Day 28.
- Complete daily surveys to review objective data (sleep duration and sleep latency) from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.

Product Use Period (Day 22 to Day 28):

- Complete Insomnia Severity Index and Generalized Anxiety Disorder-7 (Day 22 only).
- Continue nightly use of personal health tracking wearable device through Day 28.
- Complete daily surveys to review objective data (sleep duration and sleep latency) from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.
- Administer nightly dose of study product 30-60 minutes prior to lying down in bed through Day 28.

End of Study (Day 29):

- Complete Insomnia Severity Index and Generalized Anxiety Disorder-7.
- Complete surveys to review objective data (sleep duration and sleep latency) from wearable device collection and answer questions about their prior night's sleep quality and level of alertness since waking.
- Complete Experience Survey.

7.0 DATA COLLECTION AND MANAGEMENT

7.1 Data Collection Elements, Source, and Method of Collection

For recruitment purposes only, a data set limited to name, email, telephone number, and Study ID number will be generated manually. For analysis, data from the assessments and sleep data will include the Study ID number and demographic factors (age, gender, race, ethnicity), medications, and supplements.

7.2 Data Management

Research Data Capture System

This project will be utilizing People Science's proprietary platform, CHLOE. All data is securely stored on People Science Amazon Web Services HIPAA compliant servers. The platform contains modules for building and managing forms / surveys, landing pages, marketing outreach with tracking tools for recruitment, audited electronic consent forms, data management and analytics using an integrated relational database. Data from completed assessments will automatically be collected for analysis. Study monitoring can be done using reporting features.

7.3 Data Management at Study Completion

For longer term storage of the data that will reduce risk of a data breach while still permitting that the data be verifiable (audited) the dataset will be de-identified - no names, etc., and all dates turned into time- and coded, and the key to the code will be housed in a separate location. The data will be maintained under password protection in the database.

8.0 CODING OF DATA

The data set for recruitment (name, telephone number and Study ID number) and the data listed in Section 7.1 for analysis will be stored on a password secured database with access only to designated study team members and the PI.

9.0 STATISTICAL CONSIDERATIONS.

9.1 Sample Size Estimation and Justification

We anticipate needing to screen approximately 200 individuals to enroll up to 80 individuals and achieve a final sample size of approximately 47 evaluable participants. For our primary outcome (i.e. change in average sleep quality VAS scores), we assume a common standard deviation = 2 and a conservative 0.50 correlation between VAS scores. We will have at least 90% power to detect a mean VAS score difference of 1 with alpha = 0.05 using a two-sided Wilcoxon signed-rank test for the difference between dependent means with a final sample of 47 participants. Previous research on participants with insomnia and depression have suggested that single item sleep quality score can effectively detect meaningful changes in sleep quality over time relative to lengthier questionnaires.[16]

The secondary objectives include evaluating changes in the ISI, GAD-7 and daytime alertness VAS score. As above, we anticipate at least 90% power to detect a 4.5-point change in the ISI and GAD-7 with an expected standard deviation of 5. For daytime alertness, we anticipate at least 90% power to detect a 1-point change with an expected standard deviation of 2.

9.2 Projected Study Timeline - Accrual, Data/Sample Collection, Completion

The final sample size for this observational study will be 47 participants.

We anticipate screening, enrollment and data collection to be complete in 3-4 months. Study closeout will be complete in 2 weeks, Data analysis will be complete in 2 months and a CSR and lay summary will be complete in 3-4 weeks. Altogether, the study duration is estimated to be 8 months.

The final analysis will take place after approximately 47 evaluable patients have completed all final study instruments. These activities will be completed approximately 29 days after enrollees initiate participation in the study.

9.3 Evaluable Participants

Participants will be considered evaluable for analysis if:

1. They complete all the study assessments, with at least 60% completed daily assessments in each arm (Product Use vs. No Product Use); AND
2. Objective sleep data from personal wearable devices are collected.

9.4 Covariates and Subgroups

Demographic and baseline values will be collected and analyzed on all participants. Data on age, gender, race/ethnicity, medical diagnoses, sleep prescriptions, sleep supplements, alcohol and cannabis use, smartphone operating system (Android or iOS), and use of personal health tracker

(e.g. Apple Watch, Fitbit) will all be collected and included in univariate, bivariate, and multivariate analyses. Subgroup analyses will be conducted to examine differences in outcome by all covariates available.

9.5 Missing Data

Missing data will be imputed with a value of "999". The proportion of missingness will be evaluated among all covariates and outcome variables. If data are missing on a variable in under 5% of cases and the assumption of missing completely at random can reasonably be made, only observed data will be used in the analysis. If a variable is missing within a range of 5%-40% of cases, use of multiple imputation will be evaluated. Regression analyses will be conducted using only complete cases.

9.6 Statistical Analysis Plan

The primary objective of this study is to determine the impact of Sip2Sleep® use on symptoms of sleep disturbance, as measured by the change in sleep quality VAS scores from 47 participants. Univariate statistics will be generated to describe the distribution of patient characteristics and outcome data. Continuous variables will be described using means, standard deviations, minimums and maximums while categorical variables will be described using counts and percentages. Sleep quality VAS scores will be compared from baseline pre-treatment; and at end of study (post-treatment) of the same individuals. We will enroll up to 80 participants to achieve at least 90% power to detect a mean change in sleep quality VAS scores of 1 points (SD=2) from baseline with a type I error of 0.05 (two-sided) assuming a paired means, dependent Wilcoxon Signed-Rank test. We are testing the null hypothesis that there is no difference between pre-treatment and post-treatment mean sleep quality VAS scores within study participants. Summary statistics will be generated, and paired differences between pre-treatment and post-treatment sleep quality VAS scores will be reported, along with 95% confidence intervals.

Additionally, parametric linear mixed models will be employed to simultaneously account for correlated observations and adjust for confounding variables (Proc Mixed, SAS). Several covariance structures, including compound symmetry and unstructured, will be evaluated by comparing AIC and BIC to identify optimal model fit. Random slope and intercept will also be considered in a similar manner. Patient characteristics (i.e. age and sex) will be included in adjusted models a priori for confounding control. Directed acyclic graphs will be employed to select other potential confounding variables and identify biases during the model fitting process. Large differences will be further examined and may help identify where further calibration of estimation models are needed.

Stratified and interaction analyses will be employed to detect between-subgroup differences in outcomes. Specifically, we will test the difference in sleep quality VAS score change between sexes and those who reported moderate-to-severe insomnia disorder on the ISI (i.e. ISI score > 14) and those who did not (i.e. ISI score ≤ 14). Testing of these differences will be conducted by including 2-way product terms between the exposure and covariate of interest in linear mixed modeling. A significant interaction will be defined by an interaction coefficient with a p-value < 0.05.

9.7 Reporting Conventions

Confidence intervals and p-values will be reported at two decimal places, except when p-values are less than 0.01. P-values less than 0.01 will be reported as "< 0.01" and p-values less than 0.001 will be reported as "<0.001".

9.8 Quality Assurance of Statistical Programing

SAS 9.4 will be used for all data analyses in a Microsoft Windows environment. All analysis code will include the author's name, date/time of writing, reference to location and nature of inputs, reference to any parent code, and detailed comments to aid in its interpretation and implementation. A secondary statistician will have access to raw data and the opportunity to independently create the main analyses. They will also be given access to the primary code to review its validity.

10.0 STUDY COMPLIANCE AND REPORTING OF DEVIATIONS FROM APPROVED PROCEDURES

Deviations

A deviation is a divergence from a specific element of a protocol and that occurred without prior IRB approval. Deviations from the approved protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. All deviations from the protocol will be documented in study source documents and promptly reported to the IRB.

Reporting Deviations

Investigators may deviate from the protocol to eliminate immediate hazards for the protection, safety, and well-being of the study subjects without prior IRB approval. For any such deviation, the PI will notify the IRB, within 5 calendar days of its occurrence by electronic submission of a deviation notice.

11.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

The study team will be familiar with anticipated and unanticipated adverse experiences. The Principal Investigator (PI) is responsible for monitoring protocol conduct and reporting to the Institutional Review Board (IRB).

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Ethical and Regulatory Standard

Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

Regulatory Standard

This study is to be conducted in compliance with the IRB approved protocol and according to applicable federal, state, local and tribal laws including the following:

- US Code of Federal Regulations (CFR) governing clinical study conduct: Title 45 Part 46 – Protection of Human Subjects
- US Code of Federal Regulations relating to the Health Insurance Portability and Accountability Act of 1996: Title 45 Part 164 – Security and Privacy – Subpart E -
    - Subpart E—Privacy of Individually Identifiable Health Information
- State of California Health and Safety Code, Title 17, for research conducted in California

In addition, this study is to be conducted in compliance with applicable policies and procedures of the IRB(s) of record, applicable institutional research policies and procedures, applicable institutional clinical policies and procedures, and applicable NIH policies and procedures.

Institutional Review Board

The protocol, informed consent form(s), recruitment materials and all participant materials will be submitted to the IRB of record for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendments to the protocol or consent materials will require review and approval by the IRB before the changes are implemented in the study.

Per the federal regulations at 45 CFR 46 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent process and its documents prior to initiation of the study. All institutional, NIH, Federal, and State of California regulations must be fulfilled.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning participant recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the investigator before the study is initiated.

Any amendment to the protocol document and accompanying informed consent documents, as developed and provided by the PI, will require review and approval by the IRB of record before the changes are implemented in the study.

12.2 Risk Benefit Considerations

Discomforts, Risks, and Risk Mitigation

- Risks associated with the Survey: The questions used in this survey may cause temporary discomfort or distress to the participant. The survey is designed to be simple and short and is a commonly used tool in clinical studies for sleep. The participant may choose not to complete the questionnaire.
- Risks associated with Breach of Confidentiality: There is a small risk that people who are not connected with this study will learn of the participant's identity or personal information. The study staff will be GCP trained and will utilize best practices when using the data platform to ensure participant privacy protections.

Risk Level Determination

The risks to the study are minimal or unanticipated due to appropriate mitigation measures (e.g. breach of confidentiality, loss of internet access). This research meets the federally defined definition of minimal risk (45CFR 46.102(j)).

Direct benefit to research participants

Research participants have the opportunity to engage with scientists in tracking their sleep and use of the Sip2Sleep product. They will receive $25 upon completion of study activities.

Importance of the knowledge that may reasonably be expected

This research is significant and important because it facilitates an innovative way of science where participants can be engaged to learn about their own response to their chosen intervention and the Sponsor and the public may gain knowledge about a potentially effective and safe sleep remedy.

12.3 Participant Characteristics

Research equity

This research has no direct exclusions related to gender. There are also no direct exclusions related to race or ethnicity.

Vulnerable Populations

Pregnancy and lactation are exclusions due to the unknown risks of product use to fetuses and newborns.

There are exclusions for individuals with specific sleep diagnoses that require medical intervention.

Volunteers with impaired decision-making capacity are excluded.

Volunteers unable to personally provide informed consent (including but not exclusive of inability to speak and read English, hearing or sight impaired, etc.) will be excluded from participating in this research.

12.4 Financial Obligation, Burden, and Compensation to Participants

Completing research activities (not from results/findings or injury)

Research activities will be conducted virtually.

Participants will receive compensation for their time. A $25 gift card will be provided by study staff to participants upon study completion.

Research results or clinical findings arising from research activities

Due to the nature of the study, it is unlikely that research results or findings from research activities will result in further medical-related expenses for the participant.

12.4 Confidentiality/Sharing/Publication

Return or Clinical Use of Research Results

Participants will be shown their study data in real time as they go through the data visualization modules in the CHLOE platform.

Research results will be shared with participants at completion of data analysis. The results of this research may help the participant make decisions in future product purchases and participate in future research studies.

There are no anticipated burdens or financial obligations to research subjects.

Confidentiality

All documents and electronic data will be stored on secure, password-protected computers. Participant confidentiality will be strictly held in trust by the investigators, study personnel, and sponsor. No identifiers will be used in any subsequent publication of these results.

Information/Data Retention, Future Use, and Sharing

Prior to the completion of this research, information will be coded, destroyed, de-identified, or provided to a privacy officer.

Publication

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996. Neither the complete nor any part of the results of the study carried out under this protocol, nor

any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide the sponsor with all data derived from the study.

12.5 Alternatives to Participation, Withdrawal, and Early Termination

Alternatives to Participation

The individual can choose not to participate.

Participant Withdrawal from Research/ Research Activities

Research activities are limited to five weeks.

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented.

12.6 Informed Consent, HIPAA Authorization, and California Subject's Bill of Rights

Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Operational details specific to the consenting process that occurs prior to any research evaluations/interventions are described in Section 6.0.

All participants will undergo virtual electronic informed consent after they are determined to qualify for the study. An electronic informed consent document will describe the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other IRB approved information. In addition, the experimental participant's bill of rights and the HIPAA research authorization form will be provided. Prospective research participants will be informed that they may withdraw from the study at any time and for any reason without prejudice. Prospective research participants will be afforded sufficient time to consider whether to participate in the research.

Virtual informed consent will be conducted through the app-based consent form at the participant's convenience. After reading the consent, participants will be able to contact study staff about any study related questions. Once the prospective participant expresses full understanding, virtual informed consent will be obtained through electronic signature from either the prospective participant before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements. A copy of the signed consent document will be available to the participant within the CHLOE app. The signed consent must be maintained by the investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Privacy Authorization

The informed consent process will include a privacy authorization compliant with 45CFR164.508(c) via the inclusion/incorporation of:

- all core elements specified in 508(c)(1) including the signature of the individual (or representative) and date of signature,
- all required statements specified in 508(c)(2)
- the plain language requirement as specified in 508(c)(3), and

- the provision to the participant (or representative) a copy of the signed authorization (508(c)(4)

State of California Human Experimentation Requirements

This research involves the collection of information via validated questionnaires and obtaining information from the medical record. Research activities do not encompass those that are requisite for a participant to be involved in a "medical experiment" as defined by California State Law 24174. The 'California Experimental Subject's Bill of Rights' will be administered as part of the informed consent process; as part of that process participants will receive a copy of the 'Bill of Rights' marked with their signature.

12.7 Investigator Conflict of Interest

Investigators will disclose any conflict of interest from People Science.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor prior to participation in this study. All investigators will follow the conflict of interest policy.

13.0 REFERENCES

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