Mount Sinai

Icahn School of Medicine at Mount Sinai
Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital
Mount Sinai Queens
New York Eye and Ear Infirmary of Mount Sinai
Mount Sinai St. Luke's
Mount Sinai West

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Amendment
IRB-18-00343
Noah zimmerman

Table of Contents

2. Summary - Title

Protocol Title

Data Driven Health Decisions in the Wild: A Platform for Actionable N-of-1 Studies

Principal Investigator [redacted]

When the application is complete, it will be sent to the PI for submission

When the application is complete, it will be sent to the PI for submission

Primary Department Genetics and Genomic Sciences

When the application is complete, it will be sent to the PI for submission

Application Initiated By [redacted]

Lay Summary

The growing consumer-grade molecular and digital wellness market is generating unprecedented volumes of information to support decision-making around individual health. Current trends suggest the demand for personalized health information, tools, and services will continue to rise in the next decade. What is missing is a reliable, individualized way to turn this data into action. Dialogue around consumer health often ignores the disconnect between measurements and goals-for example, monitoring one's weight is not the same as losing weight, and counting steps is not the same as lowering blood pressure. If individuals are to benefit from data, they must be able to relate changes in their personal data to targeted changes in actions and outcomes. There is a great need and opportunity to adapt the tools and capabilities of modern computer science, statistics, and clinical trial design to the needs of individual patients and consumers. Our team at the Institute for Next Generation Healthcare (INGH) has created a smartphone app and study platform to allow individuals to design, implement and analyze methodologically sound, statistically robust studies of their personal health data.

IF Number IF2247892

3. Summary - Setup

Funding Has Been Requested / Obtained	No
Application Type	Request to Rely on Mount Sinai IRB
Research Involves	Prospective Study ONLY
Consenting Participants	Yes
Requesting Waiver or Alteration of Informed Consent for Any Procedures	Yes
Humanitarian Use Device (HUD) Used Exclusively in the Course of Medical Practice	No
Use of an Investigational Device to Evaluate Its Safety or Effectiveness	No
Banking Specimens for Future Research	No
Cancer Related Research that Requires Approval from the Protocol Review and Monitoring Committee (PRMC).	No

Is this Cancer Related Research? Cancer Related Research is defined as research that has cancer endpoints or has a cancer population as part of or all of its targeted population. This includes protocols studying patients with cancer or those at risk for cancer.

Clinical Trial	Yes

**** A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).***
**** Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.***

Drugs / Biologics	Yes

**** Drugs / Biologics That Are Not a Part of Standard Practice***
**** Controlled Substances***
**** Drugs / Biologics Supplied by the Research Sponsor or Purchased with Study Funds***

Ionizing Radiation for imaging or therapy, including X-Ray, Fluoroscopy, CT, Nuclear Medicine, PET andor Radiation Therapy:

*** Purely for standard of care:**	No
*** In frequency or intensity that exceeds what is necessary for standard of care:**	No

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Hazardous Materials	No

**** Recombinant DNA***

**** Viral Vectors***
**** Plasmids***
**** Bacterial Artificial Chromosomes***
**** Toxic Chemicals, Potentially Toxic Medications, Carcinogens***
**** Autologous Cell Lines***

Request Use of Clinical Research Unit Resources No

4. Summary - Background

Objectives

Our objective is to evaluate users' ability to complete and interpret results from studies run on our N-of-1 platform.

Research Questions:
1. Do N-of-1 studies conducted on our platform result in meaningful and actionable results for individuals?
2. What factors affect an individual's ability to complete an N-of-1 study?

We have created a smartphone app and study platform that together allow individuals to design, implement, and analyze methodologically sound, statistically robust studies of their personal health data. The focus of the platform will be the creation of single-participant randomized crossover studies, known as N-of-1 studies. The platform employs informatics-based intelligence that automates study design and analysis while simultaneously maintaining high standards of statistical rigor and reproducibility.
These novel methods and tools are designed to empower individuals to make rational, data-driven choices about their own health, maximizing the benefit we all receive from new and existing sources of personal health data.

Background

The growing burden of chronic disease in the U.S. and the economics of accountable care are driving a shift toward proactive approaches to disease prevention and health maintenance. At the same time, precision medicine studies continue to reveal substantial heterogeneity in the manifestations of even the most common chronic diseases. The bulk of morbidity and mortality in the U.S. arises from conditions with a significant lifestyle component (e.g. type II diabetes), and responsibility for monitoring and maintaining health largely falls on individuals.

Recent advances in molecular biology, sensors, and digital health technology underlie rapidly growing market availability of products and devices for measuring and monitoring individual health. A vast array of wearable devices, smart home monitors, and health tracking apps provide an unprecedented view of individuals "in the wild". Products and services from companies such as 23andMe (genomics) and uBiome (microbiome) provide customers with health information once accessible only to researchers. The growing digital health market is generating unprecedented volumes of information to support decision making around individual health, and current trends suggest the demand for personalized health information, tools, and services will continue to grow in the next decade.

What is missing from this technological and scientific growth is a reliable, individualized way to translate data into action. If we as a society want to prevent diabetes, heart disease, and other chronic illnesses that kill millions of Americans each year, we must empower individuals to address precursor conditions like obesity, hypertension, and depression. Dialogue around consumer health often fails to address the profound disconnect between measurements and outcomes/goals; e.g. monitoring one's weight is not the same as losing weight, and counting steps is not the same as lowering blood pressure. Data are only useful if they can help individuals identify interventions that work for them. The combination of diet, exercise, drugs/supplements, activities, and lifestyle changes that targets an individual's particular set of health problems is unique to him or her, and it is dependent on a complex web of factors including genetics, environment, and personal lifestyle. If individuals are to benefit from data, they must be able to relate changes in their personal data to targeted adjustments in actions and outcomes. This effectively necessitates conducting a robust trial at the level of the individual to determine the most promising recipe of personal lifestyle adjustments to effect change.

To address these challenges, we have developed a unified statistical framework for producing consistent, interpretable study results from diverse N-of-1 study designs. Our analysis framework is the backbone of our initial software platform, which includes modules for study design, data ingestion, data analysis, and visualization of results.

To test this platform, we plan to deploy a single N-of-1 study design across a population of approximately 500 individuals to test the cognitive effects of caffeine in combination with a safe, prevalent compound ("L-theanine"), compared to the effects of caffeine alone. Each individual will participate in his/her own study, with treatments ("caffeine alone, caffeine + L-theanine") applied in sequence to assess whether L-theanine has a cognitive effect beyond that of caffeine alone for that person. The software platform will connect wearable devices, health trackers, and survey instruments that correspond to health goals outlined in this prototype N-of-1 study design.

It is important to state explicitly that the research objectives for this protocol are not related to the efficacy of L-theanine and caffeine. This specific study is designed to allow us to efficiently recruit and enroll subjects so that we may evaluate the underlying statistical methods and software platform for executing N-of-1 studies. The following

protocol sections are divided into (1) descriptions specific to the general N-of-1 platform, and (2) descriptions specific to the prototype study.

Primary and Secondary Study Endpoints

Primary endpoints:
o Study completion: Percent of individuals that complete their N-of-1 studies after study initiation
o Meaningful results: Percent of individual N-of-1 studies that yield statistically conclusive results, for the comparisons (a) caffeine vs. baseline, (b) L-theanine + caffeine vs. caffeine alone

Secondary endpoint:
o Adherence: Percent of total actions required for the study (e.g. completing the intervention and assessment) successfully completed, by individual and in aggregate.

Protocol Was Already Approved by the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB) Under a Different Principal Investigator	No

Protocol Was Previously Submitted to an External(non-ISMMS) IRB	No

5. Research Personnel

Name/Department	Role/Status	Contact	Access	Signature Authority	Phone	Email
[redacted]	Principal Investigator /	[redacted]				
	ARC /					
	ARA /					
	ARA /					
	ARC /					
	ARA /					
	ARA /					
	ARA /					
	ARA /					
	RN /					

6. Sites

Site Name	Icahn School of Medicine at Mount Sinai
Other External Site Name	
Contact Details	
Approved	
Approval Document	
Funded By Mount Sinai	
Other IRB	

7. Subjects - Enrollment

Site Name	Icahn School of Medicine at Mount Sinai
Subjects To Be Enrolled	
500	
Total Number of Subjects to be Enrolled Across All Listed Sites Above (Auto Populated)	500

8. Subjects - Populations

Inclusion Criteria

N-of-1 platform: Anyone that lives in the US may download our N-of-1 study app from the Apple App Store. Only the US Apple App store will have the app available (effectively blocking people from outside the US from downloading the app)

Prototype study: Inclusion for the prototype study will be determined through a pre-consent screener survey. Inclusion criteria for enrollment into the study will include:
1. Adult 18 years of age and older
2. Regular caffeine drinker
3. Able and willing to give informed consent and to comply with the requirements of this study protocol
4. Possession of an iPhone

Exclusion Criteria

N-of-1 platform: None

Prototype study: Exclusion for the prototype study will be determined through a pre-consent screener survey. Exclusion criteria for enrollment into the prototype study will include:
1. Unable to read English or not willing to provide consent in English
2. Under 18 years of age
3. Pregnant or breastfeeding
4. Anyone with a contraindication for caffeine (a health problem that inhibits an individual from drinking caffeine)

The pre-consent screener will assess for age, pregnancy/breastfeeding status, and contraindications.

Enrollment Restrictions Based Upon Gender, Pregnancy, Childbearing Potential, or Race	Yes

Justify Restriction(s)

Caffeine poses health risks to babies for women who are pregnant or breastfeeding.

Age Range(s)	18 to 64 Years, 65 Years and Over
Targeted Population(s)	Adults - Healthy Controls

Other Aspects that Could Increase Subjects Vulnerability

N-of-1 platform & prototype study: Employees/students of Mount Sinai will not specifically be targeted for the app or study, but there is a chance they will enroll due to the app's open, country-wide availability.

Beta-testers of the app will include individuals who expressed interest in the research project as it was being developed. They are likely to be friends and family of the research team, and they will be testing the app before it is fully launched on the Apple App Store. Friends and family may feel pressured to use the app even if they don't want to.

Safeguards to protect Subjects rights and welfare

N-of-1 platform & prototype study: Undue influence will be reduced through the absence of an economic or work-related incentive. Participants will also have the opportunity to consent remotely to the prototype study, which would relieve potential pressure of agreeing to participate in the presence of research staff.

Re: beta testers--We will ensure that individuals asked to be beta testers know that downloading and using the app is completely optional.

9. Subjects - Participation

Duration of an Individual Subjects Participation in the Study

Prototype study: Up to 1 month

Duration Anticipated to Enroll All Study Subjects

N-of-1 platform: indefinite
Prototype: indefinite

Estimated Date for the Investigators to Complete This Study Within two years

Procedures for Subjects to Request Withdrawal

N-of-1 platform: If an app user chooses to delete their N-of-1 app account, they may do so in the settings section of the app. This will not withdraw the user from the prototype study, though they will not be able to continue with study assessments and logs if they delete their account.

Prototype study: If a study participant chooses to withdraw from the prototype study, they may do so within the app. They will also be able to withdraw by contacting the research team through a provided email address available on the app and provided on the app website (n1app.org). A participant's decision to withdraw will not be questioned and will not require justification. If the participant withdraws from a study and requests that the data be destroyed, all data associated with that account will be removed from the database. Any result already analyzed or published will not be able to be destroyed; this type of destruction is impossible because of the nature of the research results, which are statistical, aggregated, and anonymous.

A participant's previously-collected data may still be used by the study team unless the participant explicitly requests that all data be deleted. We will not continue to collect additional participant data related to the prototype study. Study withdrawal does not inhibit them from participating in a different study on the N-of-1 app in the future, once other IRB-approved studies are made available. Withdrawal also does not inhibit them from restarting this prototype study at a later date (they would need to provide consent again).

Procedures for Investigator to Withdraw Subjects

N-of-1 platform: App users will be blocked from using the app if they are found to be misusing the app in any way, at the discretion of the research team. Misuse may warrant an initial warning to the user and subsequent removal of the users N-of-1 app account.

Prototype study: Participants of the prototype study may be withdrawn without their consent only in rare instances after continued notice from the research team. This withdrawal will be at the research team's discretion based on the magnitude of the issue. For instance, a participant may be withdrawn from the study if they are found to be using more than the recommended dose of L-theanine or caffeine to a point at which they introduce risk of harm to themselves.

If an app user or study participant is withdrawn without their consent, they will receive an email from the study team indicating that their account has been terminated.

Participants Will Be Recruited Yes

Recruitment Method(s) Facebook, Twitter, Other Website, Other

Specify Other Recruitment Method

N-of-1 platform: To promote our study app and recruit people to investigate and engage with the platform, we will advertise on our INGH website (nextgenhealthcare.org), HD2i website and mailing lists (hd2i.org), N1 app website (n1app.org), and Mount Sinai Health System websites and postings. We may recycle/re-use language from existing, IRB approved documentation (e.g. onboarding screens, consent module) for recruitment. For all advertisements that include language that has not already been reviewed, they will be IRB-approved before use. We will also use Google Adwords and other advertising outlets online, as well as community bulletin boards and websites such as patientslikeme.org to promote our N-of-1 study app. We may also develop business cards to spread the word about the platform using terminology already approved by the IRB (template business card attached; QR code sends you to the App Store to download the app; some elements may change such as logo, sizing, etc. There is no study-specific language on the business card). As the N-of-1 app will be listed publicly on the U.S. Apple App store, it is

also considered a recruitment method and so the app description will also be IRB-approved before use. We may change language in advertisements slightly over time but it will remain fundamentally equivalent (sentence ordering, sizing, clarification of ads).

Prototype study: Specific to our prototype study, we will employ a variety of recruitment methods to ensure we enroll a diverse sample:
1. Posting on the Mount Sinai trials website (http://icahn.mssm.edu/research/clinical-trials)
2. Advertisements about our work placed in local Mount Sinai media and flyers (e.g., department monthly newsletters, flyers hung in appropriate areas in Mount Sinai, Mount Sinai Weekly Academic Update, etc.)
3. Advertisements on Internet websites (e.g. nextgenhealthcare.org, N1app.org).
4. Social Medial postings (e.g. Facebook, Twitter, Reddit https://www.reddit.com/r/Nootropics/)
5. Recruitment via related conferences (e.g. Quantified Self conference)

Recruitment for this prototype study will occur primarily through social media sites such as Reddit, Twitter, and Facebook. Recruitment will be largely targeted to individuals who have shown interest in and/or previous experience using L-theanine through posting on specific L-theanine-related webpages or within L-theanine-related social media groups. However, people may join our study without prior experience or knowledge of L-theanine, as recruitment will also include more general websites. The recruitment process will not involve any restrictions with regard to socio-demographic factors other than age, US residency, and ability to read and provide consent in English.

Beta testers: We plan to invite individuals who expressed early interest in the N1 project to be early users of the app. This likely includes friends and family of the research team. We may also invite conference attendees to be beta testers. They will serve as "beta testers" of the app in order to identify possible app-related issues before a full launch of our app. They will be contacted via email individually (email language attached). We will recruit approximately 50 beta testers before full launch of the app.

How Participants Will Be Identified

N-of-1 platform: Participants will not be identified in any particular way, as anyone in the US may download the N-of-1 app from the Apple App Store.

Prototype study: Specific to the prototype study, anyone that is over 18 years old, not pregnant/breastfeeding, with no contraindication to caffeine may join the study. These individuals will be identified through a pre-consent screener.

Beta testers: early users will be identified through word of mouth. They will likely be individuals close to the research team who expressed interest in the project during development. We may also invite attendees of related scientific conferences to sign up as beta testers or regular study participants post-launch.

Who Will Initially Approach Potential Participants Study Personnel

How Research Will Be Introduced to Participants

N-of-1 platform: The N-of-1 app will be introduced to participants through the N1 App website (n1app.org), and through a small introductory module on the app itself. There will also be an IRB-approved description of the app available on the App Store before download.

Prototype study: The prototype study will be introduced through a short educational module in the N-of-1 app. The module covers the goal, treatment blocks, measurements, outcomes, and planning stages related to the L-theanine/caffeine study. Please see attachment to view sample module/study flow.

How Participants Will Be Screened

N-of-1 platform: There is no screening necessary for participants to download the N-of-1 study app. Since the app is only available in English and in the US, those eligibility criteria are assumed to be met through the ability to download the app.

Prototype study: To assess eligibility for the prototype study, participants will be given a short survey after the introductory research module, and before the consent module. This pre-consent screener survey will cover age and pregnancy/breastfeeding status, and will ask if individuals have other known contraindications to caffeine such as cardiac health issues. Individuals who are ineligible will receive a notification that they cannot participate. Because these criteria may change (e.g. a woman stops breastfeeding), app users can go back into the study later and re-take the eligibility survey if their status changes.

10. Procedures - Narrative

Description of the Study Design

N-of-1 platform: The N-of-1 study app is designed to provide individuals with a number of studies that may help them achieve actionable wellness-related results that fit within their lifestyles. After an individual chooses a study and meets the inclusion criteria, he/she will be prompted with a number of study design options. These may include treatment options (e.g. exercise, meditation, caffeine consumption), study duration options (e.g. 2 weeks, 1 month, 6 months), and assessment options (e.g. n-back test, color test, NIH health surveys). Broadly, the goal of this app is to provide individuals with the option of creating a study that best fits their personal health questions and lifestyle. The app will collect the following data from each user during the account creation process:

i) Year of birth
ii) Email address
iii) Gender
iv) Password

We will then send a welcome email to the participant to verify their email address. The sample email language attached to this protocol may change slightly over time to enhance informedness where we see fit. The N-of-1 study app will allow users to connect their phone calendar and wearable devices, such as Fitbit, or other apps, such as the Nokia Health app, to the N-of-1 platform. Users may choose to connect whatever devices/apps they have that are available for connecting. App users may also choose to share their data with researchers outside of Mount Sinai within the settings of the app, and they will be doubly prompted before they may opt in to this option. Additionally, when users engage in studies on the app, they may choose to share their study data and results via their personal social media channels. This would only allow them to share basic numerical/graphical depictions of their study outcomes, and would not include any identifiable information or conclusive/diagnostic results.

Considering this is an online, remote, and individualized study platform, monitoring subjects for safety and risk must differ from conventional researcher-subject interactive studies. Thus, we will provide participants with an electronic method in which they should report any questions, concerns, or abnormal events they believe to be related to the study. This will be available in the app at all times, for all available studies. If a note is submitted with an adverse event or concern, research study personnel will contact the participant as soon as possible for additional information and will subsequently inform Mount Sinai of the event.

The app will include an onboarding and study flow that first introduces the concept of N-of-1 studies, initiates registration, explains the available studies, walks the participant through the consent process, and then manages participant study activities, procedures, and results. We have attached a sample flow to this protocol that is specific to the prototype study. Some of the general language or presentation in this flow may change slightly during app development and adjustment (e.g. wording change, font size), but the overall meaning will remain fundamentally equivalent. Study-specific screens will change when future studies have been approved. We will also include an FAQ section for each study. We may add questions to the FAQ as the study progresses based on participant feedback, but have provided as an attachment a sample of the types of questions we will include.

Prototype study: For the prototype study, there will only be one available study and participants may not choose the design of the study. Additionally, they will not connect any other devices or apps to the N-of-1 platform. To test the success of our N-of-1 platform, we have decided to investigate the effects of L-theanine, an amino acid derived from tea leaves, and caffeine, on cognition. L-theanine has been granted GRAS (Generally Recognized As Safe) status by the Food and Drug Administration, and there are no known reports of adverse events associated with L-theanine usage. Studies suggest that L-theanine may improve cognitive performance, and caffeine is commonly used to improve alertness and response time. (https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=209 ; https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm269524.pdf)

Using L-theanine and caffeine, the purpose of the prototype study is to allow a single individual to measure the effect of 2 different treatments on up to 3 measures of cognitive performance.

Active Comparator: Caffeine-alone (50-400 mg, based on choice of beverage)
Experimental: Caffeine (approximately 50-400 mg, based on choice of beverage) + L-theanine (approximately 250 mg)

Cognitive performance measures (descriptions in the procedures section):

1. Creative thinking: Remote Associates Test
2. Selective attention and processing speed: Stroop Test
3. Visual attention and task switching: Trail Making Test

The effects of the [caffeine + l-theanine] combination will be compared to baseline measures without intervention and to [caffeine-alone], to test the hypothesis that the blend of ingredients will enhance cognitive outcomes greater than caffeine alone.

This study is a single individual, multiple crossover study that will last a maximum of 27 days. We will randomize total study length, treatment arm length, and number of cognitive tests provided in order to assess adherence. Study participants will also be randomly assigned a study block length, which may be 1, 2, or 5 days. Studies may last 5, 15, or 27 days depending on which length the participant is randomized into. We are also randomizing notification levels within the app, so that participants may receive two different levels of notifications about the study they are in (light and moderate).
The beta test version of the study will last only approximately 11 days but will remain fundamentally equivalent otherwise.

Before beginning the study, the participant will select the time of day during which they want to achieve maximum productivity (e.g. during their normal working hours). The participant will have the option of using a standardized dose of caffeine, which is available over the counter in pill form, or selecting a caffeinated beverage of their choosing. If participants choose a caffeinated beverage, they will be prompted to choose a drink based on their ability to consume it daily over the course of the intervention period.

Since the study is looking at individual outcomes, the consistency of caffeine dosage across individuals is not an outcome-related concern. Furthermore, the precise quantity of caffeine is not critical to the study design, though the App will prompt the subject for an approximate amount based on their caffeine treatment selection. Individual subject consistency in caffeine intake is the most important treatment factor related to the study outcome.

The first study block is a baseline assessment in which the user completes up to 3 assessments at the specified time every day for up to 7 days, without taking any intervention. After baseline, the subject will begin alternating between the two interventions based on their randomly-assigned block length. On the intervention days, participants will ingest a single dose of either the active comparator (caffeine-alone) or the experimental combination (caffeine + l-theanine). Sixty minutes post-intervention, participants will take cognitive assessments via the study app. The cognitive assessment task block will take ~5 minutes to complete.

The total length of the study will be a maximum of 27 days (LN + baseline), but the number of blocks (N) will vary based on L (the randomly-assigned block length).

L	N
1	20
2	10
5	4

The app will prompt the participants as to when they should take their assessments and when to transition from one study arm to another. At his/her specified time, each participant will be prompted by the application to take one of the treatments under investigation according to the study calendar, and then be reminded to complete the cognition assessments 60 minutes after confirming treatment.

During the study, the app will collect data from the assessments taken during each study arm. Data collected includes:
1. Baseline survey/assessment scores
2. Survey/assessment scores during each study arm
3. Compliance information about interventions and assessments (# of missed assessments, missed transitions from one study arm to another, etc.)
4. Additional notes as desired by the individual study participant
Individual results will be processed and provided to the participant via the study platform after they have completed the study. Intermittent results will not be returned to participants for risk of influencing the study outcome.

In order to deliver on our messaging of getting "actionable results" and encourage motivated users to spend more time with our platform, we will also offer the opportunity for participants to enroll in a longer study after completing their initial study. This is particularly aimed at users enrolled in the 5 day studies, but it will be made available to all users who have completed a study. Upon successful completion of the initial study, the platform will display a screen informing the user that they have "unlocked" additional study lengths, thus allowing the user to start a new study. The user will be able to choose their study length from the 3 available study lengths (5, 15, and 27

days). The user will have to repeat the onboarding and consent process and will sign another consent document (it will be the same consent form as originally signed for the first study). The onboarding and study procedures will remain the same beyond allowing the participant to choose between 5, 15, and 27 days for study length. At launch, data from the 2 studies will not be grouped. They will be treated as 2 independent studies and analyzed independently. We anticipate adding a "grouped analysis" feature in the future. (New study screens attached to bottom of "OnboardingFlow" document)

Description of Procedures Being Performed

N-of-1 platform: not applicable

Prototype study: Each participant will spend alternating study blocks consuming either a single caffeinated beverage/ caffeine supplement (averaging 50-400mg), or a combination of caffeine and l-theanine (averaging 50-400mg caffeine and 250mg l-theanine). Each participant will also take up to 3 daily assessments, located in the N-of-1 app, addressing different cognitive outcomes.

1. Creative thinking: Remote Associates Test (RAT)
The RAT tests an individual's "creative" cognition by presenting them with 3 words and requiring the individual to come up with a fourth associated/criteria-linking word.
For example, an individual may be prompted with the following: sleeping, bean, trash. They would then try to come up with a linking fourth term, which in this case is "bag".

2. Selective attention and processing speed: Stroop Test
The Stroop Test is a measurement of executive function/reaction time which assesses the ability of the subject to attend alternatively to reading printed color words and noticing the color those words are printed in.

3. Visual attention and task switching: Trail Making Test
Similar to "connect the dots", the Trail Making Test presents the individual with 25 numerically-denoted dots that they must connect in order as fast as possible while maintaining accuracy.

The cognitive assessments are designed to closely approximate their paper-based equivalents, as appropriate. However, in some cases we must make design decisions when translating a paper-based test onto a mobile platform that could impact the raw outcome measure. For example, the Stroop Test measures reaction time, which is influenced by the precise placement of buttons on the iPhone touch screen. These differences make it impossible to compare results from the N1 App to normative population-level data for the assessments. For the present study this is not an issue, as we are only interested in subject-level differences between different treatments and baseline.

While the Stroop Test and Trail Making Test will be provided in their standard versions available through Apple ResearchKit implementations, the RAT will be abbreviated for the purpose of this study. Caffeine and l-theanine consumption, as well as assessment taking, will occur at a consistent time designated by the individual participant at the start of the study.

Description of the Source Records that Will Be Used to Collect Data About Subjects

n/a

Description of Data that Will Be Collected Including Long-Term Follow-Up

N-of-1 platform:
i. Email address
ii. Gender
iii. Year of birth
iv. Password
v. General app usage details (e.g. number of times logging in/opening app)

Prototype study:
i) Pre-consent screener responses
ii) Post-study survey answers
iii) Assessment scores
iv) Self-reports of treatment compliance
v) Self-reported notes of events
vi) Method of treatment
vii) Date/time of current study arm
viii) Date/time of assessment
ix) Length of study arm blocks

First and last name will be collected for the sole purpose of obtaining consent.

Research Requires HIV Testing No

11. Procedures - Genetic Testing

Genetic Testing Will Be Performed No

Guidance and Policies > Future Use Data Sharing and Genetic Research

12. Procedures - Details

Surveys or Interviews Yes

Type of Instruments Being Used Standardized

Names of Standardized Instruments

Remote Associates Test
Stroop Test
Trail Making Test

(Apple ResearchKit version details here: http://researchkit.org/docs/docs/ActiveTasks/ActiveTasks.html#stroop)

Audio / Photo / Video Recording No

Deception No

Results of the Study Will Be Shared with Subjects or Others Yes

How the Results Will Be Shared

N-of-1 platform: Newly published research findings that result from the overall outcomes of the N-of-1 study app will be shared with app users/study participants via established channels such as the INGH website and mailing list, and n-of-1 website (n1app.org) and mailing list.

Prototype study: Via the study app.
Participants will receive their individualized study results at the end of their study. Participants will not receive intermittent results for risk of study bias. These results will be in the form of basic statistical data as well as graphical depictions of their study experience. Upon request at the completion of the study, participants will also have the option to have their raw data securely emailed to the email address they provided.

When the Results Will Be Shared

Prototype study: Each individual will be able to view their results from within the N-of-1 app at the end of their study. Aggregated study results will be shared with app users via established mailing lists once published.

13. Procedures - Compensation

Compensation for Participation No

14. Consent - Obtaining Consent

Consent Process Adult Consent

Where and When Consent Will Be Obtained

N-of-1 platform: The N-of-1 study app itself does not require a user to engage in study activities, and is not clinical research itself. Therefore, there is no consent associated with downloading and registering for the app. Downloading the app will not require the user to enter any identifiable information into the app. Registering for the app will require that the user enter personal information such as email address and year of birth. This will occur before the app user chooses to consent, and thus participate, in the prototype study.

Although there is no consenting before a user creates/registers on the n-of-1 app, we have included a notice before account registration that informs app users that their information may be stored and used for platform analysis and enhanced user experience regardless of whether they engage in a study. They will also be informed that this sort of platform analysis will not require the use of their name or email address.
When an app user chooses to participate in the prototype study, they will go through a full consent process which includes HIPAA authorization. The waiver is solely for registering and entering basic contact information to create an account on the n-of-1 app. This is the same type of information that would be required to sign up for any internet service or app.

Prototype study: We are requesting an alteration of the consent process due to the digital and remote nature of this project. The consent process will take place electronically and remotely via the N-of-1 study app. Similar in design and function to the approved consent module for the Resilience Project at Mount Sinai, this consent process will include a short, self-guided electronic consent module that clearly presents the most integral parts of the consent form (see attached Consent Module). After the module, the patient is presented with the full, long form PPHS consent document. The participant will be provided an option to contact the research staff during regular business hours if they have questions about the consent form and prototype study. The consent form will cover HIPAA Authorization related to clinical data usage. The extended study consent form will be provided after a participant clicks that they are interested in continuing their study (after completion of initial study).

Participants will sign an electronic signature pad after reviewing the full consent form. Their signature and timestamp will be digitally placed on the consent (in line with directive at bottom of consent form) and the signed/stamped consent will be subsequently provided to the user in the study app or it will be sent to them securely via the email address provided during study app registration. After the initial study, participants will be offered the option of re-doing their study but in an extended version. If they choose to do so, they will have to re-consent to the same form, which explains the subsequent extended option too.

Initially, the consent module and long-form will only be available in English. If it is determined that alternative language options should be made available, we will request a modification to this protocol and include translated consent documents.

Waiting Period for Obtaining Consent

Considering that the consent process is remote and that patients/participants may take as much time as needed to review the consent and decide whether or not they want to participate, there is no defined waiting period.

SOP HRP-090 Informed Consent Process for Research Is Being Used No

Specify Why SOP HRP-090 Is Not Being Used

N-of-1 platform: n/a

Prototype study: While we are following the majority of HRP-090 SOPs, one difference is that the long form consent document will be provided to the participant electronically/remotely, and they will subsequently provide a digital signature to consent to participate in the prototype study. This consent will be recorded electronically in our database.
Because the consent process is taking place without the presence of any research staff, we have supplemented the long form consent document with an educational consent module to ensure that the participant fully understands the purpose of the study. We also provide each person with the option of contacting a research staff member remotely via email or phone during regular hours.
Documenting consent electronically and remotely rather than on paper and in person has been done before at Mount Sinai. Our consent process (including the informative, educational consent module before presentation of

the long form consent) is based on previously approved projects at Mount Sinai that use electronic/remote consent (Resilience Project and Lab100).

PPHS Worksheets, Checklists and SOPs

Process to Document Consent in Writing	Will Use Standard Template
Non-English Speaking Participants Will Be Enrolled	No

Justification for Not Enrolling Non-English Speaking Participants

N-of-1 platform & prototype study: Initially, the app, consent module, and long-form consent will only be available in English. If it is determined that alternative language options should be made available, we will request a modification to this protocol and include translated consent documents.

15. Consent - Waiver of Informed Consent

Requesting Waiver For

electronic documentation of informed consent

Type of Waiver Alteration of Informed Consent

How the Research Involves No More Than Minimal Risks to Participants

This research does not involve any procedures or activities that do not exist or that people would not engage in during regular life.

How the Waiver / Alteration Will Not Adversely Affect the Rights and Welfare of Participants

The waiver is simply to allow for electronic documentation of consent as opposed to a paper consent form. This will not affect the rights and welfare of participants since we are still obtaining full, informed consent. The only difference is the digital format of the consent process.

Why It Is Not Practical To Conduct this Research Without a Waiver or Alteration of Informed Consent

We must alter the consent process because of the project's remote and digital nature. It is not practical for us to obtain additional unnecessary information from participants in order to go through a paper consent process considering we plan to recruit up to 500 participants from across the country.

Plans for Providing Participants with Additional Pertinant Information After Participation Where Appropriate

Because the consent process is taking place without the presence of any research staff, we have supplemented the long form consent document with an educational consent module to ensure that the participant fully understands the purpose of the study. We also provide each person with the option of contacting a research staff member remotely via email or phone during regular hours. This option to contact research staff will remain constant throughout the participant's engagement with the N-of-1 platform.

How the Consent Process Will Be Altered

We are requesting an alteration of the consent process due to the digital and remote nature of this project. The consent process will take place electronically and remotely via the N-of-1 study app. Similar in design and function to the approved consent module for the Resilience Project at Mount Sinai, this consent process will include a short, self-guided electronic consent module that clearly presents the most integral parts of the consent form (see attached Consent Module). The language in this module may change slightly over time, but the fundamental meaning will always remain the same. After the module, the patient is presented with the full, long form PPHS consent document. The participant will be provided an option to contact the research staff during regular business hours if they have questions about the consent form and prototype study. The consent form will cover HIPAA Authorization related to clinical data usage.

Consent for the prototype study will be documented electronically and submitted before participants proceed with any study procedures.
Consent documentation will be in line with New York State electronic signature guidelines as delineated in the Electronic Signatures and Records Act.
Documentation will be in the form of an electronic signature section after review of the long-form consent document. To ensure identification of the participant, this signature documentation is in conjunction with required log-in to the study app in which the consent form resides. Date and time of consent is electronically recorded, and a dated copy will be made available to each participant via email or on the study app.

Participants will have a dated copy of their electronically signed consent form available on the study app or it will be sent to them securely via the email address provided during study app registration.

Justify the Need for this Alteration

The remote and digital nature of our project justifies our need for an electronic consent process as opposed to an in-person, paper consent process.

16. Consent - Documents

Consent Documents

Type	Long-form consent
Name	
Upload	[redacted]

Consent Templates

17. Data - Collection

Health Related Information Will Be Viewed, Recorded, or Generated Yes

Description of Health Information That Will Be Viewed, Recorded, or Generated

N-of-1 platform: none

Prototype study: Cognitive assessment scores, pregnancy/breastfeeding status

Non-Health Related Information Will Be Viewed or Recorded Yes

Description of Non-Health Information That Will Be Viewed or Recorded

N-of-1 platform: Year of birth, email address, gender, post-study survey responses, general app usage data

Prototype study: study adherence, study notes/logs

Name will be recorded for the sole purpose of obtaining consent. Names, email addresses, and IP addresses will be stored separately from study information using a linking code.

HIV / AIDS Related Information Will Be Viewed or Recorded No

Data That Will Be Viewed, Recorded, or Generated Contains ANY of the Following Directly Identifiable Information Yes

Will Be Viewed Email Address

Will Be Recorded Name, Internet Protocol (IP) Address, Email Address

Data Collection Sheet

A Data Collection Sheet is required if you are either performing a retrospective review, or your study meets the category of exempt 4 research, or your study meets the category of expedited 5 research. Please upload it here.

Data Collection Source(s) Participant

18. Data - HIPAA

Obtaining HIPAA Authorization Yes

How PHI Will Be Protected from Improper Use or Disclosure

We will be obtaining HIPAA authorization after the user registers their account on the N-of-1 platform. This means that they will provide us with their email address, year of birth, and gender before we obtain HIPAA authorization. To mitigate this, we have included a note before account creation indicating that we are collecting this information for platform analysis and to enhance user experience on the platform. None of their identifiable information will be used for research purposes. Basic contact information is collected as is done for most app/platform-specific projects, studies, and accounts.

Subjects' privacy will be protected through industry-standard electronic security.
Participants' study data and results will be stored and attached to their study ID, which effectively serves as a linking code. Profile/account information will be stored separately from study data and results. De-identifying the research data in this way enhances project security and protects participants' confidentiality.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research No

Justification for Retaining PHI Indefinitely

No, because the research is ongoing and PHI and results will be kept for as long as the participant has allowed access to the data within the app. Participants will be able to view their own results indefinitely. Should the user decide to remove access to their data, they can do so by deleting their account within the app. Deleting the app from their device will not remove access to their data. This will be made explicitly clear to the user in the consent module.

PHI Will Be Shared Yes

Description of PHI that Will Be Shared

N-of-1 platform: By default, only the participant and designated study team members will have access to the participant's account information and study data.
Participants can change their sharing preferences at any time within the settings of the app. Participants may choose, moving forward, to share their study data with external researchers. These changes will take effect once a participant opts in to global sharing in the app settings. Name, contact information, and other directly identifiable information will never be included in externally shared study data.
There is a precedent for research participants to dynamically set and adjust their data sharing preferences. As an example, such dynamic preference setting is a feature of the mPower Mobile Parkinson's Disease Study, led by researchers at Sage Bionetworks, as well as the Resilience Project Study led by researchers at Mount Sinai. Data sharing language in our consent form is similar to that in the Resilience Project Study consent form, in order to follow this precedent.

Justification for Sharing PHI

N-of-1 platform: De-identified PHI will only be shared with approved researchers who have received IRB approval for their research from their designated institution. It is up to the individual app user as to whether or not they want to share their data with external researchers.

With Whom Directly PHI Will Be Shared

N-of-1 platform: If an app user chooses to share their data globally, study data will be directly shared with the individuals listed on the IRB-approved study that is requesting access to N-of-1 data. This will not include any directly identifiable information such as name and email address.

PHI Can Be Obtained By Members of the Research Team, Researchers at Mount Sinai, Researchers Outside Mount Sinai

PI must attest to the following.

**** I assure that the protected health information (PHI) will not be disclosed to any other person or entity not listed on this form except where required by law or for the authorized oversight of this research project. If at any time I want to reuse this PHI for other purposes or disclose it to other individuals or entities I will seek approval from the IRB.***

19. Data - Storage

Location Where Data Will Be Stored

N-of-1 platform: Data will be de-identified in accordance with the HIPAA Privacy Rule and subsequently stored using secure, HIPAA-compliant electronic data storage (Amazon Web Services GovCloud, "AWS GovCloud").
All participants will be assigned a unique identifier (study ID) that is linked to their study account. Participant identifiable information (name, IP address, email address) will be stored separately from study data with a=the linking code. The linking code file will be stored separately and securely in an encrypted electronic file with limited access. The de-identification process will follow the HHS Safe Harbor guidelines. Data stored on the app cannot be accessed by other apps on the user's device, with the exception of any app that the user authorizes access to within the N-of-1 app.

Prototype study: Researchers accessing de-identified data from the prototype study will not be able to identify participants or re-link identifiable data through the unique identifier.
Access to study data is granted only to a limited list of users based on study participant preference and the identifiable database will only be accessible to direct members of the study team. All web applications used to access data will use an industry-standard encryption mechanism for data at rest and in motion (based on AWS GovCloud SOPs--see attached document for further explanation).
To the best of our ability, the system is designed such that no PHI should leave the secure environment. Identifiers will be mapped, masked, and stored separately. Data will be labeled with de-identified randomly generated codes. It will not be possible to map this identifier back to the study subject without the mapping key which will be isolated on AWS GovCloud.
In summary, our approach applies multiple layers of protection: 1: a HIPAA compliant secure computing environment where protected data having identifying information is kept, maintained and limited to protocol personnel on an as needed basis, and 2: a high-performance computational lab environment where only de-identified portions of data are exported. Moreover, all identifiers in structured data are masked at all times in all environments when possible.

How will the data be stored? With a Code That Can Be Linked to the Identity of the Participant

Research Personnel Responsible for:

Accessing Data

Receipt or Transmission of Data

Holding Code That Can Be Linked to Identity of Participants

Research Personnel Responsible for:

Accessing Data

Receipt or Transmission of Data

Holding Code That Can Be Linked to Identity of Participants

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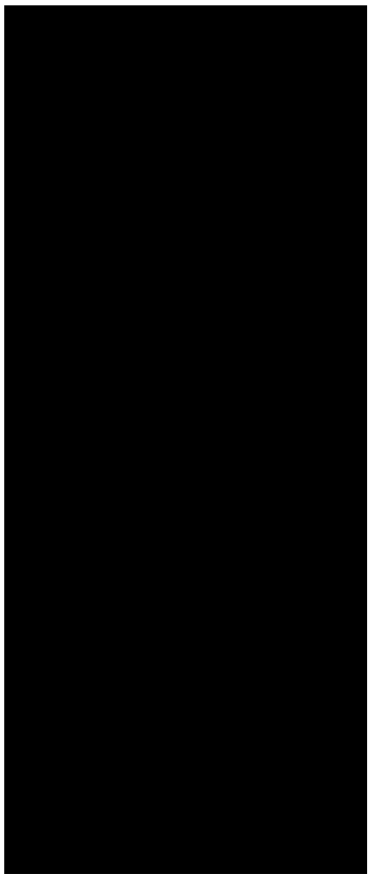

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Receipt or Transmission of Data

Holding Code That Can Be Linked to Identity of Participants

[redacted]

Duration Data Will Be Stored

Indefinitely

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission

Subjects' privacy will be protected through industry-standard electronic security.

Participants' study data and results will be stored attached to their study ID. Profile information (name, email address) will be stored separately from study data and results. De-identifying the research data in this way enhances project security and protects participants' confidentiality.

All members of the research staff will be certified to work with PHI and certified in protection of human subjects. In particular, all staff will have completed at least CITI and HIPAA Basics certification before being given access to the data.

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)

N-of-1 platform: Our two outcomes of interest at the platform level are (a) proportion of studies completed and (b) proportion of studies yielding a statistically-significant result. We are also interested in assessing whether treatment block length has an effect on either of these outcomes.

For a study to be considered "complete", the subject must complete all days of treatments in addition to baseline. We will assess the proportion of complete studies overall and at the level of different L (1-, 2-, or 5-day blocks), treating the proportion complete as a binomial random variable and using the associated binomial test of proportions to establish differences. We also want to see where most subjects drop out, so we will produce Kaplan-Meier curves for study exit for L=1, L=2, and L=5 and compare them using the log-rank test, as well as visually.

A study will be considered to have yielded a statistically-significant result if the coefficient on z is significantly different from zero at the 95% confidence level in at least one of the three models; that is, if taking caffeine (relative to baseline, with or without L-theanine) produces an effect on cognitive performance measured by at least one of the three tests we chose. This effect may be positive or negative in different individuals. Our analysis of the proportion of studies yielding a statistically-significant result will mirror our analysis of the proportion of studies complete, as described above.

Prototype study: The individual N-of-1 studies will be analyzed as follows. There are three outcomes of interest: (a) RAT, (b) Stroop, (c) Trail Making. Each of these will be analyzed separately. Because both caffeine and L-theanine are short-acting, we do not anticipate carryover effects between subsequent treatment blocks. Each day represents one independent sample from the same subject, so standard fixed-effects regression models can be used. However, we do anticipate a learning effect with regard to the individual tests - people get better at the tests the more they take them - so we will account for that in our models by incorporating a term for "time since start of test". We anticipate that this improvement effect will be linear in time. The overall models will have the form:

$y \sim a + bx + cz + dt + \text{error}$

where a is an intercept term, x is 1 if in treatment block B (caffeine + L-theanine) and 0 otherwise, z is 1 if in treatment block A or B and 0 otherwise, and t refers to time since start of study (in days, numeric). The coefficient on z is the estimated effect of exposure to caffeine on cognitive performance, since caffeine is present in both block A and block B. The coefficient on x is the additive effect of L-theanine when taken in addition to caffeine. The coefficient on t is the linear improvement effect on cognitive test performance with time. There will be three models like this in total (one for each of our three cognitive outcomes). Each model will represent up to 27 total points (e.g. 7 baseline, 10 for treatment A, 10 for treatment B).

The results reported to our users will be the coefficients b and c in the equation above, for all three outcomes, and the associated 95% confidence intervals on those coefficients. We will present these summary measures graphically as means plus error bars, and we will also provide a mechanism for users to view the raw test results from tests taken within the different treatment regimes next to each other on the same graph.

20. Data - Safety Monitoring

More Than the Minimum Data Safety Monitoring Will Be Done No

The following minimum requirements apply to all projects, including retrospective reviews of medical records, use of tissue samples, and many minimal risk studies, such as observational and survey research. Because these minimum requirements apply to all studies, a specific written DSMP will not usually be required for projects that do not pose greater than minimal risk to subjects. The MSSM PPHS may alter the required level of monitoring if appropriate.

For all projects, the principal investigator must have a plan to assure that data integrity will be maintained during its collection, storage and analysis. All research projects must adhere to MSSM recommendations on the storage of research data. Loss of data containing identifiable information is reportable to the IRB within 5 business days.

Any problems concerning the consent process and any subject complaints should be monitored by the investigator. Reports of such problems must be made at least annually. The discretion of the protocol director will guide the need to report these problems immediately or more frequently.

The principal investigator is, typically, the monitoring entity for the minimum DSMP. When a principal investigator is not a faculty member, the supervising faculty member must be responsible for the data and safety monitoring aspect of the protocol.

Will the Research Include Data Coordinating Center Activities? No