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CLINICAL RESEARCH PROTOCOL

CONFIDENTIAL

Medidata Solutions Inc.

Protocol: MOVE-2014

**A PILOT OPEN LABEL CLINICAL TRIAL TO EVALUATE THE COMBINED
IMPACT OF TWO MOBILE HEALTH PRODUCTS ON HEALTH OUTCOMES
IN OVERWEIGHT ADULTS WITH TYPE 2 DIABETES**

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STUDY TITLE**A PILOT OPEN LABEL CLINICAL TRIAL TO EVALUATE THE COMBINED
IMPACT OF TWO MOBILE HEALTH PRODUCTS ON HEALTH OUTCOMES
IN OVERWEIGHT ADULTS WITH TYPE 2 DIABETES****Principal Investigator:**

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Date: August 8, 2014

The Research Group/Principal Investigator reserves the right to update or change the protocol prior to IRB submission in order to maintain the most current standards in research. The Sponsor will be notified in such an event.

SYNOPSIS

Study Title:

A PILOT OPEN LABEL CLINICAL TRIAL TO EVALUATE THE COMBINED IMPACT OF TWO MOBILE HEALTH PRODUCTS ON HEALTH OUTCOMES IN OVERWEIGHT ADULTS WITH TYPE 2 DIABETES

Study Number:

MOVE-2014

Sponsor

Medidata Solutions Inc.

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Purpose:

The purpose of this study is to explore the effect of 8-weeks use of the Medidata Patient Cloud (a mobile application for capturing data directly from subjects, enabling entry of diary and quality of life data into internet-enabled devices) in combination with an activity tracker (Fitbit Flex) on health outcomes in overweight people with Type 2 Diabetes.

Primary Efficacy Objective:

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on markers of glucose control including glucose, insulin, fructosamine and HgbA1c.

Secondary Efficacy Objective:

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on changes from baseline in body weight.

Tertiary Efficacy Objective:

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on adherence to recommended therapy (nutrition and exercise recommendations) via dichotomous questionnaire for nutrition and the activity tracker for exercise (steps per day).

Quaternary Efficacy Objective:

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on quality of life as measured via the PROMIS® Global Health questionnaire.

Exploratory Efficacy Objectives:

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on quality of sleep as measured via the activity tracker (sleep efficiency score).

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on adherence to recommended therapy (exercise recommendations) via the activity tracker (active minutes) for exercise.

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) as compared to the Medidata Patient Cloud alone on all efficacy endpoints except those provided by the activity tracker. This objective applies only if 5 or more of the subjects' activity trackers function for less than 4 weeks.

Study Design:

Prospective, open-label, pilot clinical trial.

Study Population:

A total of 20 subjects will be enrolled, with each subject receiving the Medidata Patient Cloud and Fitbit Flex activity tracker.

Test Products:

Products - Medidata Patient Cloud in combination with the Fitbit Flex

Duration of Study:

Excluding the screening visit, each subject completing the study will participate for approximately 8 weeks, with follow-up visits separated by 4 weeks \pm 5 days.

Efficacy Assessments:**Efficacy variables** consist of:

- Changes from baseline to 8 weeks in glucose, insulin, fructosamine and HgbA1c.
- Changes from baseline to 4 and 8 weeks in body weight.
- Changes from baseline to 4 and 8 weeks in compliance with nutrition goals as measured via dichotomous questionnaire.
- Changes from baseline to 4 and 8 weeks in compliance with exercise goals as measured by steps per day (provided by the Fitbit Flex).
- Weekly changes over 8 weeks as compared to baseline in quality of life as measured by the PROMIS® Global Health questionnaire (global physical health and global mental health subscale scores and social and overall health scores).

Exploratory efficacy variables consist of:

- Changes from baseline to 4 and 8 weeks on quality of sleep as measured via the sleep efficiency score (provided by the Fitbit Flex).
- Changes from baseline to 4 and 8 weeks in compliance with exercise goals as measured by active minutes (provided by the Fitbit Flex; requires subject input of data).

Safety Assessments:

Safety variables consist of adverse events and subjective remarks.

Safety endpoints consist of the changes in the safety variables listed above from baseline to end of study.

There is no formal safety objective for this study.

Statistical Methods:

All acquired variables will be summarized by time point and by product. Numerical variables will be presented as mean, standard deviation, count, median, and range (minimum to maximum value). Changes from baseline will be summarized and presented in the same way. Numerical variables and their changes from baseline will also be displayed graphically, as plots of mean value vs. time. The graphs may contain vertical error-bars around the mean values, indicated standard errors of the mean, if, in the opinion of the statistician, this would make the graphs more informative. Categorical variables will be presented as tabulations of counts and percentages of totals.

For each continuous variable, the mean change from baseline to each subsequent time point, or between two non-baseline time points, will be tested for nominal significance by the paired Student t test, or by appropriate non-parametric test if non-normally distributed.

For each categorical variable (for instance, if we end up with a ‘cloud only group’ and a ‘fitbit with cloud group’) comparing the difference in the distribution of categories between the different product groups will be tested for nominal significance by the Fisher Exact test if possible, or by the Chi-Square test if necessary.

All p-values appearing in these summarizations will be considered descriptive, not inferential. No final statistical conclusions will be drawn from them, but they will be referred to in the interpretation of the changes.

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ENDORSEMENTS

Protocol Number: MOVE-2014

Test Product(s): Products – Medidata Patient Cloud in combination with the Fitbit Flex

Study Title:

A PILOT OPEN LABEL CLINICAL TRIAL TO EVALUATE THE COMBINED IMPACT OF TWO MOBILE HEALTH PRODUCTS ON HEALTH OUTCOMES IN OVERWEIGHT ADULTS WITH TYPE 2 DIABETES

I, the undersigned, have reviewed this protocol and agree to:

- conduct the clinical study in compliance with Good Clinical Practices, applicable law as described in the protocol;
- obtain protocol approval by an institutional review board (IRB) and to comply with IRB requirements for ongoing review and reporting;
- comply with procedures for data recording and reporting;
- permit monitoring, auditing and inspection by the sponsor and relevant regulatory agencies;
- retain study-related documents according to legal requirements and as agreed to with the sponsor.

Investigator:

(printed name)

(signature)

(date)

1 PURPOSE AND OBJECTIVES

1.1 Purpose

The purpose of this study is to explore the effect of 8-weeks use of the Medidata Patient Cloud (a mobile application for capturing data directly from subjects, enabling entry of diary and quality of life data into internet-enabled devices) in combination with an activity tracker (Fitbit Flex) on health outcomes in overweight people with Type 2 Diabetes.

1.2 Primary Efficacy Objective

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on markers of glucose control including glucose, insulin, fructosamine and HgbA1c.

1.3 Secondary Efficacy Objective

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on changes from baseline in body weight.

1.4 Tertiary Efficacy Objective

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on adherence to recommended therapy (nutrition and exercise recommendations) via dichotomous questionnaire for nutrition and the activity tracker for exercise (steps per day).

1.5 Quaternary Efficacy Objective

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on quality of life as measured via the PROMIS® Global Health questionnaire.

1.6 Exploratory Efficacy Objectives

To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on quality of sleep as measured via the activity tracker (sleep efficiency score).

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To explore the impact of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) as compared to the Medidata Patient Cloud alone on all efficacy endpoints except those provided by the activity tracker. This objective applies only if 5 or more of the subjects' activity trackers function for less than 4 weeks.

2 INVESTIGATIONAL PLAN AND METHODS

2.1 Study Overview

This is a pilot, open label clinical trial to explore the efficacy of the Medidata Patient Cloud when used in combination with an activity tracker (Fitbit Flex) on patient health outcomes (compliance with nutrition and exercise recommendations) in adults with Type 2 diabetes. The study will last approximately 8 weeks (excluding the screen visit) with eligible subjects seen at a baseline and 2 follow-up visits (at weeks 4 and 8).

Eligibility will be determined at the screening visit (with all screening procedures performed after the Informed Consent process). Screening procedures will include determining the subjects' height and weight (BMI of 25 to 34.9 kg/m² is inclusionary), reviewing the medical history and current medications, checking vitals including blood pressure and heart rate (a blood pressure \geq 140/90 is exclusionary) and performing an electrocardiogram (ECG). Blood will be collected at the screening visit and a comprehensive metabolic panel, complete blood count with differential and HgbA1c will be used for assessing study eligibility.

At the baseline visit, subjects will have their body weight, blood pressure and blood markers of glucose control (fasting glucose, fasting insulin and fructosamine) measured. Subjects will participate in a lifestyle modification instructional/motivational session which includes development of a personal care plan. Subjects will then be instructed on how to use the Medidata Patient Cloud and Fitbit Flex. Part of the Cloud app instruction will include how to complete a questionnaire through the app; the instruction will include subjects completing the questionnaire, both to maximize understanding and to obtain the baseline assessment of quality of life.

After 4 and 8 weeks of Medidata Patient Cloud and Fitbit Flex use, subjects will return to the study site for follow-up assessment. At these visits, body weight and blood pressure will be measured. At the week 8 visit, blood markers of glucose control (fasting glucose, fasting insulin, fructosamine and HgbA1c) will be obtained. Subjects will complete the questionnaire for assessment of quality of life, through the app, at the study site, following 4 and 8 weeks use of the mobile health products. Subjects will also complete the questionnaire weekly at home. Compliance with the nutrition recommendations will be assessed using dichotomous questionnaires and compliance with the exercise recommendations will be assessed using the Fitbit Flex activity tracker.

2.2 Study Rationale

The Medidata Patient Cloud is a mobile application that allows subjects to complete study questionnaires and diaries using their iPhone, iPad or iPod touch.

An activity tracker is a device that can track an individual's daily activity. The activity tracker selected for this study is the Fitbit Flex. The Fitbit Flex is a rubber wristband that tracks daily physical activity by counting the number of steps taken each day. The Fitbit

Flex synchronizes wirelessly to an iPhone, iPad or iPod touch so that the subject can see his/her steps accumulating in real-time.

Medidata will send daily messages about nutrition and exercise to the subjects' iPhone, iPad or iPod touch, through SMS text messages.

In this pilot study, the sponsor Medidata will explore the effects of combining the Medidata Patient Cloud with the Fitbit Flex and daily nutrition and exercise messages on health outcomes including body weight and glucose control in overweight subjects with Type 2 Diabetes. The sponsor will explore if the combination of the two devices motivates subjects to comply with lifestyle modifications including eating healthier and increasing physical activity.

The goal of this pilot study is also to gather information, including potential difficulties with the technology aspects of the study, so as to facilitate design of the follow-up larger study.

2.3 Study Design

Prospective, open-label, pilot clinical trial.

A total of 20 subjects will be enrolled, with each subject receiving the Medidata Patient Cloud and Fitbit Flex activity tracker.

2.4 Duration

Excluding the screening visit, each subject completing the study will participate for approximately 8 weeks, with follow-up visits separated by 4 weeks \pm 5 days.

2.5 Study Population

Per the U.S Census Bureau, 2012 American Community Survey, for Miami-Dade County:

Race	Estimate	Percent
White	2,010,643	77.6%
Black or African American	497,478	19.2%
American Indian and Alaska Native	7,773	0.3%
Asian	44,047	1.7%
Native Hawaiian and Other Pacific Islander	2,591	0.1%
Some other race	31,092	1.2%
Ethnicity		
Hispanic or Latino (of any race)	1,666,035	64.3%

2.5.1 Inclusion Criteria

1. Male and female subjects, aged 18 to 60 years, who are English or Spanish speakers.
2. BMI 25 to 34.9 kg/m²
3. Subject has type 2 diabetes with HgbA1c < 8.0%
4. Subject's glucose is controlled with either diet alone or oral agents that do not cause hypoglycemia (e.g. Metformin, DPP-4 inhibitors, Thiazolidinediones, Alpha-Glucosidase Inhibitors and GLP-1 agonists).
5. Subject is motivated to increase their activity and make other lifestyle changes.
6. Subject has:
 - A compatible Apple mobile device with the iOS 7 operating system installed:
 - iPhone 4S or newer
 - iPad 3 or newer
 - iPad Mini
 - iPod touch 5th gen (2012 model) or newer
 - 500MB of free space on the iPhone, iPad, or iPod touch
 - A valid mobile phone number to receive daily updates via SMS text messaging
 - An active iTunes account/password to install study-related software ("apps")
 - Access to Wi-Fi or a mobile data plan to send study data
7. Female subject is surgically sterile, post-menopausal or agrees to use an acceptable method of birth control as defined in section 2.7.
8. Subject agrees to not use any new vitamin and/or mineral supplement until after study completion.
9. Subject agrees to not take any dietary or herbal supplements or products until after study completion. Seven-day washout period prior to study inclusion allowed.
10. Subject is willing and able to comply with the protocol including:
 - a. Attending 3 visits, approximately 2 hours each
 - b. Wearing and inputting required information into the Fitbit Flex activity tracker
 - c. Receiving alerts from the Medidata Patient Cloud
 - d. Working on making nutrition and exercise changes over the 8-week study period
 - e. Using and updating his/her iPhone, iPad, iPad Mini or iTouch as per study requirements (e.g. downloading the iOS7 operating system, downloading the Medidata Patient Cloud and Fitbit Flex apps, and receiving daily text messages).
11. Subject is able to understand and sign the informed consent to participate in the study.

2.5.2 Exclusion Criteria

1. Subject has any of the following medical conditions:
 - a. active heart disease
 - b. uncontrolled high blood pressure ($\geq 140/90$ mmHg)
 - c. renal or hepatic impairment/disease
 - d. Type I diabetes
 - e. bipolar disorder
 - f. active psychiatric disease
 - g. Parkinson's disease
 - h. unstable thyroid disease
 - i. immune disorder (such as HIV/AIDS)
 - j. any medical condition deemed exclusionary by the Principal Investigator (PI)
2. Subject has a history of cancer (except localized skin cancer without metastases or in situ cervical cancer) within five years prior to screening.
3. Subject is taking oral agents that can cause hypoglycemia (e.g. sulfonylureas, meglitinides and insulin).
4. Subject is taking or has taken in the past 28 days any supplement or medication (prescription or over the counter) for weight loss (see section 2.6.2); 28-day washout required for study inclusion.
5. Subject is on an unstable dose of medication (defined as fewer than 90 days at the same dose).
6. Subject is currently taking any medication deemed exclusionary by PI.
7. Subject exhibits evidence of hepatic or renal dysfunction as evidenced by ALT, AST, AP being ≥ 2 times the upper limit of normal or serum creatinine value ≥ 2.0 mg/dl or other clinically significant abnormal clinical laboratory value per PI discretion.
8. Subject has a clinically relevant abnormality as defined by the PI or interpreting physician with respect to the electrocardiogram (ECG).
9. Subject has a QTc interval > 450 msec for males and > 470 msec for females.
10. Subject has a history of drug or alcohol abuse in the past 12 months.
11. Subject has begun/stopped smoking ≤ 6 months ago OR has plans to begin/quit smoking.
12. Subject has experienced a weight loss or gain greater than 4.5 kg (approximately 10 lbs) in the past 3 months.
13. Subject is pregnant, lactating, or planning to become pregnant during the study period.
14. Subject has any condition or abnormality that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data.
15. Subject has taken an investigational product within 30 days of study enrollment (visit 2).

2.6 Concomitant Medications and Other Substances

2.6.1 Substances Permitted During the Study

Subjects may take the following substances during their participation in this study:

- Vitamins and/or minerals subject was taking prior to starting the study (same frequency as prior to study start). If the subject was not previously taking vitamins and/or minerals, he/she will be asked to not start taking any during the study.
- Any medications evaluated by a medical investigator at screening for which the dose is unchanged for at least 90 days before screening and throughout the study. Examples include:
 - Thyroid hormone replacement therapy
 - Antihypertensive and antihyperlipidemic medications
 - Oral diabetes agents that do not cause hypoglycemia including:
 - biguanides [metformin, (Glucophage) long-acting metformin (Glucophage XR, Glumetza, Fortamet)
 - DPP-4 inhibitors [linagliptin (Tradjenta), saxagliptin (Onglyza), sitagliptin (Januvia)]
 - Thiazolidinediones [pioglitazone (Actos), rosiglitazone (Avandia)]
 - GLP-1 agonists [exenatide (Byetta/Bydureon), liraglutide (Victoza)]
 - Alpha-glucosidase inhibitors [acarbose (Precose), miglitol (Glyset)]
 - SGLT2 inhibitors [Dapagliflozin (Farxiga)]
 - Combination medications: Janumet (sitagliptin and metformin), Actoplus Met (pioglitazone and metformin), Avandamet (rosiglitazone and metformin)

2.6.2 Substances not permitted during the study

Subjects may not take the following substances for at least 28 days before randomization (Visit 2) or throughout the study. Any subject taking these substances during the study will be evaluated by the PI.

- Any prescription medication or dietary supplement for weight loss such as:
 - Prescription medications: Benzphetamine (Didrex), Diethylpropion HCl (Tenuate), Phentermine (Adipex-P), Phendimetrazine (Ionamin), Tartrate (Bontril PDM), Sibutramine (Meridia)
 - Over-the-counter medications or supplements: Acai Pure, Alli, BioSlim, Brazilian Slim, CarboExpel, Cravex, CurvaTrim, Cylaris, Everslim, Hoodia Gordonii, Hoodia Maxx, Hydroxycut, Lean System 7, Leptopril, Leptoprin, LiDa Daidaihua, Lipobind, Lipovox, Ma Huang, Nanoslim, Nuphedragen, Nuphedrine, Orovo, Phentermine, Proactol, Proshape RX, Xerisan ASA

- Oral diabetes agents that may cause hypoglycemia including:
 - insulin
 - sulfonylureas [chlorpropamide (Diabinese), glimepiride (Amaryl), glipizide (Glucotrol, Glucotrol XL), glyburide (DiaBeta, Glynase PresTab, Micronase), tolazamide, tolbutamide]
 - meglitinides [repaglinide (Prandin), nateglinide (Starlix)]
 - combination medications: Glucovance (glyburide and metformin), Metaglip (glipizide and metformin), Avandaryl (glimepiride and rosiglitazone), Duetact (glimepiride and pioglitazone), Prandin (repaglinide and metformin)

Subjects may not take the following substances for at least seven days before randomization (visit 2) or throughout the study. Any subject taking these substances during the study will be evaluated by the PI.

- All dietary and herbal supplements.

2.7 Acceptable Methods of Birth Control

All female subjects will be considered of childbearing potential unless they are:

- Surgically sterilized (defined as having had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
- Post-menopausal, defined as naturally induced (last menses > 1 year before screening) or surgically induced

Female subjects of childbearing potential are required to use a reliable method of birth control from the screening visit until their study participation has ended. Acceptable birth control methods include:

- Double-barrier method (condoms with spermicide, diaphragm with spermicide)
- Hormonal contraceptives (vaginal rings, patches, oral birth control pills)
- Hormone implants
- Long-term injectable contraceptives
- Intrauterine devices
- Vasectomized partner with vasectomy performed \geq 6 months prior to the screening visit
- Same sex partner
- Abstinence

2.8 Discontinuations

The PI and sponsor may discontinue a subject's participation in the study at any time if it is in the subject's best interest to do so. Such a decision may be precipitated by an adverse event; inter-current illness; clinically important change in vital signs, physical

examinations or laboratory test results; pregnancy; or poor compliance with the study visits.

Subjects may withdraw from participation in the study at any time during the study for any reason. A subject's decision to withdraw will not cause the subject to lose any benefits to which he or she is entitled.

If a subject prematurely withdraws from study participation, the reason for the withdrawal must be recorded in the source documents. Record the primary reason for premature withdrawal according to the following categories:

- **Adverse Event-** subject experiences an intolerable event, which may or may not be related to a study procedure
- **Withdrawal of Consent-** a subject may withdraw from the study at any time
- **Protocol Violations-** if a subject is found to be enrolled in violation of the protocol, or if he/she fails to adhere to the protocol requirements
- **Lost to Follow-Up-** subject stopped coming for study visits and the study staff were unable to contact the subject (see section 5.4)
- **Other-** the subject was discontinued for a reason other than those listed above, such as relocation away from the research site, the need for exclusionary concomitant medication, or if a female subject becomes pregnant during the study.

If a subject is discontinued, all efforts will be made to carry out the closeout procedures described under Visit 4, below.

3 STUDY PRODUCTS AND CONTROLS

3.1 Study Controls

3.1.1 Diet

Subject will be required to fast (no food or beverage other than water, no caffeine) after midnight the night prior to visits 2, 3 and 4 for standardizing conditions for weight measurements and efficacy laboratory assessments.

A lifestyle modification instructional and motivational session will be performed with the subjects at visits 2 and 3 and a nutrition care plan will be developed. The nutrition care plan will include three specific nutrition goals to work on between visits 2 and 3 and three specific nutrition goals to work on between visits 3 and 4. The nutrition care plan will also include nutrition information to explain and assist subjects in following each goal. Subjects will be provided a printed copy of the nutrition care plan so as to facilitate adherence with the nutrition recommendations.

For visit 2, the three nutrition goals will be the following:

1. Increase intake of fruits and vegetables; eat vegetables with every lunch and dinner and eat fruit for desserts and snacks.
2. Drink only beverages without calories.
3. Eat less fast food and when eating fast food, make healthy choices.

For visit 3, the three nutrition goals will be the following:

1. Keep starch portions to one cup per meal.
2. Choose lean meats and keep the portion to the size of the palm of your hand.
3. Eat less high fat foods and choose healthy fats versus unhealthy fats.

Subjects will receive texts throughout the study that reinforce the nutrition goals.

3.1.2 Exercise

Subjects will be provided a Fitbit Flex at visit 2. The coordinator will instruct the subject (print and verbal instruction) on how to use it.

The lifestyle modification instructional and motivational session performed with the subjects at visits 2 and 3 will also include an exercise/activity component.

At visit 2, subjects will be instructed to do their usual activity and exercise for the first week so a baseline average number of steps per day can be obtained. Using the baseline average number of steps per day, weekly step per day goals will be developed. The exercise goal for the study will be to increase steps per day by 10% each week. In other words, if the baseline average number of steps per day is 2500, the goal for week 2 would be 2750 steps per day ($2500 \times .10 = 250 + 2500 = 2750$) and the goal for week 3 would be 3025 steps per day ($2750 \times .10 = 275 + 2750 = 3025$) and so on.

Subjects will be taught how to develop the weekly step per day goals using their baseline number. Subjects will be provided a handout which will guide them in developing the step goals. Subjects will also be called on Day 8 to assist and ensure the steps per day goals for weeks 2, 3 and 4 have been developed. The handout will also include the exercise goal of increasing active minutes per day and information on how to meet the exercise goals.

At visit 3, the steps per day goals will be developed for weeks 5, 6, 7 and 8.

Subjects will receive texts throughout the study that reinforce the exercise goals.

3.2 Study Product

3.2.1 Product Description

Product 1- Medidata Patient Cloud

The Medidata Patient Cloud is a mobile application for capturing data directly from subjects, enabling entry of diary and quality of life data into internet-enabled iOS devices (iPhones, iPads, iPad minis, and iTouches). The data captured by this application automatically synchronizes with the Medidata Clinical Cloud. Forms to collect subject data will be set up using Medidata's Rave Architect, a visual form designer that allows non-programmers to configure and update the forms used by Rave for collecting, reviewing, cleaning and exporting subject data. The Medidata Clinical Cloud is not designed to diagnose, prevent, or treat disease or other conditions.

Product 2- Fitbit Flex

The Fitbit Flex is an activity tracker worn on the wrist that tracks several biometric parameters, including steps walked, activity minutes, sleep duration, and sleep efficiency. The Fitbit uses a three-dimensional accelerometer to sense user movement. It measures steps taken, and combines it with user data to calculate distance walked, calories burned, activity duration and intensity. It uses an OLED display to display information on device 'mode' (sleep versus awake). It also measures sleep quality by tracking periods of restlessness, how long it takes the wearer to fall asleep, and how long the wearer is asleep.

3.2.2 Product Use Instructions

Subjects will be provided the Medidata Patient Cloud and Fitbit Flex at visit 2. The coordinator will instruct the subject on how to use both mobile devices (print and verbal instruction). Subjects will leave the study site following completion of visit 2 using the Medidata Patient Cloud and Fitbit Flex.

Subjects will be instructed to wear the activity tracker daily throughout the 8-week study period. If the subject's activity tracker breaks or is lost or stolen, the subject will let the coordinator know as soon as possible. The study sponsor will replace the activity tracker (if it is broken, lost, or stolen) one time during the study period. Subjects will be

encouraged to come to the site to pick up the replacement activity tracker as soon as possible versus waiting for the scheduled visit.

Subjects will also be instructed to use the Medidata Patient Cloud daily (to either receive the daily text or to complete the weekly questionnaire).

Subjects will stop using the Medidata Patient Cloud for study purposes the day of visit 4.

3.2.3 Product Compliance

Subject compliance with the Medidata Patient Cloud will be determined based on the total number of questionnaires completed and submitted during the 8-week study period. Subjects must complete at least 6 out of 8 questionnaires to reach the 75% threshold for compliance and be included in the Per-Protocol population.

Subject compliance with the activity tracker will be determined based on activity (steps) recorded on the device. If the subject does not have any steps recorded on a given day, it will be recorded as a non-compliant day. Subjects need to reach 80% compliance (45 days wearing the device out of 56) in order to be included in the Per-Protocol population.

3.2.4 Product Delivery and Return

At the time of delivery to the study site, the investigators or designees will sign or confirm receipt of delivery as outlined in the MRA's Standard Operating Procedures manual for nutraceutical studies. An inventory sheet will be completed and the inventory sheet with all relevant receipts from delivery will be kept in the regulatory binder (for the activity trackers).

At the study conclusion, the sponsor will be contacted by an MRA designee regarding return of any leftover activity trackers.

4 STUDY PROCEDURES

4.1 Informed Consent

An informed consent form (ICF) will be written in accordance with established criteria of the Institutional Review Board (IRB) and the appropriate federal regulations (eg, 21 CFR Parts 50 and 56) to describe the study plan, procedures, and risks. The investigator, the sponsor, and the IRB must all approve the ICF and any ICF amendments or administrative changes before they are used.

Investigators will ensure that each subject is clearly and fully informed of the purpose, potential risks, and requirements of study participation. Written informed consent must be obtained from each subject before performing any screening or other study procedures.

The rights, safety, and well-being of the study subjects are the most important considerations and come before the interests of the study.

4.2 Medical History

A Medical History will be performed at the screening visit to collect information on past and current medical conditions, surgical history, allergy information, and concomitant or recently taken (in the past 90 days) medications including over the counter (OTC) non-prescription products, nutritional supplements, herbals, and investigational products.

4.3 Physical Examination

Subjects will undergo a physical examination at screening for determining eligibility.

The physical examination will include examination of the head, ears, eyes, nose, throat, neck, chest (body site), skin, heart and lungs and the gastrointestinal, musculoskeletal and neurological systems. The individual performing the examination will characterize their findings as normal or abnormal (and if abnormal, of clinical significance or not of clinical significance).

4.4 Anthropometrics and Vital Signs

At the screening visit, subjects will have their height, weight, blood pressure and heart rate measured. At the follow-up visits, weight, blood pressure and heart rate will be measured.

The following guidelines will be used for the weight measurement: subjects will be weighed in a gown, without shoes, after voiding completely. Subjects will also fast after midnight the night prior to visits 2, 3 and 4.

At the screening visit, the blood pressure will be used to assess study eligibility. If the blood pressure is $\geq 140/90$ mmHg, the subject will be allowed appropriate time to rest and the blood pressure will be repeated. If the repeat reading is $\geq 140/90$ mmHg, the

subject will be deemed ineligible to participate in the study. Both readings, if applicable, will be recorded in the source and Case Report Form.

At the follow-up visits, if the blood pressure is $\geq 155/95$ mmHg, the subject will be allowed appropriate time to rest and the blood pressure will be repeated. If the repeat reading is $\geq 155/95$ mmHg, investigator assessment of significance is required. Both readings, if applicable, will be recorded in the source and Case Report Form.

The following guidelines will be used for the blood pressure and heart rate: subjects will sit in a chair, resting, for at least 5 minutes prior to taking the measurements. Measurements will be done with subjects in a seated position and the subject's left arm will be used.

4.5 Electrocardiogram (12-lead)

At the screening visit, the investigator or qualified designee will administer a 12-lead ECG. Results will be analyzed for overall normality (normal, borderline, abnormal; if borderline or abnormal, not clinically significant or clinically significant) and QTcB interval (using Bazett's heart-rate correction formula). Any ECG abnormalities must be considered not clinically significant (NCS) for the subject to be enrolled.

4.6 Testing Equipment and Devices

The following testing equipment, devices and instruments will be used in this study:

- Digital Weight Scale – Detecto (Webb City, MO) or other comparably calibrated scale (weight measurement)
- Stadiometer – Cardinal Detecto ProDoc Series, DHRWN Digital Height Rod or other comparably calibrated stadiometer (height measurement)
- BMI will be calculated using the equation $\text{Weight (kg)} / [\text{Height (m)} \times \text{Height (m)}]$.
- Sphygmomanometer – Welch Allyn Spot Vital Signs LXi or other comparably calibrated sphygmomanometer (blood pressure and heart rate measurements)
- Urinary Pregnancy Tests – will be performed at all visits for females of childbearing potential
- Electrocardiogram (ECG) – Spacelabs Burdick, Inc. Deerfield, WI or comparable 12-lead ECG machine (12-lead ECG tracings)
- Screening Laboratory Assessment – Tests to be done include comprehensive metabolic panel (glucose, BUN, Cr, AST, ALT, AP), complete blood count with differential (WBC, RBC, Hgb, Hct) and HgbA1c. These tests will be done at visit 1 to determine eligibility.
 - Additional laboratory tests may be performed to determine eligibility or to assess subject safety as per PI discretion.
- Efficacy Laboratory Assessment – Tests to be done include glucose, insulin, fructosamine and HgbA1c. Glucose, insulin and fructosamine will be done at visits 2 and 4 and HgbA1c will be done at visit 4.

4.7 Study Questionnaires

- Dichotomous Questionnaire for Visit Readiness – will be administered at visits 2, 3 and 4. Each subject will be asked:
 - Have you done any of the following:
 - Eaten or drank any foods or beverages other than water since midnight last night?
 - Had any caffeine since midnight last night?
 - Taken any new vitamins or minerals since the screening visit?
 - Taken any dietary or herbal supplements since 7 days prior to visit 2?
 - If subject answers “yes” to any of the questions above, a protocol deviation will be completed as needed.
- Dichotomous Questionnaire for Nutrition Compliance – will be administered at visits 3 and 4.
 - At visit 3, each subject will be asked:
 - Are you eating more fruit since your last visit?
 - Are you eating more vegetables since your last visit?
 - Are you drinking only beverages without calories?
 - Are you eating less fast food?
 - Are you making healthier choices when you eat fast food?
 - At visit 4, each subject will be asked:
 - Are you keeping your starch portions to one cup per meal?
 - Are you eating less high fat foods (including sweets and junk food)?
 - Are you choosing lean meats?
 - Are you keeping your meat portion to the size of the palm of your hand?
 - Are you choosing healthy fats versus unhealthy fats?

- PROMIS® Global Health questionnaire - PROMIS® stands for Patient Reported Outcomes Measurement Information System. It is a 10-item questionnaire (9 items use a 5-point scale and 1 item a 10-point scale) designed to measure patient-reported health status for physical, mental, and social well-being. PROMIS® can be used as primary or secondary endpoints in clinical studies of a wide variety of chronic conditions and in the general population. The data collected in PROMIS® provides researchers with important patient-reported information about the effects of intervention that cannot be found via traditional clinical measures. Subjects will complete PROMIS® weekly (questionnaire asks how the subject has been feeling in “the past week”) through the Medidata Patient Cloud. Subjects will be encouraged to program reminders into the calendar on their mobile device to ensure they complete the questionnaires on time. Subjects will have a 48-hour period following the reminder message to complete the questionnaire. PROMIS® Global Health questionnaire produces two subscale scores: global physical health (4 items) and global mental health (4 items). Two items (ability to carry out social activities and roles and “In general, would you say your health is excellent/very good/good/fair/poor”) are not used in a summary score, but instead are used as individual scores. For each subscale, a higher score represents better physical or mental health.

5 DESCRIPTION OF STUDY VISITS

5.1 Testing Protocol (Schematic)

Test	Screening	Baseline Visit	Phone Call	Interim Visit	Final Visit
Visit	1	2		3	4
Day ^a	-28 to -1	0	8	28	56
Informed Consent Process	X				
Review Inclusion/Exclusion Criteria to determine study eligibility	X				
Review Medical/Health History	X				
Pregnancy Test (urinary HCG)	X	X		X	X
Anthropometrics (Height, Weight)	X ^b	X		X	X
Calculate BMI (kg/m ²)	X				
Vitals (Blood Pressure, Heart Rate)	X	X		X	X
Screening ECG	X				
Perform a Physical Examination	X				
Screening Laboratory Assessment ^c	X				
Provide the study requirements handout (explain study/visit requirements)	X				
Dichotomous questionnaire for visit readiness		X		X	X
Lifestyle modification instructional/motivational session and development of a personal care plan (print and verbal instruction)		X	X ^d	X	
Efficacy Laboratory Assessment ^e		X			X
PROMIS® Global Health questionnaire Completion ^f		X			
Provide the Activity Tracker (Fitbit Flex) and Medidata Patient Cloud and instruct/review how to use (print and verbal instruction).		X		X	

Test	Screening	Baseline Visit	Phone Call	Interim Visit	Final Visit
Visit	1	2		3	4
Day ^a	-28 to -1	0	8	28	56
Dichotomous questionnaire for nutrition compliance (includes specific questions for each nutrition goal); review/reinforce the importance of compliance as needed.				X	X
Assessment of exercise compliance (using steps per day); review/reinforce the importance of compliance as needed.				X	X
Assess compliance with the Activity Tracker (Fitbit Flex) and Medidata Patient Cloud; review/reinforce importance of compliance as needed.				X	X
Concomitant Medications	X	X		X	X
Adverse events monitoring		X		X	X

^aThe screening visit will occur within 28 days of the randomization visit. Visits past visit 2 will have a window of ± 5 days and be at approximately the same time of day ± 120 minutes.

^bHeight will be done at visit 1 only.

^cThe screening laboratory assessment will include a comprehensive metabolic panel, CBC and HgbA1c and will be done under fasting conditions. If the subject has blood test results deemed unacceptable for participation by a medical investigator, he or she will not be enrolled.

^dCoordinator will call the subject to assist in the development of the weekly exercise goals.

^eThe efficacy laboratory assessment will include glucose, insulin and fructosamine. The assessment will also include HgbA1c at visit 4.

^fPROMIS Global Health questionnaire will be completed by the subjects via the Medidata Patient Cloud at visit 2. Subjects will also complete the questionnaire at home via the Medidata Patient Cloud weekly over the course of the study. At visits 3 and 4, coordinator will remind subjects to complete the questionnaire for that week if not already completed. If not already completed, subjects may complete the questionnaire on site.

5.2 Specific Visit Procedures

5.2.1 Visit 1 (Screening Visit)

The screening visit begins after written informed consent has been obtained from the subject. Following the informed consent process, qualified study personnel will perform the following assessments:

- Informed Consent Understanding Questionnaire
- Clinical Conductor was checked prior to the screen visit
- Review inclusion and exclusion criteria

- Evaluate Medical/Health History including medical and surgical histories and allergy information
- Review current medications (see section 4.2)
- Perform a urine pregnancy test (HCG) for females of childbearing potential
- Measure screening anthropometrics and vital signs: height (cm), weight (kg), blood pressure and heart rate (see section 4.4)
- Have the data spreadsheet calculate BMI (kg/m²)
- Perform an ECG (see section 4.5)
- Perform a Physical Examination
- Collect blood for the screening laboratory assessment (CMP, CBC and HgbA1c)
- Provide and review the study requirements handout (provide written and verbal instructions on the study and visit requirements)
- Schedule visit 2 in the next 28 days. Let subject know that the 3 visits need to be scheduled at approximately the same time of day (\pm 120 minutes). Remind subject to:
 - Not eat or drink any foods or beverages other than water, no caffeine, after midnight the night prior to the visit;
 - Not take any new vitamins or minerals;
 - Not take any dietary or herbal supplements; and
 - To bring the iPhone, iPad, iPad Mini or iTouch that he/she wants the Medidata Patient Cloud and activity tracker installed onto to the visit. Subjects will be instructed to have the device upgraded to iOS 7 or higher (if necessary) **prior** to the visit and to bring their iTunes password to the visit to allow download of the Medidata Patient Cloud.

5.2.2 Visit 2 (Day 0)

- Clinical Conductor was checked prior to the randomization visit
- Administer the dichotomous questionnaire for visit readiness
- Monitor adverse events
- Review concomitant medications
- Perform a urine pregnancy test (HCG) for females of childbearing potential
- Measure anthropometrics and vital signs: weight (kg), blood pressure and heart rate (see section 4.4)
- Collect blood for the efficacy laboratory assessment (glucose, insulin and fructosamine)
- Perform the lifestyle modification and motivational session and develop the personal care plan (provide written and verbal instructions including instruction on the specific nutrition and exercise goals).

- Provide subject with the Activity Tracker and Medidata Patient Cloud and do an extensive instruction on how to use (provide written and verbal instructions on how to use; subjects will leave visit 2 with the Activity Tracker and Medidata Patient Cloud functioning).
- Have subjects complete the PROMIS® Global Health questionnaire through the Medidata Patient Cloud.
 - Instruct subject on the process of completing the PROMIS® Global Health questionnaire weekly throughout the study.
 - Assist subject in programming reminders into the calendar on their mobile device to ensure he/she completes the questionnaires on time.
- Obtain from subject his/her preferred phone number and let subject know that the coordinator will call after the first 7 days of wearing the activity tracker to assist with the development of the steps per day goals.
- Schedule next visit on Day 28 \pm 5 days at approximately the same time of day as visit 2 (\pm 120 minutes). Remind subject to:
 - Not eat or drink any foods or beverages other than water, no caffeine, after midnight the night prior to the visit;
 - Not take any new vitamins or minerals;
 - Not take any dietary or herbal supplements; and
 - To wear his/her activity tracker and bring his/her iPhone, iPad, iPad Mini or iTouch to the visit.

5.2.3 Phone Contact (Day 8)

- Assist subject with the development of the steps per day goals for weeks 2, 3 and 4.
- Reinforce the importance of compliance with the exercise and nutrition goals.

5.2.4 Visit 3 (Day 28)

- Administer the dichotomous questionnaire for visit readiness
- Monitor adverse events
- Review concomitant medications
- Perform a urine pregnancy test (HCG) for females of childbearing potential
- Measure anthropometrics and vital signs: weight (kg), blood pressure and heart rate (see section 4.4)
- Administer the dichotomous questionnaire for nutrition compliance; review/reinforce the nutrition goals from visit 2 as needed.
- Review subjects' compliance with the steps per day goals; review/reinforce the exercise goals from visit 2 as needed.
- Review subjects' compliance with using the activity tracker and Medidata Patient Cloud; review/reinforce the importance of daily use as needed.

- Continue the lifestyle modification and motivational session and continue to develop the personal care plan (provide written and verbal instructions including instruction on additional nutrition and exercise goals).
- Remind subject to complete this week's PROMIS®; if subject has not yet completed this week's PROMIS®, the subject may complete it on site.
- Schedule next visit on Day 56 ± 5 days at approximately the same time of day as visit 2 (± 120 minutes). Remind subject to:
 - Not eat or drink any foods or beverages other than water, no caffeine, after midnight the night prior to the visit;
 - Not take any new vitamins or minerals;
 - Not take any dietary or herbal supplements; and
 - To wear his/her activity tracker and bring the iPhone, iPad, iPad Mini or iTouch with the Medidata Patient Cloud installed to the visit.

5.2.5 Visit 4 (Day 56)

- Administer the dichotomous questionnaire for visit readiness
- Monitor adverse events
- Review concomitant medications
- Perform a urine pregnancy test (HCG) for females of childbearing potential
- Measure anthropometrics and vital signs: weight (kg), blood pressure and heart rate (see section 4.4)
- Collect blood for the efficacy laboratory assessment (glucose, insulin, fructosamine and HgbA1c)
- Administer the dichotomous questionnaire for nutrition compliance.
- Review subjects' compliance with the steps per day goal.
- Remind subject to complete this week's PROMIS®; if subject has not yet completed this week's PROMIS®, the subject may complete it on site.

5.3 Visit Window Policy

The visit window for the study is ± 5 days. If a subject returns for his/her visit outside of this window, the following policy will be followed regarding sponsor notification:

- If the subject returns for his/her visit outside of the window and has still been using either of the mobile health products, the sponsor will be notified via the final study report.
- If the subject returns for his/her visit outside of the window and is not using either of the mobile health products, the sponsor will be notified via email as soon as possible for consultation regarding subject's continuation in the study. No subject identifying information will be included in the email.

5.4 Follow-up Phone Contact

Qualified study personnel will call, text and/or send e-mail messages to subjects to remind them of pending study visits.

Any subject lost to follow up will receive three phone calls and a certified letter for the purpose of obtaining data through a closeout visit and maximizing subject retention. All phone or e-mail communication will be documented in the subject's source chart.

In addition to the scheduled phone contact, subjects may be called between study visits to assess progress.

6 ADVERSE EVENTS

6.1 Monitoring for Adverse Events

An adverse event (AE) is any undesirable symptom or occurrence experienced by a subject during a clinical trial. It may or may not be considered related to the study product.

Assessment of an adverse event (AE) involves: subjective reports from the subject, observation by members of the research team and clinically significant abnormal laboratory results.

The following information will be collected for all AEs:

- Date of onset
- Description of the AE
- Severity
- Relation to study product
- Action taken with the study intervention
- Outcome
- Date of resolution

If treatment was required for the AE, this will be recorded including the type of treatment, duration and any other relevant details.

Adverse event information will be captured on source documents. The investigator will sign off on each individual adverse event.

6.1.1 Timing

AE information collection will begin after the subject signs consent and end at the close of the final visit. AE's that are unresolved at the final visit will be followed for 30 days or until the subject's medical condition returns to normal or until a clinically satisfactory resolution is obtained per the PI.

6.1.2 Severity

AE severity (intensity) will be classified as mild, moderate, or severe according to the following definitions:

- **Mild:** causing no limitation in normal activities
- **Moderate:** causing some limitation in normal activities
- **Severe:** causing significant limitation in or the inability to perform normal activities.

The PI will assess and assign the severity of all reported AE's.

6.1.3 Relationship

The PI is responsible for determining the relationship between an AE and the study products.

The relationship will be classified as one of the following:

- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an etiology other than the trial product
- Definitely not related: the event is not related to the study product

Expected adverse events are those events which are reported to the study site by the sponsor or those that can be found in the peer-reviewed literature. By definition, unexpected adverse events are those events which are not reported to the study site by the sponsor and not found in the literature, or are not consistent with the specificity or severity described by the sponsor or in the literature.

An unanticipated problem is an unforeseen event that occurs during the course of a research trial that potentially increases the risk to participants or others; adversely affects the rights, safety, or welfare of participants; or affects the integrity of the study. All unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB and sponsor.

6.2 Monitoring for Serious Adverse Events

A serious adverse event (SAE) is defined by federal regulation as any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization (social admissions excluded), results in a persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is an important medical event.

6.2.1 Timing

Any SAE occurring in a subject after providing informed consent and until 30 days after completing the study will be recorded and reported.

6.2.2 Reporting

All SAE's, whether related or unrelated to study product, whether expected or unexpected, must be reported to the sponsor within 24 hours of site knowledge of the event.

All SAE's will also be reported to the IRB based on the IRB's requirements and guidelines.

If an ongoing SAE changes in its intensity or relationship to study product or additional information becomes available, a follow-up SAE report will be sent to the sponsor and IRB.

It is the sponsor's decision whether or not an SAE should be reported to the Food and Drug Administration (FDA).

6.3 Risks with the Study Product

6.3.1 Medication Interactions

There are no known medication, supplement or food interactions noted by the sponsor.

6.3.2 Contraindicated Medical Conditions

There are no known contraindicated medical conditions with the use of this product per the sponsor.

6.3.3 Possible Adverse Events

There are no known AE's reported by the sponsor.

7 DATA MANAGEMENT, STATISTICAL METHODS, AND ANALYSIS

7.1 Data Management

Data will be recorded onto case report forms (CRFs) by MRA staff in Medidata RAVE (EDC). The computerized data will be anonymized; subject identifiers will be limited to *two*-digit ID numbers. Data files will be retained in a physically secure location, and regular backup copies will be created and stored in a separate secure location. Data files will be password-protected when transmitted to the statistician for analysis via SAS on Demand. Prior to transmission, MRA staff will correct any discrepancies and address any queries requested by the monitor.

Subjects will enter data directly into the Medidata Patient Cloud in the form of responses to the PROMIS® Global Health questionnaire. This data integrates electronically into Medidata RAVE.

Data from Fitbit Flex devices is gathered wirelessly by Fitbit Flex and stored in their web-based servers. Medidata RAVE will pull this data into the eCRF via API (application programming interface) calls with the Fitbit cloud.

Protocol deviations will be documented by the study coordinators and reviewed by the statistician and PI for determination of whether or not they invalidate efficacy data. All protocol deviations will be included in the final study report.

All subjective remarks made by the subjects about the Medidata Patient Cloud and/or Fitbit Flex will also be included in the final study report.

7.2 Examination of Data

All data elements will be evaluated by the statistician for reasonableness and consistency, and any suspicious or impossible values will be referred back to MRA for verification or correction. All numerical variables will be tested for normality, and data found to be substantially non-normally distributed will be subjected to standard normalizing transformation (e.g.: logarithmic, square root, etc.). Variables remaining non-normally distributed even after transformation will be analyzed by appropriate non-parametric methods.

7.3 Data Lock and Unblinding

After all suspicious entries and queries in the database have been resolved; the database will be formally “locked” by the statistician or data management. A PDF version of the eCRFs will be provided to MRA for archiving.

7.4 Statistical Analysis

7.4.1 Analytical Populations

The **Safety** population consists of all subjects who wore the Fitbit Flex and used the Medidata Patient Cloud for at least one day and who had any subsequent encounter with MRA.

The **Per-Protocol** (PP) population consists of all subjects who completed all scheduled visits, had no protocol deviations that (in the judgment of the principal investigator) would have invalidated their efficacy data, and were at least 75% compliant with the Medidata Patient Cloud and at least 80% compliant with the Fitbit Flex. If a subject is only slightly outside the allowable compliance limits, the principal investigator can include that subject in the PP population.

The **Intent-to-Treat** (ITT) population consists of all subjects who completed all scheduled visits, had no protocol deviations that (in the judgment of the principal investigator) would have invalidated their efficacy data, but were less than 75% compliant with Medidata Patient Cloud and less than 80% compliant with the Fitbit Flex.

If 5 or more subjects have activity trackers (both the original and the replacement trackers) function for less than 4 weeks, the following analytical populations will be explored:

The **Complete Activity Tracker** population consists of all subjects who used their activity tracker for greater than 4 weeks.

The **Incomplete Activity Tracker** population consists of all subjects who used their activity tracker for less than 4 weeks.

If a subject discontinues from the study after participating less than one week, the site has the option to recruit an additional subject. The safety data from the discontinued subject will be utilized.

7.4.2 Safety and Efficacy Variables and Endpoints

Safety variables consist of adverse events and subjective remarks.

Safety endpoints consist of the changes in the safety variables listed above from baseline to end of study.

There is no formal safety objective for this study.

Efficacy variables consist of:

- Changes from baseline to 8 weeks in glucose, insulin, fructosamine and HgbA1c.
- Changes from baseline to 4 and 8 weeks in body weight.
- Percentage of subjects that have achieved the nutrition goals as measured via dichotomous questionnaire at 4 and 8 weeks.

- Changes from baseline to 4 and 8 weeks in compliance with exercise goals as measured by steps per day (provided by the Fitbit Flex).
- Weekly changes over 8 weeks as compared to baseline in quality of life as measured by the PROMIS® Global Health questionnaire (global physical health and global mental health subscale scores and social and overall health scores)

Exploratory efficacy variables consist of:

- Changes from baseline to 4 and 8 weeks on quality of sleep as measured via the sleep efficiency score (provided by the Fitbit Flex).
- Changes from baseline to 4 and 8 weeks in compliance with exercise goals as measured by active minutes (provided by the Fitbit Flex; requires subject input of data).

7.4.3 Descriptive Summarization

All acquired variables will be summarized by time point and by product. Numerical variables will be presented as mean, standard deviation, count, median, and range (minimum to maximum value). Changes from baseline will be summarized and presented in the same way. Numerical variables and their changes from baseline will also be displayed graphically, as plots of mean value vs. time. The graphs may contain vertical error-bars around the mean values, indicated standard errors of the mean, if, in the opinion of the statistician, this would make the graphs more informative. Categorical variables will be presented as tabulations of counts and percentages of totals.

For each continuous variable, the mean change from baseline to each subsequent time point, or between two non-baseline time points, will be tested for nominal significance by the paired Student t test, or by appropriate non-parametric test if non-normally distributed.

For each categorical variable (for instance, if we end up with a ‘cloud only group’ and a ‘fitbit with cloud group’) comparing the difference in the distribution of categories between the different product groups will be tested for nominal significance by the Fisher Exact test if possible, or by the Chi-Square test if necessary.

All p-values appearing in these summarizations will be considered descriptive, not inferential. No final statistical conclusions will be drawn from them, but they will be referred to in the interpretation of the changes.

7.4.4 Safety Analysis

All safety analyses will be conducted on the Safety population, defined in Section 7.4.1, above.

Changes in quantitative (numerical) safety endpoints (defined above) will be tested for significance by the paired Student t test, or appropriate non-parametric test if necessary. Categorical efficacy variables will be tested for significant changes over the course of intervention by the Fisher Exact test.

AE's will be listed, MedDRA encoded, grouped by general type of event (gastrointestinal, neurologic, cardiac, etc.), and cross-tabulated by event type.

Subjective remarks will be categorized to the extent possible.

7.4.5 Efficacy Analysis

The main efficacy analysis will be conducted on a Per-Protocol (PP) basis, using the PP population, defined in Section 7.4.1, above. If, in the judgment of the statistician, an excessive number of subjects were excluded from the PP population, an exploratory analysis may also be conducted on an Intent-to-Treat (ITT) basis, using the ITT population, defined in Section 7.4.1, above. And if 5 or more subjects have activity trackers function for less than 4 weeks, an exploratory analysis may also be conducted comparing the Complete Activity Tracker and Incomplete Activity Tracker populations as defined in Section 7.4.1, above.

The primary, secondary, and quaternary efficacy objectives will be evaluated in the following manner: the distribution of values will be examined to determine if they fit the assumption of normality sufficiently to use the desired parametric test, or if not appropriate steps to normalize the distribution and/or non-parametric test will be used (see 7.2 above). For tests involving 2 time points (e.g. testing change in glucose level from baseline to week 8), a dependent samples t test will be utilized. For tests involving 3 or more time points (e.g. testing if there is an overall change in body weight from baseline until study end), a repeated-measures ANOVA will be used.

The tertiary efficacy objective will be evaluated through the use of summary statistics. For the nutrition goals, the percentage of subjects who have met the goals will be determined from the dichotomous questionnaire with the results evaluated in a descriptive manner. Additional evaluations of changes in percent of subjects complying with the goals may also be conducted if there appears to be a change in said compliance values. For the exercise goals, compliance will be determined in the following manner: First, a baseline reading for average number of steps per day, as measured by the Fitbit Flex, for the first week of the study, will be gathered for each subject. Next, a goal of 110% (baseline + 10% of baseline) will be set for the following week (Week 2). The average number of steps per day for Week 2 will be calculated and compared to the goal for determination of whether the individual subject met the Week 2 goal. The percentage of total subjects who successfully met the Week 2 goal will be determined and evaluated. This procedure will be repeated for all subsequent weeks (Weeks 3, 4, 5, 6, 7 and 8), with each week plus 10% of the goal from the previous week.

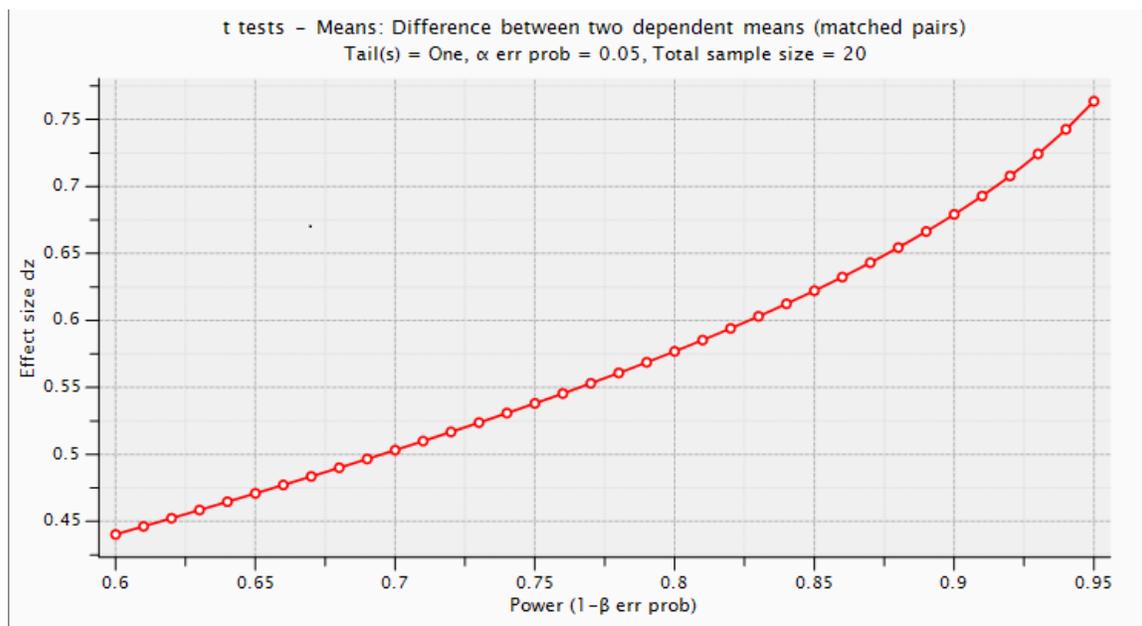
The exploratory efficacy objectives will be evaluated in the same ways as described above, but the interpretation of their significance will be in accordance with the procedure described in Section 7.4.7, below.

If 5 or more subjects have their activity trackers function for 4 weeks or less, an attempt will be made to explore the differences in outcomes between the Complete Activity and Incomplete Activity Tracker populations.

7.4.6 Power and Sample Size Considerations

Because the target enrollment for this study was specified by the sponsor as 20 subjects, this section will present the results of calculations of the relationship between power and effect size for various endpoints for a study with this number of subjects.

In order to achieve a power of .80 (i.e. an 80% probability of detecting a true effect of the product) at an alpha level of .05 (one-tailed), an effect size of approximately 0.60 will need to be achieved (see Figure 1 below). This means that the subjects will need to show an improvement of 0.60 standard deviations on each measure. As an example, using the prior weight loss data from Miami Research Associates, the typical variability is 5 pounds ($SD = 5$ lbs). Therefore, for the study to have sufficient power to detect a real decrease in body weight, a loss of 3 lbs (0.60×5 lbs) will be needed. Similar changes in the other markers will be required to meet the specified power.

Figure 1:

7.4.7 Control of Inference Errors

As this is not a pivotal Phase-III clinical trial, it is not required to control the *study-wise* Type-1 error rate to a specified alpha level (such as 0.05). Each efficacy endpoint will be considered an independent question of interest, and will be tested independently at the 0.05 alpha level ($p \leq 0.05$ required for a conclusion of statistical significance). When interpreting statistical results, it must be kept in mind that, for each endpoint, there is a 5% chance that random fluctuations alone can produce a significant p-value ($p \leq 0.05$), even in the absence of true efficacy with respect to that endpoint, and when many such endpoints are tested, there is an increased likelihood that one or more of them may achieve nominal significance ($p \leq 0.05$) in the absence product efficacy. Multiple testing will be taken into account when the results of the efficacy analyses are interpreted by the statistician in the Final Statistical Report.

7.5 Final Report and Final Research Closeout Binder

A Final Report will be prepared which will describe the design of the trial, the data management methods, the parameters studied, and the statistical methods used. It will present the results in the form of graphs and tables, with significance levels and interpretations.

A Final Research Closeout Binder will also be prepared which will include copies of the IRB approved study materials, correspondence with the IRB, adverse event pages for each subject, protocol deviations if any occurred, the electronic database and the Final Report. The binder serves as a record of the overall study process.

8 ABBREVIATIONS

Term	Definition
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
cm	centimeter
CMP	Comprehensive Metabolic Panel
Cr	Creatinine
CRF	Case Report Form
DPP-4	Dipeptidyl Peptidase - 4
ECG	Electrocardiogram
FDA	Food and Drug Administration
GLP-1	Glucagon-like Peptide 1
HCG	Human Chorionic Gonadotropin
Hct	Hematocrit
Hgb	Hemoglobin
HgbA1c	Hemoglobin A1c
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ID	Identification
IND	Investigational New Drug
iOS	i Operating System
IRB	Institutional Review Board
ITT	Intent to Treat

kg	kilogram
kg/m ²	kilograms per meters squared
lbs	pounds
MedDRA	Medical Dictionary for Regulatory Activities (coding system for AEs)
mg/dl	milligrams per deciliter
mmHg	millimeters of mercury
MRA	Miami Research Associates
msec	Millisecond
NCS	Not Clinically Significant
OLED	Organic Light-Emitting Diode
OTC	Over-the-Counter
PI	Principal Investigator
PP	Per Protocol
QTcB	Heart Rate corrected QT interval using Bazett's formula
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
WBC	White Blood Cell

9 REFERENCES

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10 APPENDIX – PROMIS GLOBAL HEALTH QUESTIONNAIRE

PROMIS v.1.1 - Global

Global Health

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Global02	In general, would you say your quality of life is:	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Global03	In general, how would you rate your physical health?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
		Completely	Mostly	Moderately	A little	Not at all
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

PROMIS v.1.1 - Global

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always						
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5						
		None	Mild	Moderate	Severe	Very severe						
Global08	How would you rate your fatigue on average?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5						
Global07	How would you rate your pain on average?.....	<input type="checkbox"/> 0 No pain	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10 Worst imaginable pain