Study Protocol and Statistical Analysis Plan

Title of Study: iSTEP - an mHealth Physical Activity and Diet Intervention for Persons With HIV

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ABSTRACT

People who live with HIV (PLWH) experience a high incidence of neurocognitive deficits and HIV-associated non-AIDS (HANA) disorders, including cardiovascular disease (CVD), metabolic dysfunction, and autonomic decline. While antiretroviral treatment (ART) has reduced AIDS-related morbidity, both the virus and the medications are associated with lipid disorders that also increase CVD risk, including dyslipidemia and lipodystrophy. Consequently, the development of effective lifestyle interventions to reduce the incidence of HIV-associated neurocognitive disorders (HAND) and decrease metabolic disorders is a high priority. Physical activity (PA) has been utilized as an effective tool to improve health in PLWH, but may not be sufficient by itself to improve lipid levels. Existing PA interventions in PLWH typically required strenuous PA and significant resources that limit feasibility for many people living with the disease. Recent work indicates that interrupting periods of sedentary behavior (SB), independent of PA, also has a significant beneficial effect on metabolic function, but SB has not been well-studied in PWLH. Mediterranean-style diets (MedDiet) are also effective at improving CVD risk factors in HIV-uninfected individuals and are reported to reduce cognitive decline in persons at risk for Alzheimer's disease, but have not been widely tested in PWLH. We recently developed a novel and personalized Short Message Service (SMS) mobile phone text messaging intervention (iSTEP) that is designed to increase moderate PA in PLWH. Our objective is to expand upon this work and conduct an RCT examining the efficacy of iSTEP in combination with a mobile mHealth MedDiet intervention tailored to PLWH. 150 PLWH will be randomly assigned to a control group (n = 50), a 6-month iSTEP group with just a PA/SB intervention (n = 50), or a 6-month intervention with both PA/SB and MedDiet components (n = 50), where participants receive daily interactive SMS/MMS messages designed to increase moderate PA, reduce SB, and promote adherence to a MedDiet, including walnut consumption. PA/SB will be quantified by accelerometer, Fitbit step counts, and self-report, while MedDiet adherence will be assessed by self-report (Diet History Questionnaire and weekly SMS feedback) and also objective measures (polyunsaturated fatty acid levels - PUFA in blood). We will also conduct a follow-up assessment 6 months after the end of the intervention (accelerometer, neurocognitive testing, PUFA levels) to assess PA and MedDiet adherence. We hypothesize that iSTEP (both intervention arms) will increase PA, reduce SB, and improve neurocognition compared to control; the iSTEP + MedDiet group will demonstrate improvement in CVD risk factors and neurocognition compared to the PA intervention alone. Findings from this proposal will lay the groundwork for development of novel large-scale mobile PA/diet interventions dedicated to treating HAND and improving cardiovascular health for PLWH.

SCHEMA

iSTEP - an mHealth Physical Activity and Diet Intervention for Persons With HIV

DESIGN: Our objective is to assess the efficacy of a mobile phone text message intervention (iSTEP) designed to increase moderate physical activity (PA), reduce sedentary behavior (SB), and improve diet in people living with HIV (PLWH) in order to improve neurocognitive function and reduce cardiovascular disease (CVD) risk. This is a randomized RCT where participants are enrolled into one of three conditions: 1) a Control Group; 2) a PA intervention; 3) a PA + Diet intervention focused on encouraging a Mediterranean-style diet (MedDiet).

POPULATION: PLWH

STRATIFICATION: none

REGIMEN OR INTERVENTION
Assignment to 24-week control group, PA intervention, or PA + Diet Intervention

1.0 Introduction

HIV-associated neurocognitive disorders (HAND) remain a significant problem for PLWH and are linked to metabolic and cardiovascular disorders. Approximately 30-60% of persons living with HIV (PLWH) manifest some form of neurocognitive impairment, including deficits in executive function, attention, and memory collectively referred to as HIV-associated neurocognitive disorders (HAND)[1]. Growing evidence indicates that metabolic syndrome (MetS) is an important factor that increases the risk and severity of neurocognitive impairment (NCI) in PLWH. MetS is frequent in PLWH, reported to be present in 47% of 2247 individuals during a 3-year period of participation in an AIDS Clinical Trials Group RCT study[25]. MetS also increased the odds of neurocognitive decline in a sample of 643 PWLH patients with assessments at 6-month intervals[26]. NCI severity in PLWH correlates with waist circumference (WC), a measure of abdominal obesity[27]. Despite the efficacy of antiretroviral therapy (ART), PLWH continue to experience excess levels of morbidity and mortality linked to HIV-associated non-AIDS (HANA) disorders, including cardiovascular disease (CVD), metabolic dysfunction, and autonomic decline[6, 7, 28]. CVD is now emerging as a major non-AIDS complication, with up to 20% of HIV+ individuals exhibiting a moderate to high 10-year risk of myocardial infarction (MI)[29]. Contributing factors to CVD and MI risk include a pattern of lipid abnormalities, including increased serum triglycerides, lower high-density lipoprotein cholesterol (HDL-C), and higher low-density lipoprotein (LDL) cholesterol[30]. PLWH also exhibit impaired autonomic nervous system (ANS) function indicated by decreased heart rate variability (HRV), a marker of poor vagal tone predictive of future CVD complications and higher rates of mortality[31, 32]. While healthy individuals exhibit a high degree of HRV, reflecting the ability of the ANS to adapt quickly to physical or psychological challenges in the environment[33], reduced HRV persists in virus-suppressed PLWH taking ART and is linked to hypercholesterolemia[34, 35]. CVD risk is also clearly increased by the use of ART itself, with a reported 26% relative increase in MI per year of ART exposure during the first 4-6 years of use[36]. In summary, HAND, MetS, and elevated CVD risk are closely related and remain prevalent in PLWH; there is thus a significant unmet need to find effective strategies to address these ongoing issues[5].

Physical Activity (PA) may provide many benefits for PLWH. PA provides a myriad of health benefits, including treating cardiometabolic disorders and improving HRV in persons with CVD, pulmonary disorders, and obesity[37-39]. Previous work in younger PLWH has shown that aerobic and resistance PA interventions improve fitness, reduce body fat, and normalize the lipid profile[40, 41]. However, these studies involve rigorous PA conducted at gym facilities, a methodology that is not widely feasible for HANA treatment in PLWH with frailty and limited resources[8-10, 42]. Although strenuous PA may not be suitable for many PLWH, increasing moderate PA, including walking, has significant health benefits and may improve metabolic and autonomic function[43-46]. For example, increasing step counts by 2,000-3,000 a day decreases total cholesterol[47], less than 3 hours of light PA per week reduces mortality for subjects with metabolic syndrome[48], and low-intensity walking also improves HRV[39, 49]. CVD risk may be significantly reduced by modest lipid changes, e.g., increasing HDL-C by 5 mg/dL, reducing LDL-C by 10 mg/dL and triglycerides by 40 mg/dL, or lowering percent body fat by 1% and BMI by 1 kg/m^2 [50, 51]; these effects can be achieved by moderate PA such as walking in HIV-uninfected persons[52]. However, exercise interventions in PLWH have also reported that PA may not improve lipid levels in a population challenged by both the virus and harmful side effects of ART[23]; these data suggest that an intervention approach that targets multiple modalities (PA, diet) may be more optimal.

Sedentary behavior (SB) is not well-characterized or addressed in PLWH. Sedentary behavior

(SB), defined as sitting or reclining during waking hours with low energy expenditure (1.0 to 1.5 metabolic equivalents), is a distinct construct from PA and has recently been identified as a significant contributor to all-cause mortality, increased CVD risk, and poor metabolic function[14, 53-55]. While moderate PA may occur during a small proportion of the day, adults in developed countries spend 55-70% of their time engaged in SB[54]. Both the quantity and duration of SB intervals are related to metabolic health and have adverse cardiometabolic consequences even for physically active individuals[14-16, 54, 56-59]. Every hour of daily sitting time is associated with a 2% increase in all-cause mortality, with a jump to 5% for sitting 7 or more hours per day[60]. However, simply interrupting periods of SB, even with very short intervals (a break of 60 seconds or more) with light PA (standing, walking a few feet) has demonstrated benefits for metabolic function, including improvements in triglyceride levels, HDL-C, glucose metabolism, and insulin sensitivity[43, 53, 55, 58, 61-63]. Unfortunately, SB has not been well-characterized in PLWH and little work has been done to modify this behavior in this population.

A Mediterranean-style diet (MedDiet) that includes walnut consumption may benefit both CV function and neurocognition. PLWH are reported to have poor diet quality, including higher fat consumption and lower fiber intake compared to HIV-uninfected individuals[64, 65]. Several diet interventions focused on reducing saturated fat intake are reported to improve the lipid profile (reducing triglycerides, total cholesterol, and LDL-C levels) [66-69], including significant improvements within a 6-month timespan[66, 68]. However, limited changes have been observed for HDL-C, potentially resulting from an emphasis on reducing saturated fat (a traditional low-fat diet), but not on increasing exposure to polyunsaturated fats, in line with a MedDiet approach[19]. The primary MedDiet objectives include consumption of monounsaturated and polyunsaturated fat sources, fruits and legumes, and whole grains[70], including: 1) 3 or more servings of fish and seafood per week (a serving is generally equivalent to ½ to 1 cup of food); 2) 3 or more servings of nuts or seeds per week; 3) virgin olive oil for cooking (> 1 spoonful/day); 4) selected white meat (poultry); 5) fruit and vegetables (> 1 serving per day); 6) 2 or more servings of legumes per week; 7) whole grain breads. Eating white bread, white rice, red meat, processed pastries, cream and butter is discouraged. A large 12-month MedDiet study (PREDIMED) (7 years and 8000 participants[71]) randomized persons into 3 groups: a low-fat diet condition, a MedDiet group with an emphasis on virgin olive oil (VOO) intake, and a third MedDiet group with daily nut consumption (1 ounce per day of nuts, including walnuts). MedDiet administration led to many benefits, including: 1) a 30% reduction in CVD incidents for the MedDiet groups compared with the low-fat control[72, 73]; 2) decreased oxidative stress[74, 75]; 3) lower risk for CVD events generated by abdominal obesity[76]; 5) improved cognition compared to the low-fat diet (Mini-Mental State Examination and Clock Drawing Test)[77]. Importantly, other studies demonstrate that MedDiet improves metabolic function (lower cholesterol, triglycerides) after only 3 months[78].

Polyunsaturated fatty acids (PUFA), and omega-3 PUFA (n-3 PUFA) from sources such as walnuts may have significant benefits for brain health and cognition[79]. Walnuts contain high levels of α-linoleic acid (ALA), which is converted to PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These PUFAs contribute to brain health via several mechanisms, including stimulating neurogenesis, improving energy transport to the brain, reducing inflammation, and activating brain-derived neurotrophic factor (BDNF)[80, 81]. Administration of walnuts (80 mg/day) to rats for 4-8 weeks improved cognitive performance on a radial arm water maze[82], with optimal performance observed with a 6% walnut diet, equivalent to 1 ounce of daily walnut intake in humans (as with PREDIMED)[79]. Nut consumption was also associated with improved working memory and reduced stroke risk in the PREDIMED cohort[83]. Administration of n-3 PUFAs for 6 months also reduced cognitive decline in patients with Alzheimer's disease[81, 84, 85].Finally, preclinical studies indicate that combining PA and n-3

PUFAs may optimize cognitive improvement; DHA supplements enhanced the beneficial effects of exercise in rats (12 days) on cognition and BDNF-related synaptic plasticity[86]; one week of exercise in rats combined with n-3 PUFA treatment increased markers of synaptic plasticity and glutamate receptor expression beyond either condition alone, biomarkers that correlated with improved performance on the Morris water maze[87]. In summary, these findings suggest that a MedDiet approach augmented with walnut consumption, in combination with PA, may successfully reduce CVD risk and neurocognitive deficits in PLWH.

mHealth interventions improve PA and diet. Mobile health (mHealth) text messaging interventions have promoted a variety of health behaviors, including increasing PA and reducing body fat and cholesterol over periods as short as 12 weeks[88] [89-91]. Although Short Message Service (SMS) protocols have been developed to improve medication adherence in PLWH[92, 93], this methodology has not been utilized to promote PA or diet interventions in this population. In addition, few studies have specifically targeted SB in PLWH[94]. Participant feedback has focused on three themes: adding a competitive component to iSTEP (allowing participants to compare their PA with others), being able to track their SB, not just steps, and the inclusion of diet as part of the intervention. Here we propose to conduct an mHealth intervention that examines the efficacy of a PA/SB intervention alone compared to PA/SB + MedDiet condition designed to improve neurocognitive performance and reduce CVD risk in PWLH with HAND and metabolic syndrome.

2.0 STUDY DESIGN

We will recruit 170 community-dwelling PLWH (20 for focus groups, 150 for the RCT) using the services of the UCSD HIV Neurobehavioral Research Program (HNRP) and the associated NIMH-funded HIV Neurobehavioral Research Center (HNRC) (P30 MH062512) and the Translational Methamphetamine AIDS Research Center (TMARC) (P50 DA026306). These centers have supported numerous multidisciplinary endeavors among PLWH over the past 20+ years and facilitate PLWH recruitment from the San Diego area and comprehensive neuromedical testing. While we will include participants who have previously engaged in research studies at the HNRP, we will also use our community outreach facilities to recruit PLWH who have not previously participated in research; this approach will enable a more appropriate representation of the general population and maximize the number of available participants. Recruitment and testing will be facilitated by an extensive research team.

3.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

3.1 Inclusion Criteria

3.1.1. Ability of participant to provide informed consent.

3.1.2 Age 18 or older.

3.1.3 HIV infection documented at the University of California, San Diego (UCSD) HIV Neurobehavioral Research Program (HNRP) or assessed by an HIV test at screening

3.1.4 proficient in English

3.1.5 Physically capable of participating in moderate PA as screened by the Physical Activity Readiness Questionnaire

3.1.6 Consent from primary care physician to participate in the study

3.1.7 Able to consume walnuts - no nut allergies

3.2 Exclusion Criteria

3.2.1. Any physical conditions that would prevent moderate physical activity or where moderate physical activity would represent a health risk for the individual, including a history of myocardial infarction or stroke

3.2.2 Unwillingness or inability to participate in daily text messaging

3.2.4. Tree nut allergy that would prevent walnut consumption or other food restrictions that would prevent participation in the Mediterranean-style diet intervention (e.g., unable to eat fish or use olive oil for cooking).

4.0 CLINICAL MANAGEMENT ISSUES

4.1 Adverse Events

We have taken great care to minimize the risks associated with text messaging in this study, including eliminating any information in the SMS content that could identify the HIV status of the participants. For example, we will not use any medication names in messages (e.g., identifying an HIV medication) or include content that could be used by a third party to identify a particular medical condition, but will utilize generic messages that ask about relevant physical conditions and limitations (e.g., do you have muscle aches today?). We will not include any personally identifiable information such the name of the participant in the SMS content sent to each subject or stored on mobile phones provided to participants. Text messages will include geographical landmarks such as nearby locations to engage in PA or the names of specific grocery stores to purchase food items; there is a risk this information could be accessed by an unauthorized person if the cell phone is lost or stolen.

Participants may experience anxiety or embarrassment related to one's personal PA or diet behavior (e.g., a lack of physical activity) or feelings of inadequacy with limited progress during the intervention. Participants in the focus groups may experience nervousness from participating in a group process activity or speaking in front of others regarding the issues that may affect PA or diet. Participants will be motivated to engage in moderate PA, including walking, and light PA to reduce and interrupt SB. No vigorous PA will be required. Some participants may experience mild muscle fatigue or soreness. Standard clinical interview procedures, including administration of PA and diet questionnaires, pose little risk to

participants.The blood draw procedure includes the risk of minor discomfort, bruising, fainting, or dizziness.

As with any HIV study, one potential risk is that of breach of confidentiality wherein a person's HIV status, sexual behaviors, or other sensitive information might be disclosed, resulting in embarrassment or prejudicial treatment by others. We will adhere to the standard risk management protocol in this regard, including use of participant identification numbers, locked data cabinets, and password protected computer databases. To ensure confidentiality, only the participant's code number will appear on all data forms as is standard at the HNRP. All paper-based records, forms, and data are kept in a locked interior file room. All medical records and demographic data also are locked in file cabinets within the file room. Computer records are protected by standard measures that limit access to the data to selected research project personnel. The electronic data are protected by multiple levels of password access, including to individual machines, the server, and to the central database. An HNRP Confidentiality Committee performs regular inspections to monitor procedures. In addition, the HNRP is protected from subpoena of confidential records by a Federal Certificate of Confidentiality.

4.2 Clearance from Primary Care Physician

Participants will be excluded for any physical conditions that would prevent moderate PA or where moderate PA would represent a health risk for the individual, including a history of myocardial infarction or stroke, pain in the chest when exercising, chronic joint problems aggravated by exercise, or a history of falls or balance problems. To minimize the probability of adverse events, participants will be screened for medical conditions using the Physical Activity Readiness Questionnaire; any indication of physical conditions that preclude moderate PA will result in the exclusion of the participant from the study. As an additional safeguard, each participant’s PCP will be contacted, with participant consent, to verify if there are any medical issues that would prevent involvement in this study. Study personnel will initially contact the physician by phone, after receiving written consent from the participant, to determine if the PCP is willing to provide medical clearance for the intervention. If the participant’s doctor agrees to do so, we will mail the PCP a medical clearance form that describes the SMS study and lists the options for moderate PA, such as walking, household activities (e.g., gardening). The form will provide the physician with the option to endorse study participation, deny participation due to known risks, postpone clearance contingent on further medical assessment, or acknowledge that they lacked adequate knowledge of the patient’s medical history to make an informed decision. The form will also allow the PCP to indicate that some activities, but not others are appropriate for the patient (e.g., walking is acceptable, but not climbing stairs). If the participant is enrolled, this information will be incorporated into the SMS prompts they receive. We will request that the PCP mail the completed form back to the PI. Participants will not be permitted to start the intervention until this written medical clearance is received. If the participant reports an adverse event or contraindication to moderate PA during the intervention (e.g., muscle soreness, shortness of breath), he or she will be suspended from the study until written medical clearance is again provided by the PCP. This will involve a second medical clearance form that will describe the adverse event and allow the PCP to indicate if the individual can resume the program, should discontinue, or if more evaluation is needed.

Ongoing medical treatment for HIV will not be altered or modified in any way for research

purposes. All subjects will be provided with PA safety and injury prevention recommendations before beginning the study, including instructions on warming up and stretching activities. Participants will be counseled that it is appropriate to gradually increase their PA (e.g., increase step counts by 10% per week) to reduce the risk of musculoskeletal injury and adverse events. During the initial enrollment and screening process, participants will be asked to phone the PI if any adverse events occur during study participation. In an emergency situation where participants are in need of immediate help as a result of an adverse event, the participants will be informed that they should first call 911 and then report the incident to the study staff as early as possible. Participants will also be contacted by telephone on a monthly basis by the PI to inquire about any adverse events, including chest pain, dizziness, or falls. Subjects will also receive regular text messages that will solicit information about any adverse events associated with their PA and any affirmative responses will be received by the PI who will contact the participant. In the case of any adverse events, participant PA activities will be immediately discontinued and the subject's PCP will be contacted to coordinate appropriate evaluation and treatment. Participant text logs will be monitored on a daily basis to ensure that no serious problems have occurred and to supervise each individual's continuing participation in the study. Participants are informed that they may withdraw from the research at any time if they find any aspect objectionable.

5.0 STATISTICAL ANALYSIS PLAN

5.1. Analyses.

For all analyses, two-sided tests with significance level α=0.05 will be used. Where necessary, assumptions for parametric testing will be checked prior to analyses. If assumption of normal distribution is not met, variable transformation (e.g., log) or nonparametric methods will be used. Randomization scheme should insure comparability of the groups on demographic and medical characteristics. Baseline characteristics will be compared between the groups using ANOVA for numeric values (e.g., age) and chi-square test for categorical variables (e.g., gender). Baseline characteristics found to be different between the groups will be used as covariates in the primary analyses to control for possible effect of group differences on the outcomes. For the primary analysis, PA outcomes will be measured at 2 visits (baseline (BL) and 24 weeks) with the exception of accelerometer and 7DPAR data, which will be measured at 3 visits (BL, 24 weeks, and 48 weeks); cognition and cardiovascular risk factors will also be assessed at 3 visits. Mixed models analyses will be conducted with a) the inclusion of all available data, assuming values missing at random; b) the baseline carry forward (BOCF) imputation method; and c) including only the participants who complete the study. For Hypothesis 1.1, changes in numeric outcomes measuring PA (e.g., time spent on PA, time spent on sedentary behavior) from baseline to week 24 (to week 48 for accelerometer/7DPAR measures) will be compared between the iSTEP and control groups using mixed effects models with subject-specific random effect. Subject-specific random effects will estimate individual changes in outcomes (slopes) as well as individual baseline values (intercept) to take into account natural variability in measured values between subjects. The models will regress PA measures on group (iSTEP vs. control), time (2 time points), and their interaction. A significant interaction term ($p<0.05$) would indicate a significant treatment effect or, in other words, significant differences in mean changes in outcomes over time (slopes) between the two treatment groups. Mixed effects model with terms for group, time (3 visits), and their interaction will be used to evaluate effect of iSTEP intervention on changes in accelerometer values. In explorative analysis, we will compare daily

changes in PA variables measured daily (step count, time spent in PA, and time in SB) between iSTEP and control groups using similar method as above, except using many time points (days) instead of just 2 or 3. For Hypothesis 1.2, Global Mean T-score will measure cognitive performance at all visits; practice effect correction will be applied to values measured at the 24 and 48 weeks. Again, mixed effects model with subject-specific random effect will be used to regress T-score on group (iSTEP vs. control), time (3 time points), and their interaction. We hypothesize that a significant interaction term will show that the slope representing an improvement in cognition will be the smallest for the control group and the largest for the iSTEP group. Similarly, for Hypothesis 2.1, changes in multiple numeric outcomes related to cardiovascular disease risk factors (e.g., cholesterol) will be evaluated with separate mixed effects models. The models will regress the outcomes on group (control, iSTEP PA/SB, iSTEP PA/SB + MedDiet), time (3 time points), and their interaction, including subject specific random effect. We hypothesize that a significant interaction will be observed and that it will show greater improvements in the outcomes for iSTEP groups, with iSTEP PA + MedDiet group having the best results. Similar approach will be used for Hypothesis 2.2, were changes (slopes) in Global Mean T-scores will be compared between the iSTEP PA/SB + MedDiet and iSTEP PA/SB groups and between the iSTEP PA + MedDiet group and controls. Additional analyses: We will conduct exploratory analyses using mixed models to assess changes in diet markers (omega-3, DHA, EPA, percent fat intake on the DHQ) over time to assess if there are group differences and if these markers predict CVD/NP outcome. Multiple regression analyses will be conducted across all participants to examine which factors (PA amount, SB change, MedDiet Score) significantly predict NP and CVD risk factors, including metabolic measures and inflammatory markers at the 6-month and 12-month visits. We will collect Likert scale data that identify what aspect of iSTEP is most useful (e.g., step self-monitoring, step count goals, types of PA/SB messages, comparing PA data to other PLWH) and conduct regression analyses to identify factors (e.g., PA barriers, SMS adherence) that best predict study outcome and PA/diet maintenance.

5.2 Power Analysis

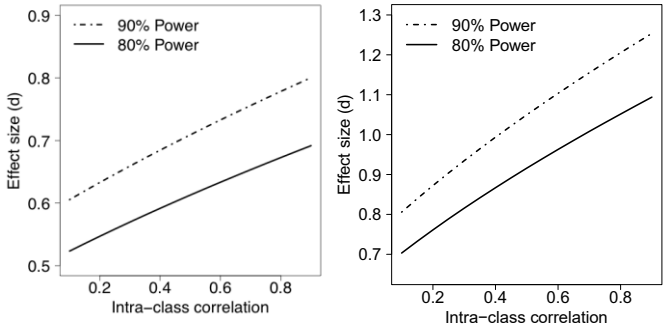

Figure 1a. Comparing changes in PA outcomes between iSTEP group (n = 40 after 20% dropout) and controls (n = 40 after 20% dropout) from BL to week 24. **Figure 1b**. Comparing changes in accelerometer data, cardiovascular disease risk factors, or cognitive outcomes between iSTEP PA+MedDiet and either of the other two groups (n = 40 for each group after 20% dropout) from BL to 48 weeks.

For all power calculations 20% dropout rate is assumed based on prior mHealth diet interventions[119], leaving N=40 for each of the three groups. For mixed effects models comparing change in outcomes over time between groups, estimates of power depend on intra-class correlation (within-subject correlation of outcomes measured at different times) and number of total visits, including baseline. For models based on 2 visits (hypothesis 1.1, except accelerometer), there will be at least 80% power to detect a medium to large effect size, Cohen's d, for the difference in mean change in outcomes from baseline to week 24 visit (Fig 1a). For models based on 3 visits (accelerometer /7DPAR values in hypothesis 1.1; hypotheses 1.2 through 2.2), there will be at least 80% power to detect a large effect size, d, for mean differences in outcome changes over three visits between any of the two groups (Fig 1b).

6.0 PARTICIPANTS

6.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

6.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB.

6.3 Study Discontinuation

The study may be discontinued at any time by the IRB as part of their duties to ensure that research participants are protected.