Measuring and Monitoring Adherence to ART with Pill Ingestible Sensor System

Investigator: Honghu Liu, Ph.D., Eric Daar, MD (mPI)

1) Title

Measuring and Monitoring Adherence to ART with Pill Ingestible Sensor System

2) Objectives

The first goals of this study are to confirm the bioavailability of over-encapsulated antiretrovirals (ARVs) and to pilot the use of the PROTEUS DISCOVER® [(**P**roteus **D**igital **H**ealth **F**eedback) (Proteus Discover ®)] system to determine approaches that maximize patient acceptability and optimize the system to be utilized. The team will build a real-time data collection hub and establish an automated feedback system to send a text message when no ingestion has been detected within a pre-specified time after a scheduled dose.

Bioavailability of over encapsulated ARVs will be conducted on at least nine (modified per Letter of Amendment # 1 dated 1/29/16) commonly used ARV formulations with six patients for each medication. We will then pilot the PROTEUS DISCOVER® system in 15 patients in an iterative process in which approaches to real time data handling, over encapsulation, patch and medication delivery and text messaging are tested and patient feedback and suggestions are elicited and incorporated into the system. The second goals are to evaluate the feasibility, acceptability and sustainability of the system, and assess the system's accuracy in describing adherence and efficacy in fostering adherence. Accuracy will be described as the association between adherence measured by the PROTEUS DISCOVER® system and adherence measured by other methods including plasma drug level concentration and self-report of prescribed medications taken. Efficacy is described as the impact of the system on leveraging adherence to ART and improving selected outcomes (exploratory).

3) Background

Introduction of antiretroviral therapy (ART) is lifesaving, but adherence to ART is critical to optimize outcomes. The limitations of current adherence measures constrain our ability to develop interventions to facilitate dose-taking and most methods do not actually measure real-time ingestion of medications or allow for immediate provision of feedback in the event of missed doses. The PROTEUS DISCOVER® system addresses these limitations, but has yet to be tested in people being treated for HIV infection. The PROTEUS DISCOVER® system involves use of an ingestible sensor, an edible material that can be over-encapsulated with a readily available and standardized product (Capsugel, Greenwood, SC, USA) so it is co-ingested with prescribed medication. The ingestible sensor is activated by stomach liquid, and is sensed by a monitor-patch that is worn by the patient and contains a microchip and a tiny battery. The monitor sends a Bluetooth signal to the patient's mobile device (e.g., cell phone), which in turn sends an encrypted message to a central server, thus allowing for a real-time signal that signifies a dose has been taken. As part of this proposal, we will create a real time data receiving hub and add a system that provides real-time automated text message feedback to the patient when a dose is missed. The ingestible marker and the personal monitor are FDA-approved for safety and have the CE mark (Conformité Européenne, meaning "European Conformity") of approval, indicating they also meet European Union safety requirements.

Recent Information

Analysis of the pharmacokinetic data around a single dose of over-encapsulated tenofovir disoproxil fumarate/emtricitabine (Truvada) were completed. The assays for plasma tenofovir levels reported

relatively low Cmax (maximum serum concentration) and Tmax (time at which Cmax is observed) when compared to historical data for this medication when not over- encapsulated. Although the team does not believe these differences in drug levels are clinically significant, for scientific rigor and patient safety we propose to repeat the assays using a modified study design. For this study for each of 6 individuals to be studied we will collect pharmacokinetic data after ingestion of non over-encapsulated dose and then this will be repeated in the same patient with the over-encapsulated pill. This strategy will allow us to compare levels between the pill with and without over-encapsulation in the same individual. We will attempt to study the same 6 individuals included in the original study; however, if a subject is no longer taking truvada or otherwise unavailable, he/she will be replaced with another subject who is currently taking this medication.

Recent Information

Analysis of the pharmacokinetic data around a single dose of over-encapsulated tenofovir alefanamide/emtricitabine/bictegravir (Biktarvy) were completed. The assays for plasma bictegravir levels reported relatively low when compared to historical data for this medication when not over-encapsulated. For scientific rigor and patient safety we propose to repeat the assays using a modified study design. For this study for each of 6 individuals to be studied we will collect pharmacokinetic data after ingestion of non over-encapsulated dose and then this will be repeated in the same patient with the over-encapsulated pill. This strategy will allow us to compare levels between the pill with and without over-encapsulation in the same individual. We will attempt to study the same 6 individuals included in the original study; however, if a subject is no longer taking biktarvy or otherwise unavailable, he/she will be replaced with another subject who is currently taking this medication.

4) Setting of the Human Research

Describe the sites at which your research team will conduct the research.

Recruitment of study subjects will take place at the CDCRC building and at Harbor-UCLA Medical Center – Building N-24.

The study will be conducted by the LA Biomed at Harbor-UCLA HIV Medicine Group located in CDCRC Building. Recruitment will take place at the Harbor-UCLA HIV Clinic.

Los Angeles BioMedical Research Institute at Harbor UCLA Medical Center

Dr. Daar will serve as one of the multiple PD/PI on this project. He will oversee the efforts conducted by his group in the development of protocol and implementation of various stages of the proposed study. This will include getting IRB approval, recruiting, enrolling and retaining study subjects and assuring appropriate acquisition of data. He will then be involved in data clean up, analysis and then reporting of research findings.

University of Nebraska Medical Center

Dr. Fletcher will contribute to the design of a sampling scheme for when to obtain blood samples for quantitation of antiretroviral drug concentrations. Antiretroviral drug concentrations in the blood samples will be quantified in Dr. Fletcher's laboratory, the Antiviral Pharmacology Laboratory using UPLC/MS/MS methods. Dr. Fletcher will contribute to the pharmacokinetic analysis and interpretation of the data generated.

Yale University
Dr. Rosen will serve as the Subaward Principal Investigator and will be responsible for supervision and day-to-day management of all aspects of the study in New Haven. Dr. Rosen will be responsible for assisting with the development of the Proteus system, and will store and analyze the qualitative data collected describing patients' experience with the system. He will provide content area and clinical expertise to Dr. Liu, with whom he will speak weekly.

5) Resources Available to Conduct the Human Research

Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

The study sample will be recruited through HIV clinics at Harbor-UCLA Medical Center and its satellite clinic in Long Beach, California. The clinics care for approximately 1,250 underserved patients, including 50% Hispanic and 25% African American and 20%women. The study subjects are expected to reflect the diversity of the clinic patient population with good representation of women, Hispanics and African Americans.

Drs. Daar (mPI) and Corado (Co-I) care for patients in these clinics and have substantial experience in studies of HIV treatment and prevention, including measurement and intervention of adherence to ART and wireless monitoring of adherence to ART.

Enrollment:
Pilot phase (Bioavailability and Feasibility):
54 subjects were enrolled and completed participation in the bioavailability phase of the study. In an effort to increase the number of possible candidates for the Trial Phase of the study, the team would like to enroll 12 more subjects to evaluate the bioavailability of 2 newly approved anti- HIV medications:

Biktarvy® (bictegravir, emtricitabine and tenofovir alafenamide) – 6 subjects
Symtuza™(darunavir, cobicistat, emtricitabine and tenofovir alafenamide) – 6 subjects

The pilot phase of the study has already been completed 15 subjects were enrolled.

Modified per LOA # 1 dated 1/29/16

Trial Phase: 120 subjects will be enrolled; about 150 subjects will need to be screened to meet our goal. To date 30 subjects have been approached and 10 have enrolled to the study.

Describe the time that you will devote to conducting and completing the trial within the agreed trial period.
Describe the number and qualifications of your staff, their experience in conducting research, their knowledge of the local study sites, culture, and society.

The members of the study team at LABioMed are: Eric Daar, MD, Principal Investigator; Katya Calvo, MD, Co-Investigator, Lisa Siqueiros, Study Coordinator; Pedro Chavez, Study Coordinator, Ramiro Correa, Study Coordinator and Mario Guerrero, Site Manager. All the members of the team have more than 2 years of experience performing HIV research. All of them are well versed in the consenting

process and all other aspects of research. All of them have obtained certifications regarding the GCP, HIPAA and Protection of Study Volunteers in Research from the IRB and are very familiar with the study.

Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

The PI and Co-I are members of the Harbor-UCLA HIV clinic; they will be readily available during the study period. Patients attending the Harbor-UCLA HIV clinic will have access to medical and psychological care through this clinic.

Describe your facilities.

The facilities and other resources available at UCLA as well as Harbor-UCLA, Nebraska Medical Center and Yale university include everything needed to undertake and successfully execute and complete the proposed study "Measuring and Monitoring Adherence to ART with Pill Ingestible Sensor System" . Page 14-19 of Stud Grant.

Regulatory: All regulatory material is coordinated through the Site Manager with the assistance of the specific research coordinator involved in each project. The Site Manager maintains the regulatory files for all studies being performed at LA Biomed and process initial IRB submissions, clarification memos and protocol amendments. In addition he coordinates correspondence and maintains the regulatory files of all safety reports. Safety reports are first registered by the coordinator and then sent to the PI for evaluations.

Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

All project staff will receive this training as provided by the UCLA, Harbor- UCLA, Yale and Nebraska Medical Center Office of Compliance and Office of Privacy and Information Security, Data collection and management procedures at UCLA, Harbor-UCLA, Yale and Nebraska Medical Center are fully compliant with HIPAA.

The research team will meet weekly to review the overall progress of the study, and discuss progress of each subject in the study. All members of the research team will be familiar with procedures for identifying and reporting possible adverse reactions. All adverse events are reported using the Institutional Review Board(IRB) standard template for reporting adverse events.

The over-encapsulation of the antiretroviral medications will be performed at the LABioMed Investigational Drug service by Roxanne Tanuviceanu, Pharm D. and Arlette Nazarians, Pharm D.

6) Study Design

a) Recruitment Methods

Describe when, where, and how potential subjects will be recruited.

Recruitment of study subjects for all Stages of this study will take place at the HIV clinic at the LABioMed CDCRC building and the Harbor -UCLA Medical Center – Building N-24. A satellite HIV

clinic in Long Beach - Tom Kay Clinic - will also serve as a referral site for the study.

Primary care providers will be informed about the study and requirements for participation. They will talk to potential subjects and refer them to the study staff if interested.

Describe the source of subjects.
The Harbor-UCLA HIV Clinic is the second largest public HIV clinic in Los Angeles County, with approximately 1,000 HIV-infected persons followed at this facility and approximately 250 followed at a satellite clinic in Long Beach. These patients are ethnically diverse with approximately 50% being Hispanic, 25% African-American and nearly 25% female.

Describe the methods that will be used to identify potential subjects.
See below – "Recruitment"

Describe materials that will be used to recruit subjects. Include copies of these documents with the application. For advertisements, submit the final copy of printed advertisements. When advertisements are taped for broadcast, provide the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the HSC reviews the final audio/video tape.

Recruitment: Both active and passive recruitment approaches will be used to recruit participants:

a. Clinic-wide information sessions will be conducted by the research team on a regular basis.
b. IRB approved posters, flyers, and brochures will be posted and readily available in each clinic;
c. Potentially eligible patients will be identified by conversation with the primary care providers. The primary care providers will ask potential participants if they are interested to participate in the study. If they agree, a research assistant will they interview the subjects to evaluate their interest. If they express interest a consent form will be provided; if they agree to participate, they will be asked to sign the consent form. .

   Recruitment will also occur by direct recruitment of patients, fliers, and advertisements. Direct recruitment will be done by direct invitation by clinic staff. Patients who are appearing for their regularly scheduled visit will be asked by a member of the clinic staff if they are interested in learning more about the study from a member of the research staff. If a patient expresses interest in learning more about the study, the patient will be contacted by a member of the research staff.

Interested patients will be interviewed by a member of the research staff to determine eligibility for participation and to be enrolled. The staff member will explain the study, and if the patient is interested in participating, will read the informed consent. The patient will be given a copy of the informed consent.

Describe the amount and timing of any payments to subjects.

Subject Compensation.
Subjects in the bioavailability portion of the study will receive $80 for the study.
Subjects participating in the pilot phase of the study will receive $50/visit.
Subjects participating in the Trial phase study will receive $50 (cash) for screening and follow up visits and $150 (check) at baseline (for completing the PK evaluations – Modified per Amendment dated

b) Inclusion and Exclusion Criteria for all Stages of study

Describe how you will screen for eligibility.

Primary care providers will be informed about the study and requirements for participation. They will talk to potential subjects and refer them `to the study staff if interested.

Inclusion criteria:

1. HIV-infected individuals in HIV care
2. Receiving ART with sub-optimal adherence estimated by either patient (self-reports < 90% adherence over last 28 days) or treating clinician (e.g., based on gaps in treatment (e.g. missed appointments) or viral load elevations within last 6 months that the treating clinician attributes to possible nonadherence) **[This will not be an inclusion criteria for bioavailability portion of the study]**;
3. Demonstrate ability to take over-encapsulated antiretroviral medications at the time of screening 4- Able to provide informed consent.

Exclusion criteria:

1. Inability to follow the study procedures manifested during the intake, as evidenced by mental confusion, disorganization, intoxication, withdrawal, risky or threatening behavior
2. Pregnancy (Evaluated during the screening visit through a pregnancy test.

c) Local Number of Subjects

Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be enrolled and screen, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Pilot phase (Bioavailability and Feasibility): 54 subjects were enrolled and completed participation in the bioavailability phase of the study.

In an effort to increase the number of possible candidates for the Trial Phase of the study, the team would like to enroll 12 more subjects to evaluate the bioavailability of 2 newly approved anti-HIV medications:

Biktarvy® (bictegravir, emtricitabine and tenofovir alafenamide) – 6 subjects Symtuza™(darunavir, cobicistat, emtricitabine and tenofovir alafenamide) – 6 subjects

Trial Phase: 120 subjects will be enrolled; about 150 subjects will need to be screened to meet our goal.

d) Study-Wide Number of Subjects

Not Applicable

e) Study Timelines for this proposal

Timeline	Project year	Year 1				Year 2				Year 3				Year 4				Year 5			
	Project quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Stage I: Preparation Stage	Establish the real time data collection procedures and system.																				
	Develop the real time patient feedback software system.																				
	Setup over-encapsulation procedures and logistics																				
Stage II: Pilot Stage	Confirm bioavailability of over-encapsulated antiretrovirals																				
	Pilot real time data collection and automated patient feedback texting system																				
	Debriefing/summary/revising																				
Stage III: Trial Stage	120 Patients will be screened, recruited, randomized to PROTEUS DISCOVER® and Usual Care (UC) groups																				
	Complete 16-week trial & collect data																				
	Complete 12-week post trial follow-up																				
Analysis & Dissemination	Data analysis, presentation, and publication.																				

Describe the primary and secondary study endpoints.

Describe any primary or secondary safety endpoints.

f) Study Endpoints

1. Pilot Stage

a. **Bioavailability of over-encapsulated ARVs**: Blood level of each drug will be tested on blood sample drawn before the dose (time 0) and at 1, 2, 4, and 6 hours post a witnessed dose to establish maximum concentration (Cmax). Blood levels of Bictegravir will be evaluated as per protocol amendment dated 12/26/18

b. **Pilot to test procedures, process, operations and patients' reactions to the PROTEUS DISCOVER® system.** Qualitative survey data collected over phone at day 3 and 14 of study and then face-to-face at weeks 4, 8, 12 and 16. Interviewers will collect feedback on what is and is not working with the system, including everything from taking the over- encapsulated pills, being monitored, wearing the patch, receiving text messages and collecting recommendations for changes to the system.

2. Trial Stage

Outcome Measures

The primary outcomes:

- Adherence to ART measured by PROTEUS DISCOVER® system for 16 weeks, including both percent of prescribed medication taken.
- Drug level concentrations from blood draw. Drug level concentration will used to define

adherence. We will measure drug level concentration 3 times at baseline to make sure that we can detect it (the 1st one to detect previous adherence, the 2nd and 3rd to detect current adherence), and weeks 4, 8, 12, 16, 20, 24, and 28. Drug level concentration adherence will be quantified with a novel pharmacokinetic-based approach as published. Brundage et al. described the pharmacokinetic-based method of estimating adherence based on intrapatient variability. Fletcher et al. described a sparse sampling method of measured drug concentrations translated into a single metric of exposure (e.g. amount of drug in the body) as a measure of adherence. Self-Reported Medication Adherence will be determined with a widely-used measure of self-reported adherence for percent of prescribed dose taken during the preceding seven days. This tool is easy to use and has been significantly associated with virological and immunological outcomes. Self-reported adherence will be measured at baseline, and week 4, 8, 12, 16, 20, 24, and 28. Due to its potential bias, self- reported adherence will be calibrated by drug level concentration to leverage its accuracy and used in analysis when calibrated self-report adherence is appropriate to be used.

The secondary outcomes:

- Viral Load and CD4 will be measured at baseline, week 4, 8, 12, 16, and 28.
- Process Measures: Patient perceptions and acceptability of the PROTEUS DISCOVER® system will be measured at baseline, and week 4, 8, 16, and 28. These will be evaluated by quantitative (first) and then qualitative interviews. The items in the quantitative interview will be rated on five-item Likert scales ranging from very strongly disagree to very strongly agree. Domains to be assessed will include overall satisfaction (would recommend to friend, would use outside of study setting, satisfied with system), utility, and specific items such as helpfulness and convenience. In addition, we will ask participants to rate specific items specific to the PROTEUS DISCOVER® system (comfort of patch, comfort receiving text messages) and issues that were identified during the qualitative interviews during the pilot stage.

Analytical approaches for Each of the Aims:

Specific aim 1: Evaluate the feasibility, acceptability and sustainability with the PROTEUS DISCOVER® system for measuring and monitoring adherence to ART among HIV-infected patients.

Hypothesis 1a. Greater than 70% of the patients assigned to the PROTEUS DISCOVER® system will rate that the system fits with their routine activities and daily living (feasibility). To test this hypothesis, we will perform analyses in two levels: (1) Obtain point estimates of ratings about the PROTEUS DISCOVER® system and conduct one group binomial test of the proportion with answers that indicates a fit (or better fit). This will be done at each of the time point of baseline, and weeks 4, 8, 16 and 28; (2) Repeated measures analyses to examine change over time. Generalized linear mixed models (GLMM) will be used to model the changes of ratings over time controlling patient characteristics (e.g., demographics, regimen type (single/multiple pill), and viral load (detectable or undetectable)). GLMM can model not only global fixed effects (e.g., the regimen type), but also random effects (e.g., change over time within a person). Patients' rating of automated text feedback system will also be evaluated and analyzed.

Hypothesis 1b. Fewer than 15% of patients assigned to the PROTEUS DISCOVER® system will discontinue use of the system during the course of the study (acceptability). To test this, we will use

similar approaches of one group binomial and GLMM as described in H1a to test acceptability through rate of discontinuing use of the PROTEUS DISCOVER® system. We will document the number of participants who complete the study, and how much technical assistance they need and receive. We will use non-inferiority tests for one proportion to compare acceptability with prefixed proportion at 15%.

Hypothesis 1c. The rate of discontinuing use of the PROTEUS DISCOVER® system will not increase over the course of the 16-week monitoring period (sustainability). To test this, we will use GLMM to model dropping off from using the PROTEUS DISCOVER® system and evaluate if there is a significant increase over time through parameter estimate of time (fix effect part) in the model. We will also document the number of participants who complete the study; and how much technical assistance they need and receive to assist the analysis.

Specific aim 2: Evaluate the accuracy of the PROTEUS DISCOVER® system in measuring adherence.

Hypothesis 2a. Adherence determined by the Proteus pill ingestible sensor system will be highly correlated with adherence determined by blood drug level of ARVs within the PROTEUS DISCOVER® group. Drug level concentrations from blood draw will be obtained for patients in both of the PROTEUS DISCOVER® and Usual Care (UC) groups to serve as an objective norm. We will use the pharmacokinetic-based method of assessing adherence based on intrapatient variability, or use the sparse sampling of measured concentrations translated into a single metric of exposure (e.g. amount of drug in the body) as a measure of adherence. Full parametric correlations (e.g., Pearson correlation (r)) between adherence measured by sensor and by drug level will be calculated and tested.

Hypothesis 2b. the correlations between adherence measured by the Proteus pill ingestible sensor system and adherence measured by drug level concentration of ART will be significantly higher than the correlation between self-reported adherence and drug level concentration of ART in the UC group. Daily adherence measured will be displayed by a scatter plot with a moving average (e.g., seven-day moving average) during the intervention period to show the trend. The strength of association between adherence measured by the Proteus pill ingestible sensor system versus adherence measured by drug level concentration of ART will be determined by calculating the Pearson correlation (r). Statistical significance tests between two correlation coefficients will be conducted.

Specific aim 3: Evaluate the efficacy of the PROTEUS DISCOVER® system for monitoring and facilitating adherence to ART. To leverage its accuracy, self-reported adherence will be calibrated by adherence measured through drug level concentration by a calibration model fitted with data from both PROTEUS DISCOVER® and UC groups. The calibrated self-report of adherence will be used in analysis of Hypothesis 3a. The level of adherence to ART of the PROTEUS DISCOVER® group will be modeled by adding quadratic term of time into GLMM, or by using generalized additive mixed model (GAMM), to evaluate the adherence trend change over time for 28 weeks. The adherence change trend before and after 16 weeks will be compared.

Hypothesis 3a. Adherence as measured by drug level concentration and calibrated self-report will be higher in the PROTEUS DISCOVER® group than in the UC group. Group-based trajectory models will be used to analyze ingestible sensor adherence pattern. GLMM will be used for modeling

adherence to ARV across the contact periods. A group (PROTEUS DISCOVER® or UC) dummy variable will be included in the model to test if the level of adherence is different between the two groups. If the distributions are substantially skewed, we will evaluate categorized clinical cut-off values using generalized estimating equation (GEE) analysis. For possible non-linear relationships between outcomes and time, we will add quadratic term of time into GLMM, or use GAMM. In addition, we will evaluate possible group differences in demographics (e.g., gender, race) and control for these variables in modeling outcomes.

Hypothesis 3b. use of the PROTEUS DISCOVER® system will be associated with lower levels of particular patterns of non-adherence than the UC group over time. We will make full use of machine learning and data mining methods to identify statistically significant patterns in the data. The machine learning and data mining methods we will use include tree models [e.g., classification and regression trees (CART), random forests, Boosting, Generalized Additive Models]; we will use GLMM and GAMM to model adherence between PROTEUS DISCOVER® and UC group over time to determine if it differs between groups. For possible non-linear trend, a quadratic term of time will be added into the GLMM model. We will also use GAMM modeling graphically show the change trend over time.

Hypothesis 3c. use of the PROTEUS DISCOVER® system will be associated with lower viral loads and higher CD4 counts than the UC group. GLMM and GAMM will be used to model viral load and CD4 of patients in the PROTEUS DISCOVER® group and the UC group across the contact periods (baseline and follow-ups) to evaluate a group x time interaction.

Hypothesis 3d. differences in adherence and virologic and clinical outcomes between the PROTEUS DISCOVER® and UC groups will be sustained during the 12 week follow-up after discontinuation of the PROTEUS DISCOVER® system. GLMM/GEE and GAMM will be used to model the adherence and virologic and clinical outcomes including parameterization that can distinguish the 16-week trial and the 12-week follow-up periods.

g) Procedures Involved in the Human Research

Study Design.

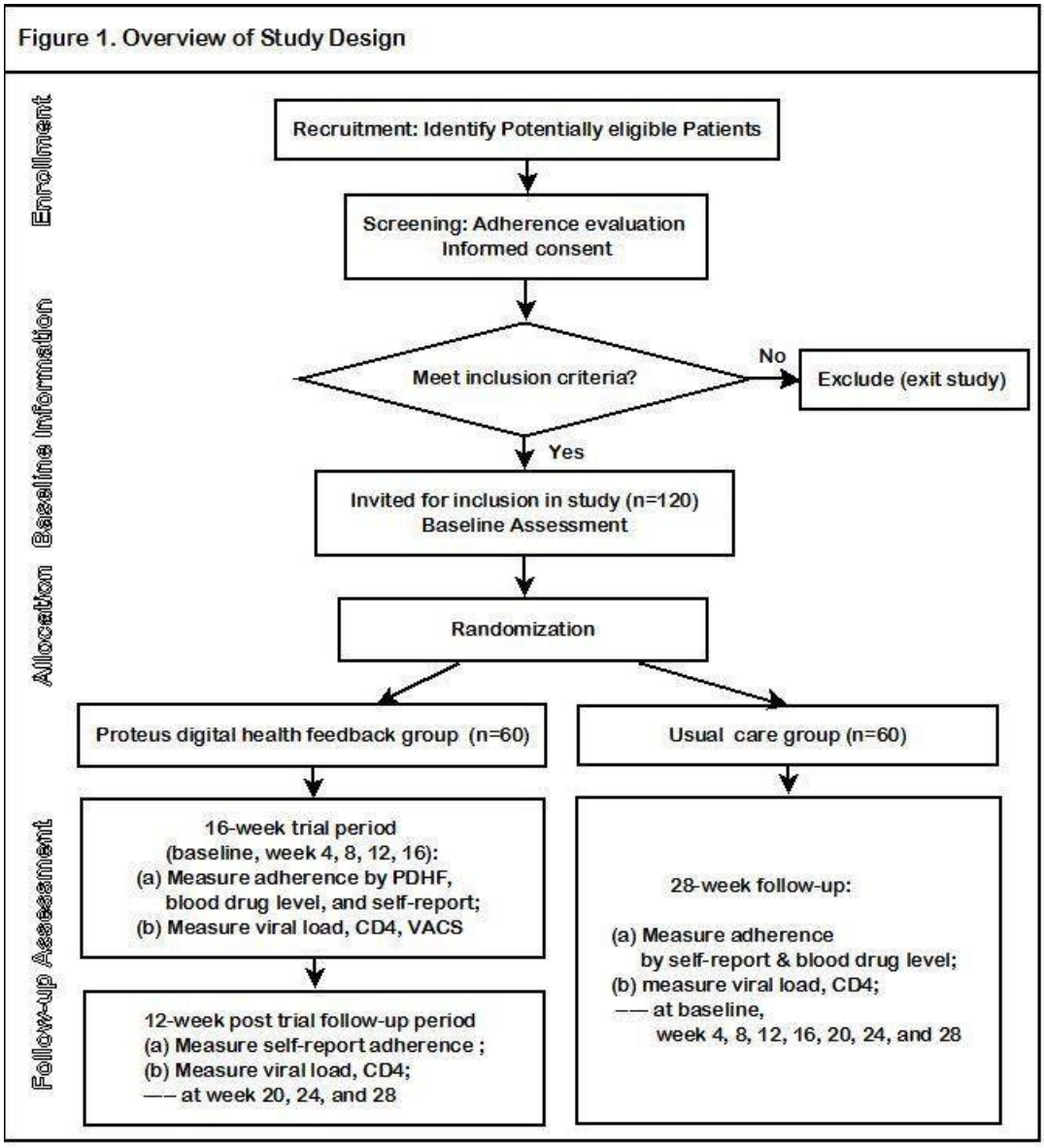
The study team propose to develop a data receiving hub and add to these components an automated text message that is sent to the patient when a dose is missed. The ingestible sensor and patch monitor system is already FDA-approved as safe, but has yet to be tested in HIV infected patients in clinical setting. The first goals of this study are to confirm the bioavailability of overencapsulated antiretrovirals (ARVs) and to pilot-test the use of the PROTEUS DISCOVER® system in 15 participants prescribed ARVs to test and identify approaches that optimize the use of this measuring and monitoring system. The next goals are to determine the system's feasibility, acceptability, sustainability, accuracy and efficacy in fostering ART adherence. Feasibility, acceptability and sustainability will be assessed by patients' rating of the system and the rate of dropping off from using the system. Accuracy will be evaluated by the associations between adherence to ART measured by the PROTEUS DISCOVER® system and other adherence measures such as plasma drug level concentrations of ARVs and self-report. Efficacy will be assessed by comparing adherence of participants assigned to the PROTEUS DISCOVER® system and participants assigned to usual care (UC) over time, with exploratory outcomes of viral load and CD4. We will recruit 120 of HIV-infected patients 18 years or older with sub-optimal adherence. Participants will be randomized to receive the PROTEUS DISCOVER® system or UC for 16 weeks with monthly assessments. The durability of

effects of the PROTEUS DISCOVER® system after stopping the use of the system will be determined during a 12-week follow-up stage. In summary, we will evaluate the feasibility, acceptability and sustainability of using the PROTEUS DISCOVER® system; assess the accuracy of the PROTEUS DISCOVER® system in measuring adherence to ART; and evaluate the efficacy of the PROTEUS DISCOVER® system for monitoring and leveraging adherence to ART.

The study goals will be achieved through three operational stages:

(1) Stage I—Preparation Stage will build the foundation and set up the needed systems and procedures. This first stage will involve setting up the real time data collection system, developing the system to deliver real time patient feedback via text messages, and setting-up over- encapsulation procedures and logistics through the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center Investigational Pharmacy.

Figure 1. Overview of Study Design



(2) Stage II—Pilot Stage will confirm bioavailability of over-encapsulated ARVs and pilot-test and optimize the procedures and systems developed in Stage I to ensure smooth operations in the trial stage of the study. At least five different ARVS will be tested among six patients each for a total of 30 patients. Second, we will pilot-test and optimize the procedures and systems developed in Stage I with 15 patients. During this pilot, we will assign patients to use the PROTEUS DISCOVER® system for 16 weeks. Some of the specific aspects of the system we will be evaluating, and possibly modifying are: (a) the real-time data collection process through mobile device, (b) the real time automated patient feedback texting system, (c) methods for over- encapsulating tablets, and (d) patients' acceptability with the PROTEUS DISCOVER® system, including automated text feedback message.

(3) Stage III—Trial Stage is shown in Figure 1. In the first 16 weeks, we will test overall utility (including feasibility, acceptability and sustainability) of the PROTEUS DISCOVER® system, its accuracy for measuring adherence and its impact on enhancing patients' level of adherence and selected outcomes. Durability of any observed effects will be examined during a 12-week post-Proteus system follow-up period.

Justification of Trial Stage Study Durations:
Duration of testing PROTEUS DISCOVER® system: The sixteen weeks was chosen because it is long enough to test feasibility and acceptability and to detect an effect of many effective adherence-promoting systems. It is also long enough to detect problems with sustained use of the system (e.g. fatigue with using the patches, use of an on-line pager system to increase adherence to antiretroviral medications, etc.) The system is likely to become easier to use in future years with longer-lasting patches and lower costs but studies like this one are necessary to establish proof of concept and the PROTEUS DISCOVER® system's feasibility, acceptability, accuracy and efficacy in a clinical population.

Duration of follow-up for retention of effects: A twelve week follow-up is long enough to detect rapid dissipation of any effects of using the PROTEUS DISCOVER® system. The PROTEUS DISCOVER® system is being tested in this early stage study as a standalone system, without other efforts to effect long-term adherence improvement (e.g. with a behavioral intervention.) Although ideally we would conduct longer-term testing of the system in order to address questions about long-term use, we decided against such a design because of the cost such testing would entail and the need to first establish feasibility, acceptability, accuracy and short-term effects.

Provide a description of all procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks. Include procedures being performed already for diagnostic or treatment purposes and differentiate between these and the procedures performed solely for the research.

Pilot Stage

a. **Bioavailability of over-encapsulated ARVs**: Eligible patients will be identified that are already on stable regimens with one of the drugs of interest including TDF/FTC, ABC/3TC, TDF/FTC/EFV, ABC/3TC/DTG, TDF/FTC/EVG/COBI, TAF/FTC/EVG/COBI and when approved TAF/FTC and TAF/FTC/RPV (Modified per LOA 1 dated 1/29/16) . The study will evaluate 6 patients on each of the drugs of interest. All participants will be counseled to ensure compliance with their HIV medications. Participants will be queried as to the number of doses of HIV

medications not taken in the previous 3 days, and this number will be recorded. The time and date of all doses of HIV medications taken the day prior to the PK study day will be recorded on a case (study) record form (CRF). The PK study will not be performed if a participant reports missing any doses of HIV medication on the day prior to the PK study. If this situation occurs, the participant will be counseled about medication adherence, and a repeat PK study may be performed ≥ 5 days later. On the day of the PK study, the participant will come in, have a pre-dose (time 0) blood sample obtained, take an observed dose and have blood drawn at 1, 2, 4, and 6 hours post dose. The time of doses of HIV medications given on the day of the PK study, and the exact time that blood samples are obtained, will be recorded on a CRF. Drug concentrations will be determined in Antiviral Pharmacology Laboratory at University of Nebraska Medical Center. We will compare observed Cmax values with those from published literature. The finding that Cmax values are within the expected range will confirm the lack of any adverse effect of over- encapsulation on absorption. If this is not the case we will exclude the drug in question from the Pilot and main study.

Subjects taking a Tenofovir/Emtricitabine (FTC/TDF, Truvada) will be asked to complete two 6-hr evaluations. One without over-encapsulation and one other in which the medication will be over-encapsulated as described above.

Subjects taking a Tenofovir alefanamide/Emtricitabine/Bictegravir (FTC/TAF/BIC, Biktarvy) will be asked to complete two 6-hr evaluations. One without over-encapsulation and one other in which the medication will be over-encapsulated as described above.

The study will evaluate six (6) subjects on each of these drugs for a total of 12 additional subjects. The total number of subjects to be enrolled to the bioavailability phase of the study will be 66 (54 already enrolled and complete) . The process of evaluating the bioavailability of these two new drugs will be similar to what was done for the other drug combinations as described above.

b. **Pilot to test procedures, process, operations and patients' reactions to the PROTEUS DISCOVER® system.** Fifteen patients including at least 6 women and 4 Hispanics who meet inclusion criteria will be provided the Proteus system and a mobile phone that is programmed for study-related communication, data upload, and data review. These individuals will pilot the use of the PDHS system to identify approaches that optimize the procedures and operation process. This phase of the study will be for 16 weeks. At initial orientation they will have the Proteus app installed on their smart phones, and if they don't have one we will provide. The system will be explained with pictures and graphics, and a handout summarizing the information will be provided. An initial debriefing will occur three days after beginning to use the system and again at week 2, both by phone and then at week 4, 8, 12 and 16. In face-to-face data collection visit. During the visits interviewers will be trained in principles of qualitative interviewing with semi-structure format seeking feedback on what is and is not working with the system, including everything from taking the over-encapsulated pills, being monitored, wearing the patch, receiving text messages and collecting recommendations for changes to the system.

Trial Stage

Overview. The schedule of assessment administration is summarized in table 3 below. Table 3. Schedule of Assessment Administration

Measure (From survey and lab test)	Screenin	Baselin	Week						
Screening and Baseline Measures									
	-30	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Baseline Characteristics Questionnaire	**X**								
HIV History	**X**								
Tolerability of Ingesting encapsulated pill	**X**								
Outcome Measures									
Adherence measured by sensor		**X**	**X**	**X**	**X**	**X**			
Self-reported medication adherence for both groups	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Drug level concentration from blood draw for both groups		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Viral load/CD4	**X**		**X**	**X**	**X**	**X**			**X**
Randomization		**X**							
Process Measures									
Patient perceptions and acceptability of the PROTEUS DISCOVER® system			**X**	**X**		**X**			**X**

[1]Continuous measure on daily basis from baseline through week 16.

A research assistant will complete the baseline assessments within 30 days of screening using computer-based and paper-based assessments. Responses will be directly entered into a computer database by the research assistant. Once entered, all responses will be anonymous and no personal identifying information will be recorded. The research assistant performing the follow- up assessments will do the best to remain blinded to the randomization allocation. In the event of missed visits, at least six attempts will be made to contact patients by telephone and letter. Even if a contact was not successful at any follow-up visit, further attempts will be made at each subsequent scheduled study visit. Table 3 summarizes the assessment schedule. Patients will be compensated for completing the baseline assessment ($40) and for each follow-up assessment ($40).

- Screening and Baseline Assessments. Patients will be screened with research assistants to complete Eligibility Form, informed consent, and consent to contact with providers to determine current medication regimen, determining if the patient meets suboptimal adherence criteria and tolerability of over-encapsulated pill. Patient interview will be audio taped.
- Baseline Characteristics Questionnaire. Socio-demographics, including, age, gender, race/ethnicity, language, educational level, marital status, source of income and residential status, will be collected.
- HIV History. A brief HIV clinical history will assess years since HIV diagnosis, years on HIV treatment, current HIV regimen, overall pill burden, and disease co morbidity.

Trial Stage

This will include randomization to PROTEUS DISCOVER® group or UC group for 16 weeks (Figure 1). During these 16-weeks, adherence of the PROTEUS DISCOVER® group will be measured by

pill ingestible sensor, plasma drug level and self-report, and adherence of the UC group will be measured only by plasma drug level and self-report. After 16 weeks there will be a post PROTEUS DISCOVER® follow-up period where all subjects will be followed for an additional 12 weeks during which adherence of both groups will be measured by plasma drug level and self- report as outlined in Table 3.

The objective adherence measure of drug level concentration will be obtained to serve as norm for patients in both groups throughout the 28 weeks with blood draw schedules of three samples at baseline [(to establish patient specific response bases) at times 0 (before taking anti-HIV medicines) and 2 and 6 hours after taking the medications)] and one sample each at weeks 4, 8, 12,16, 20, 24 and 28. With three blood draws scheduled around the time of an administered dose to establish patient-specific pharmacokinetics. The schedule of blood draws relative to drug administration and other conditions will be specified for each drug by Dr. Fletcher. During the trial phase, the date and time of all doses of HIV medications taken the day prior and the day that blood concentrations are obtained will be recorded on a case (study) record form (CRF). Plasma HIV RNA and CD4 cell count will be obtained with the same time schedule as drug level blood draw. This same blood draw schedule of plasma HIV RNA and CD4 cell count outcome with the drug level concentrations will enable us to blind patients for drug level concentration test to reduce "white coat" effect on adherence as assessed by drug levels. Patient surveys of demographics and baseline information will be done at baseline. Perceptions of wearing the patch, use the PROTEUS DISCOVER® system, automated texting feedback system and others will be done at weeks 4, 8, 16, and 28.

Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

(1) Proteus Ingestible Sensor and Monitor

The system consists of an ingestible sensor and an externally worn adhesive monitor, the patch-monitor. Together, the ingestible sensor and patch-monitor can be used to directly confirm whether, when, or how many doses of prescribed medication are actually taken.

(2) Proteus Digital Health Feedback System with Real Time Data Collection

Building on the available Proteus devices, we will design and create a PROTEUS DISCOVER® system (Fig. 2) to transmit the adherence data using mobile technology to allow treatment monitoring that is, direct confirmation of the type, dose, date and time of oral pharmaceutical ingestion using wirelessly observed therapy (WOT). We will set up a REDCap database system on a UCLA-based server. When the patch-monitor comes into proximity of the patient's mobile phone, the monitor's stored data are encrypted and transmitted via Bluetooth to the patient's phone. The phone sends the data using industry standard encryption (the same encryption utilized by banks) to a secured, centralized data center for storage and processing at UCLA. Processed data can then be relayed for display to the patient and/or medical professionals, as designated by the patient. The WOT system directly confirms adherence to oral medication electronically and wirelessly, eliminates the need for direct observation by a health worker and allows anytime, anywhere, objective confirmation of dosing.

(3) Automated Text Feedback System

We will use a secure and confidential web-based interface to send a short message service (SMS) text when a dose has not been ingested within a pre-determined time, informing the participant that

a dose was missed. We will build on our experience in the CARE study and that of other groups to do the following:

a) Customize with patients the schedule of messages (what window qualifies as a missed dose, and how soon after a dose is missed a text message is sent)
b) Customize the content of the text messages. Options offered to patients will include use of a code for medication-taking to disguise the message if seen by someone else (e.g. message to "eat your veggies"), exhortations ("remember your health, take the dose" or "remember your mom, take your meds"), or more HIV specific messages (e.g. "efavirenz was due at 8PM").

(4) Over-Encapsulation Procedures

Ingestible Sensors will be assembled in conjunction with device carriers. Proteus will directly provide sensors inside a placebo of a tablet dose form (about 3mm in diameter and 1mm in thickness). We will use over encapsulation with capsules provided by Capsugel (Greenwood, SC, USA) which has been used in other Proteus studies. This will provide a vehicle to combine any solid-dosage drug product inside a capsule with an Ingestible Sensor tablet dose form. ARVs of various form factors (e.g., a tablet or a capsule) can be placed inside the capsule along with the Ingestible Sensor tablet dose form. With the over-encapsulation method, the Ingestible Sensor, the drug product, and the standard excipient materials are completely contained within the capsule. Over-encapsulation provides an Ingestible Sensor-enabled dosage form with a familiar appearance to patients. Over encapsulation will be performed and handled by the Investigational Pharmacy at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and will be done to one of the pills to be taken at a given time to an individual. If taking multi-pill regimen the verification that the other medications were taken will be accomplished by self-report and plasma drug level monitoring.

Data sharing plan:

This project will adhere to the spirit and letter of the NIH guidelines on data sharing as published online at: NIH Data Sharing Policy,

http://grants1.nih.gov/grants/policy/data_sharing/

and to University Intellectual Property policy. We will create final merged and de-identified analytic files (no any PHI) that include behavioral and adherence measures and make them as widely and freely available as possible for educational, research, and nonprofit purposes while safeguarding the privacy of subjects and protecting confidential and proprietary data. We will be sensitive to situations in which even de-identified data could lead to "deductive disclosure" of participants' identities. Our approach to data sharing will include (1) Sharing data via website, particularly the summarized and aggregated results. (2) Sharing data through an electronic copy of the data sets. (3) Sharing data through a hard copy of summarized information. (4) Sharing data and findings through national academic meetings and conferences.

h) Data Management

Describe the data analysis plan, including any statistical procedures. Provide a power analysis.

Sample Size Calculation and Power Analysis

Sample size calculation and power analysis was conducted based on the primary outcome of adherence to ART. Using repeated measures analysis with intra-subject correlation of 0.1, a type I error of 0.05, a type II error of 0.2, and average number of available data points six, 60 subjects in

each of the PROTEUS DISCOVER® and UC groups will enable us to detect an effect size as small as 0.23 between the two groups, which is statistically and clinically meaningful. Thus, we will have sufficient statistical power to carry out the analyses for aims 2 and 3 (analyses for plasma HIV RNA and CD4 count are exploratory). For analyses of aim 1, 60 subjects in the PROTEUS DISCOVER® group will enable us to obtain stable point estimates. Thus, we have sufficient power for the study.

Stage I—Preparation Stage
PROTEUS DISCOVER® system with Real Time Data Collection

Building on the available Proteus devices, we will design and create a PROTEUS DISCOVER® system (Fig. 2) to transmit the adherence data using mobile technology to allow treatment monitoring that is, direct confirmation of the type, dose, date and time of oral pharmaceutical ingestion using wirelessly observed therapy (WOT).

We will set up a REDCap database system on a UCLA-based server. When the patch-monitor comes into proximity of the patient's mobile phone, the monitor's stored data are encrypted and transmitted via Bluetooth to the patient's phone. The phone sends the data using industry standard encryption (the same encryption utilized by banks) to a secured, centralized data center for storage and processing at UCLA. Processed data can then be relayed for display to the patient and/or medical professionals, as designated by the patient. The WOT system directly confirms adherence to oral medication electronically and wirelessly, eliminates the need for direct observation by a health worker and allows anytime, anywhere, objective confirmation of dosing.

Automated Text Feedback System

We will use a secure and confidential web-based interface to send a short message service (SMS) text when a dose has not been ingested within a pre-determined time, informing the participant that a dose was missed. We will build on our experience in the CARE study and that of other groups to do the following

- customize with patients the schedule of messages (what window qualifies as a missed dose, and how soon after a dose is missed a text message is sent)
- customize the content of the text messages. Options offered to patients will include use of a code for medication-taking to disguise the message if seen by someone else (e.g. message to "eat your veggies"), exhortations ("remember your health, take the dose" or "remember your mom, take your meds"), or more HIV-specific messages (e.g. "efavirenz was due at 8PM").

Stage III—Trial Stage

The third stage will test overall utility (including feasibility, acceptability and sustainability) of the PROTEUS DISCOVER® system, its accuracy for measuring adherence and its impact on enhancing patients' level of adherence and the effect on virologic and clinical outcomes (exploratory), the retention of its impact on keeping up with adherence and improvement of plasma HIV RNA and CD4 cell count after the 16-week usage of the PROTEUS DISCOVER® system. For this stage, we will recruit 120 HIV/AIDS patients with sub-optimal adherence to ART. Patients will be observed and followed up for a total of 28 weeks, with the initial 16-week trial period including the PROTEUS DISCOVER® versus UC, and a subsequent 12-week post trial follow-up period where both groups receive UC alone.

Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.
Describe any procedures that will be used for quality control of collected data. Describe how data and specimens will be handled study-wide:

- *What information will be included in that data or associated with the specimens?*
- *Where and how data or specimens will be stored?*
- *How long the data or specimens will be stored?*
- *Who will have access to the data or specimens?*
- *Who is responsible for receipt or transmission of the data or specimens?*
- *How data and specimens will be transported?*

Research participants will be interviewed by specially trained research assistants, using standardized assessment instruments. Subjects will also complete self-report rating forms. All assessments will be recorded directly into a computer database and monitoring system. Participants' names will appear only on the consent form, the HIPAA authorization form, medical records, and a "key" form kept by the Project Director. With the exception of the "key" form linking subject ID numbers and names, research records will contain only the subject's study ID number (and no patient identifiers), and medical records will contain only subject names (and no subject ID numbers).
Research staff will have access to patient names only during active participation

Clinical Site Monitoring and Record Availability

UCLA will review the individual subject records, including consent forms, CRFs, supporting data, and medical records to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records.

i) Confidentiality

Describe the local procedures for maintenance of confidentiality.

All evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by UCLA, NIH or other government agencies as part of their duties to ensure that research subjects are protected.

All research information is considered confidential. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. Right to privacy for participation in this research will be protected through anonymous coding of research data and proper storage of research records.

a. Limits to confidentiality: These limits include disclosure of acute suicidality, homicidality, or abuse of a minor, as is standard in clinical practice. Research data will be identified by code number and will not include names, although enrollment records must also be kept and these records will include names.

b. Data Collected: The study forms have been designed to avoid collecting identifiable information;

no Protected Health Information (PHI) will be collected on study forms. We generally collect only protocol session dates. These dates are changed to 'number of sessions completed' when data sets are anonymized and released to other investigators. All computers used by research staff are password protected.

c. Enrollment Records Containing PHI: Clinical enrollment records are kept separate from research data, and are not available without a client's written consent. Participants' names will appear only on the consent form and the HIPAA authorization form, kept by Dr. Daar. Both P.I.s (Drs. Liu and Daar) will keep a "key" form that links the study IDs to their names; this form will be stored on a secure server separate from the study data. Research data will also be collected from the treating clinicians such as initial eligibility information. To allow clinicians to provide information candidly, data collected from clinicians will be kept confidential from both third parties and the patients being enrolled. Only researchers officially appointed to work on this project will have routine access to protected health information. The sponsor, and agencies or departments with responsibility for research compliance will have access to protected information if necessary for oversight of study conduct (e.g. review that consent forms are completed properly). These other agencies include: Institutional Review Boards, Office of Research Compliance, government representatives, when required by law, UCLA Harbor Medial Center Clinic representatives, the Department of Health and Human Services, and the Food and Drug Administration. At the conclusion of the study, all locator data will be destroyed. Source data will be sent to a secure location (Iron Mountain) and will be destroyed 7 years after publication of the study results.

d. Preparation of Reports: The research records will be used to prepare reports that do not include client identification.

e. Staff training: All project staff will receive this training as provided by the UCLA, Harbor-UCLA, Yale and Nebraska Medical Center Office of Compliance and Office of Privacy and Information Security, Data collection and management procedures at UCLA, Harbor-UCLA, Yale and Nebraska Medical Center are fully compliant with HIPAA.

f. Certificate of Confidentiality: The study team has applied for a Certificate of Confidentiality to minimize the risk of forced disclosure in a legal or other proceeding. The Certificate, and the study consent form, will indicate the exceptions to confidentiality in which information may be disclosed without a patient's consent including danger of imminent harm to self or others, abuse or neglect of a child, and abuse or neglect of an elderly person.

g. Patient Behavior: Administrative termination will be considered if the patient's behavior is incompatible with safe completion of the research protocol.

h. Release of study information at Conclusion of Study: Patients who are enrolled in the study will have a debriefing session at the conclusion of their study participation at which they will review their adherence data (including ARV blood level data) with the research assistant. Patients will also be offered the study data to present to their providers if the patient chooses to do so

i. Difficulties providing informed consent: As noted earlier, participants will be asked questions at the time of enrollment to determine whether or not they understand key aspects of the study procedures. In addition to the usual consent procedures, the researcher obtaining consent will document the

discussion of the study, including questions raised by the participant.

- *Where and how data or specimens will be stored locally?*

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 subject, except as necessary for monitoring by the NIH, study monitors, OHRP, or other government agencies as part of their duties to ensure that research subjects are protected.

No laboratory specimens will be stored at this site. All test required for the study will be performed in real time.

Study visits will be performed in private rooms at the CDCRC and CTSI

- *How long the data or specimens will be stored locally?*
  Data will be stored locally until 2 years after the completion of the study
- *Who will have access to the data or specimens locally?*
  Only study personnel associated with the study will have access to the data
- *Who is responsible for receipt or transmission of the data or specimens locally?*
  The study coordinator will be responsible for receipt and transmission of data to the collaborating institutions
- *How data and specimens will be transported locally?*
  Data and specimens will be handled by the local study personnel

Audio-recordings: To make sure that the subject's confidentiality and privacy are protected, the following steps will be taken:

- We will ask subjects to provide informed consent for taping some of the sessions. However, they have the right to refuse taping. If they agree to taping, they have the right to stop taping at any time during the session.
- Audio recordings will be treated as confidential research records. The tapes will be stored in a locked cabinet and labeled with the subject's unique identifier code number and the date of the session. The audio-taped files will be encrypted with password protection. Access to audiotapes will be limited to members of the research team.
- Secure email system and secure FTP site will be used to transfer the research data (including *audio* recordings) between the data collection site at LABioMed, UCLA research team and the Yale research team.

j) Provisions to Monitor the Data to Ensure the Safety of Subjects

This is required when Human Research involves more than minimal risk to subjects.

Describe the plans to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Data and Safety Monitoring Plan

We are planning to use a reliable and secure system for data collection, monitoring and reporting that we have used in our clinical trial for the past 10 years. It consists of a database hosted on a network

of secure servers that will be used to collect and store data on server-based applications. New assessments are easily programmed and added to specific studies. All connections to the systems are secured and encrypted using 128-bit strong encryption protocols and only authorized users are able to access the system. All data is stored in encrypted files, and multiple backups of the system and all data are maintained. The system monitors participant progression through the study and reports are generated for the project director and Principal Investigator (PIs) when assessments are not completed. Additional reports can be provided on study logistics to monitor study progress and protocol compliance. At the completion of the study, or at any point during the study, all data collected can be transferred to the PIs or DSMB in the form of electronic data files using the format predetermined for reviewing. At the request of the PIs, all data from its systems including the backups can be erased.

Data monitoring procedures involve an organizational structure of clearly defined tasks assigned to all research personnel involved in the conduct of this study. The organizational structure used to ensure quality of data in this project include: 1) extensive training and close supervision of research assistants in data collection; 2) direct entry of most data at time of collection; and 3) utilization of on-line error-checking procedures. The PIs will supervise data procedures. All error corrections will be fully documented in the research records of the study. All research personnel will be required to participate in and document training in protection of human subjects and the responsible conduct of scientific research.

Data entry and review in this study will be conducted using a web-based data collection and monitoring system – REDCap. The REDCap system is designed to fulfill strict requirements of a clinical trial regarding data collection, monitoring, and reporting from the recruitment of participants to the delivery of data sets suitable for statistical analyses at the end of the trial. Briefly, the user of this system, after connecting to the server using a secure connection protocol, is presented with on-screen forms that allow information to be entered. Data is entered directly into web-based assessment forms or is transferred from other records when they are available (e.g. urine screens, HIV markers). The system monitors the subject progression along his/her schedule and this information is used for reporting.

The research team will meet weekly to review the overall progress of the study, and discuss progress of each subject in the study. All members of the research team will be familiar with procedures for identifying and reporting possible adverse reactions. All adverse events are reported using the Institutional Review Board (IRB) standard template for reporting adverse events. The PI at the site of the adverse event will review all adverse events, classify the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grade the severity of the event, utilizing the FDA's definition of serious adverse events, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious unanticipated or anticipated adverse events will be reported immediately to the IRB and to NIH. Adverse events will be reported in summary form at least annually to the IRB. The summary will include the number of subjects enrolled and a summary of graded adverse events to date, using the chart format included in the UCLA University Data Safety and Monitoring Plan template. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

The PI is responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should discontinue enrollment.

Safety monitoring plan: In this study we will use the FDA definition of SAEs. The P.I. at the site the SAE was detected will be responsible for reporting it.

Any SAEs will be immediately reported to the P.I. Reports will include a description of the event, relevant progress notes and records, and a summary of recent contacts with the patient. This summary will include any warning signs of the adverse event, the patient's general state and any information suggesting a causal link between study participation and the event. These will be reported to the UCLA and LABioMed at UCLA-Harbor IRBs and to the NIH Grants Project Officer within 3 working days.

Patients with HIV have an extremely high frequency of medical and psychiatric difficulties. Therefore, changes in physical or psychiatric condition, medication regimen or the presence of medication side effects are not untoward and do not constitute adverse events. It is extremely unlikely that the study procedures would exacerbate any of these. Anticipated adverse events include complaints about the study procedures, and any occurrence in which the patient attributes discomfort, harm or disability to the study procedures.

In this study, assessment for adverse events will be a routine part of every study and visit and phone call. SAEs and AEs will be screened for in the timeline follow-back. Operationalized, any report that a patient required overnight treatment in any facility (emergency room, detoxification, hospitalization) will constitute an SAE, as will any report of death, serious disability or hospitalization or death of another individual due to direct action of patient.

Every year, Drs. Daar and Liu (Co-PI at UCLA) will review study enrollment-to-date, SAEs and AEs, urine toxicology test results, side effect reports and other data as it deems necessary. A written summary including this information will be provided to the two IRBs with the protocol renewal and to NIH with the grant renewal.

k) Withdrawal of Subjects

Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

The study doctor may stop subjects from taking part in the study at any time without their consent if the study is cancelled, subjects are not able to attend visits as required, or their doctor thinks is not in their best interest.

Describe any procedures for orderly termination.

Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

7) Risks to Subjects

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the HSC's consideration, describe the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Blood Drawing: Participants will have ten blood draws (three at baseline and at months 1-7) as a result of their participation in the study. Blood drawing can cause some pain and result in a hematoma. Plasma HIV RNA and CD4 cell count will be obtained with the same time schedule as drug level blood draw. This same blood draw schedule of plasma HIV RNA and CD4 cell count outcomes with the drug level concentrations will enable us to blind patients for drug level concentration test to reduce "white coat" effect on adherence as assessed by drug levels. We will ask patients to get permission to withhold information from them about the purpose of the blood draw.

Rating Scales and Assessments: These are all noninvasive and should not add risk. The major inconvenience is the time it takes to complete the assessments and that they may be somewhat tedious to complete.

Monitoring System-Related Risk: *Refer to current version of Investigator Brochure for the study device.*

The ingestible marker and the personal monitor of the monitoring system are FDA-approved for safety and have the CE mark (Conformité Européenne, meaning "European Conformity") of approval, indicating they also meet European Union safety requirements. The potential risks include:

1- Nausea
2- Vomiting
3- Constipation
4- Difficulty swallowing the pills
5- Bitter taste
6- Abdominal cramping (very rare)
7- Stomach pain (very rare)
8- Asthma attacks
9- Non-cardiac chest pains
10- Risk that participants could find the co-encapsulation pill (which includes the sensor) is larger and thus less comfortable to swallow than the antiretroviral (ARV) medication alone:
11- Risk that participants could find wearing patch uncomfortable:
12- Possible skin irritation/itchy/allergic, although very rare in prior trials.
13- Risk that Proteus system inaccurate
    - Risk that message sent even though the medication was taken, and patient takes a second dose of the medication because he/she mistakenly thinks the dose was missed when it was not;
    - Risk that reminder not sent when med missed;
    - Risk that Proteus system associated with worse adherence than existing method of taking medication.
14- Risk that over-encapsulation alters pharmacokinetics.

Risk from resistant strains of HIV: Risk that patients may not take medications due to over-encapsulation or other study-related issues and that this could be associated with emergent drug

resistance.

Loss of Confidentiality. There is the possibility that confidential information obtained during the study will be disclosed, given the social and legal sanctions associated with HIV status, and psychiatric symptoms. Patient names and other identifying information will not appear on research records. Text message reminders will be messages patients choose to receive, with as much or as little HIV-related information as they choose.

Audiotaping of Interviews:

During the study we would like to audio record some of the sessions with the study staff. The purpose of this is for the study team to hear your opinion about the system and how we can make it better. .

- Recordings will be reviewed by members of the research team who are trained to review recordings.
- Recordings will be identified by number only. Names will not be noted by the study staff or reviewer on any recordings.
- Subjects may choose to stop being recorded at any time and can still be in the study. This decision will not change their care in any way.
- All study recordings will be kept in locked file cabinets and/or password protected computers. Only study staff will have access to them. Study records (including audio recordings) will be stored until the completion of the study
- Information from the recordings may be published or shared in study reports in aggregate to help describe the sessions and how they were conducted, but names or other data that might reveal personal information will not be revealed in any reports or writings that may result from this study.

If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Subjects cannot take part in this study if they are pregnant or planning to become pregnant. The risks of the PROTEUS DISCOVER® system to a pregnant woman and her fetus (unborn baby) are not known. Women who are having sex that could lead to pregnancy must agree not to become pregnant while taking part in this study.

Monitoring System-related risk:

- Risk that participants could find the over-encapsulated pill (which includes the sensor) is larger and thus less comfortable to swallow than the ARV medication alone:
    - Screening will include taking the over encapsulated product prior to enrollment and we will monitor and offer regular pills to anyone who reports this is impacting them.
- Risks hat participants could find wearing patch uncomfortable (e.g., Skin irritation, itchy, allergic)
    - we will warn participants of this possibility, and ask them to stop using the patch if it is consistently discomforting.
- Risk that Proteus system inaccurate
    - Risk that message says med not taken when actually was
      – this is very rare
      – will warn participants of this possibility

  - Risk that reminder not sent when med missed
    - was not an issue in Centralized Off-site Adherence Enhancement (CARE) automated system but will monitor this
- Risk that Proteus system associated with worse adherence
  - will have Data Safety and Monitoring Board (DSMB) with semi-annual unblended review of study data

Blood Drawing: Participants will have ten blood draws (three at baseline and at months 1-7) as a result of their participation in the study. Blood drawing can cause some pain and result in a hematoma.

Plasma HIV RNA and CD4 cell count will be obtained with the same time schedule as drug level blood draw. This same schedule of plasma HIV RNA and CD4 cell count outcomes with the drug level concentrations will enable us to reduce "white coat" effect on adherence assessed by drug levels. We will ask patients to get permission to withhold information from them about the purpose of the blood draw.

Risk that over-encapsulation alters pharmacokinetics. To address this there will be a lead in study to assure approximate bioequivalence of commonly used ARVs when taken with, compared to without over encapsulation.

Risk that patients on study may take drugs less frequently, such as if they are bothered by over encapsulation of medications and that this could result in emergence of resistant strains of HIV Because periods without ARV medication may allow resistant strains of HIV to emerge, we will institute procedures to insure that interruptions in effective ARV associated with using the Proteus system are promptly remedied. These safety procedures include:

a. Reminding participants of their right to switch to their usual medication-taking system at any time. We will make clear to participants that one aim of the study is to learn if the Proteus system is acceptable to patients, not to insist they use it whether they like it or not. Note that the study analyses involve intent-to-treat, so we will follow patients assigned to the Proteus condition, whether they continue to use the Proteus system or not. Thus, there is no financial incentive for patients to use the Proteus system in order to continue to receive payments for study participation. We will make this clear to participants upon enrollment.

b. We will ask people who "strongly disagree" with a statement about the Proteus system being "convenient" (or similar concept such as "usable") if they feel it is in any way making it less likely, compared to the way they usually take their medication, that they will take their medication as prescribed. Participants who feel the Proteus system is making adherence less likely will be encouraged to discontinue use of the Proteus system and use another way to take medications. We will, however, allow participants who want to continue using the Proteus system to do so. These patients may be judging that overall, the Proteus system is likely to help them take their medication as prescribed, despite some inconvenience, because it has offsetting advantages (knowing one is monitored, reminder system).

8) Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the HSC's consideration, the probability, magnitude, and duration of the potential benefits.

Benefits to Participants: Patients enrolled in this study may have enhanced adherence which could improve their medical condition. *Payment for participation during the Pilot and trial Study*: Patients will be paid for completing data collection assessments with a research assistant according NIH standards.

Benefits to Others: If the PROTEUS DISCOVER® system is effective, it might be adopted by other treatment facilities. This project may demonstrate the benefit of a system to help patients improve their adherence to ART. Given the enormous health, economic and societal costs of progression of HIV, the risk-benefit ratio is favorable.

The Benefit/Risk ratio: The potential benefits realized of the device system are substantial, and the risks posed by the device system are small. The benefits of study participation outweigh the risks.

Importance of knowledge to be gained
Overall, the study risks are reasonable in relation to the importance of the potential benefits for both the participants and science that reasonably can be expected to result. The risks associated with participating in this study can be categorized as minimal.

9) Provisions to Protect the Privacy Interests of Subjects

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.
Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.
Indicate how the research team is permitted to access any sources of information about the subjects.

The study doctors and staff will do everything they can to protect their privacy. In addition to the efforts of the study staff to help keep their personal information private, the study team has applied for a Certificate of Confidentiality from the Department of Health Services. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about their participation.

Measures to protect privacy

- Use a private setting for completing sensitive surveys or interviews
- Collect only the minimal amount of information necessary
- Avoid and limit the collection of identifiable information, and/or signatures
- Use discrete recruitment methods to eliminate identification of participants based on a stigmatizing or sensitive condition
- Confirm the participant's identity at the first encounter
- Never discuss the participant's case with anyone without the participant's permission (including family and friends during off-duty hours)
- Never leave hard copies of forms or records where unauthorized persons may access them

When on-site:

- Conduct interviews in a private room.

- Never discuss cases or use participant names in a public area such as hallways or elevators
- If a staff member or health care worker requests participant information, establish his or her authority to do so before disclosing anything
- Keep records that contain participant names and other identifying information in closed, locked files
- Carefully protect computer passwords or keys; never give them to unauthorized persons
- Don't leave sensitive or confidential information on an answering machine that other people can access

At the end of the study the study team will create final files (no any PHI) that include behavioral and adherence measures and make them as widely and freely available as possible for educational, research, and nonprofit purposes while safeguarding your privacy and protecting confidential and proprietary data. We will be sensitive to situations in which even de-identified data could lead to "deductive disclosure" of their identity Our approach to data sharing will include (1) Sharing data via website, particularly the summarized and aggregated results. (2) Sharing data through an electronic copy of the data sets. (3) Sharing data through a hard copy of summarized information. (4) Sharing data and findings through national academic meetings and conferences.

10) Compensation for Research-Related Injury

If subjects are injured because of this research, emergency medical care will be available. The care will not necessarily be free of charge. Financial compensation for any injury from this research is not available. If they are injured because of this research, they should first try to contact the principal investigator. If they cannot reach the investigator, they may call the hospital emergency department. They can also call the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Compliance Office, for further information on the availability of medical treatment or compensation.

11) Economic Burden to Subjects.

None

12) Consent Process

Indicate whether you will you be obtaining consent, and if so describe:

- *Where will the consent process take place*
- *Any waiting period available between informing the prospective subject and obtaining the consent.*
- *Any process to ensure ongoing consent.*
- *Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)."*

This site will follow the HRP-090 SOP regarding the consenting process.

Consent forms for the human subjects are obtained face-to-face, by the designee in a private office or exam room, and the consent forms are explained to them fully. The subjects are then asked if they have any questions and if everything is understood, they are asked to sign the consent form in front of a witness.

Plenty of time will be provided to the subject to make decisions about study participation. They will be allowed to take the consent form home and when they are ready to begin they can return to the

study site to sign the consent form.

Non-English Speaking Subjects

- *Indicate what language(s) other than English are understood by prospective subjects or representatives.*
- *If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language.*

Spanish speaking individuals will be invited to participate. Study documents will be translated to Spanish. Bilingual study personnel will be available during the consenting process

13) Process to Document Consent in Writing

Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be documented in writing.

Written Documentation of Consent SOPs (HRP-091) will be followed.
Consent: Voluntary informed consent will be obtained from all patients prior to participation. Consent will be obtained by a member of the research team after the research procedures and risks associated with participation have been explained to the candidate. Participants will be informed that they are free to decline participation and withdraw from the study at any time and that neither action will adversely affect their relationship with study personnel or their clinic staff. A signed copy of the consent form will be provided to all potential patients.

Consent to Obtain Baseline Information from Clinicians: Patients will provide written informed consent at the time of screening for the research staff to interview their treating clinicians to confirm the patients' regimen so that patients are counseled to take the correct regimen

14) Vulnerable Populations

If the Human Research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

HIV-infected individuals who with problems to maintain adherence to antiretroviral medications will be included in the study.

Indicate specifically whether you will include or exclude each of the following special populations:

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

All above populations will be excluded.

15) Drugs or Devices

If the Human Research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators

Ingestible Sensors will be assembled in conjunction with device carriers. Proteus will directly provide sensors inside a placebo of a tablet dose form (about 3mm in diameter and 1mm in thickness). We will use over encapsulation with capsules provided by Capsugel (Greenwood, SC, USA) which has been used in other Proteus studies. This will provide a vehicle to combine any solid-dosage drug product inside a capsule with an Ingestible Sensor tablet dose form. ARVs of various form factors (e.g., a tablet or a capsule) can be placed inside the capsule along with the Ingestible Sensor tablet dose form. With the over-encapsulation method, the Ingestible Sensor, the drug product, and the standard excipient materials are completely contained within the capsule.

Over-encapsulation provides an Ingestible Sensor-enabled dosage form with a familiar appearance to patients. Over encapsulation will be performed and handled by the Investigational Pharmacy at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and will be done to one of the pills to be taken at a given time to an individual. If taking multipill regimen the verification that the other medications were taken will be accomplished by self-report and plasma drug level monitoring.

The patches and smart phones will be handled by the study staff under the supervision of the authorized investigators.

16) Multi-Site Human Research

If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites

This study is a collaboration with investigators at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Daar), UCLA (Liu), University of Nebraska (Fletcher) and Yale (Rosen). All patient enrollment and follow-up will be exclusively conducted at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

The research team will meet weekly via teleconference to review the overall progress of the study, and discuss progress of each subject in the study. All members of the research team will be familiar with procedures for identifying and reporting possible adverse reactions.

17) Community-Based Participatory Research

Describe involvement of the community in the design and conduct of the research.

The LABioMed/Harbor-UCLA HIV Clinical Trials Unit has a local Community Advisory Board (CAB). The CAB meets monthly. Meetings are publicized through emails to our community partners. The CAB is an open group and currently consists of 10-15 community members from a variety of racial/ethnic/gender populations. Further, it represents many community organizations, as well as people living with HIV/AIDS, many of whom have participated in clinical trials at each of the sites. The meetings consist of educational and scientific discussions regarding HIV-related treatments and care. These have included new drugs for treatment naïve patients, diagnosing and managing cognitive impairment, therapeutic vaccines, and updates from national and international conferences. The remainder of each meeting is spent in review of currently enrolling trials, reviewing and commenting on CAB drafts of future studies, and other CAB business.

18) Sharing of Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Results of laboratory tests will be provided as soon as they are received. Final results of the study will be disseminated through direct mail to study participants and presentations at group forums.