Studying the Effectiveness of Non-Invasive Glucose Sensors in Patients With Diabetes: The SENSOR Study

NCT # 02800044

Document date: 8/15/2017

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1.PROJECT TITLE

Studying the Effectiveness of Non-Invasive Glucose Sensors in Patients with Diabetes: The SENSOR Study

2. PRINCIPAL INVESTIGATOR

Edward C. Chao, DO

3. FACILITIES

UCSD Medical Center, Hillcrest; and the UCSD Clinical and Translational Institute, Center for Clinical Research

4. ESTIMATED DURATION OF THE STUDY

1 year

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Self-testing of glucose by patients involves needles, which can cause discomfort or inconvenience; these and other factors can lead to decreased willingness to perform these checks that are vital to diabetes management. While technology has evolved, we currently do not have available a glucose monitoring device that is needle-free. We are studying a glucose sensor that adheres to the skin, similarly to a temporary tattoo. This sensor has not yet been tested in individuals with diabetes, and we will examine its accuracy and acceptability in these patients. Results from this clinical trial could serve as the basis for further development of a non-invasive, wearable glucose sensor that can provide measurements of glucose levels continuously.

6. SPECIFIC AIMS

Specific Aim 1: To gather initial data to permit a future assessment of the feasibility, accuracy, reliability, and validity of a wearable glucose sensor, compared with SMBG, in patients with DM.

Specific Aim 2: To evaluate whether patients with DM will find this sensor to be acceptable to use.

7. BACKGROUND AND SIGNIFICANCE

Self-monitoring of blood glucose (SMBG) can both facilitate and hinder adherence in patients with diabetes mellitus (DM). Readings are crucial to successfully managing this disease, as they provide real-time information on hypoglycemic and hyperglycemic excursions. SMBG can also help guide titration of medications, and can encourage patient engagement.[1] There is a correlation between increased frequency of SMBG and more optimal hemoglobin A1c (HbA1c) in type 1 DM (T1DM) and type 2 DM (T2DM) patients.[2,3,4] There are drawbacks. Patients may find piercing the skin to check glucose up to several times a day uncomfortable and obtrusive.[5] SMBG offers only a snapshot of the patient's glucose at the time of testing.

Continuous glucose monitoring (CGM) can reveal glucose trends. A subcutaneous sensor transmits interstitial glucose readings approximately every five minutes. Yet, sensor insertion requires a needle.[6] Patients still must test SMBG about 4 times per day to calibrate the sensor.[6] CGM is less accurate with low or rapidly rising glucose. A non-invasive glucose monitor, the GlucoWatch, was discontinued due to problems with accuracy and tolerability.

Compounding these challenges is the surging number of individuals with DM. Every 19 seconds, an American 20 years of age or older is diagnosed with DM.[7] Patients with T2DM have a 2- to 4-fold increased risk of cardiovascular disease, stroke, and peripheral vascular disease compared with non-diabetic individuals.[8] Diabetes is the leading cause of blindness, non-traumatic lower-limb amputation, and renal failure in the US.[9] The total costs of diagnosed DM in the US in 2012 were $245 billion, an increase of 41% from 2007.[10] If current trends continue, by 2050, 1 in 3 Americans could have DM.[11] Greater patient engagement with glucose monitoring can potentially lead to reduced risk of complications of diabetes, improved outcomes, and enhanced quality of life.

There is thus an unmet need for a non-invasive glucose monitoring device. UCSD nanoengineers developed a flexible, ultra-thin sensor adherent to the skin, similar to a temporary tattoo.[12] Preliminary data from seven individuals without DM demonstrated correlation between glucose measurements from this sensor and a glucometer.[12] This proposed study would be the first to examine this sensor in individuals with DM, and would serve as the basis for future development of a continuous, non-invasive sensor. We hypothesize that compared with a glucometer, a tattoo sensor can accurately measure glucose in patients with DM.

8. PROGRESS REPORT

Not applicable

9. RESEARCH DESIGN AND METHODS

We will enroll in this pilot clinical study a total of up to 50 patients between the ages of 18-75 with diabetes of any type, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), or diabetes secondary to etiologies such as pancreatitis; or to medications, such as steroids: defined as having a fasting plasma glucose (FPG) $\geq$ 126 mg/dL, or hemoglobin A1c (HbA1c) $\geq$ 6.5%. Participants will wear a tattoo sensor placed by study staff on one to three visits, on up to three different days (participants can elect to perform all measurements on one day), at various times: 1) fasting (before breakfast), 2) at least 1 time point between 15 to 200 minutes after consuming a meal, and 3) during and 4) 15 minutes after exercising aerobically for 15-30 minutes (walking at a moderate pace, or pedaling on a stationary bicycle, at up to 80% of maximum heart rate). Participants will warm up for 5 minutes before exercising and cool down for 5 minutes after completing the exercise session. We will obtain at least three sensor readings from each of these four time points, for a minimum total of 12 sensor readings. (We will compare participants' glucose levels as detected by a tattoo sensor, with at least 3 corresponding simultaneous fingerstick glucose readings, (measured by a glucometer, used as standard of care for those with diabetes). There will be a minimum of 12 glucometer readings, one for each of the above times. The total number of sensor and glucometer readings combined will be at least 24. We will monitor for acceptability and any discomfort through both verbal feedback and a brief, written questionnaire. Participants will be informed of their sensor and glucometer data. We will advise participants that only the glucose readings from the glucometer are non-experimental, and are considered accurate.

Participants can elect to perform exercise on a stationary bicycle; this portion of the study will be done at either the UCSD Clinical and Translational Research Institute's Center for Clinical Research, or the UCSD Exercise and Physical Activity Resource Center (EPARC). Those who are unable to or prefer not to exercise on a stationary bicycle, can choose to walk at either the UCSD Clinical and Translational Research Institute's Center for Clinical Research, of if a UCSD SBHP inpatient, at the UCSD Hillcrest Senior Behavioral Health Program (SBHP) Inpatient Unit. Study staff will monitor all participants during and after all exercise sessions.

All of the sensor components are printed onto temporary tattoo paper; the sensors are self-adhesive and are disposable. By applying a mild electrical current to the epidermis, sodium ions, and in turn, interstitial fluid glucose molecules, migrate toward an electrode. This process is termed reverse iontophoresis. An electrochemical sensor that is part of the tattoo detects the electrical charge strength of glucose to measure the glucose level.[12,13]

Prior *in vitro* and *in vivo* research conducted in the laboratory setting on human participants has demonstrated the efficacy of these sensors.[12] This work was conducted in the laboratory of Dr Joseph Wang. However, these sensors have not been validated in a clinical population previously. We will conduct this study in both outpatient and inpatient settings: the UCSD Clinical and Translational Research Institute's Center for Clinical Research, and the UCSD Senior Behavioral Health Program (SBHP), respectively. Individuals from this population may have conditions, such as depression, that may hamper their self-management of their diabetes. The inpatient setting offers the ability to simultaneously monitor other factors like dietary intake, degree of physical activity, and medication use. We can measure these parameters more precisely, as these are regularly and closely monitored and documented by nursing staff or other individuals. As many patients do not usually record such data as extensively, this information is more accurate than patient recall. In order to validate sensor use, mapping these covariates is essential, and the inpatient setting will allow us to measure these parameters efficiently, and without additional cost. Since one of the study sites is the UCSD geriatric psychiatry inpatient unit (the UCSD Senior Behavioral Health Program Inpatient Unit), some patients will have comorbid psychiatric diagnosis. We will not recruit any patients with cognitive impairment, to ensure that all participants have the ability to provide informed consent.

Since this is a pilot, single-arm study that is collecting preliminary data, we will use simple descriptive statistics to assess the glucose readings. The number of participants anticipated for enrollment is thus not based on statistical power analysis.

Sensor and glucometer values will be analyzed to determine the extent that these correlate in patients with diabetes; we will determine measures such as the mean, median, and standard deviation at the different time intervals.

10. HUMAN SUBJECTS

Participants who express interest after learning about the study from their physician or, if a geropsychiatry inpatient, from Dr. Sewell's team, reading the flyer describing this clinical trial, or reading the study description on ResearchMatch will be asked to sign an informed consent form.

We will recruit up to a total of 50 participants, ranging in age from 18 to 75, both male and female, without regard to ethnic or racial background. All prospective participants must have diabetes. Potential participants must be able to carry out the tasks required by the study. Participants must be able to read and speak English.

Inclusion criteria for the study will be:

1) An existing diagnosis of diabetes mellitus, either T1DM or T2DM, or any other type or etiology of diabetes
2) Absence of cognitive impairment, as demonstrated by a Montreal Cognitive Assessment (MOCA) score greater than 26; those individuals with questionable cognitive ability will be screened with this instrument.
3) Ability to provide informed consent for participation.

Exclusion criteria are:

1) Individuals without diabetes
2) Those who have a MOCA score of 26 or less
3) Those who cannot speak or read English. We are limiting participation to those who read and speak English, as this is a pilot study of a small number of participants, that will very unlikely offer the prospect of direct benefit from participating.
4) Individuals who have a cardiac, respiratory, or other condition that would preclude safely exercising at a moderate pace. Along with a medical history and physical examination by the PI, we will administer the Physical Activity Readiness Questionnaire (PAR-Q) to help determine those who may safely exercise for this study. One or more "yes" responses does not necessarily exclude an individual from participating.
5) Individuals who have frequent hypoglycemia, hypoglycemia unawareness, or who are at high risk for hypoglycemia.

We will provide compensation totaling $50 for all participants who complete all 3 study visits, and follow the sensor monitoring protocol. Those who complete 2 visits receive $25, and individuals who complete 1 visit will receive $15.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Internal medicine physicians and family medicine physicians will recruit prospective participants during regularly scheduled office visits. Dr. Sewell's team will recruit potential participants from the inpatient Geropsychiatry Unit. Potential volunteers will be provided flyers by their respective providers, and advised to contact Dr. Chao. We will also use ResearchMatch to identify potential participants. The proposed recruitment message is on a separate document entitled, "ResearchMatch Message to Potential Participants." Selection will be subject to meeting the inclusion and exclusion criteria detailed above. All individuals who qualify will be offered a place in the study on a first-come, first-served basis.

12. INFORMED CONSENT

Dr. Chao or another study team member will provide each prospective study participant information about the study and answer any questions. Should the individual agree to participate, he will obtain informed consent. Informed consent will occur in UCSD Hillcrest or the UCSD CTRI Center for Clinical Research. The potential participant will be given sufficient time to decide whether s/he would like to take part in the study. S/he will be provided the informed consent form and given the option to take this with him/her, if more time is desired. Every effort will be made to minimize any possibility of undue influence or coercion - the individual will be reminded both verbally and in the written consent form that participation is entirely voluntary, the decision to participate or not will not affect his/her health care, and that s/he can withdraw at any time. Informed consent will be obtained before any study procedures will be conducted, including screening procedures.

The participant will be given a copy of the signed informed consent forms, and the Experimental Subject's Bill of Rights. The originals shall be kept in the regulatory file. Additional copies will be filed in the participant's medical record.

13. ALTERNATIVES TO STUDY PARTICIPATION

The alternative is not to participate in this study and to undergo usual care.

14. POTENTIAL RISKS

There is a slight risk of skin irritation from the wearable, adhesive epidermal sensor. A preliminary study of this sensor on individuals with diabetes found no complaints of skin irritation or significant discomfort.[12] We will minimize potential risk by asking patients to wear these sensors for brief periods (of several minutes maximum), and will apply isopropanol to the region of the skin where the sensor was affixed. If any participant develops a rash, we will immediately remove the sensor and apply isopropanol. Should irritation persist or not resolve, we will advise the participant to consult with a physician. Reverse iontophoresis may cause transient, mild skin edema, which should completely resolve within one hour. When comparing sensor readings with a glucometer's readings, using a lancet to pierce the skin can cause slight pain, and potentially carry a slight risk of infection. We will minimize the latter by practicing hygienic technique.

Exercising can involve a slight risk of injury, such as muscle strain, whether walking or using a stationary bicycle. These forms of exercise entail significantly lower risks of falls or tripping. While there is a very small risk of a cardiac event (<1 in 12,000), this is minimized in healthy and physically active individuals. We will decrease this risk by monitoring participants closely during and after exercise sessions, and excluding any potential subjects with any pre-existing cardiac or metabolic condition. Exercising can also potentially cause hypoglycemia - a low blood glucose (70 mg/dL or lower), with or without symptoms such as shakiness and sweating.

Should a participant have an abnormal glucose reading - either hypoglycemia or hyperglycemia, we will immediately verify the individual's glucose level by checking on a glucometer. If the glucose is low (70 mg/dL or lower), we will provide standard of care: 15 g of carbohydrate (equivalent to 4 ounces (1/2 cup) of fruit juice, or 3 glucose tablets, or 1 small tube of Instaglucose), and will recheck glucose with a glucometer 15 minutes after the participant consumes the source of glucose. If the glucose remains low, we will repeat the above procedures until the level is corrected. If the participant has a profoundly low reading with loss of consciousness, we will inject glucagon and have the patient be evaluated further in the emergency room. Should hypoglycemia occur during an exercise session, a session may be rescheduled or cancelled as warranted.

If the reading is markedly elevated (e.g. too high for the glucometer to provide a numerical reading), we will advise the participant to undergo evaluation and treatment in the emergency room. For levels that are not as elevated, we will instruct the patient to monitor, and contact his or her primary care physician regarding possible medication adjustment. We will report all instances of abnormal glucose levels to the patient's primary care physician. The study physician will not make recommendations regarding titrating participants' usual diabetes medication regimens.

This non-invasive glucose sensor is a non-significant risk device, as it does not meet the definition of a significant risk device. This sensor does not have have the potential to pose a serious risk to the health, well-being, or safety of participants, and is similar to a new laboratory assay of blood glucose. Thus, an Investigational Device Exemption application is not required.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Risks will be minimized as much as possible, as the study team will closely monitor the participant while wearing the sensor. If the participant may warrant emergency care, such as having symptoms including chest pain, shortness of breath, dizziness, or markedly elevated blood pressure with vision changes and/or severe headache, we will contact 911 so that the patient can transported to, as well as evaluated and treated at the nearest emergency room.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Data from study volunteers will be de-identified at the beginning of the study. Each participant will be assigned a unique identifying number that will be used in all data sets. A list that assigns each study participant a code number will be stored electronically in a secured file that is password-protected. Access will be limited to only the Principal Investigator, Co-Investigators, and study staff.

17. POTENTIAL BENEFITS

Participants will unlikely receive direct benefits from this study in the short-term. The results from this study could assist in further development of a non-invasive (needle-free) continuous glucose monitoring device.

18. RISK/BENEFIT RATIO

The minimal potential risks associated with this study - including skin irritation, and piercing the skin - should be far outweighed by the insights that this study can provide, and the data that can inform potential future development of a non-invasive continuous glucose monitoring system.

19. EXPENSE TO PARTICIPANT

Participants will not incur any expenses related to completing this study. Study participants will be responsible for all travel expenses to and from the study site. The study team will furnish all supplies and equipment, including the wearable glucose sensors.

20. COMPENSATION FOR PARTICIPATION

We will provide compensation totaling $50 for all participants who complete all 3 study visits, and follow the sensor monitoring protocol. Those who complete 2 visits receive $25, and individuals who complete 1 visit will receive $15.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Edward Chao, DO, is an internist and endocrinologist at the VA, and is an Associate Clinical Professor at the UCSD School of Medicine. Joseph Wang, DSc, is Chair and Distinguished Professor of Nanoengineering, whose lab developed the tattoo sensor. Ipsit Vahia, MD, is Medical Director of Geriatric Outpatient Services at McLean Hospital, and holds a faculty appointment at UCSD; he was the former Director of Research, Senior Behavioral Health at the UCSD Stein Institute for Research on Aging. Daniel Sewell MD, is Medical Director of Senior Behavioral Health Program. Victor Legner, MD is the Clinical Services Chief for UCSD Geriatric Medicine. All investigators are CITI-certified.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

UCSD Academy of Clinician Scholars Faculty Development Award, UCSD Clinical and Translational Research Institute Clinical Research Pilot Project Grant

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

We do not anticipate any impact on nursing or laboratory staff.

27. CONFLICT OF INTEREST

The PI and co-investigators do not have conflicts of interest.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Since some individuals in the UCSD SBHP Inpatient Unit may have conditions, such as psychosis or dementia, that may limit or preclude them from being able to provide informed consent, or to understand and follow the study procedures, we will use the MOCA to help assess for decisional capacity. We will first ask all prospective participants to state what their understanding of this study is - including topics such as the study's purpose, potential risks and benefits, and the voluntary nature of this clinical study. If an individual does not appear to understand any facet, we will attempt to further explain, answer questions, or repeat applicable information from the Informed Consent. Should these efforts appear unsuccessful, or decisional capacity is uncertain, we will undertake further assessment by administering the MOCA. Should the individual fail this decisional capacity assessment, we will neither seek surrogate consent, nor enroll this individual in this study.