Certificate of Action

Board Action Date: 08/14/2023	**Work Order Number**: 1-1683646-1
Sponsor: CARI Health, Inc.	**Protocol Approval Expires**: 08/07/2024
Sponsor Protocol Number: 003 **Amended Sponsor Protocol Number:**	**Continuing Review Frequency**: Annually
IRB Tracking Number: 20233500	
Protocol Title: Assessing methadone dose taken using electrochemistry	

THE FOLLOWING ITEMS ARE APPROVED:
Baseline Questionnaire #38098796.0 - As Submitted (source: wcg irb 3 baseline questionnaire 073123)
Clinical Trial Agreement #38098789.0 (source: synergy clinical trials agreement_encrypted_)
Clinical Trials Study results #38098794.0 (source: clinicaltrials isfstudy2results)
DPV MTD+EDDP Data in PBS Gold SPE
DPV MTD in aISF TerraSensor #38098791.0 (source: dpv mtd+eddp data gold spe in pbs _ dpv mtd terrasensor in aisf = 07312023)
Eligibility Screener Questionnaire #38098787.0 - As Submitted (source: wcg irb 3 eligibility screener questionnaire 073123)
Experimental Research Subject's Bill of Rights #38098790.0 - As Submitted (source: bill_of_rights)
Follow-up questionnaire #38098786.0 – As Submitted (source: wcg irb 3 follow up questionnaire 073123)
MEM Elution Final Report #38098792.0 (source: cytotoxicity report from nelson)
Revised Protocol (07-29-2023) (source: irb 3 research protocol clean 081023)

Please note the following information about this review:
The Board determined that the use of the device(s) in this research is non-significant risk.

The Board requires that all subjects must be able to consent for themselves to be enrolled in this study. This means that you cannot enroll incapable subjects who require enrollment by consent of a legally authorized representative.

ALL WCG IRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

Consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization submitting shall promptly communicate or provide, and where necessary cause each investigator to promptly communicate or provide, the following information relevant to the protection of human subjects to the IRB in a timely manner:

- Upon request of the IRB, a copy of the written plan between sponsor or CRO and site that addresses whether expenses for medical care incurred by human subject research subjects who experience research related injury will be reimbursed, and if so, who is responsible in order to determine consistency with the language in the consent document.
- Any site monitoring report that directly and materially affects subject safety or their willingness to continue participation. Such reports will be provided to the IRB within 5 days.
- Any findings from a closed research when those findings materially affect the safety and medical care of past subjects. Findings will be reported for 2 years after the closure of the research.

For Investigator's Brochures, an approval action indicates that the IRB has the document on file for the research.
When the Board approves subject materials and/or advertisements, any redline changes that were provided by the submitter or required by the Board for approval will remain visible in the outcome document(s); however, recipients are expected to accept the tracked changes in the document before using. Do not make any additional modifications (including font size and visual effects) to the approved materials.
If this study includes data monitoring committee/data safety monitoring board, please note that the reports of all meetings of this committee should be submitted to the IRB even if the outcome of the meeting results in no changes to the study.

This is to certify that the information contained herein is true and correct as reflected in the records of WCG IRB. WE CERTIFY THAT this IRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) REGULATIONS, AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Federal regulations require that the IRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WCG IRB when the expiration date is approaching.

Thank you for using WCG IRB to provide oversight for your research project.

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Natasia Courchesne-Krak, CARI Health

Investigator List

The following PIs received some or all of the approvals specified in this Certificate of Action (COA). Please review the COA for each PI listed below to confirm which approvals apply for each PI.

Bari, Mohammed

Assessing methadone dose taken using electrochemistry
IRB Research Proposal
Protocol # IRB003
July 29, 2023

BACKGROUND INFORMATION

Sponsor: CARI Health, Inc.
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INTRODUCTION

A. Type of Research

Proof of concept: Pilot Study

B. Purpose/Objective of the Study

CARI Health's long term goal is to develop a minimally-invasive wearable Remote Medication Monitor (RMM) that provides continuous, real-time data on methadone levels in interstitial fluid (ISF). An RMM could be used as a medication adherence monitor and would allow for the physician, counselor, patient, or family member to remotely verify that a physician-prescribed dose has been taken. Such a verification system can allow methadone clinics greater flexibility in the provision of take-home doses and thus retain more patients in opioid treatment programs.

The purpose of this IRB protocol is to evaluate the early safety and feasibility of detecting methadone in the interstitial fluid (ISF) of subjects taking prescribed daily doses of methadone by using a minimally-invasive remote medication monitor (RMM).

We propose the following study aims:

Aim 1: Determine if an RMM <u>can assess</u> the status of taking a prescribed dose of methadone. To complete this aim, the peak and trough concentrations of a witnessed methadone dose will be assessed in ISF collected through the surface of the skin using existing ISF extraction methods and assessed outside the body via differential pulse voltammetry **(DPV)**. We hypothesize that the peak and trough blood samples will correlate with the level of methadone in ISF.

Aim 2: Determine if an RMM <u>can continuously assess</u> the status of taking a prescribed dose of methadone over time. To complete this aim, the pharmacokinetic profile of a witnessed methadone dose will be assessed in ISF continuously from the surface of the skin using the RMM for up to 6 hours. We hypothesize that a clinician can recognize a dose taken from the RMM generated measurement of the methadone in the ISF.

C. Background of the Study

Although reported biosensors have been successful in the identification and quantification of several important biomarkers, most of these devices require invasive means to achieve access to blood samples, thus resulting in pain and suffering on behalf of the individual. Furthermore, only a handful of these devices can provide a

continuous real-time measurement of analytes [1]. Thus, there is a need for a minimally-invasive device that can overcome the limitations faced by current technology. Wearable sensors have been receiving considerable attention recently due to their great promise for on-body monitoring of a wide range of relevant parameters for healthcare, fitness and biomedical applications [2-3]. While most current wearable technologies focus on monitoring physical parameters, there is tremendous interest in developing wearable chemical sensors to monitor important biomarkers for health and fitness applications [4-5]. Remarkable progress has been made in developing wearable electrochemical sensors that detect metabolites and electrolytes in human biofluids [4].

Human ISF from the skin (tissue fluid) contains many physiologically relevant biomarkers with a similar composition to that of blood in terms of salts for dehydration analysis, alcohol for sobriety testing, glucose, insulin and ketone for monitoring glycemic conditions, lactate as an anaerobic stress biomarker, glycerol for obesity monitoring [1,6] etc. Several research groups have shown a close correlation of concurrent metabolite levels in ISF to those in blood [7,8-9]. Indeed, efforts have been made to develop continuous ISF glucose monitoring systems as a viable replacement for invasive and painful fingerstick-based blood glucose testing [10-11]. In these systems, for ISF glucose, the ISF was forced to flow toward the skin surface through a process known as reverse iontophoresis [12]. However, for continuous analyte monitoring, constant access to the sampled biofluid (ISF) is necessary, which can be achieved using a microneedle-based device in a minimally-invasive manner. One of the first examples of microneedle-based devices that were tested in humans were developed for drug and vaccine delivery by Prausnitz and coworkers in the 1990's [13]. Since these reports, multiple microneedle-based platforms have been FDA approved and are commercially available or clinically applied [7].

An ideal ISF sensor must be well-suited to operate in the complex anatomy of skin tissue with minimal inconvenience to the wearer. The sensor must also integrate wireless data transmission capability for real-time readout over long distances. During operation, once the ISF reaches the electrode surface, the target analyte is quantified using electrochemical techniques (amperometry/potentiometry) sometimes coupled with specific analyte recognition (*i.e.,* enzymatic oxidation/reduction etc.) [11-14].

DPV

The methadone and metabolite assay uses a voltammetric technique called DPV which is not limited to measuring redox currents at single potentials but can be scanned across a wide range of potentials. In short, DPV is using three different types of electrodes/microneedles: working electrode (WE), counter electrode (CE), and reference electrode (RE). A potentiostat applies a sweeping voltage between the WE and the RE while detecting an electrical current flowing from the WE to the CE (or vice versa). The current is proportional to the concentration of an analyte that can be reduced or oxidized at a specific voltage in the sweep. If no analyte is present (at a given potential) only a baseline signal (due to ion conduction) will be detected. If, however, a specific analyte is present and can be reduced or oxidized within the swept voltage range, the current will show a peak at that specific voltage, which is so low that it can not be felt by the patient.

Electrochemical Assay

The electroanalytical performance of the sensor is strongly dependent on the surface structure and composition of the WE. Our assay uses a proprietary electroactive carbon composite (EAC) that is applied onto a "test strip or microneedle based electrode (WE)". This coating has independently passed tests for cytotoxicity and is considered biocompatible. The 3 electrodes of the sensor are the WE, CE and RE. The electrochemical assay does not comprise a 'recognition chemistry' layer, i.e., an enzyme, an aptamer or a molecular imprinted polymer that exclusively binds to or reacts with a specific molecular substrate (analyte). The assay is capable of detecting multiple substances (i.e., methadone) in the ISF while it is indwelling in the dermis or after being collected with an extraction device.

The complete sensing solution comprises a precision analog front-end (AFE) chip ("potentiostat") that is

controlled by a microprocessor (MCU). The AFE sets voltages and measures the current between the different types of electrodes (i.e., WE, RE and CE). The DPV waveform consists of an increasing staircase ramp superimposed on a square wave, whereby the waveform parameters (start/end voltage, scan rate, Epulse, Estep, etc) are selected to optimize the performance of the invention. The potentiostat applies the DPV waveform directly across the WE and RE and controls the CE accordingly to generate whatever voltage and current is required to maintain the WE and RE voltages. The electrochemical current that flows from CE to WE (or vice versa) is relayed to the Bluetooth Low Energy Communication Module module for transmission to a smartphone or laptop.

Initial studies of the microneedle sensor device have been performed in the lab for demonstration of sensing methadone/EDDP levels in artificial ISF [list of prior studies provided below]. Attractive performance was achieved non-enzymatically using a proprietary coating over platinum microneedle electrodes. Thus, the microneedle sensor device can be readily expanded toward realization of real-time, on-body testing on humans to offer useful insights into patients daily dosing of methadone.

Additional prior relevant studies and references include:

- Toxicity level of the microneedle coating material based on standard and independent cytotoxicity studies (see attached cytotoxicity report from Nelson showing the EAC1 coating used in our assay is not cytotoxic).
- Methadone in ISF (see attached clinicaltrials.gov results and Enzyme official study reports).
- Data on the ability of the proprietary assay to quantitatively detect methadone and EDDP
- Related work by others [15] showing proof of concept in humans for phenylalanine dose taken, and reference [16] for tylenol dose taken

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PARTICIPANT SELECTION

D. Inclusion and Exclusion Criteria

Aim 1 and 2 (up to N = 20):

- **Inclusion criteria for methadone group includes:**
  - Age 18-70.
  - A prescription for methadone for chronic pain at a dose of 10mg or more for at least one week.
  - Taking methadone as prescribed during the last 4 days before consent to participate in the study.

- **Exclusion criteria for methadone group includes:**
  - Age <18 or >70.
  - A condition preventing or complicating ISF collection
  - Conditions may include dermatological (skin) condition
  - bleeding diathesis
  - immunodeficiency
  - recent blood donation
  - anemia
  - end stage renal disease
  - liver cirrhosis
  - cancer
  - congestive heart failure
  - bleeding diathesis
  - tuberculosis (TB)
  - active severe depression
  - suicidal ideation
  - mania symptoms.

- Pregnancy
- intending to become pregnant during the course of the study
- Enrolled in a substance use disorder treatment program
- Under a conservatorship.

B. Sex

and the potential benefits that may result from this research. Women of childbearing potential are eligible to participate in this study. Acceptable methods of birth control include abstinence, meaning a total lack of any sexual activity, as well as the use of oral contraceptives (the "pill"), contraceptive injections, intrauterine device, double-barrier method (diaphragm or condom + spermicidal cream), contraceptive patch, or male partner sterilization. Pregnant women will not be included.

C. Racial/Ethnic Origin

There will be no racial/ethnic enrollment restrictions in this proof of concept study.

D. Vulnerable Populations

Vulnerable populations such as pregnant women, children, fetuses, wards of the state, severely cognitively impaired individuals, patients in treatment for opiate use disorder, as well as prisoners and institutionalized individuals will not be included in this pilot study.

E. Age

Subjects under the age of 18 will not be included in this study. Older adults are known to metabolize substances differently and have thinner skin than younger adults, as such those over 80 will also not be included in this study.

STUDY DESIGN / METHODS / PROCEDURES

We will conduct a non-randomized, non-blinded, feasibility study at a single center in the United States. The study will include up to 20 subjects of an equal number of male and female adults (ages 18–70) who have a prescription for methadone for chronic pain. In **Aim 1**, we will determine if an RMM can assess the status of taking a prescribed dose of methadone, using biosamples (i.e., ISF, blood) collected from subjects and tested in a laboratory setup. Biosample collections and pharmacokinetic monitoring will take up to 6 consecutive hours. By completing this aim, we will determine if a physician is able to recognize the peak and trough concentrations of a witnessed methadone dose by DPV or LC-MS data using one of the three available ISF extraction methods described later in this protocol (i.e., Samplimy, Kiffik, or Prausnitz). In **Aim 2**, we will determine if an RMM can continuously assess the status of taking a prescribed dose of methadone over time, by inserting the intradermal microneedle sensing elements of the RMM in the subjects' skin. The electronics for the RMM prototypes will consist of commercially-available benchtop potentiostats like the PalmSens Sensit BT (https://www.palmsens.com/product/palmsens4/) or CH Instruments 660D (https://www.chinstruments.com/) and will not be in direct contact with the skin. Biosample collections (i.e., ISF, blood) and pharmacokinetic monitoring will occur over a 6 hour period. By completing this aim, we will determine if a physician is able to recognize a pharmacokinetic profile of a witnessed methadone dose via data collected using intradermal microneedle sensing elements worn continuously on the skin. Completion of Aims 1-2 will require two separate visits.

A. Summary of the Research Design for Aims 1-2

Subject Recruitment Strategy: Up to 20 adults ages 18-80 years of age will be recruited to participate in this study. Subjects will be recruited from pain management clinics and primary care physicians providing control of chronic pain with methadone prescriptions. Human subjects research will be performed at Synergy Research Centers (https://www.synergyresearchcenters.com) in San Diego which is a well-established clinical trial company that provides appropriate staff and facilities to conduct this study.

Study Procedures: As described in detail below, all subjects will participate in a 1) pre-screening phone call, 2) two in-person clinical visit(s) which will include a urine toxicology test, pre dosing blood samples, microneedle and/or

electroporation+suction device application depending on whether it is the first (Aim 1) or second (Aim 2) visit, post dosing blood samples, and a post-microneedle application follow-up call approximately 2 days after sensor removal. As such, there will be two in-person visits. On the first day visit (Aim 1) we will test whether the **RMM** can assess taking a prescribed methadone dose periodically for up to 6 hours. On the second day visit (about 1 month after the first visit; Aim 2), we will test whether the **RMM** can assess taking a prescribed methadone dose continuously for up to 6 hours.

- **Screening (up to 10 minutes)**
    a. Potentially eligible subjects will be identified by the research team and clinical staff through pain clinic referrals. The screening process may occur in-person or online. However, subjects will use an online screening process in both situations while final consent will be obtained electronically in person at the research facility.
    b. Study eligibility will be conducted by the clinical research coordinator (CRC). See the supplemental material for specific questions.

- **Consent (up to 10-30 minutes):**
    a. If the potential subjects meet the inclusion criteria, do not meet the exclusion criteria, and agree to learn more about the study, the CRC will send the study consent document link via an online Good Clinical Practice (GCP) compliant program to the subject for review.
    b. The CRC will walk the subjects through the consent and answer any questions the subject might have online and again in person. As such, there will be no paper consents.

- **Initial questionnaire (up to 15-30 minutes):**
    a. If the potential subjects agree to participate as indicated by their online signature on the consent, they will be assigned a computer-generated Subject ID code and will be asked to complete the online baseline questionnaire in a GCP compliant data collection program (see the supplemental material for specific questions).
    b. The questionnaire will include the following:
        i. Demographics (e.g., age, sex, race, ethnicity)
        ii. Past and current diseases or medical conditions
        iii. Previous operations or medical procedures
        iv. Any medicines, vitamins, minerals, and herbal remedies that the person is currently taking
        v. Diet and exercise habits
        vi. Tobacco, alcohol and other substance use history
        vii. Previous pregnancy history (if female)
    c. The CRC will schedule an in-person clinical visit for the subjects if needed. Subjects will be instructed to take their medications as prescribed by their physician (e.g., dose, dosing times). As such, the in-person visits will be scheduled around the subjects usual dosing time. Subjects will also be asked to abstain from alcohol and non-prescribed substances at least 24 hours before their in-person assessment.

- **In-person study visit within 7 days after the initial consent and online assessment is completed:**
    a. **Physical assessment (up to 30 minutes; Aims 1-2)**
        i. The in-person assessment may include the following:
            1. Limited physical exam:
                a. Height and weight measurements
                b. Feeling for the pulse
                c. Listening to the heart and lungs with a stethoscope
                d. Measuring blood pressure using a sphygmomanometer
            2. Changes in medications in the past week
            3. Use of substances (e.g., opioids, alcohol) in the past week
            4. Urine toxicology test to confirm no other substance use

b. **Prescribed dose of medication (5 minutes; Aims 1-2)**
    i. Participants will be asked to take their prescribed methadone medication at the study site. Study personnel shall observe that a dose has been taken.

c. **Blood sample collections (5 minutes each; Aims 1-2)**
    i. At medication peak and trough, a standard venipuncture blood sample will be collected by a certified clinician. These samples will be used for comparative analysis with the sensor's ISF Methadone Readings and LC-MS assays of the extracted ISF samples.

d. **Visit 1 ISF samples collected by 1 of 3 potential methods.**

1. ISF is collected from subjects using one or more of three published extraction methods (i.e., Samplimy, Kiffik, or Prausnitz). The subject is asked for a preference of location (dorsal side of right or left upper arm, or alternatively ventral side of right or left forearm) and the clinician applies the appropriately selected method to collect ISF. If more than one of the three ISF collection methods are applied then it will be applied on the same upper arm or forearm areas by the physician at least 10 cm apart. Participants will have the opportunity to decide whether they are willing to have more than one of the extraction methods administered.
    a. **Samplimy Method** (microneedle patch and applicator as per (Ribet et al., 2023): First applied 1 hour prior to dosing and continued every 15-30 minutes until 4 hrs after dosing (total of 5 hours). An applicator will ensure consistent control of the force and speed of attaching the intradermal microneedle and the pressure required for microneedle extraction [17].
    a. **Prausnitz Extraction Method** (manual microneedle application): As described in our IRB 002 (#20222142) approved and completed study, a minimally invasive microneedle array will be used in conjunction with a standard vacuum pump. Microneedles (without the patch) will be inserted and removed multiple times (~10) to collect about 1 µ1 of ISF. This approach has been well tolerated with faint visual evidence of micropores in the skin in previous studies, including ours [18].
    b. **Kiffik Method:** A certified physician will place the Kiffik device on the participant's preferred arm. ISF collection will start 2 hrs prior to taking the participant prescribed methadone dose and will end prior to dosing with repeat collections after dosing every 2 hrs until 6 hrs of collection time has ended. Thus, a total of 3 samples will be collected from each participant [19].

e. **Visit 2 ISF samples collected by 1 of 3 potential methods .**
    i. The steps listed above (section d #1) will be repeated for visit two (Aim 2), however, in addition to having ISF collected from the skin, the subject will also be applied with up to 3 RMM device(s) and continuously wear them for up to 6 hours. This will replicate how other standard of care continuous monitoring devices (e.g.CGMs) are worn (e.g., https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes/continuous-glucose-monitoring). The continuously monitored levels will be compared to the ISF extracted levels as well as the peak and trough blood levels as explained in the analysis section of this protocol.

f. The RMM device will consist of a microneedle sensor array wired to a benchtop potentiostat like the PalmSens Sensit BT or CHI 660D. Data will be continuously collected using either bluetooth or data cables. Computer programs will be used to record, measure and analyze methadone and its metabolite levels in the collected sample data. The resultant Differential Pulse Voltammograms will be translated into pharmacokinetic data and securely stored for analysis by the lead research staff.

g. Up to 6 hrs after the application is complete, the microneedles will be removed, the insertion area inspected and a sterile bandage covering will be supplied to the area.

h. Subjects will be monitored before, during, and 15 minutes after the application to report their tolerability, pain, and experience. Their responses will be documented on a secured google drive spreadsheet, which will be encrypted with a password that adheres to secure GCP certified online storage medium requirements.

- **Method of sample preservation**
  a. Blood samples will be centrifuged and plasma will be kept in the refrigerator.
  b. Collected ISF samples using the single hollowed microneedle with absorbent paper devices will be prepared as outlined by Bird Rock Laboratories and Federico Ribet (developer of the Samplimy method).
  c. Collected ISF samples will be analyzed at the time of study and frozen after analysis
  d. All samples will be transported to the laboratory within 7 days of collection and stored in the refrigerator.

- **Follow-up call/visit (15 minutes)**
  a. Approximately 2 days after the microneedle application, subjects will be contacted by the CRC via phone. Subjects will be asked to report their tolerability, pain, and experience. Their responses will be documented in a secure online storage medium.

- **Compensation:**
  a. **Day 1 (Aim 1):** Subjects participating in the first part of this study will be compensated with an online visa gift card worth up to $250 for their participation. Subjects will be compensated $25 for the initial online assessment (up to 15-30 minutes), $25 for the in-person physical exam (up to 30 minutes), $130 ISF sample collections (up to 6 hours), $50 using the standard venipuncture with vacuum tube based blood collection (1 pre and 1 post sample per day), and $20 for the follow-up call (up to 15 minutes).
  b. **Day 2 (Aim 2)**: Subjects participating in the second part of this study will be compensated with an online visa gift card worth up to $250 for their participation subjects will be compensated $25 for the online assessment (up to 15-30 minutes), $25 for the in-person physical exam (up to 30 minutes), $130 for ISF sample collection, continuous sensor application, and data collection (up to 6 hrs), $50 using the standard venipuncture with vacuum tube based blood collection (1 pre and 1 post sample per day), and $20 for the follow-up call (up to 15 minutes).
  c. All subjects will also be provided with 2 meals, snacks, and non-alcoholic beverages during their stay at the study site.

There will be no paper data stored in locked filing cabinets or offices. A unique subject ID code will be created in analytic databases and be used to link all data in an individual file because such linkage is critical for communication with the subject. Research data will be separated from identifying data. All data will be stored on secure password protection servers. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. The research sites used in this study have well established systems for protection of confidential subject information. All computers and files containing confidential information will be password protected and monitored by study staff. As such, the data will be limited to a small number of project investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

B. Analysis of Study Results

All the biological samples collected in this study (e.g., ISF (1 ul), blood (2ml), will be tested for methadone and its **r** metabolites at a laboratory that has experience with these types of samples. Urine will be tested for illicit substances to inform eligibility on site with urine drug testing strips.

Concentrations of methadone and its metabolites (EDDP, EMDP, and methadol) will be measured in the

collected ISF, and blood samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The study will analyze the data using noncompartmental pharmacokinetic analysis to determine the pharmacokinetic parameters of methadone in the ISF and blood.

Published protocols will be followed for quantitation of methadone and its metabolites.
Determination of the dose taken will be accomplished by the physician using the 2-4hr slope of change in concentration of methadone in the ISF after a witnessed stable dose. The physician may also use the ratio of the area under the ISF dose curve (AUC) for a witnessed individual stable methadone dose divided by the individuals sensed and extrapolated 24hr witnessed/unwitnessed ISF dose curve AUC. (A ratio close to 1.0 confirms compliance to a full dose taken, less than .5 or greater than 1.5 suggests noncompliance. See Rostami et al Poster reference)

ISF samples collected using the Samplimy or Kiffik method will be assessed using the RMM in the same way that they will be assessed in vivo but with modifications as outlined in the phenylalanine dose taken example study. Concentration determinations from analyte peaks in the Voltammograms will be correlated to the trough and peak blood methadone levels.

All samples will be safely stored and processed according to Good Clinical Practice Guidelines. None of them will be used for any DNA analysis.

C. Monitoring
N/A

D. Storage of Data
The original electronically signed consent forms will be stored in a secure password protected file online via the Adobe Sign BA agreement based Storage Service. Only the research team members (Principal Investigators/Co-Investigators) and the CRCs will have access to identifiable private information.

An electronic data sheet casebook using GCP certified software will be used for each subject enrolled in the study. The appropriate data sheet will be completed online by the CRCs after each visit. All data collected for the study will be reviewed for quality assurance, data entry, and statistical analysis. All electronic forms will be reviewed for completeness; evident recording errors will be rectified by contact with the appropriate clinical staff. All data sheets will be reviewed by a research team member before final data entry submission. Laboratory Data will be entered within two (2) weeks of a receipt from the independent laboratory. Any corrections will be made electronically.

All biological samples will be stored and processed through standard IRB approved procedures. Subjects will consent to allow their deidentified biological samples to be stored for future use.

All team members will be GCP certified and trained to protect identifiable private information (e.g., signed consent). Deidentified research data will be kept separate from identifiable data in secure GCP certified online locations for the duration of the study. This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of GCP regulations. These requirements are stated in global regulations as well as “Guidance for Good Clinical Practice,” International Conference on Harmonization (ICH), and the most recent guidelines of the Declaration of Helsinki of Technical Requirements for Registration of Pharmaceuticals for Human Use.

E. Confidentiality of Data
Due to the sensitivity of the health information, strict precautions will be employed to protect confidentiality. Subjects will be informed that their participation in the study is voluntary and they may choose to not participate or withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. All study personnel will be compliant with GCP regulations.

Risks associated with confidentiality will be minimized by collecting and storing data securely. There will be no paper data stored in locked filing cabinets or offices. A unique Subject ID code will be created in analytic databases. The unique Subject ID code will be used to link all data in an individual file because such linkage is critical for communication with the subject. Research data will be separated from identifying data. All data will be stored on secure servers using password protection. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. All bio-samples will be labeled with the subject's ID number. As such, no identifying information will be listed on the bio-samples. All computers and files containing confidential information will be password protected and monitored by study staff. The data will be limited to a small number of project investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

RISK/BENEFIT ASSESSMENT

A. Risks

The risks of participating in the study include the potential for discomfort or pain during the insertion and removal of the microneedles and the potential for infection at the insertion site. There is also a small risk of bleeding or hematoma formation. The benefits of participating in the study include the potential for better pain management through improved understanding of the pharmacokinetics of methadone in the interstitial fluid. Subjects may also experience mild allergic reaction to adhesives, bleeding, bruising, infection, pain or discomfort, scarring or skin discoloration, skin inflammation, thinning, discoloration and/or redness. Although unlikely, hospitalization due to infection is possible. Based on clinical studies and post market data available for a similar approach, it is expected that the occurrence of any adverse events will be low.

As with most research involving human subjects, loss of confidentiality or breach of privacy is a risk. The proposed study involves data collected over the internet and in person. Data will be transferred to and from the online data system electronically, and stored on secure servers through Synergy Research Centers.

B. Prevention of Risks Study staff will monitor subjects for any adverse events described in the next section. The CRA will also contact the subjects two days after each procedure to assess their tolerability, pain, and experience. All potential adverse events will be assessed and reported when necessary.
As mentioned, risks associated with confidentiality will be minimized by collecting and storing data securely. There will be no paper data (e.g., test forms) stored in locked filing cabinets/offices. A unique subject code will be created in analytic databases, as mentioned. The unique Subject ID code will be used to link all data in an individual file because such linkage is critical for data analyses. Research data will be separated from identifying data. All data will be stored on secure servers using password protection. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. All computers and files containing confidential information will be password protected and monitored by study staff. As such, the data will be limited to a small number of project investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

C. Adverse Events

Below is a list of the potential adverse effects (e.g., complications) associated participating in this study:

- Mild allergic reaction to adhesives
- Mild bleeding
- Mild bruising
- Mild or moderated infection
- Mild or moderate pain or discomfort
- Mild scarring or skin discoloration
- Mild skin inflammation, thinning, discoloration and/or redness.
- Although unlikely, hospitalization due to infection is possible.

D. Benefits

Besides the financial compensation outlined in this protocol, there is no immediate personal benefit to the subjects.

However, it is believed that these research efforts will lead to significantly improved responses to the growing opioid epidemic. Relevant information learned in this study will be managed with care and in a respectful manner. Strict protection over subject information to ensure confidentiality will be employed.

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