IRB APPROVED
AS MODIFIED
Aug 03, 2022

RESEARCH SUBJECT CONSENT FORM

TITLE: Interstitial Fluid Collection Validation Study

PROTOCOL NO.: 002
WCG IRB Protocol #20222142

SPONSOR: CARI Health, Inc.

INVESTIGATOR: Mohammed A. Bari, MD
7922 Palm Street
West Lower Level
Lemon Grove, CA 91945
USA

STUDY-RELATED PHONE NUMBER(S): 858-278-3647
888-539-0282 (24 hours)

RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether or not you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Dr. Jon Wilensky received consulting fees from the sponsor in the past 12 months and owns private equity in the sponsor company. He is the physician that will perform the procedure for obtaining fluid from your skin. He is certified in this procedure and has previously performed it on other patients. He will not have access to your confidential patient records and will only know you by your assigned subject number. He will have access to the de-identified data but not to any personally identifiable information. Please feel free to ask any further questions you might have about this matter.

How long will I be in this research?

We expect that your taking part in this research will last about 4-5 hours total in person. This does not include travel time from your home to the study site for one day.

Why is this research being done?
The purpose of this research is to determine if common medications for opioid use disorder (i.e., buprenorphine/naloxone, buprenorphine, methadone) and their metabolites (norbuprenorphine [a metabolite of buprenorphine], buprenorphine-3-glucuronide [B3G; a metabolite in buprenorphine], ethylidene dimethyl diphenyl pyrrolidine [EDDP; a metabolite of methadone]) can be detected in the fluid under the surface of the skin by interstitial fluid sampling.

If it is confirmed that these common medications can be detected in the fluid right underneath the skin it may be possible to create a wearable product that will enable patients to prove that they have taken their medication as prescribed without having to physically visit the clinic.

Additional subjects who are not prescribed or taking any of these medications will be included in this study to act as a comparison group.

You have been invited to participate in this study because you have indicated that you have a prescription for either buprenorphine, buprenorphine/naloxone, or a take-home dose of methadone to treat opioid use disorder, and/or you meet other eligibility requirements.

What is interstitial fluid sampling?

a. Interstitial fluid sampling is a procedure where very small needles are placed in the skin to make tiny openings from which fluid under the skin can come out. Collecting this fluid with gauze material or small tubes is called interstitial fluid sampling.
b. Interstitial fluid sampling works by creating tiny openings from which fluid under the skin can come out with the help of a suction device.
c. The ultimate reason we are collecting the interstitial fluid is to develop a sensor so patients can prove that they have taken a dose of methadone without having to visit the clinic. Eventually it may provide patients with a device that allows them to receive more take home doses earlier in their treatment plan.

What happens to me if I agree to take part in this research?
If you decide to take part in this research study, the general procedures include a questionnaire (up to 15-30 minutes), an in-person a physical exam 7 days after this consent is signed (up to 30 minutes), a first blood collection (up to 10 minutes), two collections of a small amount of interstitial fluid from the surface of your skin and monitoring (up to 60 minutes each), a second blood collection (up to 10 minutes), and a follow-up call 2 days after your in-person visit (up to 15 minutes). As such, there will only be one in-person visit and the whole process will last about 4-5 hours total.

Could being in this research hurt me?
The most important risks or discomforts that you may expect from taking part in this research include 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.

Will being in this research benefit me?
It is not expected that you will personally benefit from this research. However, possible benefits to others include improvements in the response to the growing opioid epidemic.

What else should I know about this research?
Other information that may be important for you to consider so you can decide whether to take part in this research is you will be asked to abstain from alcohol and non-prescribed substances at least 7 days before your in-person clinical assessment. You will be compensated for your participation. Any subject who enrolls in the study can stop participating at any time.

DETAILED RESEARCH CONSENT

A person who takes part in a research study is called a research subject, or research participant.

If you <u>have</u> a prescription for buprenorphine/naloxone, buprenorphine, or methadone: You are being invited to take part in a research study because you are age 18-65, you do not have a condition preventing or complicating interstitial fluid collection, active severe depression (e.g., suicidal ideation) or mania symptoms, and you have not consumed/used alcohol or illicit substances (e.g., barbiturates, benzodiazepines, amphetamine, methamphetamines, cocaine, heroin, oxycodone, or other opiates) in the past 7 days. If you are a woman, you are not lactating, pregnant, or intending to become pregnant during the course of the study.

If you <u>do not have</u> a prescription for buprenorphine/naloxone, buprenorphine, or methadone: You are being invited to take part in a research study because you are age 18-65, you do not have a condition preventing or complicating interstitial fluid collection, active severe depression (e.g., suicidal ideation) or mania symptoms, and you have not consumed alcohol or illicit substances (e.g., barbiturates, benzodiazepines, amphetamine, methamphetamines, cocaine, heroin, oxycodone, or other opiates) in the past 7 days. If you are a woman, you are not lactating, pregnant, or intending to become pregnant during the course of the study.

What should I know about this research?

- Someone will explain this research to you.
- This form sums up that explanation.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don’t understand, ask questions.
- Ask all the questions you want before you decide.

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Additional subjects who are not prescribed or taking any of these medications will be included in this study to act as a comparison group.

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How long will I be in this research?
We expect that your taking part in this research online and in-person will last about 4-5 hours total. This does not include travel to the study site.

What happens to me if I agree to take part in this research?
If you decide to take part in this research study, the general procedures include a questionnaire (up to 15-30 minutes), an in-person a physical exam (up to 30 minutes), a first blood collection (up to 10 minutes), two collections of a small amount of interstitial fluid from the surface of your skin and monitoring (up to 60 minutes each), a second blood collection (up to 10 minutes), and a follow-up call 2 days after your in-person visit (up to 15 minutes). As such, there will only be one in-person visit and the whole process will last about 4-5 hours total.

- **Initial questionnaire (up to 30 minutes):**
    a. If you agree to participate as indicated by your signature on this consent, you will be assigned a computer-generated Subject ID code. You will then be asked to complete a baseline assessment. 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 you are currently taking
        v. Diet and exercise habits
        vi. Alcohol, tobacco, and other substance use history
        vii. Pregnancy or breast-feeding status (if female)
    b. Once the assessment has been completed, the Clinical Research Coordinator will schedule in-person clinical visit for you if needed. You will be instructed to take your medications as prescribed by your physician (e.g., dose, dosing times). As such, if you are in the study group (not the control group) the in-person visit will be scheduled around your usual dosing time. You will also be asked to abstain from alcohol and non-prescribed substances at least 24 hours before your in-person assessment.

- **In-person physical exam within 7 days after the consent and online assessment is completed (30 minutes)**
    a. Study groups:
        i. You will be instructed to take your medications as prescribed. As such, in-person assessments will be scheduled around your typical medication administration time.
    b. Comparison group:
        i. In-person assessments may occur at any time during the available clinic hours.
    c. The in-person assessment may include the following:
        i. Limited physical exam:
            1. Height and weight measurements
            2. Feeling for the pulse
            3. Listening to the heart and lungs with a stethoscope
            4. Measuring blood pressure using a sphygmomanometer
        ii. Report of changes in medications in the past week

iii. Urine pregnancy test for premenopausal women. If you test positive, you will be discharged, paid $50, and referred to your primary care doctor or OBGYN.
iv. Urine test to confirm no alcohol, barbiturates, benzodiazepines, amphetamine, methamphetamines, cocaine, heroin, oxycodone, or other opiates

- **In-person first blood sample collection (10 minutes)**
    a. Before the interstitial fluid collection, a standard venipuncture blood sample will be collected (about ½ teaspoon) by a certified clinician. These samples will be used for comparative analysis with the interstitial fluid. The blood draw may cause mild discomfort.

- **First microneedle interstitial fluid collection (up to 1 hour)**
    a. Interstitial fluid will then be collected by a board-certified physician with procedural skills, training, and familiarity with interstitial fluid collection.
    b. Interstitial fluid will be collected from the surface of your right or left arm (your preference).
    c. You will be prepared for the interstitial fluid collection using standard clean working techniques (e.g., prepped and draped).
    d. The procedure will involve covering the skin with a transparent film skin dressing containing a 1-cm-diameter opening where microneedle treatment will be performed.
    e. 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 (~10) times to collect about greater than or equal to 1 µ1 of interstitial fluid. A standard vacuum pump will then be administered for 20 min to draw out the interstitial fluid. Skin appearance should remain largely unchanged and result in a swift recovery as seen in a previous study. This approach has been well tolerated with minimal visual evidence of damage to the skin in previous studies.
    f. Gauze will then be used to collect the interstitial fluid from the surface of the skin.
    g. After the interstitial fluid collection is complete, a sterile bandage covering will be supplied to the area.
    h. You will be monitored for about 30 minutes and be asked to report your tolerability, pain, and experience. Your responses will be documented in a secure online storage medium provided by the research site.

- **Prescribed dose of medication (5 minutes)**
    a. You will be asked to take your prescribed medication at the study site. Study personnel may observe.

- **In-person second blood sample collection (10 minutes)**
    a. After interstitial fluid collection, a standard venipuncture blood sample will be collected (about ½ teaspoon) by a certified clinician. These samples will be used

for comparative analysis with the interstitial fluid. The blood draw may cause mild discomfort.

- **Second microneedle interstitial fluid collection (up to 1 hour)**
    a. A second interstitial fluid collection will occur at the medication peak (e.g., 2-4 hours after you take your medication).

- **Follow-up call (15 minutes)**
    a. Approximately 2 days after interstitial fluid collection, you will be contacted by the Clinical Research Coordinator via phone. You will be asked to report your tolerability, pain, and experience. Your responses will be documented in a secure an online storage medium provided by the research site.

Your interstitial fluid and blood will be tested for prescription medications and the medication metabolites described in this consent. Your urine sample will be tested for alcohol and other drugs to confirm there are no other drugs in your system.

What are my responsibilities if I take part in this research?
As mentioned, if you decide to take part in this research study, the general procedures include an online assessment (up to 15-30 minutes), an in-person assessment which will include a physical exam (up to 30 minutes), a first blood collection (up to 10 minutes), two collections of a small amount of interstitial fluid from the surface of your skin and monitoring (up to 60 minutes each), a second blood collection (up to 10 minutes), and a follow-up call 2 days after your in-person visit (up to 15 minutes). As such, there will only be one in-person visit.

Could being in this research hurt me?
The most important risks or discomforts that you may expect from taking part in this research include:

- 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.

Even though we will keep information collected in this study private, there is a possible risk of loss of privacy.

In addition to these risks, taking part in this research may harm you in unknown ways.

Will it cost me money to take part in this research?
Taking part in this research will not lead to added costs to you.

Will being in this research benefit me?
It is not expected that you will personally benefit from this research. However, possible benefits to others include improvements in the response to the growing opioid epidemic.

What other choices do I have besides taking part in this research?
This research is not designed to diagnose, treat or prevent any disease. Any subject who enrolls in the study can stop participating at any time. Your alternative is to not take part in this research.

What happens to the information collected for this research?
Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor (CARI Health, Inc.)
- People who work with the research sponsor
- Government agencies, such as the Department of Health and Human Services (DHHS), National Institute of Health (NIH), National Institute of Drug Abuse (NIDA), and U.S. Food and Drug Administration (FDA)
- WCG IRB, the Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

This study will not conduct DNA or genetic testing, or whole genome sequencing on your blood or any biological sample collected from you, and your samples will not be used to identify you in the future through DNA testing. In addition, the study will prohibit any genetic testing by any person or entity with whom your samples are shared in its contracts with those persons or entities.

Data or specimens collected in this research will not be used to identify you and will not be used for future research or distributed to another investigator for future research without your consent. For example, your interstitial fluid, blood, or urine may be used for further testing. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Interstitial fluid, blood, and urine taken from you may be used to establish products that could be patented and licensed. There are no plans to provide you with financial compensation should this occur. Your biological samples and their derivatives may have significant therapeutic or commercial value. You consent to such uses.

a. There will be use restrictions on how biological samples are used in "further testing," by this study or by any other researchers and entities with whom the samples may be shared;

b. Biological samples or test results will not be placed in publicly available biobanks;

c. Your present and/or future medical record can be accessed for 7 years and will then be destroyed. Your biological samples will be destroyed after completion of the study in 3 months and there will be no future testing.

Information about a Certificate of Confidentiality for this research:
CARI Health, Inc. has received a Certificate of Confidentiality from the government which will help protect the privacy of research subjects. The certificate protects against the involuntary release of information about subjects collected during the course of this research. The researchers involved in this study cannot be forced to disclose any information collected in this study in any legal proceedings.

However, you may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality/Authorization section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure.

Who can answer my questions about this research?
If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?
If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. The sponsor will pay any charges that are not covered by insurance policy or the

government, provided the injury was not due to your underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study doctor or sponsor.

Can I be removed from this research without my approval?
The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- It is in your best interest
- You have a side effect that requires stopping the research
- You need a treatment not allowed in this research
- The urine pregnancy test on admission suggests that you are pregnant
- Urine toxicology tests include the following substances: alcohol, barbiturates, benzodiazepines, amphetamine, methamphetamines, cocaine, heroin, oxycodone, or other opiates. You will be discharged from the study if these tests positive for any of the listed non-prescribed medications tested and you will be paid a total of $50.
- The research is canceled by the sponsor
- You are unable to have your interstitial fluid collected
- You are unable to keep your scheduled appointments

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?
If you decide to leave this research, contact the research team so that the investigator can:

- Take you off the study schedule.
- Provide you with your compensation for the steps you completed.

If you do not participate in the follow-up phone call assessment, there may be risks with this decision. These may include: Un-identified adverse events associated with the interstitial fluid collection procedure.

Will I be paid for taking part in this research?
For taking part in this research, you may be paid with a visa gift card up to a total of $250. Your compensation will be broken down as follows:

- $25 for the initial assessment (up to 15-30 minutes)
- $30 for the in-person physical exam and data collection (up to 30 minutes)
- $10 for the first blood collection (up to 10 minutes)
- $150 ($75 each) for two interstitial fluid collections and monitoring up to 60 minutes each)
- $10 for the second blood collection (up to 10 minutes)
- $25 for the follow-up call (up to 15 minutes)

You will be paid in full after your follow-up call. If you drop out before this time, you will be compensated for the steps you have completed.

Your specimens (even if identifiers are removed) may be used for commercial profit. You will not share in this commercial profit.

Statement of Consent:
I have read this information, which is printed in English. This is a language that I read and understand. Your signature documents your consent to take part in this research. You will receive a copy of this signed informed consent form as well as a copy of the Experimental Subject's Bill of Rights.

Signature of adult subject capable of consent	Date
Signature of person obtaining consent	Date