Buprenorphine Plus Baclofen to Increase Analgesia in Healthy Volunteers

NCT04251819

April 11, 2022

Buprenorphine plus baclofen to increase analgesia in healthy volunteers ("BACUP")

IRB-300004505

Manual of Operations (MOP)

Dr. Karen Cropsey & Dr. Burel Goodin

Introduction

Abuse of opioids is a significant and growing problem in the United States. In the past two decades, opioid prescriptions have quadrupled while the age of heroin initiation has decreased, suggesting that more individuals are using opioids and transitioning to heroin and potent synthetic opioids than in the past. Further, fatal opioid overdose is now the leading cause of accidental death and is the 5th highest overall cause of mortality in the US. Engaging opioid users in opioid agonist treatments has been shown to lower rates of criminal behavior, lower rates of non-opioid drug use, and increase retention in drug treatment programs, while decreasing mortality and new HIV and hepatitis infections. However, a recent study noted that 68% of patients prescribed buprenorphine had poor medication adherence, which was associated with illicit opioid use. A Cochrane review concluded that buprenorphine was less effective at retaining patients in treatment relative to methadone. One reason for lower treatment retention may be the high comorbidity of opioid use disorder and chronic pain and/or opioid-induced hyperalgesia. Buprenorphine, as a partial mu agonist, provides lower analgesia but an improved safety profile relative to full agonists like methadone. Thus, enhancing the analgesic properties of buprenorphine will provide a safer alternative for opioid use disorder patients with chronic pain/hyperalgesia.

Baclofen is a GABA receptor agonist that is FDA-approved to treat spasticity. Baclofen has an established clinical safety profile, as well as evidence to support its use in addictions, primarily with alcohol use disorders. Our preclinical evidence suggests baclofen, in combination with buprenorphine, increases the analgesic effects of buprenorphine in rodents. Using these medications together may offer an important novel strategy to increase retention in treatment and adherence to buprenorphine while preserving the safety profile of a partial opioid agonist, particularly among patients with a chronic pain condition who may be more likely to abuse illicit opioids. However, data for this approach in humans is lacking and initial evidence is needed to assess the analgesic interaction, safety, acceptability and feasibility of using buprenorphine and baclofen in humans before conducting a larger clinical trial to examine efficacy in patients.

Brief purpose of the study

The purpose of the study is to determine if baclofen will enhance buprenorphine analgesia for acute pain in healthy volunteers (non-opioid users). We will first recruit 30 healthy volunteers (Group 1) who will be administered either 4mg of Buprenophine, 5 mg of Baclofen, or 10 mg of Baclofen in order to test the effects of the drugs on pain separately.

Then, we will recruit another 60 healthy volunteers (non-opioid users; Group 2) and randomize them to either placebo, 5mg or 10 mg of baclofen (1 dose) in combination with 4 mg of buprenorphine to examine analgesia in acute pain tasks.

Measurement occurrence

Data Collection Instrument	Session 1	Session 2
Informed consent	✔	
Screening questions (survey)	✔	
Vital signs: blood pressure, heart rate, temperature, neck circumference, height/weight	✔	✔
Blood draw	✔	✔
Pregnancy test		✔
Urine drug screen		✔
Demographics questionnaire (survey)		✔
Profile of Mood States Questionnaire (POMS) (survey)	✔	✔
QST: Cold pressor task	✔	
QST: Heat pain task	✔	✔
QST: Cold pain task	✔	✔
QST: Mechanical pressure pain task	✔	✔
QST: Conditioned pain modulation task	✔	✔
QST: Pinprick pressure pain task	✔	✔
26-item Visual Analog Scale (VAS) (survey)		✔
Drug Effects Questionnaire-5 (survey)		✔
Opioid symptom checklist		✔

Accessing the shared drive

1. Click on the home button at the bottom left hand of the computer
2. Go to “Computer”
3. Click on “PBN.” Enter your blazer ID and password if necessary
4. Click on “Cropsey-Lab”
5. Click on the “BACUP” folder (this is the folder for our study)

Recruitment and eligibility

Inclusion criteria

a) 18 years of age or older;
b) In general good health (no serious chronic medical or psychiatric conditions);
c) Fluent English speaker.

Exclusion criteria

a) Pregnant or nursing;

b) Tests positive for any drug other than THC on urine drug screen;
c) Diagnosed with opioid use disorder or any substance use disorder other than nicotine;
d) Prescribed agonist treatment for opioid dependence or prescribed opioids for a medical condition;
e) Prescribed naltrexone;
f) Uses CBD products;
g) Known sensitivity to buprenorphine, naloxone, or baclofen;
h) Acute or chronic pain condition;
i) Trouble breathing or a pulmonary condition;
j) Prescribed benzodiazepines or daily use of benzodiazepines;
k) Cognitive impairment or psychiatric disorder requiring treatment.

Telephone screening

Self-referred participants will contact Tammie Quinn (205-934-8743) and be pre-screened via telephone for initial eligibility. As long as participants meet this initial eligibility criteria, they will be scheduled for a study visit. Dr. Goodin's lab will handle all pre-screening, including scheduling visits at the CRU.

To schedule a participant or modify a visit date/time, email the CRU scheduling email at cruschedule@uabmc.edu. When emailing them, refer to our CRU project number which is **2738**.

Study visits

Study session 1 (approx. 2 hours long)

Send the participant a reminder email the day before the visit. A sample reminder email is below:

> "My name is [RA name] and I am the research coordinator working on the Baclofen & Pain study at UAB. I am writing to remind you that you are scheduled for a study visit **tomorrow at 2 PM**. Please confirm whether you are still able to attend. As a reminder, the visit will take about 2.5 hours to complete and will take place in the Clinical Research Unit (CRU) on floor 15 of Jefferson Towers (625 19th St S, Birmingham, AL 35233). I am attaching directions on where to park/how to get to the CRU to this email.
>
> If you have any questions or need to reschedule, you can respond to this email or call me at 205-975-7809."

Before the visit, be sure to print out all the required paperwork:

- 2 copies of the most up-to-date IRB-approved consent form (stamped)
- Blank visit 1 data recording sheet
- Visit 1 flow sheet (double check to make sure all information is accurate, i.e., DOB and visit date)
- CRU space request form (optional, but good to have on hand just in case there is an issue)

You will also need the following supplies:

- Surface Pro and charger
- TSA laptop and charger
- Stopwatch
- Measuring tape
- Clipboard
- Pens

The QST equipment is located in the CRU. The algometer and cold pressor are located in the back of the CRU in the infusion suite. The CHEPS/TSA machine, bucket, and water pitcher used to fill the water bath are located in the closet in the nurse's station – you will need one of the nurses to unlock the door for you. It's also a good idea to give the flow sheet to the nurse who will be assisting you with the blood draw (you can ask them and they will tell you who it is). This will allow them to prepare for the blood draw.

When participants arrive at the CRU, instruct them to first sign in at the nurse's station. They will then go through the informed consent form with the RA. If they agree to participate, they will sign the informed consent form. During the consent process, participants will indicate whether or not they agree to a blood draw or storage of their biospecimens for future research (it is not required for them to consent to these in order for them to participate).

After going through the informed consent process, the RA will take some initial vitals and ask some questions:

- Ask what substances they have used in the past 24 hours (alcohol, tobacco, drugs)
- Do 3 BP/HR trials – one reading must be below 150/95 to continue in the study
    - Blood pressure machine should be in all the CRU rooms, but if there isn't one in your room then just ask a nurse for one
- Take the pt's temperature – it must be below 100.4° F to continue
- Take the pt's neck circumference using the tape measure
- Ask the nurse to take the pt's height and weight. They do not allow the study staff to do this, so one of the nurses must do it. Make sure you tell them that the readings should be in inches/pounds
    - At this point you can tell your nurse that you will need about another 10 minutes and then you will be ready to do the blood draw

Go back into the room and open REDCap (project name: Buprenorphine plus baclofen to increase analgesia in healthy volunteers). Open the participant's record – you can use the report called "Visit Date and Contact Info" to look them up by name

- Open the measure called "Subject ID" under Session 1. Enter their assigned study ID
- Open the "Medical & Psychiatric History measure." Go through all the questions with the participant, recording as much detail as possible about any conditions and medications they endorse. They will have been asked a briefer version of these questions at screening, so this is just to make sure we aren't missing anything
    - If they endorse something that you know might make them ineligible (e.g., pain conditions, taking a medication for chronic pain, prescribed opioids, etc.) you can alert the PIs/study doctor. They can decide whether or not they are eligible. But continue to go through all the questionnaires with the participant regardless
- Once you get to the "Demographics" measure, you can open the form as a survey and give the Surface Pro to the participant to have them fill out the rest of the surveys on their own. They are queued up such that the surveys will automatically flow from one to the next:
    - Childhood Trauma Questionnaire (CTQ)
    - Pittsburgh Sleep Quality Index (PSQI)
    - Perceived Stress Scale (PSS)
    - Pain Vigilance and Awareness Questionnaire (PVAQ)
    - Coping Strategies Questionnaire – Revised (CSQ-R)
    - Profile of Mood States (POMS)

If participants are deemed ineligible after any of these screening procedures, they will be considered a screening fail and will be dismissed from the study. If you are unsure whether the participant is eligible or not, consult with the PIs and study team.

When they are finished with the questionnaires, alert the CRU nurse that you are ready for them to do the blood draw. Make sure the nurse is using one 10 ml red-top tube and one 4 ml lavender-top tube (14 ml total), and that the lavender tube goes on ice after the blood is collected. They will have created labels for the tubes (generated in OnCore) and will send the samples to the CRU lab for storage and processing. Make sure the nurse records the time of blood collection and initials/signs the flow sheet. Ask for the flow sheet back from them – we will want to store these in our records in Dr. Cropsey's office.

Following eligibility determination, questionnaires, and blood draw participants will undergo a battery of pain tasks (see "Pain tasks" section for more information). Once the pain tasks are completed, the participant's information will be added to ClinCard and they will be compensated $50 for completing session 1. They will be asked to come back a week later (7 days ± 2 days) to complete session 2, where they will receive a study drug and complete the pain tasks once again. Remind the participant of their visit 2 date at the end of visit 1.

Study session 2 (approx. 4 hours long – occurs 7 ± 2 days after session 1)

A couple days before the visit, make sure that the prescription (Rx) for the study drug has been emailed to the investigational pharmacy (idsorders@uabmc.edu). Specify which study the Rx is for (2738) and the date of the visit. If you are not sending the Rx from a uabmc.edu email, it is advised to fax the form rather than emailing it as the Rx form has a lot of PHI on it. The fax number is [ask Tammie].

Before the visit, be sure to print out all the required paperwork:

- Blank visit 2 data recording sheet
- Visit 2 flow sheet (double check to make sure all information is accurate, i.e., DOB and visit date)
- Physician's order form (Rx order form) – this should also have been sent to the pharmacy prior to the visit
- CRU space request form (optional, but good to have on hand just in case there is an issue)

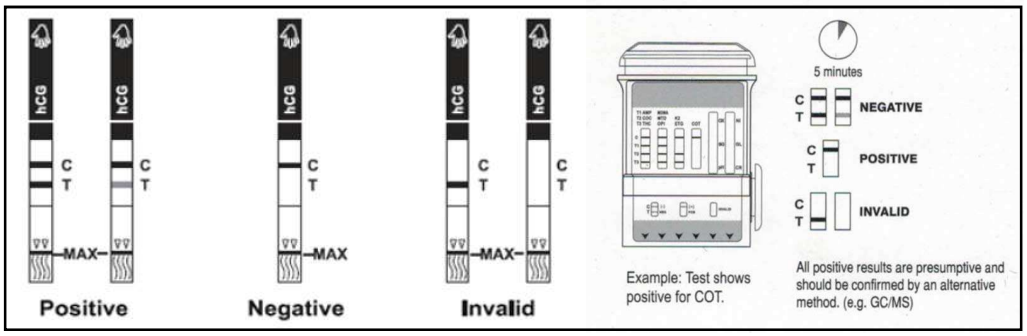
You will also need the following supplies:

- Urine drug test cup
- Pregnancy test (if female of child-bearing potential)
- Surface Pro and charger
- TSA laptop and charger
- Stopwatch
- Clipboard
- Pens

When participants arrive for session 2, they will repeat the same procedures as the beginning of visit 1 (BP/HR readings, temperature, weight). Then participants will be asked to complete a urine drug screen and a pregnancy test (if a participant is a woman of child-bearing potential). A positive drug or pregnancy test reading will result in immediate termination from the study (if they only test positive for THC they are allowed to continue)

- Pregnancy test: Hold strip vertically in urine sample for at least 5 seconds. Read results after 3 minutes.

- Urine drug screen: Have participant provide sample in urine drug screen cup. There must be enough urine to cover the black temperature indicator strip. Wait 2-4 minutes before removing the peel-off label, then wait another 5 minutes to read results.



Participants will then complete the POMS and the Opioid Symptom Checklist prior to taking the study drug. These questionnaires will be entered directly into REDCap by the participant as a survey. Then, alert the nurse that you are ready for them to give the pt the study drug. Note that it can sometimes take up to an hour for the nurse to retrieve the drug from the pharmacy, so you may have to wait a little bit.

Then participants will be administered the study drug:

- First cohort (n=30): Randomized to either 5 mg of baclofen, 10 mg baclofen ,or 300 mcg of buprenorphine (n=10 per group). **All participants in this cohort will receive one dose of one single drug compound.**
- Second cohort (n=60): Randomized to 300 mcg of buprenorphine, and either: placebo, 5 mg of baclofen, or 10 mg of baclofen (n=20 per group). **All participants in this cohort will receive a combination of drug compounds.**

Participants will be instructed to take the drug(s) orally (baclofen) or buccally as a film (buprenorphine). Following the administration of the study drug, all study procedures are identical for all groups and cohorts.

Visit timeline

The visit timeline for session 2 is as follows (represented below in 15-minute segments):

Group 1 (single compound)

-1	**0**	15	30	45	1 hr	15	**30**	45	2 hrs	15	30	45	3 hrs
Vitals, surveys, OSC	**Adm drug OSC**	Vitals	Vitals, blood draw #1, surveys	…	Vitals OSC	…	**QST**	…	Vitals, OSC	…	Blood draw #2	…	Vitals, OSC
Begin 3 hour post-dose observation …… End observation													

Group 2 (duo compound)

0	**15**	30	**45**	1 hr	15	30	45	2 hrs	**15**	30	45	3 hrs	15	30	45	4 hrs
Vitals Surveys OSC	**Adm Bup OSC**	Vitals	**Adm Bac**	…	Vitals, blood collection	Surveys	Vitals OSC	…	**QST**	…	Vitals OSC	…	…	…	Vitals OSC	…
Begin 3 hour post-dose observation …… End observation																

Participants are asked to stay for a 3-hour observation period post-drug administration as that is the amount of time it typically takes for the drug(s) to leave their system. This observation period will allow us to monitor the side effects of the medications while it is still in their system. During the observation period, participants' vital

signs will be taken periodically to monitor drug side effects. We will also administer the Opioid Symptom Checklist at various timepoints to quantify the drug's effects.

If the participant reports any severe symptoms, or if their BP/HR readings become out of range, notify a CRU nurse immediately. You may also have to call the study doctor Dr. Peter Lane (phone number: 205-531-0772). It is a good idea to alert the PIs as well. If the participant is experiencing intense symptoms, you may have to skip the QST tasks. However, try to complete all study procedures if possible.

The QST tasks will be administered 1.5 hours post-drug administration.

Following the pain tasks, participants will complete a second 14 cc blood draw at around 145-155 minutes post-drug administration.

Pain tasks (QST)

The following Quantitative Sensory Testing (QST) tasks will then be administered by the research assistant at **1.5 hours post-drug administration** to allow for maximum drug efficacy:

Stimulus modality	Area of body	Tissue stimulated	QST response measures
Thermal (contact heat) **Heat pain**	Forearm	Cutaneous	• Pain threshold • Pain tolerance • Suprathreshold pain responses • Temporal summation of pain
Pinprick pressure pain	Middle phalange Trapezius	Cutaneous Myofascial	• Pain threshold • Pain tolerance • Suprathreshold pain responses • Temporal summation of pain
Mechanical (pressure) **Pressure pain**	Forearm Trapezius	Cutaneous Myofascial	• Pain threshold • Pain tolerance • Suprathreshold pain responses • Temporal summation of pain
Conditioned pain modulation **Combined pressure and cold pain**	Forearm Trapezius	Cutaneous Myofascial	• Cold immersion as the conditioning stimulus, and pressure contact as the test stimulus
Thermal (immersion cold) **Cold pain**	Hand	Cutaneous	• Pain threshold • Pain tolerance • Suprathreshold pain responses

Cold Pain – Cold Pressor Threshold Temperature. Prior to the CPM task, we will measure sensitivity to cold pain by asking the participant to put his/her hand in the cold water bath. Participants will be instructed to immerse their non-dominant hand into a cold water bath maintained at 8, 6, and 4 degrees C for 60 seconds. They will be asked to give pain ratings using the 0-100 scale at 30 and 60 seconds at each temperature. The temperature the participant had the most moderate response to (i.e., the response closest to 50 on the pain scale) will be used for all remaining cold pressor tasks. Participants will be told they can discontinue at any time they choose – if they report a pain level of 100 at any point, discontinue the procedures.

Heat Pain – Thermal Pain Threshold and Tolerance and Heat Pain Temporal Summation. The following types of heat stimuli will be delivered:

1) A slowly increasing heat stimulus that the participant can terminate by pressing a button when it becomes painful or intolerable.
    a. **Threshold:** The RA will instruct the pt that the node will slowly heat up, and they are to press the mouse when that heat sensation **first becomes painful**. This will be repeated 3 times on 3 different spots on the pt's forearm (starting closest to the palm and moving upwards towards the elbow)
    b. **Tolerance:** The RA will instruct the pt that the node will slowly heat up, and they are to press the mouse when the pain they are experiencing becomes **intolerable**. This will be repeated 3 times on 3 different spots on the pt's forearm (starting closest to the palm and moving upwards towards the elbow)
2) A series of 5 heat pulses that are brief (about 2 seconds in duration), and we will ask the participant to rate how painful each heat pulse feels on a scale from 0-100 (0 = no pain, 100 = most pain imaginable) at the peak of each pulse. These heat pulses will be repeated at different temperatures (44° C, 46° C, and 48° C). The participant can stop the procedures at any time so that they do not experience unacceptable pain.

Pinprick Pressure Pain. The MRC Systems "Pinprick" Stimulator Set will be used for the testing of fine mechanical pressure pain perception thresholds as well as the temporal summation of mechanical pain. It allows a reproducible measurement and documentation of nociceptor activation of the skin. Thus, it enables a better diagnostic of symptoms of neuropathologic pain and the investigation of mechanisms that are connected with chronic pain. We will use the pinprick stimulators on both the middle phalange and the trapezius (shoulder). Body sites will be randomized each time. The RA will first tap the body site once and ask for a pain rating from 0-100 using the 256 mN stimulator. Then the RA will tap the same body site 10 times in a row and ask for a pain rating of the highest amount of pain they felt during those 10 taps. This will be repeated on both body sites. Then the RA will repeat the procedures with a different pinprick stimulator that is 512 mN in weight. The participant will be told to close their eyes or look away during this task.

Pressure Pain Threshold. We will use a handheld probe (Algomed, Medoc) with a small (less than ½ inch wide) rubber tip to apply pressure to the participant's forearm and shoulder. The pressure will be slowly increased, and the participant will be asked to click a button when they first feel pain as a result of the pressure stimulation. As soon as the participant presses this button, the pressure will be removed. This will be repeated 3 times on each body site: forearm and trapezius. The goal of this procedure is to have the participant tell us when they first feel pain from the pressure stimulation. This particular algometer will be used because it provides the examiner with visual feedback to maintain a consistent application rate, which is critical for maintaining high inter-examiner reliability. In order to assess pressure pain threshold, the examiner will apply a constant rate of pressure and the participant will be instructed to press a button when the sensation first becomes painful, at which time the device records the pressure in kilopascals (kPs). This will be repeated 3 times on each body site in an alternating fashion.

Combined Pressure and Cold Pain (CPM). The participant's hand will be immersed into cold water (8, 6, or 4 degrees C as designated by results from the initial cold pain task). After 30 seconds, the participant will rate the intensity of the pain from 0-100 (0 = no pain, 100 = most pain imaginable). They will keep their hand in the cold water for another 30 seconds, totaling 60 seconds of immersion in the cold water bath. Then, the pressure pain test will immediately be repeated on the opposite side of the body, and participants will again be asked to indicate the moment when they first feel pain due to the pressure stimulation by pressing a button. This task will be done 4 times in total (2 times on each body site). Just like before, the participant can stop any of these procedures at any time.

Cold Pressor Task. Following the CPM task, participants will complete the cold pressor task. They will be asked to put their dominant hand in the water at their specified temperature (i.e., 8, 6, or 4 degrees C) for as long as possible. Unbeknownst to participants, the maximum permitted immersion time will be five minutes – it is important that you do not tell them how long they will be keeping their hand in for. They will rate the intensity of the pain experienced using the 0-100 numeric rating scale at 30 second intervals and again immediately prior to hand removal. Time to removal of hand from the cold water will be used as a measure of cold pain tolerance. Participants will be told they can discontinue at any time they choose.

Questionnaires

Participants will complete the following questionnaires (in a REDCap survey format, participant enters data directly into REDCap) at 30-45 minutes post-drug administration:

- **Abbreviated Profile of Mood States Questionnaire (POMS):** This 36-item survey contains a series of descriptive words/statements that describe feelings people have. Participants are asked to self-report their current mood using a 5-point Likert scale. This survey takes approx. 5 minutes to administer.
- **26-item Visual Analog Scale (VAS):** A 26-item scale that measures subjective and physiological effects of a medication using mood states, as well as questions about the medication dose. This survey takes approx. 5 minutes to administer.
- **Drug Effects Questionnaire-5:** A 5-item questionnaire assessing drug effects. This survey takes approx. 5 minutes to administer.

The research staff running the session will also periodically administer the Opioid Symptom Checklist (OSC). This questionnaire will be administered pre-drug administration, at the time of first drug administration, 1 hour post-drug administration, 2 hours post-drug administration, and 3 hours post-drug administration.

- **Opioid Symptom Checklist (OSC):** A 13-item scale used to quantify any sedation, somnolence, and other drug effects that the participant is experiencing from the buprenorphine and/or baclofen. Participants answer true/false questions about these opioid effects. This checklist takes approx. 2 minutes to administer.

Post-observation period

Once the 3-hour observation period has concluded, and the participant has finished all the QST tasks and questionnaires, they will be free to leave. Make sure they are not experiencing any severe side effects before allowing them to leave. If they are still feeling sick, allow them to wait a bit before leaving. Because we are giving them a drug known to produce somnolence as a side effect, participants will not be allowed to drive home and must have someone pick them up from their visit. If they are not able to have someone drive them home from the visit, we will arrange for an Uber Health taxi to bring them home (free of charge to the participant).

Post-visit procedures

Following the study visits, enter all data into REDCap that was recorded on paper forms. Also be sure that the urine drug screen and pregnancy test results are entered into REDCap. Update the participant tracking SPSS database (P:\Cropsey-Lab\BACUP\6. Databases → BACUP Participant Tracking).

Adverse event procedures

In the event that a participant has severe side effects from the study medication or procedures, the study doctor and PIs should be alerted as soon as possible. Examples of severe adverse side effects would be vomiting, blood pressure reading that is too high/too low, sudden spike or drop in body temperature, etc. If any of these occur, first alert one of the CRU nurses so that they can come check on the pt. Then, call the study doctor to let them

know what occurred. You can also have the CRU nurse talk to them so that they can relay treatment information to the nurse.

If the adverse side effects become serious, the study doctor may recommend admitting the participant to the emergency room. CRU nurses will arrange a transport in this instance. You can offer to call someone to come meet the participant at the ER if they would like to have a friend/family member with them.

The day after the AE, be sure to call and follow-up with the participant to see what the outcome of the event was, if they are still experiencing any side effects, if they received any medications or treatments, etc. Once you have this information, you can draft a problem report form. Be sure to provide lots of details, including the fact that CRU nurses and the study doctor were alerted to the AE. Also include the outcome of the AE, if known. Send to the study doctor and PIs for approval before submitting to the IRB.

Compensation

Participants will be paid up to $150 ($50 for visit 1, $100 for visit 2) for participating in this study. They will be paid via ClinCard (account ending in 4505).

Greenphire ClinCard instructions

Login Information

- Log in to **www.clincard.com**
- Enter your log in and password that are provided to you. Keep in mind that you log in and password are case sensitive, so make sure to use capital letters as necessary.
- If you have difficulty logging into **www.clincard.com**, please click on the "Forgot username and password?" link, enter your email address, and click "Reset my password." This will instantly send you an email with a link allowing you to reset your password.

Note: You can also call site support team at 215-609-4378.

How to Look Up a Subject

1. Login to www.clincard.com
2. Click on "Look Up Subject"
3. Search for the subject you want to pay by entering one of the following pieces of information and click on "Search"
   a. First name and/or last name
   b. Subject ID
   c. Subject's initials
4. Click on the underlined name of the Subject
5. You will be brought to the "Subject Information" screen where you can perform any of the actions required for the subject, e.g., add another study or issue payment.
6. If the subject already exists in the system and has been enrolled in the ALL STUDY - UAB, then skip to the section on "How to Register a Subject in an Additional or Extension Study."
7. If the subject cannot be found, then you must follow the next steps and register that subject in the ALL STUDY - UAB, first.

How to Register a Subject

1. Login to www.clincard.com
2. Click on "Register Subject"
3. From the "Select Study" drop-down menu, choose "ALL STUDY – UAB"

4. From the “Site” drop-down menu, select UAB All Study (Central).
5. Enter the required information into the brief form. At minimum, you must include the subject’s first name, last name, initials, SSN, address, and DOB.

Note: If you would like the Subject to receive payment confirmations or appointment reminders, be sure the “Email (Enable)” and/or “Text Messaging (Enable)” checkboxes are selected

6. Click on the “Register” button
7. You will be brought to the “Subject Information” screen where you can enroll the subject in our study, assign a card number, make a payment, schedule an appointment reminder, replace a ClinCard or edit a subject’s information
8. If you have difficulty making a payment for the first time please call the ClinCard site support team at 215-609-4378

How to Register a Subject in an Additional or Extension Study

1. Locate the existing “Subject Information” page through the “Look Up Subject” menu tab.
2. Click on the last name of the subject to open the subject’s information tab
3. Click on the **Edit Subject** option in the list to the right.
4. Click on the **Add Study** link located under the list of the subject’s current study(ies) and select our study from the drop-down menu.
    a. Our study is the one ending in 4505.
5. Enter the new **Subject ID** and select the additional study subject **Status**.
6. Scroll to the bottom of the page, and click “Save”.
7. This will allow the subject to receive reimbursements for any additional studies on a previously assigned ClinCard.

How to Assign a ClinCard to a Subject

Once you have selected an existing subject or registered a new subject, you will be brought to the “Subject Information” screen. On the right hand side of the screen, you will see options that represent all of the actions you can perform on the Subject.

Note: If the subject already has a ClinCard assigned, you should not assign another card. (You can tell the subject already has a ClinCard if the first option in the list of options to the right-hand side of the screen is “Replace ClinCard.”)

1. Click on “Assign ClinCard” and a pop-up screen will appear.
2. In the “New Card” field, enter the 8 digit token number visible through the window of one of the ClinCard card packages you received
   Note: There is no need to open the envelope prior to providing to the Subject
3. Click on the “Assign” button
4. Once the card has successfully been assigned, you will receive a confirmation message at the top of the “Subject Information” screen
5. Now an option to “Replace ClinCard” appears. In the event that a subject loses their card, you can replace that card for them by clicking on “Replace ClinCard,” and follow the steps above, using the 8 digit token number from a new ClinCard card package

Note: This will inactivate the lost card and automatically transfer any available/pending balance to the newly assigned ClinCard

How to Make a Site Visit Payment

Once you have selected a subject or registered a new subject, you will be brought to the "Subject Information" screen. On the right hand side of the screen, you will see options that represent all of the actions you can perform on the Subject.

Note: If the subject has a ClinCard assigned, follow the next steps. If the subject has no ClinCard assigned, see the previous "How to Assign a ClinCard to a Subject" instruction section.

1. Verify that the "Study Name" field displays the name of our study. If the subject is enrolled in more than one study, you may have to select our study from the "Study Name" drop-down menu.
2. Click on "Make Site Visit Payment" and a pop-up screen will appear.
3. Select from the dropdown box which milestone the patient is being paid, e.g., Visit 1, Visit 2, etc.
4. Click on the "Pay" button
5. Once the payment has successfully been requested the "Pending Payment" area of the "Subject Information" screen will reflect the payment. It will also be reflected in your "Recent Activity"
6. Once a payment request has been approved and processed, the amount will be removed from the "Pending Payment" area and reflected in the "Available Balance" area.
7. If the subject has opted to receive email and/or text messages, the Subject will receive a payment confirmation communication when the payment is made.

How to Request Assistance

If you have questions about using the www.clincard.com Admin Portal, you may reach the ClinCard site support team by:

1. Submitting an email request through the "Support" link within the www.clincard.com website
2. Directly emailing at support@greenphire.com
3. Calling site support team directly at 215-609-4378 between the hours of 8:00AM and 10:00PM Eastern Time (Monday through Friday) in order to speak with a ClinCard team member