Official Study Title:

An innovative proof-of-concept approach to identify age-modulating drugs capable of reversing inflammation and re-setting the epigenetic clock (Topical-RAPA)

NCT number: NCT04608448

IRB Approval Date: 10-12-2021

Unique Protocol ID: HSC20200720H

Concise Summary

Important Information
This information gives you an overview of the research. More information about these topics may be found in the pages that follow. You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled and will not affect your relationship with us.

1. What problem is this study trying to solve?
You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future**.**

We know that cells in the body change the way they behave as we age, often causing inflammation that affects the cell's ability to produce new healthy cells. Safely studying the anti-aging benefits of medications administered and absorbed into the body is a challenge in older human beings. Therefore, testing anti-aging medications in a small patch of skin with little to no absorption of the medicine into the body may be a better option. It may keep research participants safer and avoid serious risks to them.

There are 2 goals of this research study: (1) to test whether age-associated changes in genes of skin cells (also known as the "epigenetic clock") are stopped or reversed by topical treatment with an investigational ointment (sirolimus, RAPA); and, (2) to evaluate whether the RAPA ointment, when topically applied to the skin for 6 months, is able to reverse changes in the immune system and inflammation that are thought to be associated with aging.

For more information, please see the ***Why is this Study being Done*** section below.

2. What will happen to me during the study and how is this different from continuing with usual care? What are all my options for treatment, including the pros and cons?
The research study team plans to enroll people age 65 to 95 in general good health. Study staff will schedule you for a total of eight (8) research visits. Visits will include informed consent and screening, physical exam and safety labs, dispensing and treatment with RAPA topical ointment, research labs (blood draws and skin samples), and monthly follow up. You will use the topical study drug on one arm and the placebo (just ointment without drug in it) on the other arm. After the treatment period, there is one last visit at the Research Unit where a researcher will perform the skin sampling procedure on your arms that causes minimal to no scarring and does not require a local anesthetic (numbing).

For more information, please see the ***What will be done if you decide to be in the research*** section below.

3. How much time will I spend on the study?
The total duration of the study is 7-8 months. Most visits are monthly and will take less than an hour except the first (90 minutes) and last visits (up to 4 hours).

4. **Could taking part in the study help me and are there risks?**
We do not know if there will be any physical benefit from using the study medication. You will be compensated a small amount of money for your time and effort after each completed visit. Previous studies have shown the topical medicine is absorbed into the skin but not into the body, and therefore, we expect it to have few side effects other than mild to moderate localized redness, rash, or itching.

We want you to report immediately to the research team when any possible side effects or other medical symptoms occur while you are in the study whether or not they seem related to the study medicine.

For more information, please *see **How could you or others benefit from your taking part in this study*** section below.

For details and a list of risks you should know about, please see the ***What are the risks of participation in the research*** section below.

5. What else should I consider before I make my decision?

Other considerations you may have about participation include the importance and limitations of applying medication to your skin every day for 6 months, as well as the value of your time to comply with appointments and phone-reporting about symptoms. Six (6) of the 8 visits will be conducted as home visits (or if you prefer, at an alternate site within 20 miles of the UTHSA) for your convenience. Only the first (Visit 0) and last visit (Visit 7) will be conducted in person at the Research Unit.

We work hard to protect the confidentiality of your personal health information and your privacy. We promise not to share information without your permission. *However, if you choose an alternative site for your "home visits" that is in a public setting, we cannot guarantee privacy.*

Please review the rest of this document for additional details about these topics and other information you should know before making a decision about participating in this research.

Consent to be part of a Research Study
To be conducted at
University of Texas Health Science Center at San Antonio (UT Health San Antonio)

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you and you will not lose any benefits to which you are entitled.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights, safety and welfare as a participant in the research. The PI for this study is Ellen Kraig, PhD, Professor at UT Health San Antonio in the Department of Cell Systems and Anatomy.

Co-Principal Investigator
The Co-Principal Investigator shares the principal investigator's responsibilities for this study. The Co-Principal Investigator for this study is Dean L. Kellogg, Jr, MD, PhD, Professor in the Department of Medicine-Division of Geriatrics, Gerontology and Palliative Medicine.

Funding
The National Institutes of Health/National Institute on Aging (NIH/NIA), a federal agency that promotes scientific research, is funding this study. This organization is providing money to UT Health San Antonio so that the researchers can conduct the study.

Purpose of this study – "Why is this study being done?"

We know that cells in the body change the way they behave as we age; this often causes inflammation at the cellular level that affects the cell's ability to produce new healthy cells. These changes are a normal part of aging. Researching the anti-aging benefits of medications administered and absorbed internally becomes a challenge for safety reasons in older human populations. Therefore, limiting the area being tested to a small patch of skin with little to no absorption of the medicine into the body systems is expected to help avoid serious risk to the participants. The researchers hope to learn two things: (1) if aging effects on skin cell genes (also known as the "epigenetic clock") are improved by topical treatments with an investigational ointment (sirolimus, RAPA) and (2) to evaluate the safety and effectiveness of the RAPA ointment when topically applied to the skin for 6 months to test its effect on reversing inflammation or immune system responses that are thought to be associated with aging. We want to establish laboratory testing that will measure markers of healthy aging.

Investigation Use of Drug
This study involves the use of an investigational drug called Sirolimus® (rapamycin, RAPA). "Investigational" means that the drug has been approved by the U.S. Food & Drug Administration (FDA) to be administered by mouth for other indications. RAPA has not been FDA-approved for topical use and is being used for research purposes in this study.

This study will help find out what effects, good and/or bad, topical RAPA ointment has on people who use it and on its effect on skin genes (DNA methylation). The safety of this drug in humans has been tested in prior research studies; however, some side effects may not yet be known.

At Visit 7 at the end of the treatment period, we will obtain the skin sample and run lab tests on skin tissue and fluid from under the skin. To generate the specimens, we will use a device called a Negative Pressure instrument (NP-2 or NP-4, Electronic Diversities, LLC) that has been used in other research studies to cause a skin blister. This method is non-invasive, carries little or no risk, and causes minimal discomfort.

Using the device creates a suction effect causing the skin to develop a small blister less than ½-inch in diameter (up to 10 millimeters) and approximately ¼-inch in height (3-4 millimeters). This process involves a small chamber of the device strapped to the inside area of your forearm situated between the wrist and elbow. See more detailed information in Visit 7 and added discussion in the Section on Potential Risks.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the study and results. You can search this Web site at any time.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you are between the ages of 65 and 95 and have been vaccinated for COVID-19 (or will have been vaccinated prior to the start of the study). In addition, you are a non-smoker in good general health without active infection or unstable disease or you are stable on treatment for existing medical conditions not taking medication(s) that would exclude you from participating.

How many people are expected to take part in this study? This study will enroll up to 75 study participants to attain at least 40 completers.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend approximately eight (8) visits with the researchers or study staff. Visits 0 and 7 will be conducted at the UT Health San Antonio [either in the Medical Arts and Research Center (MARC) FORU on first floor or in the Cell Systems & Anatomy Department Research Unit in the UTHSA Basic Science Building on second floor]. Visits 1-6 will typically be conducted as home visits (or at an alternate site within 20 miles of the UTHSA, if the subject prefers), but two of these visits (#4 and #6) may be replaced with phone calls if you feel comfortable with the application procedure and there have been no problems.

COVID-19 Screening (standard of care)

- All participants will be pre-screened by telephone questionnaires before visits are scheduled. No COVID-19 testing will be done by the research team during this study. If getting a test is indicated, we will refer you to your primary care physician for further instructions and care.
- Upon entering the facility, you will be required to wear a mask. If you do not have a mask, one will be provided for you.
- At each study visit, whether the visit is conducted in the Research Unit or in your home, the study staff will take your temperature and ask COVID-19 screening questions to document in the research record.
- For your personal safety and the safety of study staff, these COVID-19 screening procedures will be repeated at each and every visit.
- Study staff wear personal protective equipment (PPE), including masks, gloves and possibly a surgical gown depending on research activities for the visit.

Informed Consent Process
The process of explaining the study to you and all study-related activities is known as the informed consent process and is important to research ethics. We are required to obtain your voluntary consent with signatures before any information about you can be collected or stored for research purposes. After reviewing and signing this form, we will provide you a copy for reference.
We will perform an assessment of your memory and thinking by drawing a clock (CLOX test) to ensure that the consent is valid.

Screening - (Visit 0)
After you sign this form, we will carry out exams, tests, and/or procedures as described below to find out if you can continue in the study; this is called screening. We may be able to use the results of exams, tests, and/or procedures you completed before enrolling in this study. You will be told which results we will obtain, and which procedures will not have to be repeated. Some of the procedures are described below as "standard care" and would be done even if you do not take part in this research study. You will be told which ones are for "research only".

Screening Procedures
The following procedures will be performed to ensure you are eligible to participate.

Medical history – Study staff will ask questions about your history of illnesses and surgeries and record any and all medications that you take currently or may have taken recently. You will also be asked about COVID-19 vaccination as this is required for you to be eligible for study participation; the vaccine will not be provided as part of this study.

Physical examination, including

- Standard vital signs to measure your height, weight, heart rate (listen to your heart or take your pulse), blood pressure, and temperature
- Tattoos or scars on the forearms will be examined to ensure that they will not interfere with drug application.
- Physical exam similar to what you get when you visit your doctor for a routine checkup.
- Electrocardiogram (ECG/EKG) – 12 sticky pads on your chest attached to wires connected to a machine that measures your heart function
- Blood draw (safety labs for research eligibility) – Blood will be taken from a vein in your arm or hand to measure:
    - Complete blood count (CBC) to count the number of red blood cells and white blood cells
    - Blood chemistry (CMP) to check your liver function, measure the amount of sugar/ cholesterol in your blood (hemoglobin A1c and lipid panel), which will help us to determine your overall, general health
    - If you have had these tests in the last 60 days and we have access to the results, we can accept them for study purposes

This visit will take approximately 60-90 minutes. Compensation for this visit is valued at $25.00 (see Participant Payment Section for more details).

The results of the screening exams, tests, and/or procedures will be reviewed by study staff to determine whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you.

If safety lab reports show any values outside the normal range, the medical investigator will determine whether the difference is "clinically significant" or not and might choose to repeat a specific test(s) to confirm the results before determining eligibility. This could possibly require an additional or "interim" visit.

Assignment to Study Intervention
When it is determined that you will be allowed to continue in the study, you will be provided study medication and you will act as your own "control" for the study. What this means is, you will apply the active study drug to the inner surface of one forearm and the "placebo" (inactive) ointment to the other forearm.

- Topical RAPA – petrolatum ointment (like Vaseline®) with 8% RAPA in it
- Placebo – similar ointment with no study drug in it

Neither you nor the researchers will know which of your arms is receiving the study drug and which is getting placebo. This is called "double blinding." In the event of an emergency, there is a way for the researcher to find out which you are receiving.

Study Procedures - as a participant, you will undergo the following procedures:
All visits are for research purposes.

Visit 0 – consent and screening – detailed above and performed in the Research Unit

Visits 1 through 6 – conducted as home visits (or if the subject prefers, at an alternate location within 20 miles of the UTHSA) that will occur monthly, with phone follow up in between home visits. Visits 4 and 6 may instead be conducted by phone if the individual participant has been fully compliant with no adverse events. At each home visit, the study staff will:

- adhere to COVID-19 safety precautions (temperature, screening questions, masks, etc.)
- if clinically indicated, listen to your heart and take your blood pressure
- review your current health status and other medications
- ask questions about any side effects or expected/unexpected symptoms you experienced since the previous visit (called Adverse Event review)
- two weeks after home visit #1, you will receive a phone call to check on your adherence to daily study drug administration and to determine whether there have been any Adverse Events
- schedule further research visits
- prescribe and dispense study medication (Visits 1, 3, and 5)
- review clear instructions verbally and in writing that explain how to apply the ointment
- mark the skin area where medication is applied

Study Medication
At Visits 1, 3 and 5 we will deliver study medication. Using the Topi-Click® dispenser system, the container is shaped like a cylinder of stick deodorant and by turning it one time, the measured amount of medication is squeezed out for you to apply. See Risks section for more information about effects of the medication.

Each container is color coded and labeled for which arm gets which medication. For the left arm (L), you will use the dispenser color coded in Leaf Green labeled "L", and for the right arm (R) you will use the red-coded dispenser and labeled "R". We plan to mark your arm with a permanent marker that is Red on the right and Green on the left where the medication should be applied. As mentioned earlier, only the pharmacist will know which dispenser has active medication in it.

Dispensers should be stored at room temperature, not refrigerated or left in a hot car or direct sunlight. We will ask you to return all medication dispensers during the study, so we can weigh them and calculate how much medication was used from each. Please do not throw them away.

Each home visit is estimated to take up to 60 minutes and will be compensated at a rate of $10 per home visit. If home visit 4 or 6 is replaced by a phone call, it will be compensated at the rate of $10/visit. Any interim phone calls (between monthly scheduled visits) will not be compensated.

Visit 7 – we will ask you to return to a Research Unit at the UT Health San Antonio to undergo post-treatment assessments, including:

- COVID-19 precautions
- Vital signs, medical history, medication review, and post-treatment physical exam (like in Visit 0)
- Blood draw – Blood will be taken either by venipuncture or by a finger prick using single-use lancets.
    - RAPA level in blood

- Skin tissue and fluid sampling by suction blister procedure
    - Will be performed by a licensed clinical provider trained to do the procedure. No local anesthetic (numbing medicine) is required.
    - Specimens will be collected from the inner surface each forearm; at the site of topical application. Both arms will undergo suction at the same time.
        - Arm(s) will be comfortably positioned with inner side (ventral) facing up
        - Skin area will be cleaned with a mild antiseptic or alcohol pad
        - A suction chamber will be placed on each forearm and secured with straps to create a seal at the skin
        - Negative pressure console is turned on and pressures increased slowly and gradually at 30-minute intervals until a skin blister appears on each arm.
        - The blister can take from 1 to 3 hours to form fully. The fully formed blister will be approximately ½-inch in diameter and ¼-inch in height.
        - You may feel warmth and an itching sensation at the blister site during the suction procedure.
        - The researcher uses a small gauge needle to withdraw blister fluid (interstitial fluid) from each blister and transfers collected fluid from each arm to a small storage tube
        - Next the researcher uses surgical scissors or a small sharp scalpel (knife) and tweezers to remove the “roof” skin of each blister and prepares the sample for storage
        - Each blister site is medicated with antibiotic ointment and covered with a small bandage.
    - You will rest approximately 15-30 minutes before being discharged to home. The study staff will give you instructions to keep the wound(s) clean and promote healing.
    - The procedure is reported to cause minimal scarring and little to no discomfort after the procedure.

This visit will take approximately up to 4 hours and will be compensated at a rate of $200.

Visit Schedule of Activities

Visit Number	V0	V1	V2	V3	V4	V5	V6	V7
Month#		0	1	2	3	4	5	6
Goal	Consent & Screen	Pre-drug	RAPA/ Placebo	RAPA/ Placebo	RAPA/ Placebo	RAPA/ Placebo	RAPA/ Placebo	RAPA/ Placebo
COVID-19 screening	X	X	X	X	X	X	X	X
Consent	X							
CLOX test	X							
Vital signs	X							X
Medical History	X							
Consent and medication review	X	X	X	X	X	X	X	X
Physical Exam	X							X
12-lead EKG	X							
Safety Labs (fasting):								
CBC,CMP,A1c, lipids	X							
Study drug dispensed		X		X		X		
Self-reported AE		X	X	X	X	X	X	X
RAPA level								X
Phone call to assess compliance and AEs		2 wks later						
Suction Blister Proc.								
Blister fluid								X
Blister roof excision								X

Ending Participation Early

Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is stopped.

The researchers will discuss your options for medical care when your participation in this study ends.

Future Use of Your Information or Biospecimens Collected as Part of Your Participation

Identifiers may be removed and the de-identified information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

Your collected skin specimens will be stored in a locked freezer located in the UTHSA laboratory and a portion will be sent to core facilities for analysis. When the study is complete, all remaining materials will be destroyed. Specimens in the lab or sent for analysis will be labeled with your subject number and sample site (left vs. right arm), as appropriate, but will not include any personal identifying information. Your biospecimens or data derived

from your biospecimens, even if identifiers are removed, may be used for commercial profit and you would not share in this commercial profit.

Risks – "What are the risks of participation in the research?"

Risks from the research
There are no known social, legal, or psychological risks.

At the time of collection, all specimens and data are coded and stored such that so that there is no risk to the privacy of individuals or confidentiality of data. Data are stored in electronic form behind institutional electronic firewalls and/or in physically secured laboratory facilities that are patrolled by armed police forces. These procedures have adequately protected our data for decades and we believe that they will continue to be highly effective in the future.

Risks from the specific research procedures (drug(s), interventions, or procedures)
Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The following section will describe potential risks related to your participation in this research study. You should talk to the study doctor about any side effects or other problems you have while taking part in the study.

Risks and side effects related to the research include those which are:

Study Medication (Topical RAPA)
Less Likely, and not Serious
In previous human studies cited by our investigators, topical administration did not produce systemic or serious reactions. Side effects from this study will usually go away soon after you stop using the RAPA medication. In some cases, side effects can be long lasting or may never go away.

In 100 people, approximately 1 to 5 may have:
- Localized skin redness, mild rash or itching; resolves when medication is stopped
- RAPA can cause mild to moderate redness or itching at the site of application. If a clinically significant rash develops, the study medication will be stopped, and participation will cease.

Rare and Serious
Approximately 1 in 1,000 people may have an allergic reaction. Persons with any allergy or sensitivity to RAPA will not be studied. Participants will be instructed to notify the research team and get help right away if any of the symptoms of an allergic reaction occur.

Serious allergic reactions related to the oral medication include:
- Swelling of face, eyes, or mouth
- trouble breathing or wheezing
- throat tightness
- chest pain or tightness
- feeling dizzy or faint
- rash or peeling of skin

Blood draws (venipuncture)

Likely, and not Serious
In 100 people, approximately 5-10 may have:

- Bleeding, bruising, or localized pain at the site of the blood draw
- Bleeding will be seen as bruising (discoloration) at the place where the blood was obtained. The bruising usually goes away within 3 to 4 days, although sometimes it may take a week. The bruising is helped by using hot packs.

Less Likely, some may be Serious
There is a small risk, less than 1 in 100, of infection where your veins are punctured. Report to your study team any signs or symptoms of infection including localized warmth, redness, swelling or pain.

Rare and Serious
None

Blood draws (finger prick)

Likely, and not Serious
In 100 people, approximately 5-10 may have:
The specific risk associated with single use lancets and finger-stick devices is pain at the site of skin puncture.

Suction blister procedure

Likely, not Serious
In 100 people, approximately 10-20 may have:
- Localized itching at the blister site, during the suction process. Once the suction is removed, we expect the sensation to resolve spontaneously.

Less Likely, some may be Serious
In 100 people, approximately 5-10 may have:
- Ruptured blister during the suction process, which could require a repeat process. This risk is minimized by closely monitoring the blister formation and reducing suction as needed.

Rare and Serious
In 100 people, less than 1 may develop an infection.
- Blisters will usually heal on their own. The skin over the blister helps keep out infections. To minimize infection risk at suction blister sites, all subjects will have the sites treated with topical antibiotic ointment and covered with a band-aid or gauze. They will be provided with antibiotic ointment and band-aids for use at home until the sites have healed. Make sure that there is no rubbing or friction on the blister site.
- You should contact your health care provider if
    - The blister looks infected - if it is draining pus, or the area around the blister is red, swollen, warm, or very painful
    - You have a fever
    - You have health problems such as circulation problems

We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

For more information about risks and side effects, ask one of the researchers or study staff.

This study will/may include genetic testing to determine the pattern of DNA modifications in your skin cells. These patterns, called epigenetic profiles, change with age but cannot be used to identify you.

Are there Risks related to withdrawing from the study?
If you decide to withdraw from this study early, please discuss your decision with the principal investigator. The researcher may ask you to complete study withdrawal procedures at a final study visit. This visit includes returning study medication dispensers and completing some parts of the final visit.
Depending on final data collection, the visit may be done over the phone, at the home, or in the Research Unit.
There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – "How could you or others benefit from your taking part in this study?"
There is no guarantee or promise that you will receive any benefit from this study.
We hope the information learned from this study will benefit other people with similar conditions in the future.

Payments – Will there be any payments for participation?
The researchers will provide you with a MasterCard®. Compensation will be automatically credited within three days of each study visit. Your name, address and date of birth will be shared with a third-party solely for the purposes of compensation processing. This information will only be used for the administration of the compensation (ClinCard) and will be kept strictly confidential.

Visit 0, Consent/Screening	25.00	25.00
Visit 1 – 6, Home (or alternate site) follow-up visits (V4 and/or V6 may be replaced by phone calls, in some cases)	10.00	60.00
Visit 7, Post treatment testing	200.00	200.00
Manual payment, Interim Visit	Prorated at $15.00/hour	
Total Compensation all visits		$ 285.00

In addition to the compensation on the card, you may elect to receive study-related messages (text and/or email). These messages will contain information confirming that money has been loaded onto your card. If desired, you may also receive reminder messages with information about your next appointment with researchers or study staff.

Please indicate your willingness to receive study-related messages:

- □ **Yes,** I would like to participate (please select the best method(s) for communication)
  - Cell Phone (text messages)
  - Email
- □ **No,** I choose not to participate

Costs – Will taking part in this study cost anything?

Ask the researchers if you have any questions about what it will cost you to take part in this study (for example bills, fees, or other costs related to the research).

The sponsor will provide the study drug free of charge during this study. At the end of your participation you must return all unused study drug to the researcher.

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?

Protected Health Information is information about a person's health that includes information that could make it possible to figure out who it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include: your medical history, medications, and health status (based on the blood work and screening tests we perform and the information you provide), and information that is created or collected during your participation in the study, and results of blood tests and laboratory assays performed with your skin samples. In addition, we will see demographic information like your age, sex, ethnicity, and race. Since we arrange for home visits, we will also have your address. We will get the health information by asking you and running basic blood tests.

How will your PHI be shared?

Because this is a research study, we will be unable keep your PHI completely confidential. We may share your health information and your age (<u>but not your name or other identifiers besides age</u>) with people and groups involved in overseeing this research study including:

- Dr. Horvath, a collaborator at UCLA who performs the analysis of the epigenetic clock, and the laboratory facilities both at the UTHSCSA (pharmacology core) and the University of Minnesota (genomics core)
- Clinical Lab that runs standard blood analyses
- Doyle's Pharmacy (Houston) prepares the topical dispensers and retains the key to drug vs. placebo site
- Collaborators at the UTHSCSA, including statisticians and bioinformaticians (Dr. W. Koek and Dr. H. Zare).
- The DSMB, the data safety monitoring board of the Pepper Center at the UTHSCSA. This committee checks the study data on an ongoing basis to determine if it should be stopped for any reason.
- The members of the local research team

- The Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out.
- The Food and Drug Administration (FDA) and other U.S. (National Institute on Aging, NIA) and international governmental regulatory agencies involved in overseeing drug research; this study has been designated "exempt" by the FDA.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI (such as your age) may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

This study includes genetic testing to determine the pattern of DNA modifications in your skin cells. These patterns, called epigenetic profiles, change with age but cannot be used to identify you.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premium;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

How will your PHI be protected?

In an effort to protect your privacy, the study staff will use code numbers, instead of your name, to identify your health information. Subject identifiers will be used on any photocopies of your study records, on any specimens collected (blood or skin samples), and any other study materials containing health information that are sent outside of the UTHSCSA for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?

You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you need to say this in writing and send your letter to Dr. Ellen Kraig, Department of Cell Systems and Anatomy, MC 7762, UTHSCSA, 7703 Floyd Curl Drive, San Antonio, TX, 78229. If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?

The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.

You will only have access to your PHI until two years following the end of your participation in the study. Because of the type of research, you can only access your PHI when the study is done. At that time, you have the right to see and copy the medical information we collect about you during the study, for as long as that information is kept by the study staff and other groups involved.

How long will your PHI be used?
Authorization to use your PHI will expire 5 years after the last subject completes the study or on 05/31/2027, whichever occurs first.

By signing this form, you agree to let us use and disclose your health information for purposes of the study until 05/31/2027.

Contact Information – Whom can you contact if you have questions, concerns, comments or complaints?

If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact:

Primary contact:

Dean L. Kellogg, Jr, MD, PhD can be reached at 210-235-3681 (pager) or 210-788-6497 (mobile) during and after regular business hours.

Note: To use the pager, you need to have a touch tone (push button) telephone. Dial the pager number as you would any phone number. When you hear 3 short high-pitched beeps, dial in the number where you want the doctor to call you back. Push the # button, hang up and wait for the doctor to return your call.

If primary is not available, contact
Terry Q. Romo, FNP-BC can be reached at 210-617-5300 x14266 (can be reached during normal work hours) or (210) 834-7819.

Dr. Ellen Kraig can be reached at 210-367-3171.

The University of Texas Health Science Center committee that reviews research on human subjects (Institutional Review Board) will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the IRB by calling 210-567-8250, or by mail to IRB, UTHSCSA, Mail Code 7830, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900.

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.

Adult Signature Section

- You have voluntarily decided to take part in this research study.
- You authorize the collection, use and sharing of your protected health information as described in this form.

Printed Name of Subject	Signature of Subject	Date	Time (AM / PM)

Printed Name of Witness	Signature of Witness	Date	Time (AM / PM)

☐ *Check if consent and authorization obtained from an individual who is unable to read and/or write but can otherwise communicate and/or comprehend English. Have witness initial below.*
Declaration of witness: I was present for the entire consent process. _____ ←(initials of witness)

Printed Name of Person Obtaining Consent & Authorization	Signature of Person Obtaining Consent & Authorization	Date	Time (AM / PM)

☐ Consent and authorization was obtained from this individual who is unable to read and/or write but can otherwise communicate and/or comprehend English. The method used for communication with the subject was: _____.
The specific means by which the subject communicated agreement to participate was:
_____