Protocol #: HSC20190850H

NCT # 04200911

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

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.

The purpose of this pilot study is to evaluate whether a study drug, Rapamycin ("RAPA", Sirolimus, Rapamune®) reaches the brain using cerebrospinal fluid (CSF) in older adults with mild cognitive impairment (MCI) and early stage Alzheimer's disease (AD). This drug has been shown to improve cerebral blood flow, decrease neuroinflammation, and enhance memory in Alzheimer's mice models. We want to know if this medication reaches the brain in order to evaluation if this intervention may be effective for treating MCI and AD symptoms in future studies. This is also known as a "proof of concept" study.

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?

Eligible participants will have 8 clinic visits to undergo laboratory assessments of blood, receive the study medication over an 8-week period and complete pre- and post-treatment testing including: 2 visits with lumbar punctures to obtain cerebrospinal fluid; blood draw (7 out of 8 visits); memory and thinking assessments; mood and sleep questionnaires, and tests of physical functioning, all of which will be done for research purposes only. The possible benefit of participating is contributing to science, which may improve treatments for MCI and AD in the future. The cons of participating may include medication side effects, pain or bleeding from blood draws and lumbar puncture, emotional distress from assessments of memory and thinking, or fatigue from physical performance measures.

Other available treatments for early stage AD include cholinesterase inhibitors (Aricept [donepezil], Exelon [rivastigmine], Razadyne [galantamine]) and Namenda [memantine]. If you are prescribed these medications, you can continue taking them throughout the study assuming that you have been on a stable dose for at least three months. Treatment pros include established benefits for slowing the progression of the disease. The con is that these medications do not cure AD and the disease will gradually get worse over time.

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?
This study involves 8 visits over the course of approximately 12-18 weeks. Visits are scheduled 1 to 4 weeks apart. Visits last anywhere from 45-minutes to 3.5-hours. The total hours of participation may range from 15-18 hours.

4. Could taking part in the study help me and are there risks?

We cannot guarantee that you will benefit from participating in this study other than to receive study medication and study related clinical care at no cost to you, and a small amount of reimbursement for your time and travel to the clinic.

The risks associated with your participation may include medication side effects, pain or bleeding from blood draws and lumbar puncture, emotional distress from assessments of memory and thinking, or fatigue from physical performance measures.

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?

Another important factor to consider before participating is the need for you to be accompanied to visit 1 by someone who is legally authorized to represent you such as your husband/wife or child, as well as study partner (husband/wife, child) for all other study visits.

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.

Information about this form

If you are providing consent for someone else, for example your child, your next-of-kin or someone for whom you are the legal guardian or are designated as a surrogate decision maker on a medical power of attorney, please note that in the sections that follow the word "you" refers to the person you are providing consent for.

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 Mitzi Gonzales, PhD of the University of Texas Health Science Center San Antonio (UTHealth San Antonio or UTHSA), at the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases. The Co-PI for this study is Dean Kellogg, MD of The University of Texas Health Science Center San Antonio (UT Health San Antonio or UTHSA) and Sam and Ann Barshop Institute for Longevity and Aging Studies. The Co-Principal Investigator shares the principal investigator's responsibilities for this study.

Non-Profit Funding.

This study is funded by an institutional grant awarded by the Institute for Integration of Medicine & Science/Clinical and Translational Science (IIMS/CTSA) at UTHSA. This organization receives and distributes funding from state and federal sources so that the researchers can conduct the study.

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

The purpose of this pilot study is to evaluate whether a study drug, Rapamycin ("RAPA", Sirolimus, Rapamune®) reaches the brain using cerebrospinal fluid (CSF) in older adults with mild cognitive impairment (MCI) and early stage Alzheimer's disease (AD).

You are asked to participate in this clinical trial, which evaluates inflammatory and AD-related markers in the blood and cerebrospinal fluid, possible medication side effects, memory/thinking, sleep/activity, physical functioning in individuals with MCI and early stage AD.

The researchers hope to learn if this drug reaches the brain in order to evaluate if this intervention may be effective for treating MCI and AD symptoms in future studies

Title of Study: Title of Study: Cognition, **A**ge, and **R**a**P**amycin **E**ffectiveness – **D**ownregulat**I**on of th**E m**Tor pathway (**CARPE DIEM**)

This study involves the use of an FDA-approved drug called Rapamycin ("RAPA", Sirolimus, Rapamune®), that has not yet been approved by the U.S. Food & Drug Administration (FDA) for treating MCI or Alzheimer's disease.

This study will help find out what effects, good and/or bad, this drug has on people who take it and its effect on the condition/disease. The safety of this drug in humans has been tested in prior research studies; however, some side effects may not yet be known.

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 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 have been diagnosed with MCI or early stage Alzheimer's disease.

How many people are expected to take part in this study?
This study will screen approximately 60 individuals to enroll and complete all procedures and interventions on 10 people.

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 8 visits with the researchers or study staff. Your Legally Authorized Representative (LAR or legal representative) must accompany you to the first visit and your LAR/study partner must accompany you to all remaining visits.

It will be necessary for you to return to the research clinic 8 times across a period of up to 18 weeks.

Special Considerations related to COVID-19

1) You will be phone screened 1 to 2 business days before all study visits to assess for signs or symptoms of COVID-19 and for reports of recent exposure to people known to be infected with the virus. Upon arrival to the visit and before entering the research unit building, you will be screened again, have your temperature taken, and will receive a mask if you need one.

2) For added safety, participants enrolled in the study will be tested for the coronavirus also known as SARS CoV-2. Approximately 24-72 hours before starting the study drug intervention you will be tested with a nasopharyngeal swab (inserted in the nose to the back of the mouth) for rRT-PCR (Real-time reverse transcriptase–polymerase chain reaction) COVID-19 analysis. Research funds will pay for the testing. If you test positive, the investigator will refer you to your primary care physician for medical care and may withdraw you from participation in the trial. If you have completed your vaccination to COVID-19 at least one-week prior to your first dose of study drug, the rRT-PCR test may be waived with the authorization of the study doctor. It will be necessary for you to provide proof of your completed vaccination such as the card issued to you by the place where you got the vaccine or a similar record from your doctor.

3) If you develop COVID-19 signs or symptoms at any time during the study, the investigators will arrange for testing and if indicated, will refer you to your PCP for medical care. Research funds will pay for the testing. If you test positive for COVID-19 during the 8-week study drug treatment, you will be withdrawn from treatment and your study participation will stop. If you test positive for COVID-19 during the pre- or post-treatment study periods, you will be required to wait until your symptoms resolve and you receive a negative COVID-19 test before continuing your study participation.

4) **COVID-19 Vaccination:** If you decide to be vaccinated for COVID-19, at any point during the study, please notify the research team. If your vaccination occurs during the study treatment period, the research team will

advise that you stop taking the study medication for four days before and at least three days after each vaccine dose. Prior to resuming the study drug, the research team will contact you to evaluate for any new symptoms and advise you on when to resume the study drug. The temporary stop in taking the study medications will not change the total number of days that you take the study drug during the course of the research study. Your end of study treatment date will simply be extended by the number of days that the drug was withheld.

Visit 1 – Screening

Consent - Researchers will first attempt to seek consent from you. In order to have appropriate safeguards, we will assess your capacity to understand the purpose, procedures, risks and benefits of study participation using a standardized instrument (questionnaire) for assessing capacity to consent. If your capacity to consent is diminished, the researchers will obtain consent through your representative who is legally allowed to speak for you (LAR). When a LAR is necessary, the researchers will instruct your LAR to respect your will and preferences relevant to this study and we will still include you in the consent process and seek to obtain your assent (approval) for study participation

Screening – After you sign this consent to participate, exams, tests, and/or procedures may be done 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. Most of the procedures are for "research only" and if any are performed for standard of care (soc), we will inform you accordingly.

Screening Procedures
We will ask you to come in a non-fasting state to the Biggs Institute at the McDermott Clinical Sciences Building (Biggs-McDermott) located at 8403 Floyd Curl Drive on the 5th floor in Room 5.110. The following procedures will take place:

- Physical examination – we will measure vital signs (blood pressure, heart rate, respiratory rate and temperature, pulse oximetry), height , weight , and calculate Body Mass Index (BMI). We will perform a physical examination similar to what you would have when visiting your family doctor.

- Medical history and medications – we will ask you questions about your health history and a list of current and recent medications you have taken or are taking.

- Cognitive screening assessment – Using a brief assessment scale, we will evaluate your memory and thinking.

- Non-fasting blood draw to measure safety indicators, including complete blood count (CBC), comprehensive metabolic panel (CMP), hemoglobin A1c (A1c to check for diabetes), and coagulation panel (PT/PTT/INR). A urine specimen will also be collected to check your kidneys.

This visit is expected to require 2.5 hours.

The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. After receiving all test results (including laboratory data), the study investigators or research staff will call you to let you know if you quality for the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you. If there are abnormal lab results that are interpreted to be clinically significant, investigators may ask to repeat the testing or advise you to consult with your primary care provider before enrolling you in the study. If you do qualify for the study and remain interested in participating, Visit 2 will be scheduled. Within one business day of Visit 2, research staff will call you and/or your LAR/study partner to confirm the appointment and provide a reminder about fasting.

Visit 2 – Baseline Measurements Part I (within 30 days of Visit 1 [Biggs-MCD or RII-MCD])

You will be asked to return with your legal representative/study partner to the McDermott location (RII – First Floor) to undergo the first of 2 visits to collect pre-treatment (also called Baseline) measurements. You must arrive to this appointment after an 8-hour fast (nothing to eat/drink at least 8 hours before your visit, except water, as instructed).

- Vital signs – heart rate, blood pressure, respiratory rate, temperature, pulse oximetry
- Review of current medications
- Fasting Blood draw – comprehensive metabolic panel (CMP, lipid panel) and research lab work for inflammatory and AD markers
- Lumbar puncture – also known as a 'spinal tap' from which fluid is obtained.

  This procedure involves placing a needle in the lower back to obtain fluid that bathes the brain and spinal cord (this fluid is called cerebrospinal fluid or CSF). The correctly placed needle enters a sac below the actual spinal cord. The lower back is generally considered the safest site to obtain this fluid for laboratory testing.

  The physician will tell you which position they want you in for this test. It is important to be as still as you can during the procedure. There is not usually a lot of pain because a local anesthetic is used to numb the area but some patients feel a slight pressure and soreness when the needle goes in. If clinically indicated for subject safety during the procedure, the physician performing the spinal tap may opt to use fluoroscopy, an imaging technique using X-ray, to identify the correct insertion point on the spine.

  This procedure is performed for research purposes so that investigators may learn whether the study medication crosses from the bloodstream into the brain (also called the blood-brain barrier) and at what concentration the medication reaches the CSF.
- Provision of a snack (optional)

This visit is expected to require 3 hours. An appointment for the next visit will be scheduled. Within one to two business days of Visit 3, research staff may call you and/or your LAR/study partner to confirm the appointment.

Visit 3 – Baseline Measurements Part II (up to 30 days after Visit 2 [Biggs-MCD])

You will be asked to return with your legal representative/study partner to the Biggs-McDermott location within 30 days after Visit 2 for Visit 3 that will include:

- Medication review
- Adverse event (AE) review – a list of questions concerning any medical experiences related or unrelated to the research since the last visit
- Cognitive examination – we will administer a set of detailed cognitive assessments to score your memory, mental status, comprehension and thinking. Physical functioning and sensory performance measures
  - □ We will provide instruction and ask you to perform some physical performance tests that include walking on a pressure sensitive walkway to capture data on steps, balance and gait. We will measure your hand grip strength.

Visit 3 is estimated to require 3.0 hours, and at the end of Visit 3 we will confirm the scheduling of Visit 4. Within one to two business days of Visit 4, research staff may call you and/or your LAR/study partner to confirm the appointment.

COVID-19 Testing: Within one to three days of your Visit 4 appointment, you will be asked to complete COVID-19 testing with a nasopharyngeal swab (inserted in the nose to the back of the mouth) for rRT-PCR (Real-time reverse transcriptase–polymerase chain reaction) analysis. Please complete the test at the location provided to you by the study staff. Research funds will pay for your test and study staff will access your results electronically from the laboratory's secure portal. If your test is positive, research staff will call to inform you of the results. Research staff may also call you to ensure that you complete the COVID-19 test prior to study Visit 4.

Visit 4 – Study Drug Dispensing and Monitoring (within 15 days of Visit 3 – [Biggs-MCD])

You will be asked to return with your legal representative/study partner to the Biggs-McDermott location after an 8-hour fast (nothing to eat/drink, except water, at least 8 hours before your visit) within 15 days after Visit 3 for Visit 4 that will include:

- Vital signs
- Medication and records review
- Fasting blood draw for safety labs (CBC, CMP, lipid panel, HbA1c); a urine specimen will be collected to monitor kidney function
- Adverse event review – a list of questions concerning any medical experiences related or unrelated to the research since the last visit
- Cognitive Screening Assessment may be repeated if this visit is done more than 60 days after visit 1.
- Dispense study medications to take at home with written instructions
- Scheduling Visit 5 to occur

Visit 4 is estimated to require 1.5 hours or less. Scheduling of Visit 5 to occur 4 weeks (± 2 days) after Visit 4. Within one to two business days of Visit 5, research staff may call you and/or your LAR/study partner to confirm the appointment.

Visit 5 – Study Drug Dispensing and Monitoring (4 weeks ± 2 days after Visit 4 – [Biggs-MCD])

We will ask you to return to the Biggs-McDermott location with your LAR/study partner after an 8-hour fast (nothing to eat/drink, except water, at least 8 hours before your visit) for:

- Vital signs
- Weight
- Medication and adverse event review
- Fasting blood draw for safety labs (CBC, CMP, lipid panel)

- Study medication compliance/tolerability - questions regarding how often you took the study medication and any side effects
- Dispense study medications to take at home with written instructions

The estimated duration of this visit is 1 hour or less. We will also confirm scheduling of Visit 6. Within one to two business days of Visit 6, research staff may call you and/or your LAR/study partner to confirm the appointment.

Visit 6 – Study Drug Dispensing and Monitoring (3 weeks ± 2 days after Visit 5 – [Biggs-MCD])

We will ask you to return to the Biggs-McDermott location with your LAR/study partner after an 8-hour fast (nothing to eat/drink, except water, at least 8 hours before your visit) for:

- Vital signs
- Weight
- Medication and adverse event review
- Fasting blood draw for safety labs (CBC, CMP, lipid panel, PT/PTT/INR) ; a urine specimen will be collected to monitor kidney function
- Study medication compliance/tolerability (able to tolerate medication)
- Study Staff will return study medications to take at home with written instructions

The estimated duration of this visit one hour or less. We will also confirm scheduling of Visit 7 for return to the Biggs-MCD location. Within one business day of Visit 7, research staff will call you and/or your LAR/study partner to confirm the appointment and provide a reminder about fasting.

Visit 7 – Lumbar Puncture, Blood Draw, and Monitoring (1 week ± 2 days after Visit 6 – [Biggs-MCD or RII-MCD])

We will ask you and your LAR/study partner to return to the first floor of the McDermott location after at least an 8-hour fast (nothing to eat/drink, except water, at least 8 hours before your visit) and before taking your final dose of the study medication. At this visit, please plan to bring all remaining study medication with you to return to the study staff. Please make note of any study medication that may have been lost or damaged during the course of the study.

During this visit, research activities include:

- Vital signs
- Medication and adverse event review
- Fasting blood draw –CMP, lipid panel, and research lab work for inflammatory and AD markers
- Lumbar puncture to acquire CSF.
- Provision of a snack (optional)

The estimated duration of this visit is 3 hours or less. We will confirm scheduling of Visit 8 for further post-treatment measures and final follow up with disenrollment. Within one to two business days of Visit 8, research staff may call you and/or your LAR/study partner to confirm the appointment.

Visit 8 – Post treatment testing and End of Study (7-14 days after Visit 7 – [Biggs-MCD])

We will ask you and your LAR/study partner to return to the Biggs-McDermott research unitafter an 8-hour fast (nothing to eat/drink, except water, at least 8 hours before your visit) to undergo final post-treatment measures, including:

- Vitals, weight , medication review, history and physical examination
- Cognitive test battery, including all assessments from Visit 3 and one of the screening visit measures (CDR)
- Physical performance testing like in Visit 3
- fasting blood draw for safety labs (CBC, CMP, lipid panel, hbA1c) and urinalysis to evaluate your kidneys
- Provision of a snack
- Final AE review and disenrollment processing

The estimated duration of this visit is 3.5 hours. A Summary Table of all visits is shown below.

Visit Number	**Visit 1 Biggs -MCD**	**Visit 2 Biggs/ RII-MCD**	**Visit 3 Biggs-MCD**	**Visit 4 Biggs-MCD**	**Visit 5 Biggs-MCD**	**Visit 6 Biggs-MCD**	**Visit 7 Biggs/ RII-MCD**	**Visit 8 Biggs-MCD**
Visit Window		V1 + up to 30d	V2 + up to 30d	V3 + up to 15d	V4 +4w ±3d	V5 +3w ±3d	V6 +1w ±3d	V7+7-14d
Consent	X							
Reassess willingness to participate		X	X	X	X	X	X	X
CDR	X			X*				X
Vitals: BP,HR,T,RR, Pulse Oximetry	X	X	X	X	X	X	X	X
Height	X							
Weight	X			X	X	X		X
H & P	X							X
ConMeds	X	X	X	X	X	X	X	X
AE Review		X	X	X	X	X	X	X
Blood Draws, Labs, and Lumbar Punctures								
*COVID-19 RT-PCR nasal swab***				X				
Non-Fasting Blood Draw	X							
Fasting Blood Draw		X		X	X	X	X	X
CBC w diff	X			X	X	X		X
CMP and lipids	X	X		X	X	X	X	x
Hemoglobin A1c	X			X				X
PT/PTT/INR	X					X		
Urinalysis, routine	X			X		X		X
Research Labs		X					X	
Lumbar Puncture (potentially with Fluoroscopy)		X					X	
Cognitive, Physical, and Sensory Assessments								
Snack Provision (optional)		X					X	X
Montreal Cognitive Assessment			X					X
HVLT-R			X					X
Craft Stories			X					X
Benson Figure			X					X

Number Span Test			X					X
Trail Making Test A&B			X					X
Phonemic and Semantic Fluency			X					X
Multilingual Naming Test			X					X
Hayling			x					x
GDS-15			X					X
FAQ			X					X
NPI			X					X
Electronic Gait Mapping			X					X
Grip strength			X					X
Study Medication								
Compliance Review					X	X	X	
Administer in clinic							X	
Dispense next dose to home				X	X	X		
Schedule/Confirm Next Visit	X	X	X	X	X	X	X	
End of Study								
Final AE review								X
Final Forms Review								X
Follow up instruction								X
Disenrollment Note								X

**COVID-19 RT-PCR swab performed 24-72 hours prior to drug dispensing visit
*CDR will only be done if visit 4 is conducted more than 60 days after visit 1.

Assignment to Study Medication

When it is determined that you are eligible for the study, you will be prescribed and provided with the study medication. Everyone enrolled in the study takes the same prescribed treatment, which will be 1 mg of Rapamycin ("RAPA", Sirolimus, Rapamune®) daily for 8-weeks.

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

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

Human Genetics: Research involving your biospecimens will, or in the future, might include whole genome sequencing. Whole genome sequencing is the process of determining the complete DNA sequence of a person or other organism's genome at a single time. DNA is short for deoxyribonucleic acid. DNA contains

information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child

Return of Research Test Results for Genetic Tests to Subjects

It is possible that this study will identify information about you that was previously unknown, such as disease status or risk.

There are no plans to provide this information to you or your physician unless the information indicates that you may be at risk for a serious illness known at the time of testing to be treatable and it can be confirmed by a clinical laboratory. In that case, we will attempt to notify you using the contact information you have provided.

If you do not want to be notified of any of these incidental findings, please initial below.

_____ Please do not notify me of any incidental findings obtained from this research.

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 premiums;
- 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.

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.

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

Risks associated with participation in this research may be related to: a) drug administration side effects and potential drug-drug interactions, b) blood draw, c) genetic informational risks, d) cognitive assessment and semi-structured interviews/questionnaires, e) lumbar puncture, f) risks of radiation exposure, g). physical and sensory functioning assessments, h) COVID-19 swab test.

Side effects from this study will usually go away soon after you stop taking the medication or a reasonable time after a procedure. In some cases, side effects can be long lasting or may never go away.

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 the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

a) Drug Administration

Rapamycin (RAPA) (Sirolimus, Rapamune®) is FDA-approved and indicated for use as an immunosuppressant. The most common adverse events include mucositis, stomatitis, diarrhea, nausea, and acneiform rash. Many side effects are alleviated with lower dosing and shorter durations of exposure. In a recent clinical trial of elderly adults receiving 1mg RAPA daily, the same dosage to be used in this proposal, no serious adverse events occurred. The reported adverse events were limited to facial rash (N=1), stomatitis (N=1; 1 on placebo and 1 on RAPA), and gastrointestinal distress (N=2).

- Likely, and may be serious (more than or 15 out of 100 people):
  - Mucositis and stomatitis (inflammation of the mouth and tongue)
  - Mouth scores
  - Acne like rash
  - Hyperlipidemia (increased cholesterol and fat in the blood)
  - Increased blood sugar
  - Peripheral edema (swelling in the arms, legs, hands, feet)
  - Hypertension (high blood pressure)
  - Constipation
  - Diarrhea
  - Headache
  - Fever
  - Anemia (low red blood cell count or hemoglobin)
  - Nausea
  - Arthralgias (pain in the joints)
  - Pain
  - Urinary urgency (the feeling that you have to go to the restroom right away)
  - Insomnia
  - Oral paresthesia (numbness)
  - Transient numbness in mouth or other parts of the body
- Rare, and may be serious (1 to 5 people out of 100) :
  - Pneumonitis – inflammation of lung tissue, may be fatal
  - A hypersensitivity response (allergic reaction), though rare, may develop. Some signs of allergic reactions are rash, itching, hives, and shortness of breath.
  - Low platelets (increases the risk of bruising and bleeding)
  - Low white blood cells (increases the risk of developing infections)
  - Infections
  - Certain types of cancer (i.e. lymphoma and skin cancer)

- Protein in the urine which may signal a decrease in kidney function

Drug-Drug Interactions may include:

- Strong CYP3A4 Inhibitors – clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, such that dose reduction may be necessary.
- Strong CYP3A4 Inducers – carbamazepine, dexamethasone, ethosuximide, glucocorticoids, griseofulvin, phenytoin, primidone, progesterone, rifabutin, rifampin, nafcillin, nelfinavir, nevirapine, oxcarbazepine, phenobarbital, phenylbutazone, rofecoxib (mild), St John's wort, sulfadimidine, sulfinpyrazone, troglitazone, such that dose increase may be necessary.
- Live vaccinations - measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, TY21s typhoid

b) Blood withdrawal (To minimize these risks a qualified phlebotomist will perform venipunctures.)

- Likely, and may not be serious (5 to 10 out of 100 people):
  - Pain, bleeding, bruising, or swelling at the site of the needle stick
  - Fainting or light-headedness
- Less likely, and may or may not be serious (1 to 5 out of 100 people):
  - Hematoma (bleeding outside of the blood vessels
- Rare risks and complications (less than 1 in 100 people)
  - Nerve damage
  - Infection

c) Genetic Information

This study may include genetic testing. Human tissue contains genes that determine many of a person's physical characteristics, such as the color of eyes and hair. In some cases, genetic testing of tissues can be used to indicate a risk for the development of certain diseases. Genetic information is unique to each individual and could potentially be used to discover possible changes in a person's future health status or life expectancy, or that of his/her children and family members. Even though the results of genetic testing cannot be linked to you, it is possible that people of your ethnic background may be found to be at more risk for certain diseases based on future genetic research and this information might harm you in the future as a member of the group. Releasing this information to others, such as including it in your medical record, may pose a possible risk of discrimination, or increase difficulty in obtaining or maintaining disability, long-term care, or life insurance.

These risks would occur if your information is released by mistake. The measures being taken to protect your privacy are discussed below and make this possibility unlikely.

Even though the results of genetic testing may not be linked to you, it is possible that people of your ethnic background may be found to be at more risk for certain diseases based on future genetic research and this information might harm you in the future as a member of the group. Also, there may be unknown risks of genetic testing in the future.

d) Cognitive Assessment (Patient or Study Partner-Reported Outcomes include questionnaires related to cognitive symptoms, memory and thinking, functional status, sleep, and mood scales.)

- Likely, and may not be serious (less than 5-20 subjects out of 100)

- Psychosocial – you may experience embarrassment, discomfort or anxiety during memory and thinking tests

o Less likely (less than 5-20 subjects out of 100) and Not Serious:

- Uncomfortable answering questions –If you feel uncomfortable answering questions, one of the investigators will speak with you to help clarify your doubts. Your responses will be kept confidential. You do not have to respond to any question that you do not feel comfortable answering.

o Rare (less than 5 subject out of 100) and Serious:

- Breach of confidentiality- It is possible in a rare occurrence there may be a breach of confidentiality. However, the researchers have taken steps to minimize this risk such as keeping focus group audio recordings and materials in a secure, locked location.

e) Physical Functioning Assessment

o Likely, and may not be serious (approximately 5-20 out of 100 people):

- Psychosocial - heightened awareness of physical limitations may cause anxiety or embarrassment during testing, which will be mitigated by ensuring privacy
- Brief, temporary fatigue with timed short distance walking and/or using handheld dynamometer to measure grip strength

f) Lumbar Puncture (To minimize these risks, a qualified provider specifically trained in the procedure will perform the lumbar puncture; if clinically indicated, an xray called fluoroscopy may be used)

o Likely, and may not be serious (more than 5 out of 100 people):

- Temporary pain and discomfort in the back – affects up to two thirds of people having LP and rarely is it permanent
- Shooting pain down the legs at the time of the procedure is common, affecting about 10% of people having LP and it usually stops as or shortly after the needle is removed
- Bleeding – is more common if you have been taking blood thinning drugs such as Warfarin, Aspirin, Clopidogrel (Plavix, Iscover. Coplavix), Prasugrel (Effient), Dipyridamole (Persantin or Asasantin), Ticagrelor (Brilinta), Apixaban (Eliquis), Dabigatran (Pradaxa), Rivaroxaban (Xarelto).

o Less likely (1 to 5 out of 100 people), and may be serious:

- Allergic reaction to the local anesthetic (lidocaine) used for the lumbar puncture, such as swelling or rash at the puncture site
- Headache – may be severe and last up to several days and could require further treatment
- Persistent low-pressure headache due to leakage of CSF. If this type of “spinal headache” persists, it may require additional treatment. The chances of having a spinal headache depend on many factors including age, weight, and size of needle used for the LP. A spinal headache may occur up to 5 days after the LP procedure. This type of headache usually is described as more severe when upright and gets better when lying down.

  Conservative management includes adequate hydration and or drinking things high in caffeine like Mountain Dew, or strict bedrest for 24-48 hours.

  Uncommonly, if conservative treatment fails, a blood patch (injection of some of participant blood into

the lumbar puncture site to patch the CSF leak) may be required.

- Rare risks and complications (less than 1 in 100 people)
  - Bleeding at the site of the needle insertion or into the spinal canal can be immediate or delayed. Often harmless but may cause leg problems. Lower limb weakness or numbness is an exceedingly uncommon complication. It may vary from mild to severe. It usually lasts only a short time but rarely can be permanent.
  - Infection may occur at the needle site and affect the bones of the back or the spinal fluid. It is very rare but death from meningitis can occur.
  - Needle injury problems are uncommon and include occasional implantation of skin cells that can cause local lumps or tumors (dermoids). They are harmless and may need surgical removal, which is extremely rare.
  - Brain Herniation or Coning (Movement of the brain) is an exceedingly rare condition that can lead to death or severe disability. Death as a result of this procedure is ultra-rare.

g) <u>Risks from Radiation Exposure (Lumbar Puncture with Fluoroscopy):</u>

- If clinically indicated due to obesity, arthritis, scoliosis or any other condition that makes it difficult to identify the correct insertion point on the lumbar spine, the lumbar puncture will be completed with fluoroscopy, an imaging technique using X-ray. Fluoroscopy involves exposure to radiation. The amount of radiation exposure that you will receive from this procedure is equivalent to a uniform whole-body dose of 300 mrem (a unit of radiation exposure) which is approximately 0.5 times the average amount of environmental radiation exposure (620 mrem dose) that each member of the general public receives per year. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (abnormal cells) or cancer. However, the probability of harm from such risk associated with the amount of radiation exposure that you will receive from this study is considered to be low when compared to other everyday risks each member of the general public receives per year, depending on the amount of radiation you personally have been exposed to in the past, particularly in the previous year.

  If you have had radiation (like x-rays) before, please tell us now. We want to make sure that the probability of harm from the amount of radiation you will be exposed to in this study continues to be low when combined with the radiation you have received within the past year. If you are pregnant, you cannot take part in this research study. If you are able to have a baby, are not pregnant and wish to take part in this study, we will give you a urine test to be sure that you are not pregnant now. This test will be free. If you get pregnant while taking part in this study, or you think you are pregnant, please tell Dr. Gonzales right away.

h) COVID-19 Swab Test:
During the COVID-19 nasopharyngeal swab test you will have a 6-inch swab (similar to a long Q-tip) inserted into your nose into the passageway that connects the base of the nose to the back of the throat. The swab will be rotated to collect fluids. The procedure will be performed on both nostrils. This may cause discomfort, cause you to experience a “gagging” reflex, or have a lachrymal reflex “cause your eyes to become teary.”

It is possible that the COVID-19 test could produce an incorrect test result “false-negative.” If you have symptoms of COVID-19 and your test result is negative, the study doctor may stop your study treatment until your symptoms resolve and a repeat COVID-19 test is performed

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

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.

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 and/or co-principal investigator. The researchers may ask you to complete study withdrawal procedures at a final study visit. This visit includes lumbar puncture, blood draw, cognitive assessment, and physical functioning and sensory assessment. 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.

Alternative procedures or course of treatment – "What other options are there to participation in this study?"
There are other options available to you. Your other choices may include:

The standard of care for early stage AD that does not involve research is treatment with cholinesterase inhibitors (Aricept [donepezil], Exelon [rivastigmine], Razadyne [galantamine]) and /or Namenda [memantine]. There are no standard of care medications for MCI. Cholinesterase inhibitors and Namenda cannot stop the damage Alzheimer's disease causes to brain cells, but may stabilize symptoms for a limited time or slow the progression of the disease in some cases. For the current study, participants can continue treatment as usual and remain on cholinesterase medications and/or Namenda, if they have maintained a stable dose for at least three months.

Many clinical trials for MCI and AD are ongoing. A list of available trials can be found at this link after creating a secure account: https://trialmatch.alz.org/find-clinical-trials#createaccount

As no disease-modifying treatments for AD are available, the progression of the disease is similar for no treatment and treatment as usual. AD gradually progresses over time and cognitive and functional abilities become more impaired. In the severe stages, AD is associated with complications that ultimately lead to death. Individuals with MCI convert to dementia at a rate of 10-15% per year, but not all individuals will convert.

Payments – Will there be any payments for participation?

The researchers will provide you with a MasterCard®. Compensation will be automatically credited after completion 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.

A schedule of payments is shown below. The total potential reimbursement to a subject is $435 for the study for all visits, or payments may be prorated to include the last visit completed if study participation is terminated early. Manual payments for additional visits, if necessary, will be handled on an ad-hoc basis with prior approval from the funding sponsor.

Table 2. Participant Compensation

Study Visit	Compensation Amount
Visit 1: Screening and Consent	$35
Visit 2	$75
Visit 3	$75
Visit 4, 5, 6	$25 each
Visit 7	$100
Visit 8	$75
Manual Payment (unscheduled visit, lab visit, or AE)	$25

If you are paid, the money you receive may be taxable. When the total payment is $600 or more in one calendar year, the institution must report the amount to the IRS. The IRS considers it earned income and treats it like any other income.

Costs – Will taking part in this study cost anything?

While being seen at the study sites for this study, you or your health insurance company will be responsible for the cost of treatments and procedures that are ***not*** part of this study. It is important to understand that some insurance companies do not cover some costs (for example, approved drugs used in a way different from the package instructions). If your insurance company does not cover these treatments or procedures, you will be required to pay for them.

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.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the Federal Government. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer,

employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under certain circumstances. Circumstances that warrant the release of your information without your permission include: abuse and/or neglect, intention to harm yourself or others, or certain communicable diseases.

Limits of Confidentiality
Even without your consent, suspected or known abuse or neglect of a child, disabled, or elder abuse, threatened violence to self or others or other local health reporting requirements will be reported to appropriate authorities.

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 would make it possible to figure out whose 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 and blood work,
- information that we get from your medical record,
- information contained in your underlying medical records related to your medical history and treatments prior to the study,
- information that is created or collected during your participation in the study including medical and treatment history,
- information you give us during your participation in the study such as during interviews or from questionnaires, results of blood tests; demographic information like your age, marital status, the type of work you do and the years of education you have completed.

We will get this information by asking you, asking your doctor, by looking at your chart at the UT Medicine clinics at UT Health San Antonio or University Hospital.

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 with people and groups involved in overseeing this research study including:

- the company funding the study
- the company (Pfizer, Inc) that makes the study drug/device.
- the following collaborators at other institutions that are involved with the study and not affiliated with the UT IRB: Mayo Clinic and Wake Forest University Medical Center
- the Barshop Institute's Claude D. Pepper Center Data and Safety Monitoring Board (DSMB) - the committee that checks the study data on an ongoing basis, to determine if the study 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 Research offices at [the University of Texas Health Science Center at San Antonio, University Health System (UHS).
- the Food and Drug Administration (FDA) and other U.S. and international governmental regulatory agencies involved in overseeing drug or device research

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 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.

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 premiums;
- 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. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the UT Health San Antonio 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 **Mitzi Gonzales, PhD or Dean L. Kellogg, Jr, MD, PhD, UT Health San Antonio, 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.
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?

By signing this form, you agree to let us use and disclose your health information for purposes of the study until 02-28-2030. This permission to use your personal health information expires on the date noted above.

Title of Study: Title of Study: Cognition, **A**ge, and **R**a**P**amycin **E**ffectiveness – **D**ownregulat**I**on of th**E m**Tor pathway (**CARPE DIEM**)

Contact Information – Who 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 contacts:
Haritha Katragadda can be reached at *210*-450-3167 during normal work hours.

. For medical concerns after hours please contact the research doctor on call at 210-258-4605.

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.

Title of Study: Title of Study: Cognition, **A**ge, and **R**a**P**amycin **E**ffectiveness – **D**ownregulat**I**on of th**E m**Tor pathway (**CARPE DIEM**)

Research Consent & HIPAA 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: _____

Surrogate Signature Section

- You are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You also authorize the collection, use and sharing of another person's protected health information as described in this form.

Printed Name of Subject	Signature of **Subject**, indicating Assent *(If incapable of signing, person obtaining consent should initial here)*	Date	Time (AM / PM)
Printed Name of Person Giving Consent & Authorization for Subject	Signature of Person Giving Consent & Authorization ☐Family Member/☐Guardian/☐Legally Authorized Representative	Date	Time (AM / PM)
Printed Name of Witness	Witness Signature	Date	Time (AM / PM)
Printed Name of Person Obtaining Consent & Authorization	Signature of Person Obtaining Consent & Authorization	Date	Time (AM / PM)