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Alzheimer's Disease Clinical Research at SIU Medicine

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FORWARD. FOR YOU.

Objectives

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- What is a clinical trial and why do people participate?
- Clinical trial terms
- Value of clinical trials
- Why do people participate in clinical trials?
- Important information to know about clinical trials
- What is involved in a clinical trial visit?
- Clinical trial inclusion/exclusion criteria
- Current state of Alzheimer’s research at SIU

What is a Clinical Trial?

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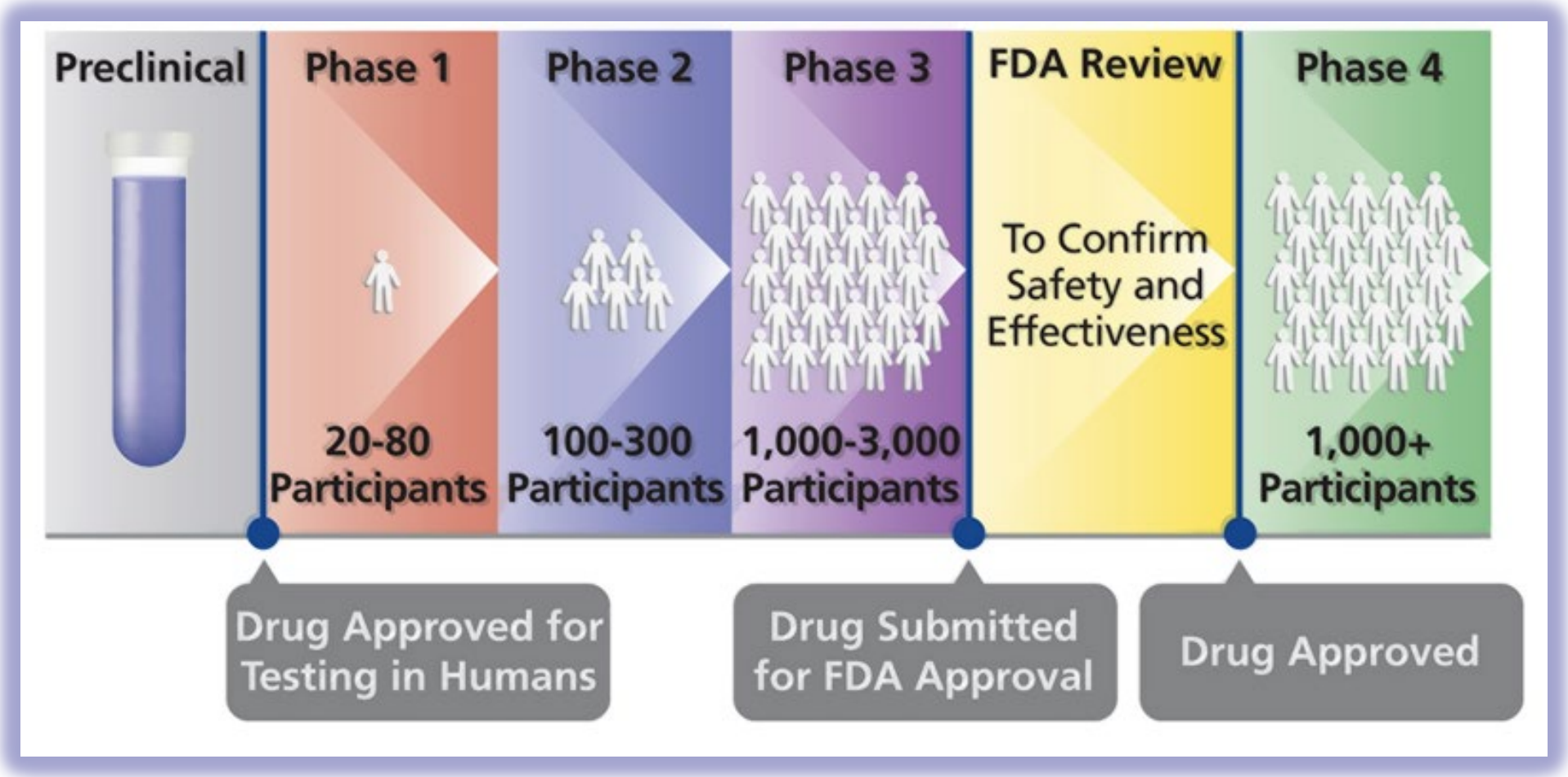
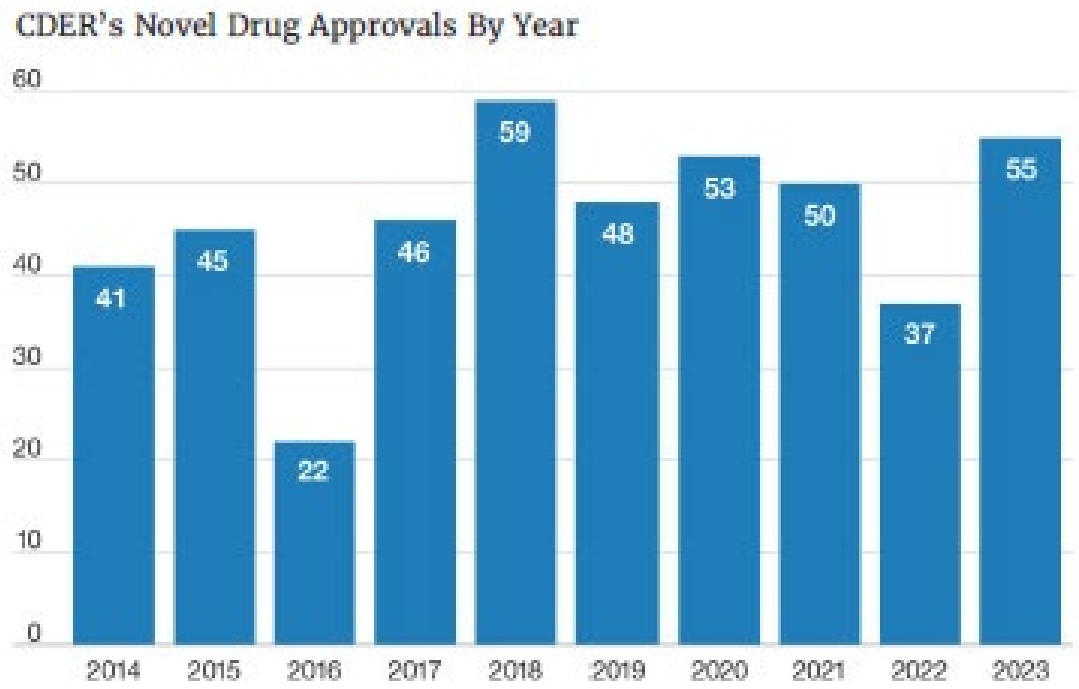
- A clinical trial is a research study that tests a medicine or therapy in people.
- Clinical research helps us answer questions about the medicine being studied.
- The medicines inside your medicine cabinet have one big thing in common; before reaching you, they went through years of research studies to ensure that they were safe for you to take.

CLINICAL TRIAL PHASES



https://ocra.fsu.edu/study-support-services/clinicaltrialsgov-administration/navigating-clinical-trials/

THE DRUG PIPELINE



www.fda.gov

- Success Rates of Drug Approvals by the FDA's Center for Drug Evaluation and Research
  - Average of 46 novel drug approvals per year
  - In 2023 16% of drugs were designated as a "Breakthrough Therapy"

Clinical Trial Terms

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THE CLINICAL RESEARCH TEAM

- Principal Investigator (PI)
- Sub-Investigator (Sub-I)
- Clinical Research Coordinator (CRC)
- Research Nurse
- Rater

TRIAL TYPES

- **Industry Sponsored –** Usually paid to be conducted by an industry organization (i.e. pharmaceutical company)
- **Investigator Initiated –** studies initiated and managed by an individual independent of a company (i.e. a physician or scientist)
- **Double-Blind** – both the study team and the subject are "blinded" to the treatment that is being given
- **Placebo-Controlled** – compares a treatment to a look-alike substance that includes no active treatment or drug
- **Open-Label** – A trial in which treatment is known to the study team and to the subject

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- **Adverse Event (AE)** – A change or medical event that occurs during a clinical trial. It may or may not be caused by the treatment received in the trial.
- **Serious Adverse Event (SAE)** – an event that results in any of the following outcomes
  - Is life-threatening
  - Causes death
  - Results in inpatient hospitalization
  - Congenital anomaly/birth defect
  - Causes disability or permanent damage

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Value of Clinical Trials and Why People Participate

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VALUE OF CLINICAL TRIALS

- New medical breakthroughs.
- Determine safety and effectiveness for the human body
- They may show that one treatment is effective over a previously used treatment
- Help reduce the burdens of disability and illness
- Developing cures!

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WHY DO PEOPLE PARTICPATE?

- Advancement of science and treatments
- To learn more about the disease or condition that they have
- To help others with the same condition or disease as them
- To obtain treatments before it is available to others
- More attention from physicians (frequent visits)
- Etc.

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Important Information to Know About Clinical Trials

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- Clinical trials are experiments.
- Risks and benefits are different for everyone.
- <u>Protecting the rights and welfare of humans is of utmost importance.</u>
- Everyone conducting a clinical trial has strict regulatory and ethical duties.
- There are independent reviewers that operate separate from the day-to-day conduct of research (Institutional Review Boards or Central IRBs)

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IS THERE PAYMENT FOR PARTICIPATION?

- For most trials, the study medicine is provided and visits are conducted at no cost to the participant.
- Some clinical trials pay or reimburse participants.
  - Payment for participation is not meant to entice subjects to participate.

Clinical Trial Visits

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STUDY PARTNER

- All of our trials that study memory loss require a study partner or caregiver that accompany the patient to each visit.
  - Spouse
  - Child
  - Friend
  - Legally Authorized Representative (LAR)

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SCHEDULE

Study Period	Screening/Baseline		At-Home Treatment		Unscheduled Visit[a]	Early Discontinuation Visit
Visit Timing	Day -42 to 0		6 weeks ± 7 days	12 weeks ± 7 days (end-of-trial) [b]		
Procedure	Screening[c] (up to 42 days before Day 0)	Baseline (Day 0)	Clinic Visit (Day 45)	Clinic Visit (Day 90)	Clinic Visit	Clinic Visit
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography information	X					
Full physical and neurological examination	X	X	X	X	X	X
Height, Weight, BMI	X					
Medical and psychiatric history (includes substance use)	X					
Urine pregnancy test (WOCBP only)	X	X	X	X	X	X
MMSE	X	X		X		
ADCS-CGIC		X[d]	X[e]	X[e]		
ADAS-Cog11		X	X	X		
ADCS-ADL		X	X	X		
DSST		X	X	X		
C-SSRS	X	X	X	X	X	X
Safety laboratory tests [c]	X	X	X	X	X	X
12-lead ECG	X	X	X	X		
Vital signs[d]	X	X	X	X	X	X

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Randomization		X				
Genetic sample (ApoE)		X				
Study intervention		X[a]	X[b]	X[d]		
Study intervention compliance review			X	X		
AE/SAE review	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
PK sampling		X		X		
Sampling for blood biomarkers		X		X		
24-hour phone follow-up		X	X	X	X	X

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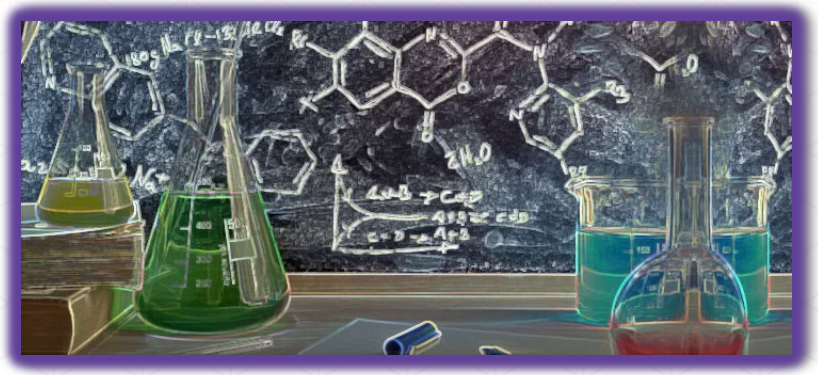
IMAGING

- MRI
- PET Scan
  - Amyloid
  - Tau
- DaT Scan

https://www.brainandlife.org/reports/advanced-imaging-can-now-detect-changes-that-foreshadow-alzheimers-years

LABORATORY TESTS

- Biomarker
- PK Sampling (pre and post drug)
- Safety labs
- Lumbar punctures (usually optional)



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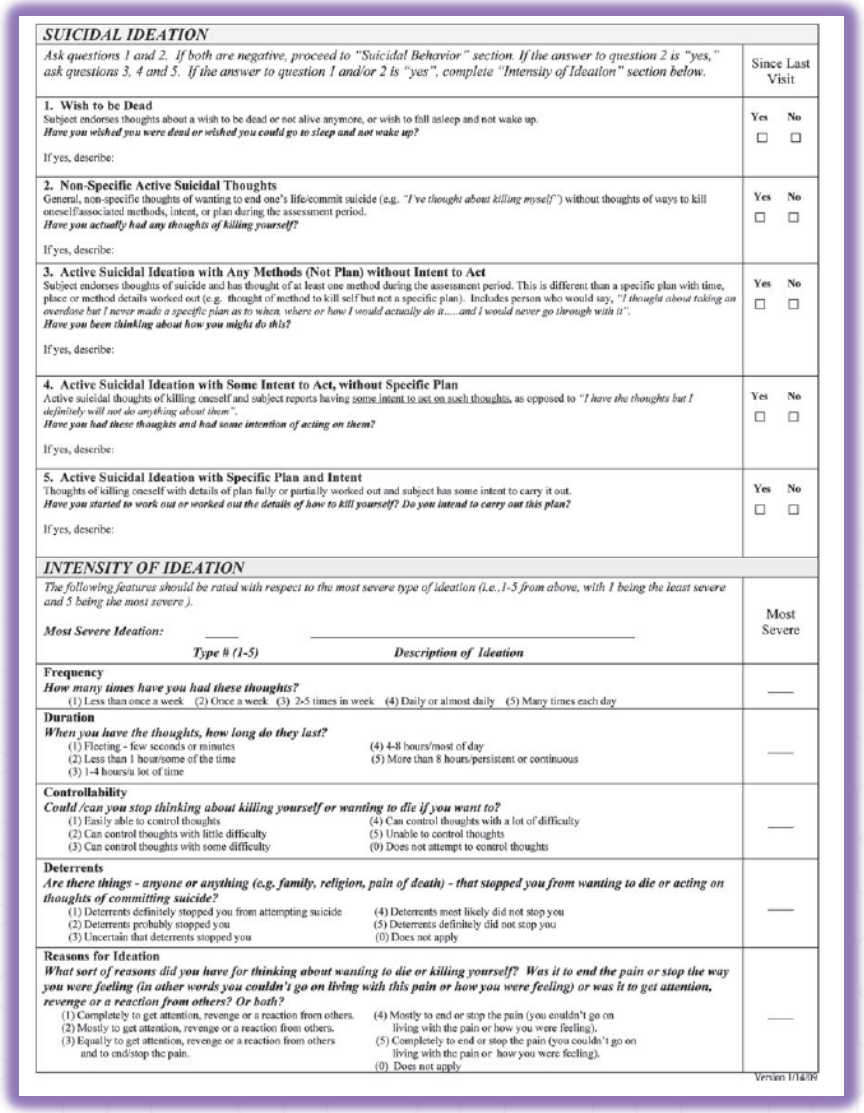
COGNITIVE TESTING

- Most clinical trials require the use of scales to help determine if the intervention being studied is effective.
- Scales commonly used in clinical trials:
  - Mini Mental State Exam (MMSE)
  - Alzheimer's Disease Assessment Scale (ADAS)
  - Montreal Cognitive Assessment (MoCA)
  - Repeatable Battery for Assessment of Neuropsychological Status (RBANS)
  - Clinical Dementia Rating (CDR)
- Caregiver Questionnaires
  - Neuropsychiatric Inventory (NPI)
  - Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)
  - Etc.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)



SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead — Yes ☐ No ☐
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

2. Non-Specific Active Suicidal Thoughts — Yes ☐ No ☐
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — Yes ☐ No ☐
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — Yes ☐ No ☐
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — Yes ☐ No ☐
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts? ____
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration
When you have the thoughts, how long do they last? ____
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability
Could /can you stop thinking about killing yourself or wanting to die if you want to? ____
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide? ____
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both? ____
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

Version 1/14/09

- Suicide risk assessment
  - Users of this tool ask people:
    - Whether and when they have thought about suicide (ideation)
    - What actions they have taken – and when – to prepare for suicide
    - Whether and when they attempted suicide or began a suicide attempt that was either interrupted by another person or stopped by their own volition

https://cssrs.columbia.edu/the-columbia-scale-c-ssrs/about-the-scale/

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OTHER LESS COMMONLY USED ASSESSMENTS

- Resource Utilization in Dementia – Lite Version (RUD-Lite)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Beck Depression Inventory (BDI)
- Etc.

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Inclusion/Exclusion Criteria

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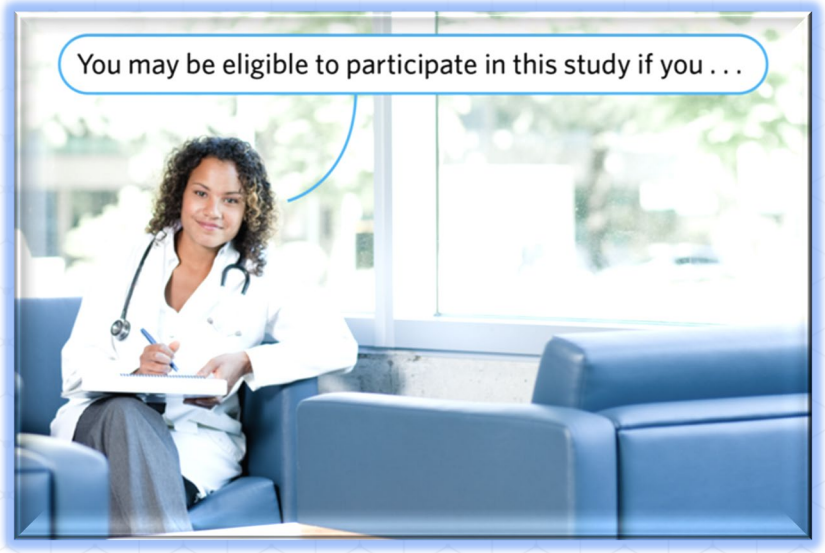
INCLUSION/EXCLUSION CRITERIA

- Inclusion criteria – characteristics prospective subjects must have if they want to be included in a study
  - Demographics
  - Medical History
- Exclusion criteria – Additional criteria that may interfere with the success of the study or increase risks for unfavorable outcomes



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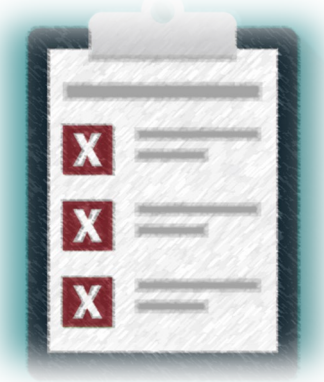
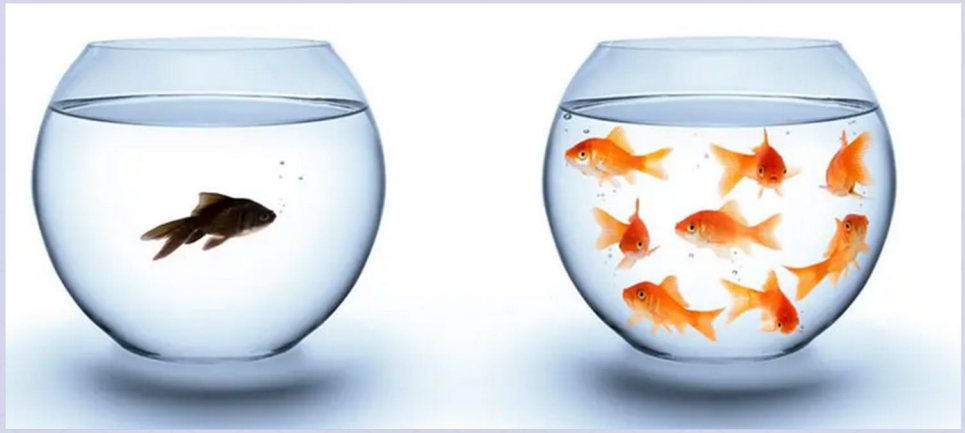
TYPICAL INCLUSION CRITERIA FOR ALZHEIMER'S TRIALS

- Age range (usually 55 to 85)
- Diagnosis of Alzheimer's disease or memory loss
- Generally in good health other than the illness being studied
- Caregiver is with the patient at least 10 hours a week and willing to accompany patients to all study visits
- Mini-Mental State Exam (MMSE)
  - Mild studies – score of 25-30
  - Moderate studies – score of 14-24
  - Severe studies – score of 0-13



EXCLUSION CRITERIA FOR ALZHEIMER'S TRIALS

- Inability to tolerate MRIs/PET scans
- BMI outside of range
- Poor venous access
- Serious medical conditions (that in the opinion of the PI preclude the patient's safe participation)
- Prohibited medications
- Recently alcohol and tobacco use



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THE MOST IMPORTANT THING YOU NEED TO KNOW ABOUT CLINICAL TRIALS

- Participants can withdraw from a clinical trial at any time for any reason.
  - Ongoing Consent
  - Keep subjects and caregivers updated on risks that may change their willingness to participate
  - Remind the patient and caregiver of the study goals and objectives

Current Clinical Trials

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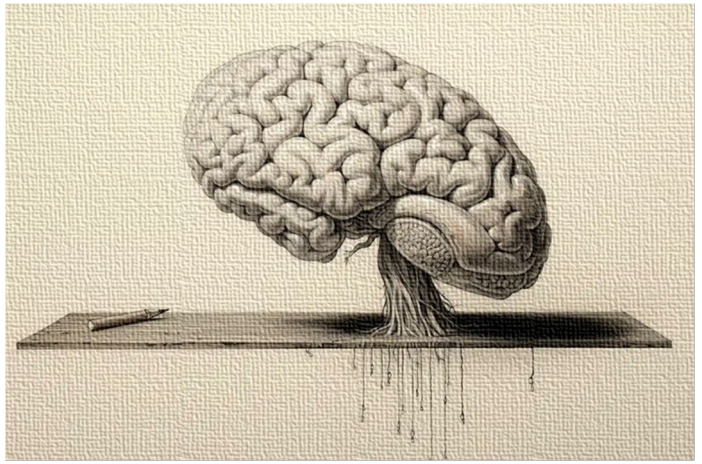
CURRENT TRIALS IN THE NEUROLOGY AND NEUROSURGERY DEPARTMENTS AT SIU MEDICINE

Alzheimer's Disease – 4 open (7 Pending)
Parkinson's Disease and Movement disorders – 1 open
Neurocritical Care – 0 open (1 Pending)
Neurosurgery – 0 open (1 Pending)
Neuromuscular – 1 open
Seizure – 5 open (1 pending)
Stroke – 1 open



https://www.siumed.edu/neuro/research.html

If you would like to enroll in our clinical trials, please complete the patient survey located at: https://www.siumed.edu/ccr/enroll-clinical-trial

ONGOING - CLOSED TO ENROLLMENT– LIFT AD OPEN-LABEL EXTENSION (ATH-1017-AD-0203)

- Open-Label Extension (OLE) – only subjects who have completed the 26 week blinded portion of study were eligible to *roll-over* into the OLE.
- The OLE is not blinded – no more possibility of placebo.
- This period runs 18 months
- Subjects will receive a daily subcutaneous injection.
- You do not have to enroll in the OLE – it is optional.

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ONGOING – CLOSED TO ENROLLMENT
LILLY I5T-MC-AACI (TRAILBLAZER 2)

- Assessment of safety, tolerability, and efficacy of donanemab in early symptomatic Alzheimer's disease.
- Phase 3 – disease modifying treatment
- Aims to slow down memory and thinking decline in early-stage AD
- Infusion every four weeks at Simmons Cancer Institute
- 78 week initial study treatment period followed by a 78 week extension treatment period, up to 44 week post-treatment period
- 50:50 chance of receiving drug initial study treatment period

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- June 2021 - Lilly's donanemab receives U.S. FDA's Breakthrough Therapy designation for treatment of Alzheimer's disease.

https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-receives-us-fdas-breakthrough-therapy

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OPEN TO ENROLLMENT– ADC-061-BENFO

- Phase 2A-2B randomized, randomized double-blind, placebo-controlled trial to evaluate the safety and efficacy of Benfotiamine in patients with early Alzheimer's disease
- Mechanism of action raises blood thiamine levels. In AD, it addresses and treats a well characterized tissue thiamine deficiency and related changes in glucose metabolism as well as post-translational modifications that are linked to thiamine dependent processes including neuroinflammation, abnormalities of advanced glycation end products, plaques and tangles, and downstream neurodegeneration

ADCS
Alzheimer's Disease Cooperative Study

NIH

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OPEN TO ENROLLMENT– ADC-061-BENFO

- 72 week treatment duration
- Will randomize 406 total participants to a 1:1:1 ratio of oral medication (1200 mg/day, 600 mg/day, or placebo)
- Currently, there is not an Open-label portion, but this may change in the future
- Key inclusion – 50-89 years old, MMSE of 20-30, MoCA of <26, positive plasma AD biomarker signature
- Sara Boarman, BS, is the Lead Coordinator for this study – you can reach her at sboarman93@siumed.edu or 217.545.6829.

ADCS
Alzheimer's Disease Cooperative Study

NIH

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OPEN TO ENROLLMENT– CAREGIVER STUDY

- Caregiver characteristics that may be associated with the optimal care of patients with AD – investigates characteristics that may predict changes in caregiving over the course of 3 years
- Investigator initiated – no treatment
- We hope to enroll 217 couples – patients and their spouse or partner (not children)
- Couples will have a one-time visit in the clinic, questionnaires mailed to them every 6 months, phone call interview every 2 months
- Key inclusion – MMSE of <24, patient and spouse at least 70 years old, patient must live at home, not in a care facility
- Stephanie Kohlrus, is the contact for this study – and can be reached at skohlrus@siumed.edu or 217.545.3013.

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Upcoming Clinical Trials

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- 2 Alzheimer's trials in start-up phases
  - 1 – estimated recruitment time is Summer 2024
  - 1 – estimated recruitment time is Fall 2024

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EARLY SUMMER 2024…

- Phase 2
- Tau Monoclonal Antibody – targets early AD
- 76-week double-blind treatment period and an 11-week safety follow-up
- 4:3:3 ratio to receive placebo, 1400 mg, or 4200 mg by infusion every 4 weeks
- Ages 50-80, MMSE of 22-30, evidence of AD pathology confirmed by PET scan, etc.

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ESTIMATED FALL 2024…

- Phase 3
- Mechanism of action is to target and remove amyloid plaques
- 76-week treatment period and 52-week extension period
- 1:1 ratio to receive placebo or 2300 mg IV infusion every 12 weeks for 3 doses
- Ages 60-85, MMSE 20-28, biomarker consistent with presence of brain amyloid pathology, positive tau PET, etc.

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LOOKING FOR CLINICAL TRIALS

- http://clinicaltrials.gov or search Clinical Trials.gov
- This is a worldwide database of privately and publicly funded clinical trials.
- As of March 2024, there are over 480,000 research studies in all 50 states and 221 countries.
  - Search for Alzheimer's disease turned up over 3,000 results.
  - Search for Dementia turned up over 5,000 results.

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ALZHEIMER'S NEUROLOGY CLINICAL RESEARCH TEAM

Jennifer Arnold, MD, PhD – Principal Investigator
Tom Ala, MD – Principal Investigator/Sub-Investigator
Cindy Womack, DNP – Sub-Investigator
Amber Fifer, PharmD, ACRP-CP – Research Assistant Professor of Neurology and Psychiatry
Andre Catalano, PharmD, MBA – Research Assistant Professor of Neurology
Stephanie Kohlrus, BA, CCRP – Senior Clinical Research Coordinator
Ann Jirmasek, BS, MA, LPC, NCC – Rater
Amy Richey, LPN – Rater
Sara Boarman, BS – Clinical Research Coordinator
Rylee Manka, BA – Clinical Research Specialist
Mary (Missy) Cartwright, RN, BSN – Research Nurse
Megan Meinke, MD – Post-Doctoral Fellow

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References

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Questions?

Alzheimer's ... it is a barren disease, as empty and lifeless as a desert. It is a thief of hearts and souls and memories.

Nicholas Sparks

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