ARCADIA-CSI Protocol Training

An ancillary study to the ARCADIA trial

Joe Broderick, Christy Cassarly, George Howard, Stephanie Kemp, Faria Khattak, Maarten Lansberg, Ron Lazar, Terina Myers, Kevin Sheth, David Tirschwell

ARCADIA•CSI
Cognition & Silent Infarcts
Thank you!

This slide-set provides you with a very brief 😊 investigator training for ARCADIA-CSI, an ancillary study to the ARCADIA trial.

Thank you in advance for taking the time to review the slides.

Once you have viewed them, please fill out the Training Attestation Form that will be posted on Training Campus (webdcu.musc.edu/campus)
The One-Minute Summary
Everything participants (and investigators) need to know

ARCADIA-CSI is a simple add-on study that won’t take much of your time. If you sign up for ARCADIA-CSI, you will:

1. Undergo annual cognitive assessments by telephone (22 minutes) during your participation in the ARCADIA study
2. Undergo a brief (15-30 minute) MRI at the end of your participation in the ARCADIA study
Background

ARCADIA Parent Trial
- Apixaban vs. aspirin for secondary stroke prevention
- 1100 patients with cryptogenic stroke and atrial cardiopathy
- 2.5 years of enrollment; 1.5-4 (median 3) years of follow-up
- No data on cognitive and neuroimaging outcomes

ARCADIA-CSI Ancillary Study
- Adds key cognitive and neuroimaging outcomes
- Integrates seamlessly with ARCADIA study visits
- Low patient / investigator burden
- Potentially high impact
Post-stroke Cognitive Decline

- Cognitive decline accelerates after stroke
- Stroke doubles the risk of developing dementia
- 30% prevalence of dementia post-stroke

Levine. JAMA 2015
Silent Infarcts

- Common
  - Prevalence 30-50%
  - Incidence up to 19% annually after TIA
- Accelerate cognitive decline
- Double risk of dementia
- Secondary stroke prevention studies have not focused on preventing silent infarcts and cognitive decline

Vermeer. NEJM 2003
Vermeer. Lancet 2007
Aims

1. To determine the effect of anticoagulation (vs antiplatelet therapy) on the slope of cognitive function after stroke (primary clinical outcome)

2. To determine the effect of anticoagulation (vs antiplatelet therapy) on the incidence of silent infarcts after stroke (primary imaging outcome)
Inclusion / Exclusion Criteria

**Inclusion Criteria**
- Randomized in ARCADIA
- Able to undergo MRI
- Able to provide self-consent for ARCADIA-CSI in English
- Score of 0-1 on NIHSS language at time of ARCADIA-CSI enrollment

**Exclusion Criteria**
- Diagnosis of dementia
- Active illicit drug use
- Psychiatric admission or ECT for major depression within last two years
- Education less than 8 years
- History of traumatic brain injury with loss of consciousness of more than 30 minutes
- ARCADIA study drug permanently discontinued
Randomization

Index stroke
Baseline MRI

Enrollment
Randomization

f/u visit

Baseline Neurocog test

Baseline MRI – only if no clinical MRI at time of index stroke

1 yr ± 3 months

f/u visit

Year 1: Neurocog test

1 yr ± 30 days

f/u visit

Year 2: Neurocog test

1 yr ± 30 days

f/u visit

Year 3: Neurocog test

1 yr ± 30 days

f/u visit

Year 4 (or exit from ARCADIA whichever occurs earlier): Neurocog test + MRI

• >3 months after index stroke
• ASAP after ARCADIA-CSI consent (when possible on same day)
• No more than 3 months after ARCADIA-CSI consent

ARCADIA-CSI Enrollment (can occur anytime after ARCADIA randomization)
Annual neurocognitive test

- 22 minute phone battery
- Covers 4 cognitive domains relevant to post-stroke cognition
- Demonstrated sensitivity to cognitive change.
- Centrally administered by trained interviewers to reduce interrater variability
- Tested in >30,000 subjects in REGARDS and CREST-2 studies
Study End MRI

- Simple protocol with standard sequences
- Preferably on 3T (1.5T acceptable)
- 15 minute scanning time
- 30 minutes total time
- MUSC will collect and store the images
- Stanford Radiology Core will analyze the images:
  - New Silent infarcts
  - White matter disease burden
  - Micro-hemorrhages
Enrollment / Baseline

Consent

MRI

Neurocognitive testing
General Consenting Guidelines

• The research subject should have an opportunity to read the consent and ask questions about anything they do not understand.
• Enough time should be given to the subject to consider whether or not to participate in the study
• The subject should know that participation in the study is voluntary and that he/she may stop the study at any time
When do ARCADIA subjects become eligible for enrollment in ARCADIA-CSI?

- When a site becomes active for ARCADIA·CSI, all patients already randomized in ARCADIA who meet the ARCADIA·CSI eligibility criteria, immediately become eligible for enrollment in ARCADIA·CSI.
- Additional patients will become eligible as the site randomizes new ARCADIA patients.
Timing of Consent

• Scenario 1: Patients who are already randomized in ARCADIA and on study drug when site becomes ARCADIA-CSI active
  • If next ARCADIA clinic visit ≤ 3 months, obtain consent during that visit
  • If next ARCADIA clinic visit > 3 months, schedule a dedicated visit for ARCADIA-CSI consent

ARCADIA-CSI consent should be obtained as soon as feasible after the patient meets ARCADIA-CSI eligibility criteria (goal is within 2 weeks and not to exceed 3 months after a patient becomes ARCADIA-CSI eligible)
Timing of Consent

• Scenario 1: Patients who are already randomized in ARCADIA and on study drug when site becomes ARCADIA-CSI active
  • If next ARCADIA clinic visit ≤ 3months, obtain consent during that visit
  • If next ARCADIA clinic visit > 3months, schedule a dedicated visit for ARCADIA-CSI consent

• Scenario 2: Patient who are consented and randomized in ARCADIA after a site becomes ARCADIA-CSI active
  • Obtain ARCADIA-CSI consent during randomization visit
The goal is to make ARCADIA-CSI as easy as possible on the subjects. In order to achieve that:

- **Do** minimize patients’ time commitment by combining ARCADIA and ARCADIA-CSI visits whenever this is convenient to the patient
- **Do** give patients the option to return for a dedicated ARCADIA-CSI visit if a combined visit would be too time-consuming or tiring.
- **Do not** ‘pile on so much’ in a single visit that it would negatively impact the parent trial and/or ARCADIA-CSI
ARCADIA subjects on study drug

Introduce study and if interested, reserve time for cognitive assessment after upcoming clinic visit

Site activation for ARCADIA-CSI

Scheduled ARCADIA visit
Introduce study
• Obtain consent
• Attempt same day cognitive test

Obtain consent
• Perform cognitive test at visit

Scheduled ARCADIA visit

ARCADIA•CSI
Cognition & Silent Infections
Introduce study & schedule appointment

Schedule cognitive test at home if same day test is not possible

Scheduled ARCADIA visit too far out
Introduce study & schedule appointment

Obtain consent
Perform cognitive test

Dedicated ARCADIA-CSI enrollment visit

New ARCADIA consent

Participant meets randomization criteria

- Schedule randomization visit
- Introduce ARCADIA-CSI
Randomize in ARCADIA
Obtain ARCADIA-CSI consent
Perform cognitive test
Patient had standard-of-care MRI post index stroke

Yes

Upload MRI to WebDCU

Radiology Core Lab Review

You will be notified if:
- MRI quality insufficient
- MRI quality insufficient or Unexpected findings on Research MRI

No

Obtain Research MRI

≤ 2 weeks of ARCADIA-CSI enrollment
Transfer of MR Images: Aspera®

- **What is Aspera®?** Aspera® is the platform by which imaging will be uploaded into WebDCU.
- **How to test Aspera®?** Download and test Aspera® before starting to enroll subjects.
- **How to use Aspera®?** Upload an MRI through a link in the subject’s eCRF.
- **Need more info?** Detailed instructions will be in the StrokeNet WebDCU User Manual that is posted in the ARCADIA-CSI Toolbox folder on WebDCU.
Baseline Neurocognitive Testing

Baseline cognitive testing should be obtained:

• At least 3 months after the index stroke
• As soon as feasible (and no more than 3 months) after the patient signs ARCADIA·CSI consent
• Preferably on the day of ARCADIA·CSI consent during a routine ARCADIA visit
Please, please, pretty please .....

• Do all you can to **obtain the neurocognitive phone assessment in clinic**

• Typically obtain neurocognitive testing following a routine ARCADIA study visit to minimize time-burden.

• If patient prefers, OK to schedule testing during a separate dedicated ARCADIA-CSI visit

• If assessment during clinic is not possible, we can call the participant at home but this not preferred because it often results in missing data.
Scheduling of Neurocognitive Testing

Detailed scheduling instructions are listed in the ARCADIA-CSI Manual of Procedures, posted in the ARCADIA-CSI toolbox on WebDCU

To get started click [this link](https://example.com) or follow the link located on the ARCADIA-CSI WebDCU page
ARCARDIA-CSI Reservation Form

All times listed are Central Standard Time. Please make sure you select the correct time.

- Please correct any errors below. Make sure to select a schedule date and time.

Participant First Name

Test

Participant Last Name

Test

Primary Phone of Participant (10 digits)

0123456789

Secondary Phone of Participant (10 digits)

0123456789

ARCADIA Subject ID

1234

Date of Birth

03/28/1971
Visit
Baseline

Communication Type
Site will call the SRU

Click calendar button below to reserve a day/time for cognitive testing. Please note that all times are Central Standard Time which is two hours after PST, one hour after MST and one hour before EST. Please make sure you select the correct time.

Calendar

Booked Date
09/23/2019

Scheduled Time
8:00 AM - 8:30 AM

Booked Message

Make Reservation
Dialing in for a Cognitive Assessment

**Step 1**
Dial 205.934.2462
• Please make sure you have completed a reservation.

**Step 2**
Talk to a live person!!
• You will get a live person when you dial in for the assessment. This person will then transfer and connect the call to the interviewer.

**Step 3**
Share your experience
• Please contact your friendly UAB team (Terina Myers) if you have any questions, complaints or ideas! We need your input to know how we are doing.
Annual Follow-Up Visits

Neurocognitive testing
Neurocognitive Follow-Up Visits

1. The first follow-up visit will be scheduled to coincide with a routine ARCADIA clinic visit (9-15 months after the baseline cognitive evaluation).

2. Subsequent evaluations are scheduled every 12 months (±30 days) thereafter to coincide with routine ARCADIA clinic visits.

3. Six weeks prior to the due date of each neurocognitive evaluation, the local ARCADIA·CSI study coordinator will be reminded by e-mail.

4. Coordinator will schedule a time for the neurocognitive evaluation on the UAB Cognitive Reservation System.
Final Visit

MRI

Neurocognitive testing
End of Study MRI

• If the patient exits ARCADIA·CSI because (s)he reaches final ARCADIA follow-up, a dedicated research MRI scan will be scheduled on the day ($\pm$ 2 weeks) that study drug is discontinued.

• If the patient exits ARCADIA·CSI because (s)he has a clinical stroke, an MRI will be obtained as soon as possible after the stroke, typically during hospital admission. If a clinical MRI has been obtained, it will serve as the final study MRI if it meets the MRI requirements.
MRI Protocol

- T1 (3D)
- FLAIR (3D)
- DWI / ADC
- GRE
- SWI / SWAN (optional)
End of Study Neurocognitive Testing

• If the patient exits ARCADIA·CSI because (s)he reaches final ARCADIA follow-up, a final cognitive evaluation will be scheduled at the time of study-drug discontinuation (± 2 weeks, preferably during the final ARCADIA visit) if ≥6 months have elapsed since the previous cognitive evaluation.

• If the patient exits the study because (s)he has a recurrent stroke or dies, the most recent neurocognitive evaluation will serve as the final cognitive assessment.
Impact of ARCADIA-CST

- Will provide large scale data on the effect of anticoagulation on silent infarction and cognitive decline
- Will yield results that are important regardless of the results of the parent trial
- Will provide deeper insight in the incidence of silent infarcts, the slope of post-stroke cognitive decline, and the relationship between them
- Will set the stage for future trials to prevent silent infarction and post-stroke cognitive decline
FAQ - MRI

Q. If baseline MRI is obtained on 1.5T, what is the preference for the final MRI?

1.5T. Try to do the follow-up scan on the same scanner as the baseline but if not possible, at least try to match scanner strength at baseline and follow-up.

Q. Is there a payment for the MRI scan?

Yes, the study covers the cost for each dedicated research MRI scan. The payment schedule for ARCADIA-CSI is listed on the StrokeNet website.

Q. Do MRI scans need to be de-identified prior to upload through ASPERA?

Yes, detailed instructions are in the WebDCU User Manual in the ARCADIA-CSI Toolbox on WebDCU.

Q. Are patients with claustrophobia eligible?

It depends on the severity of their claustrophobia. As long as they can undergo a brief (15-minute) MRI scan, they are eligible.

Q. Do MRI scans need to be read by a local radiologist?

The study does not require a read by a local radiologist of MRI scans that are obtained purely for research (and paid for by the study). The scan will be reviewed by a neuroradiologist at the core-lab and you will be informed of any significant incidental findings. However, it is possible that your institution requires a local read in addition to the central read by a neuroradiologist at the core lab.
FAQ

Q. What is the link to the Cognitive Testing Reservation System?  
   https://reservation.soph.uab.edu/Arcadia/Account/Login

Q. Can we mail the ARCADIA-CSI consent form to eligible ARCADIA participants?  
   Yes, but it is not yet cIRB approved. We will inform you by email when it is cIRB approved. At that time you should check with your local IRB if they also allow mailing of the consent.

Q. Is the subject ID number the same for ARCADIA and ARCADIA-CSI?  
   Yes

Q. Can I get a copy of these slides?  
   Yes, they are available on Training Campus
Other Questions?

• WebDCU  Faria Khattak (khattak@musc.edu)
• WebDCU Hotline  (866) 50-2016
• MRI  Max Wintermark (mwinterm@stanford.edu)
• Cognitive testing  Terina Myers (tmyers@uabmc.edu)
  (205) 996-5592
• Contract  Wren Hanson (hansonwm@ucmail.uc.edu)
• IRB  Tashia Harris (herndotl@ucmail.uc.edu)
• Enrollment / Eligibility  Maarten Lansberg (lansberg@stanford.edu)