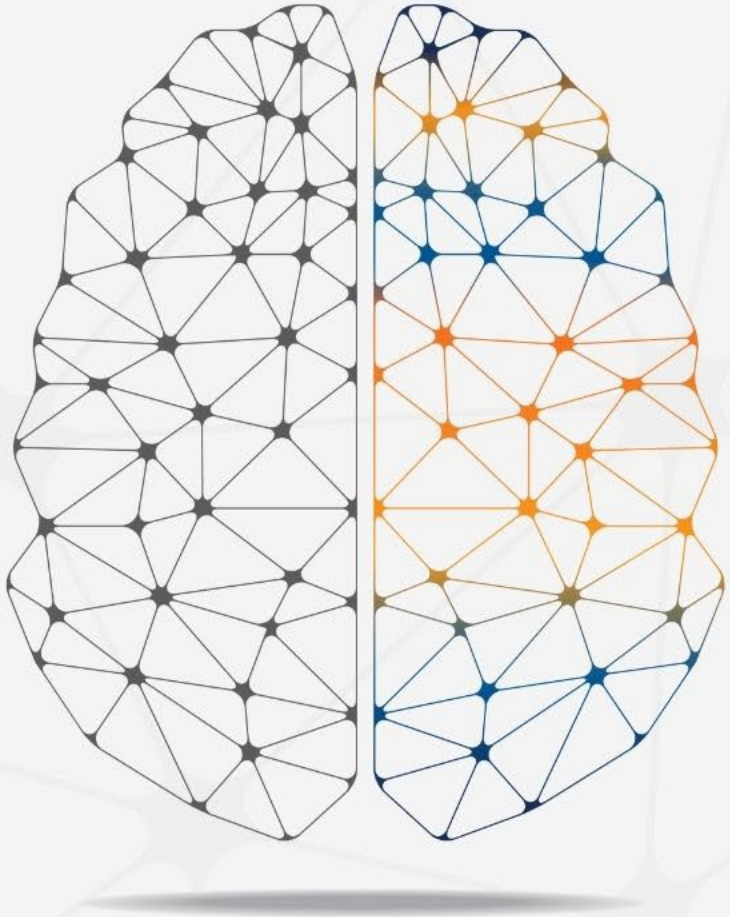


CAPTIVA

NIH StrokeNet RCC Coordinator Webinar

October 26, 2022

COLLABORATORS

National Institute of Neurological Disorders and Stroke

Clinical Coordinating Center

National Coordinating Center

National Data & Risk Factor Management Centers

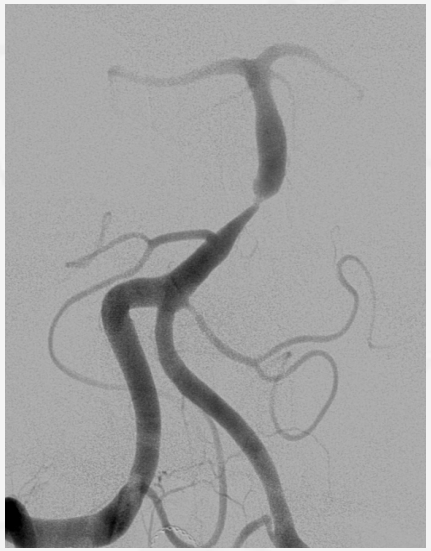
Rivaroxaban & Placebo Funding

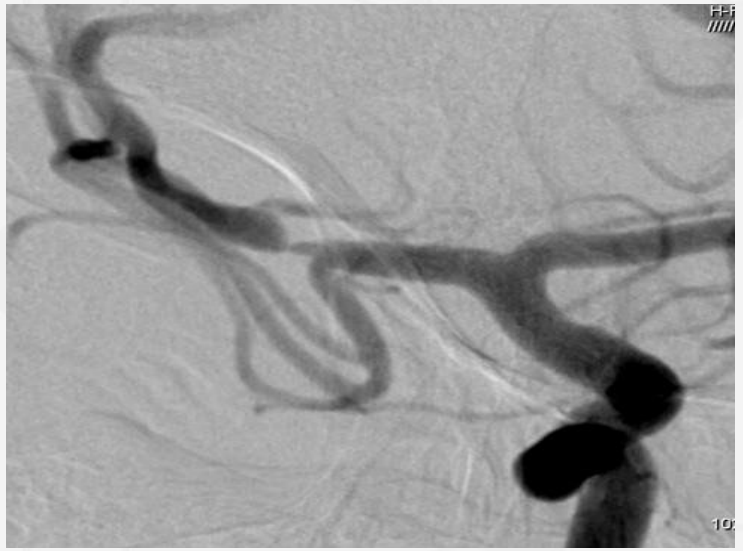
Ticagrelor

AGENDA

I. Welcome/Introductions
II. Scientific Overview
III. Site Readiness Calls
IV. Common Questions
V. Paxlovid
VI. Unblinding
VII. IRB/CTA/DOA/Regulatory Docs
VIII. Fellows Participation
IX. Questions

World-Wide Burden of Intracranial Atherosclerosis





- USA: Important cause of stroke (8-10%), especially in Blacks (15-29%), Hispanics, and Asians
- China 33–50%, Thailand 47%, S. Korea 56%
- Based on ethnic and racial make-up of world population, one of the most common cause of stroke
- Particularly High Risk of Recurrent Stroke

Rationale for CAPTIVA

SAMMPRIS *Chimowitz et al, NEJM 2011; Derdeyn et al, Lancet 2014*

	PTAS (n=224)	Medical (n=227)	
Primary Endpoint: stroke or death <30d, ischemic stroke in territory >30d, stroke or death <30d of revascularization procedure	23%	15%	P=0.02
Primary Endpoint beyond 30d	10%	10%	P=NS
Any stroke	26%	19%	P=0.046
Major hemorrhage	13%	4%	P=0.0009

Interpretation The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

Main Criticisms of SAMMPRIS

- Wingspan Stent System
- Stenting allowed within 7 days of stroke or TIA
- Included branch artery (perforator) territory infarcts
- Inexperience of US Interventionists

VISSIT Trial

Balloon-expandable Pharos stent
Zaidat et al. JAMA 2015

- Similar entrance criteria to SAMMPRIS
- Similar medical management (except LDLc < 100 mg/dl, no lifestyle intervention)
- Included sites in Europe and China
- Enrollment stopped early (112 patients)
- Peri-procedural (30-day) stroke - 25.8%
  - 17.2% ischemic stroke, 8.6% hemorrhagic stroke
- Any stroke within 30 days or stroke in terr. to 1 yr: **43.1%** in stenting group, **9.4%** in medical group) ----> NNH = 3.

CASSISS Trial

JAMA®

QUESTION In transient ischemic attack (TIA) or ischemic stroke due to intracranial atherosclerotic stenosis, does angioplasty and stenting ≥3 weeks after the index event along with standard medical therapy reduce the risk of stroke or death vs medical therapy alone?

CONCLUSION This randomized clinical trial's findings did not support the addition of percutaneous transluminal angioplasty and stenting to medical therapy for the treatment of patients with symptomatic severe intracranial atherosclerotic stenosis.

POPULATION

263 Men
95 Women

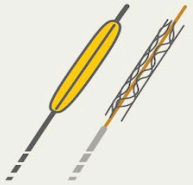
Adults with TIA or nondisabling ischemic stroke attributed to severe intracranial stenosis

Mean age: **56.3** years

LOCATIONS

8
Centers in China

INTERVENTION



380 Patients randomized
358 Patients analyzed

176

Stenting plus medical therapy
Percutaneous transluminal angioplasty and stenting plus medical therapy

182

Medical therapy alone
Aspirin and clopidogrel for 90 days (single antiplatelet therapy thereafter) and control of stroke risk factors

PRIMARY OUTCOME

Composite of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year

FINDINGS

Risk of stroke or death

Stenting plus medical therapy
8.0% (14 of 176 patients)

Medical therapy alone
7.2% (13 of 181 patients)

There was no significant difference between groups:

Between-group difference, 0.4%
(95% CI, −5.0% to 5.9%)

Hazard ratio, 1.10
(95% CI, 0.52 to 2.35)

Gao P, Wang T, Wang D, et al; CASSISS Trial Investigators. Effect of stenting plus medical therapy vs medical therapy alone on risk of stroke and death in patients with symptomatic intracranial stenosis: the CASSISS randomized clinical trial. *JAMA*. Published August 9, 2022. doi:10.1001/jama.2022.12000

Rationale for CAPTIVA

- Compelling data for clopidogrel + aspirin *(POINT and CHANCE)*
- Ticagrelor + aspirin *(THALES and PRINCE)*
- Low dose rivaroxaban + aspirin *(COMPASS and COMMANDER HF)*

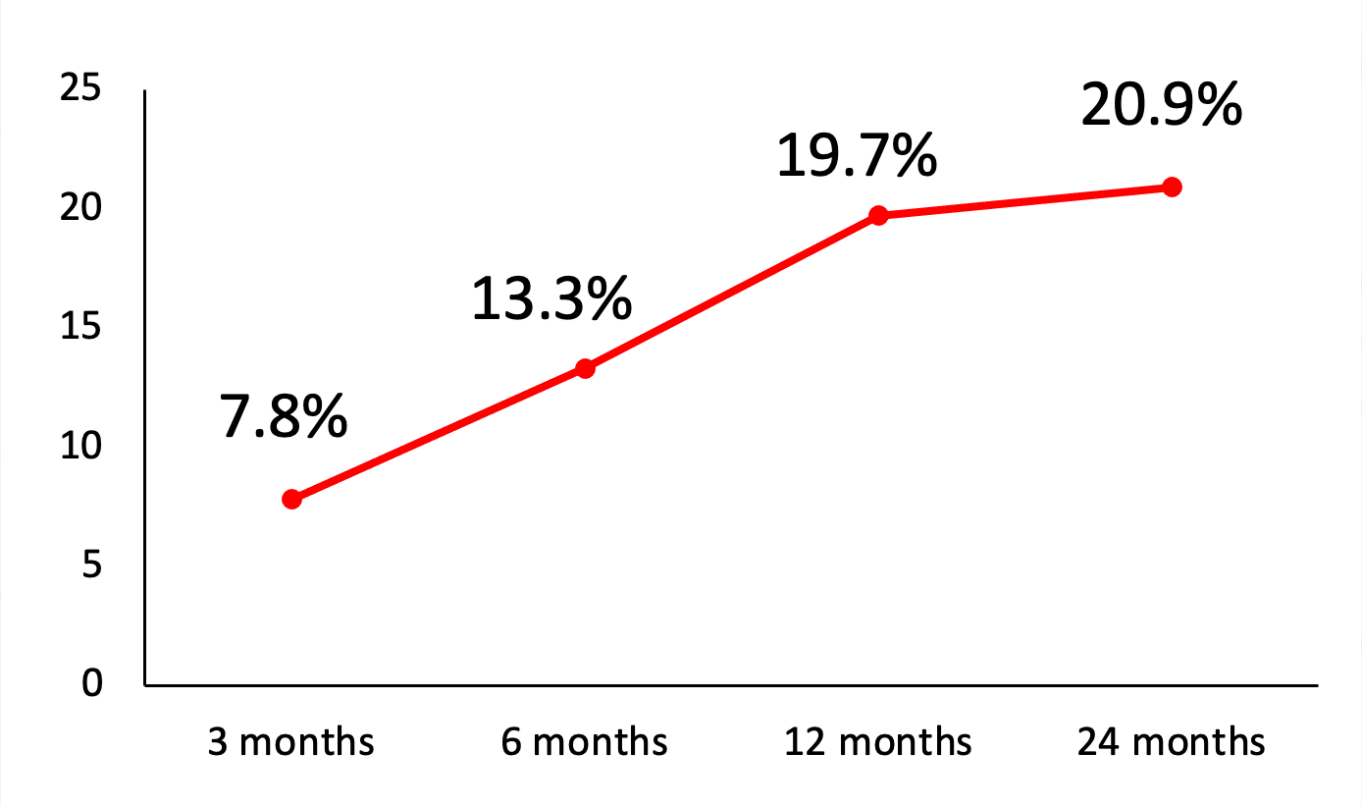
Study Design

- 3-arm, double blind Phase III Trial
  - *Ticagrelor* (180 mg loading dose, then 90 mg twice daily), or
  - *Low Dose Rivaroxaban* (2.5 mg twice daily), or
  - *Clopidogrel* (600 mg loading dose, then 75 mg daily).

- All subjects will also be treated with aspirin (81mg daily) and receive intensive risk factor management (Intervent)

Duration of Antithrombotic Therapy in CAPTIVA

- SAMMPRIS: rates of recurrent ischemic stroke in territory of stenotic artery more than doubled from 3 to 12 months
  SAMMPRIS medical arm subjects who qualified by symptomatic infarct (Lynn, personal communication)



Duration of Antithrombotic Therapy cont.

- In SAMMPRIS, 50 medical arm subjects took clopidogrel + ASA longer than 3 months for cardiac reasons *Abdul Rahman L, et al. JSCVD 2020*

	No clopidogrel beyond 3 months N=158 medical subjects	**Clopidogrel + ASA >3 months N=50 medical subjects**
Stroke >3 months	10.8%	6.0%
Major Hemorrhage >3 months	2.5%	4.0%

1683 subjects with symptomatic infarct due to 70-99% sICAS

1 year treatment & follow-up

First Stage: Safety Analysis

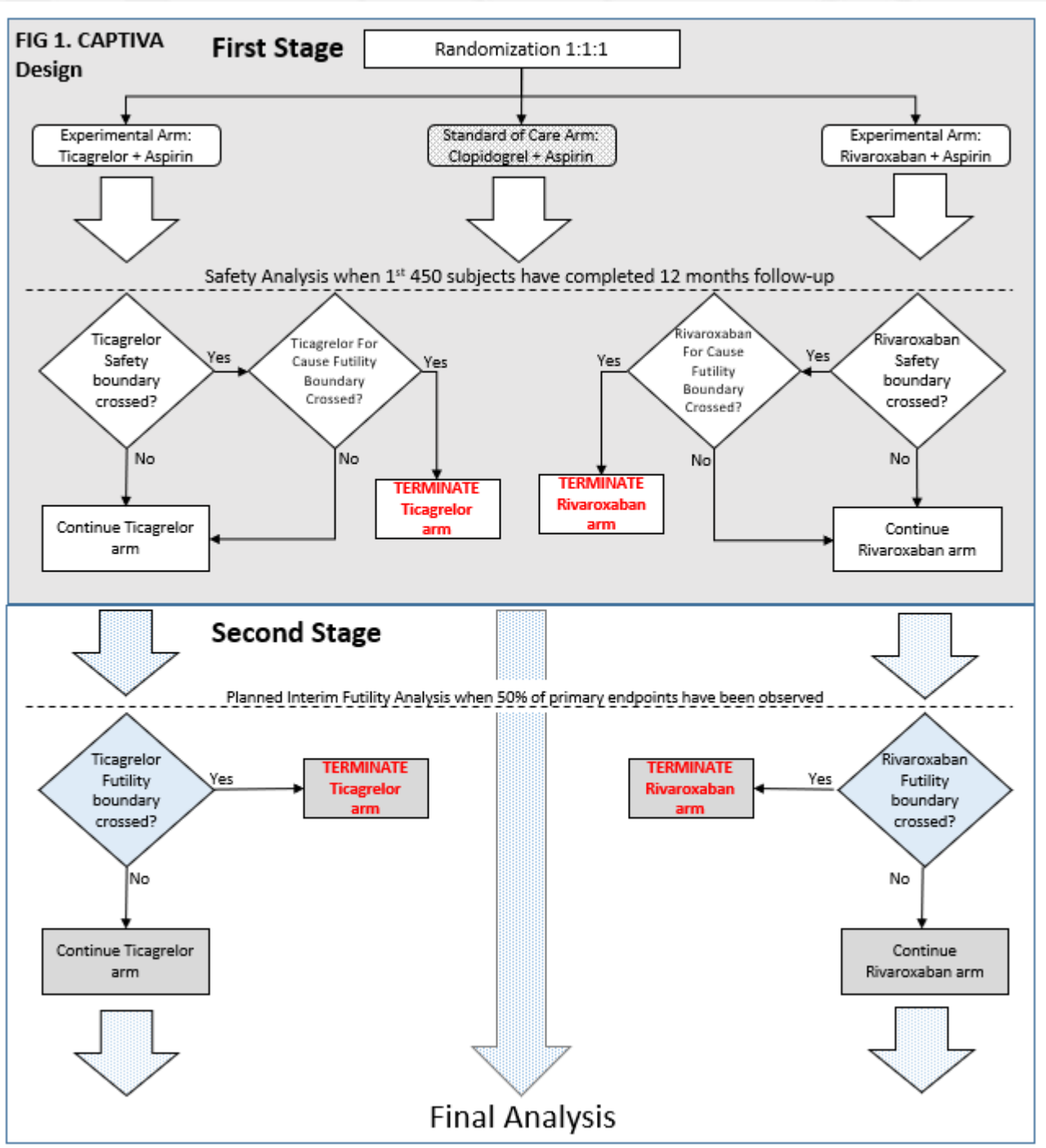
1. Parenchymal brain hemorrhage (ICH)
2. Major non-ICH hemorrhage (ISTH criteria Schulman et al, JTH 2005)

Second Stage: Primary Endpoint

1. Ischemic stroke (AHA definition Sacco et al, Stroke 2013)
2. ICH
3. Vascular death

Secondary Endpoints

1. Composite of the primary endpoint and MI
2. All stroke (ischemic and ICH)
3. Ischemic Stroke
4. Ischemic stroke in the territory of the qualifying stenotic artery
5. All death



- Safety analysis - 450 randomized subjects completed 1 year follow-up
- Identify excess risk of ICH and non-ICH major hemorrhage in the experimental arms
- Oversite by DSMB – will meet semiannually and recommend modifications to the protocol

Site Readiness Calls

PI & Coordinator complete checklist

Return to CCC

Schedule/Complete Readiness Call

Released to Enroll

SITE READINESS CHECKLIST

The purpose of this checklist is to allow sites to conduct a self-assessment to ensure that they have all the information, resources, and materials required to be "Released to Enroll". Sites must complete Section 1 and Section 2 and submit this checklist to CAPTIVA-Study@ufl.edu prior to their site readiness call.

SECTION 1: TO BE COMPLETED BY THE PRIMARY STUDY COORDINATOR

Are you aware that subjects must provide consent for themselves (LAR/family member consent is not permitted)?	☐ Yes	☐ No
Do you know where to enter the subject's contact information in WebDCU™ for INTERVENT risk factor counseling?	☐ Yes	☐ No

SECTION 2: TO BE COMPLETED BY THE PRINCIPAL INVESTIGATOR

Does your site have competing trials? If 'Yes', list: Click or tap here to enter text.	☐ Yes	☐ No
Will you notify the subject's PCP of study enrollment, request that s/he allow the study Neurologist to manage blood pressure and LDL, and provide periodic letters on risk factor control?	☐ Yes	☐ No
Will you download, review, and sign all INTERVENT reports and forward to PCP if action is required?	☐ Yes	☐ No

CAPTIVA

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

Site Readiness Calls

- As sites complete all regulatory requirements and training, a Site Readiness Call will be scheduled in place of a Site Initiation Visit.
- Primary Investigators and Study Coordinators are required to attend. You may invite Sub-Is and Pharmacy team.
- Additional information will be provided as sites approach this milestone.

Common Questions

- Dysphagia:
  - Have OT/Speech evaluation (pass)
  - Show visual reference kit to ensure compliance

- Loading Dose:
  - Subjects should not take their PM loading dose within 6 hours after their AM loading dose. Outpatient subjects who are randomized late in the day and who's PM loading dose is due to be taken within 6 hours after their AM loading dose, should skip their PM loading dose, and should wait until the next day and proceed with Day 2.
  - Hospitalized subjects should wait until the following morning to be enrolled and randomized. If a hospitalized subject is being discharged and cannot wait until the following morning for randomization, then they should be treated in accordance with the outpatient guidance listed above.
  - Aspirin can be taken at any time on the day of randomization.

Common Questions

- What if subject has additional stroke?
  - Per the protocol (page 26, section 12):
    - All subjects who are adjudicated as having a stroke during the study will continue on their assigned treatment that will remain blinded unless their treating physicians choose open-label antithrombotic therapy. These subjects will continue to be followed to one year after randomization
- Released to Enroll
  - Once the final check has been made, an email from WebDCU™ will be generated saying “RELEASED TO ENROLL”

Paxlovid Use

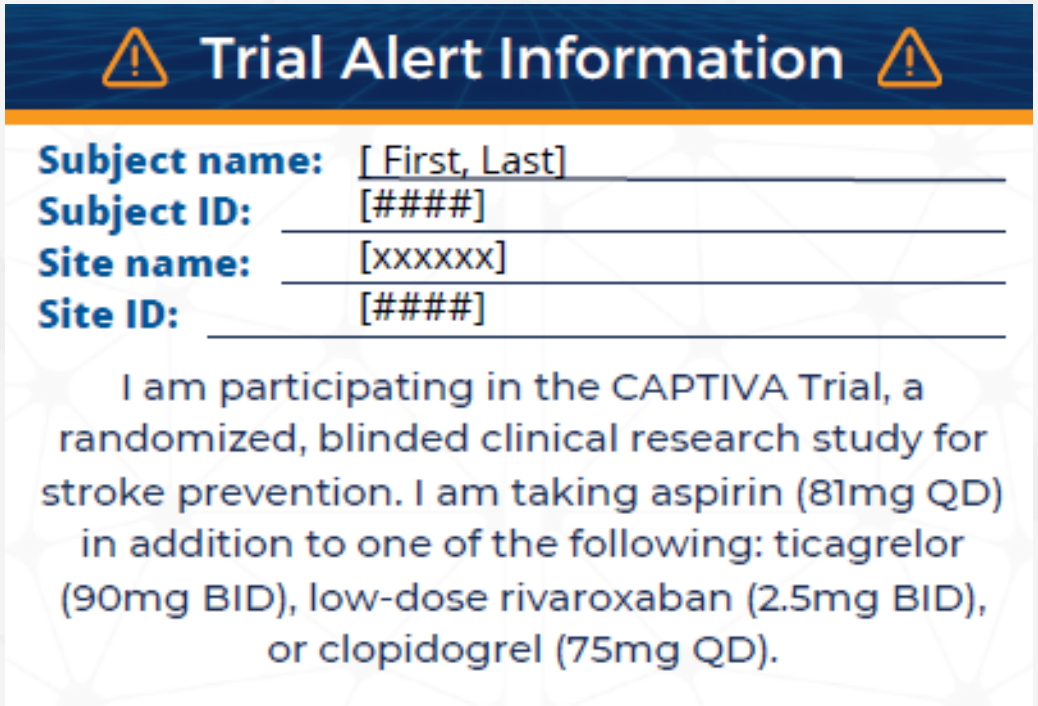
Given the ongoing pandemic, it is likely that some of the subjects enrolled in CAPTIVA will develop COVID and be prescribed Paxlovid by their primary care doctors.
Paxlovid interacts with all three study medications (clopidogrel, ticagrelor and rivaroxaban), statins and calcium channel blockers.

As such, we are recommending that if a study subject is prescribed Paxlovid, that they should **stop** their study antithrombotic medications **but continue** to take their open label aspirin during the 5 days they are on Paxlovid and for another 4 day after they stop the Paxlovid. Additionally, if they are on a statin they should hold the statin during that 9 day period. If they are on a calcium channel blocker (e.g., felodipine) site PI should consider decreasing the dose of the calcium channel blocker for that 9 day period. The link below allows you to enter any medication to review the interaction with Paxlovid.

https://reference.medscape.com/drug/paxlovid-nirmatrelvir-ritonavir-4000259#3

It is important to let your newly enrolled patients know about the interactions of Paxlovid with the study antithrombotic medications, statins and calcium channel blockers and ask that they call you if they have a positive COVID test. This will enable you to remind them to stop the study antithrombotic medications (but not the aspirin) and statin for those 9 days and allow your site PI to make a recommendation regarding lowering the dose of calcium channel blockers during the 9 day period.

Trial Alert Card / Unblinding



Front

Back

CAPTIVA

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

Expanding Sites

CAPTIVA is expanding and looking for more sites.

Do you have any leads on potential sites or know anyone interested?

Non-StrokeNet sites are welcomed

Help us spread the word!

IRB / CTA

- **CIRB Submission to Advarra**
  - Be sure to answer YES to using **e-consent** and the attestation questions even if you are not planning to use e-consent. e-consent is approved at the protocol level and by signing the attestation in your initial application allows you to use e-consent in the future without having to submit to the IRB.
  - If your local IRB is not granting a **partial HIPAA waiver** for recruitment purposes you must answer YES to the HIPAA waiver question, then YES to partial waiver. If unsure, please answer YES so it can be granted with your initial approval vs having to submit a modification.
  - Please submit your ICF to schuljd@ucmail.uc.edu and cc: sulkenay@ucmail.uc.edu prior to submitting to Advarra unless you have Mandatory Language on File with Advarra and they are creating your ICF.
  - If you have questions about your submissions, direct questions to sulkenay@ucmail.uc.edu or use the **contact IRB button** inside CIRBI.

  - **CTAs**
    - The language in the CTA is non-negotiable
    - The payment schedule can be found on the NIH StrokeNet website
      - copy-captiva__payment-schedule_final__08apr2022.pdf (nihstrokenet.org)
      - Password = **Captivatrial**
    - Please copy sulkenay@ucmail.uc.edu on emails regarding CTAs so that I can help expedite the approval process

DOA / Regulatory Documents

- **DOA**
  - If you haven't already, please submit your DOA as soon as possible for review, this will populate regulatory people documents upon acceptance
  - A suggestion to help expedite getting your site "released to enroll"
    - Start with primary study staff only (PI, PSC, RDC, PPH)
    - Add others only after they have completed all regulatory requirements
    - Responsibility "L" – upload images to AMBRA is limited to 3 individuals per site

- **Regulatory Documents**
  - **Regulatory Site Documents**
    - All documents approved by Advarra will be uploaded into the placeholder in WebDCU™ by NCC Regulatory on your behalf and you will be notified via email when that has been completed.
  - **Regulatory People Documents**
    - Protocol Training
      - Investigators and Coordinators must watch the Investigator Meeting Videos if the did not attend the virtual meeting on March 12, 2022 (Investigators must watch videos 1-11 and Coordinators 1-8); Slides for Protocol V 3.0 changes and Investigators must also watch the video on Stroke In and Out of Territory Training
    - **Pharmacy Training**
      - Pharmacists and Pharmacy Techs must review the Pharmacy MOP which satisfies the requirement for training
      - Questions, please contact CAPTIVAtrialRX@ucmail.uc.edu

Questions?

- **New Site Startup / IRB / DOA / Regulatory Documents**
  - **Amy Sulken** – NCC Project Manager – sulkenay@ucmail.uc.edu
- **CTA**
  - **Sasha Simms,** NCC Contracts **-** simmssc@ucmail.uc.edu
  - **Aimee Nance,** NCC Contracts **-** nanceae@ucmail.uc.edu
- **Site Payments NCC team**
  - **Amy Sulken** – NCC Project Manager – sulkenay@ucmail.uc.edu
  - **Paula Sinclair** – NCC Financial Administration – sinclapl@ucmail.uc.edu

Questions?

- **NCC Regulatory team**
  - **Jordyn Schultz** – Primary Regulatory Compliance Specialist - schuljd@ucmail.uc.edu
  - **Jen Golan** – Regulatory Compliance Specialist – golanjl@ucmail.uc.edu
  - **Kim Lever** – Regulatory Compliance Specialist – leverky@ucmail.uc.edu
- **NCC StrokeNet Central Pharmacy**
  - CAPTIVAtrialRX@ucmail.uc.edu

New Policy for Fellows, NPs and PAs, Participation in CAPTIVA

- Can now consent patients as long as CAPTIVA Independent Stroke Provider confirms qualifying stroke is in the territory of the stenotic artery and percent stenosis is 70-99%
- Still cannot decide and report whether subject has had a CAPTIVA adverse event independently

Final Questions?