Study Coordinator Webinar
October 29, 2014

An Introduction to CIAO-ISCHEMIA

Moderator

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NYU Cardiovascular Clinical Research Center

Housekeeping

- All participants will be placed on mute for the call.
- At any time during the presentation, you may unmute your phone by pressing *6 to ask any questions.
- You may also type any questions you have into the chat box located on the side of your screen.

Agenda

- Global Study Update
- DSMB Update
- An Introduction to CIAO-ISCHEMIA

ISCHEMIA Main Trial Update

Harmony Reynolds, MD
Associate Director of ISCHEMIA CCC
CIAO PI

1957 Enrolled

- Insufficient ischemia = 286/1957 (14.6%)
- No obstructive disease = 159/1246[1] (12.8%)
- Left Main disease = 114/1246[1] (9.1%)
- Incidental Findings = 5/1246[1] (0.4%)
- Other = 129/1957 (6.6%)
- 133 Pending Confirmation of Eligibility

1131 Randomized

As of 10/27/14

[1] Denominator = CCTA screened

Enrolled Pt Demographics (n=1957)

Mean age = 64
Female = 497 (25.4%)
eGFR 30-59 = 201(10.3%; no CCTA)

Excluded Pt Demographics (n=693)

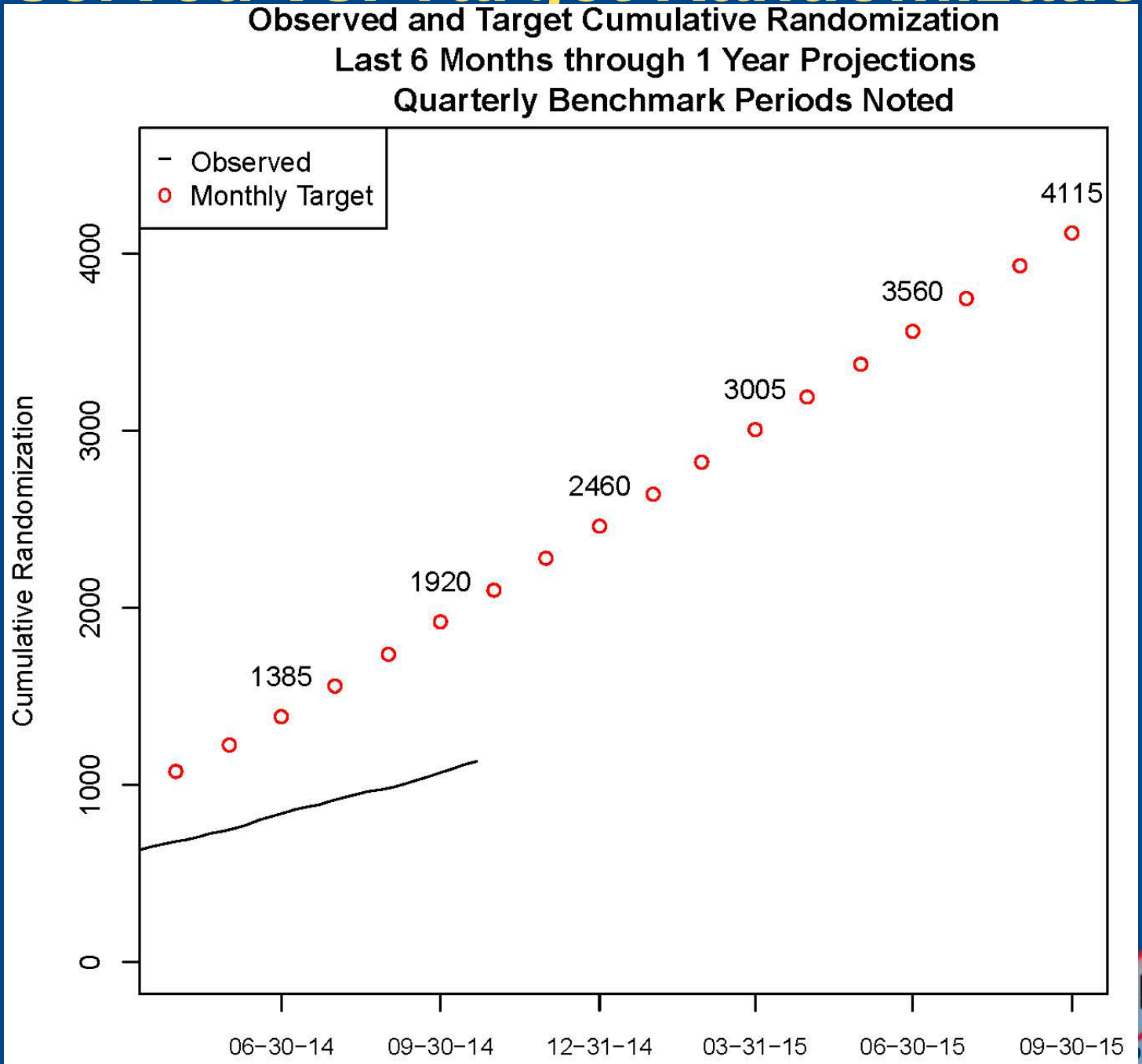
Mean age = 63
Female = 222 (32.0%)

Rand. Pt Demographics (n=1131)

Mean age = 64
Female = 245 (21.7%)
eGFR 30-59 = 145 (12.8%)

Countries	
Argentina: 14	Lithuania: 17
Australia: 8	Mexico: 12
Austria: 19	New Zealand: 11
Belgium: 2	Poland: 113
Brazil: 26	Russia: 29
Canada: 165	Saudi Arabia: 3
China: 20	Serbia: 8
France: 9	Singapore: 5
Germany: 2	Spain: 40
Hungary: 17	Sweden: 4
India: 85	Switzerland: 4
Israel: 10	Macedonia: 11
Italy: 67	United Kingdom: 136
Japan: 3	United States: 291

Observed vs. Target Randomizations



As of
10/21/14

Top Randomizers

Country	Site Name	Investigator	Study Coordinator	Enrolled	Randomized	Pending
United Kingdom	Northwick Park Hospital-Royal Brompton Hospital, London	Roxy Senior	Jo Evans, Sothinathan Gurunathan, Linda Haimbodi, Raisa Kavalakkat, Christopher Kinsey	105	**64**	4
Poland	Coronary and Structural Heart Diseases Department, Institute of Cardiology, Warsaw	Marcin Demkow	Radek Pracon, Olga Chojnacka	46	**42**	1
Canada	Montreal Heart Institute, QC	Gilbert Gosselin	Rima Amche, Magalie Corfias	66	**38**	3
India	Medical College Calicut	Mangalath Krishnan	Sajeesh Pontrasseri	47	**33**	7
Spain	Hospital Universitario La Paz	Jose Lopez-Sendon	Almudena Castro, Silvia Valbuena	45	**31**	0

As of 10/28/14

Update from DSMB Meeting

Harmony Reynolds, MD
Associate Director of ISCHEMIA CCC
CIAO PI

DSMB Meeting 10/15/14

- The DSMB approved continuation of the trial and thanks the sites and coordinating centers for their hard work
- A proposal was discussed to allow many more sites to use an exception written into the protocol allowing CCTA or randomization *before waiting for core lab confirmation of ischemia*
  - Protocol Section 5.4: **"***Sites will wait for verification of ischemia before CCTA (or, for patients who will not undergo CCTA, before randomization) unless the CCC permits an exception."*
- The operational plan was approved by the DSMB and a note about the plan will be distributed to sites for filing with the IRB/EC at the time when the DSMB update is filed

Why now?

Exceptions to waiting for core lab ischemia confirmation

- Most sites have demonstrated sufficient concordance with interpretation of stress tests by core labs
- The trial findings can be more easily applied to clinical practice based on use of local determination of the level of ischemia
- This will simplify participant workflow
- The possibility of simplifying the workflow in this way was anticipated when the protocol amendment was written. Exceptions already have been granted for a small number of sites to date.

How will it work?

Exceptions to waiting for core lab ischemia confirmation

- It is anticipated that most sites will qualify for this exception based on prior experience
- Sites will be notified by the CCC if they are granted an exception to waiting for core lab review
- If the core lab finds less than moderate ischemia on a randomized participant, the core lab will discuss the difference in viewpoint on the reading with the site
- If the site and core lab cannot come to agreement on additional cases, the site may be asked to wait for core lab ischemia review for future enrollments
- Pre-enrollment verification is still available and is particularly encouraged for borderline cases
- It is always OK to wait for core lab review if preferred

Questions?

CIAO ISCHEMIA

Changes in Ischemia and Angina over One year among ISCHEMIA trial screen failures with no obstructive CAD on CT angiography

Harmony Reynolds, MD, CIAO PI
(Associate Director of ISCHEMIA CCC)

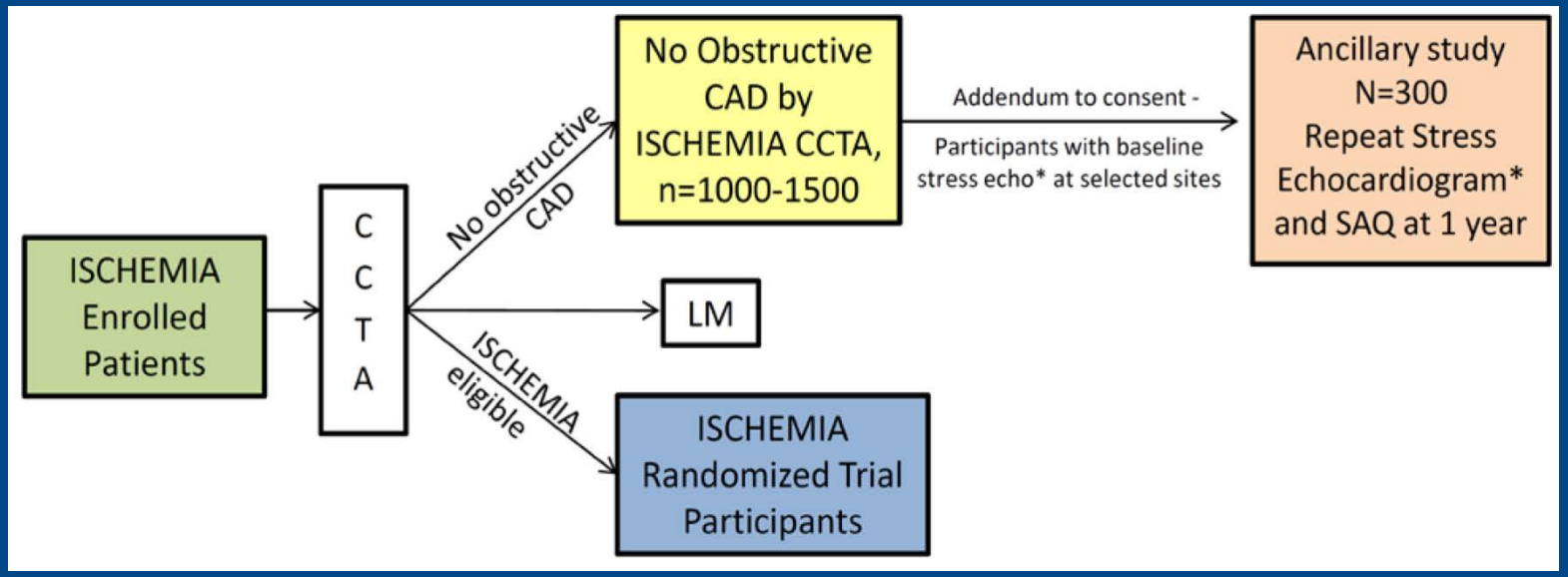
What is CIAO-ISCHEMIA?

- Target population: participants who are **screen failed out of the main study** based on **no obstructive CAD** on study CCTA
- Currently restricted to participants enrolled using **stress echo**
- May expand to include CMR in the future
- Baseline angina assessment and stress echo (used to qualify for ISCHEMIA)
- 6-month angina assessment (primarily for participant retention)
- 1-year stress echo (paid for by the study) and repeat angina assessment
- Hypothesis: Changes in ischemia and change in angina will be correlated because angina is due to ischemia
- Relationship to CCTA-measured atherosclerosis severity also to be investigated

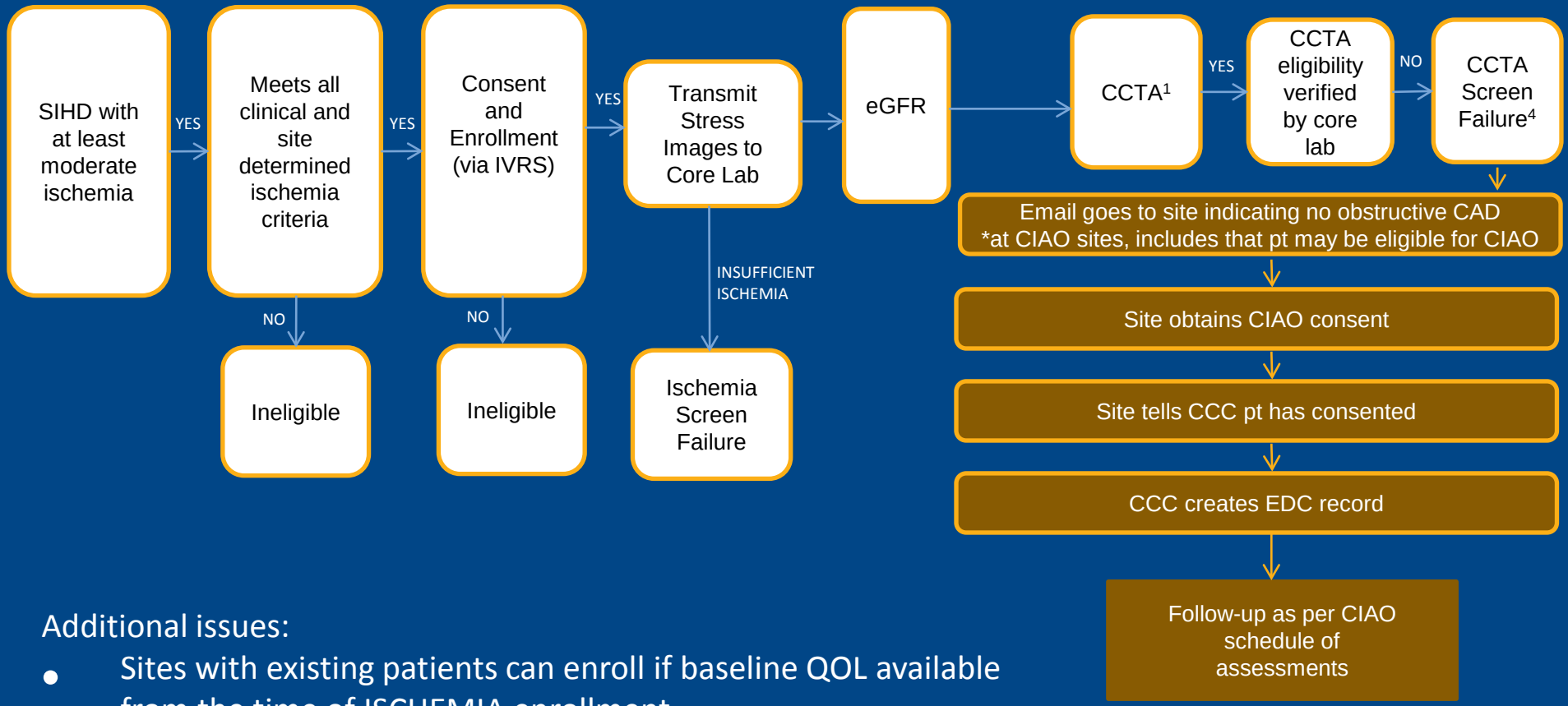
CIAO Aims

- The primary aim is to investigate the association between change in angina severity and change in severity of ischemia on stress echocardiography over one year in patients with an initial finding of moderate-severe ischemia and with no obstructive CAD on CCTA.
- *Additional objectives*
  - To describe the effect of medication classes selected by treating physicians on change in angina and change in ischemia over one year in this cohort.
  - To assess the relationship between change in angina and change in ischemia in selected subgroups (sex, age, presence/severity of atherosclerosis) in this cohort.
  - To investigate the relationship between ischemia, angina and severity of non-obstructive atherosclerosis at baseline in patients with an initial finding of moderate-severe ischemia and with no obstructive CAD on CCTA. Severity of non-obstructive atherosclerosis will be characterized by a composite score based on the number of segments affected on CCTA.
  - The association between severity of ischemia and cardiovascular events over one year will also be explored (death, MI, stroke, CV hospitalization/ER visits).

Flow of Participants into the CIAO Study:



CIAO Study Flow



Additional issues:

- Sites with existing patients can enroll if baseline QOL available from the time of ISCHEMIA enrollment
- CKD+CIAO = OK
- Prior PCI or CABG = not OK (MOO)

Where will CIAO be conducted?

- To be conducted at 100-125 sites in

Australia	Macedonia
Brazil	Mexico
Canada	Poland
France	Serbia
Germany	Spain
Italy	UK
Lithuania	US

How are sites selected to participate in CIAO?

- Selection criteria based on:
  - Use of stress echo at your site, especially previous enrollment in ISCHEMIA after stress echo
  - Location in a country where many sites use stress echo to qualify patients for ISCHEMIA
  - Existing potentially eligible participants
  - Enrollment rates
- Selected sites were provided with the CIAO consent form as part of the amendment IRB submission packet.
- If you are not sure if your site has been asked to participate, please contact the CCC.
- If your site performs stress echo and would like to participate please contact the CCC. We are accepting more sites.

CIAO Highlights

- Regulatory work−minimal. CIAO is integrated into the amended protocol (dated January 6th, 2014) as Appendix B.
- IRB approval required for short separate CIAO consent form.
- Screening: only participants already enrolled in the main trial and screen failed due to no obstructive CAD on CCTA
- Participant ID: same as in ISCHEMIA trial (e.g., 001204-003)
- Only 3 visits
- Additional reimbursement to sites (in addition to the late screen failure payments)
- Expectations: 1-3 participants enrolled in CIAO per site per year on average

What do I need to get started?

- IRB/EC approval for ISCHEMIA protocol version 2.0
- Protocol version 2.0 signature page (if not already activated for 2.0)
- Approval of the CIAO consent by the local IRB and the clinical coordinating center
- Availability of stress echocardiography
- An executed contract addendum for CIAO is *not* required by the CCC in order to enroll CIAO participants but will be required before payments can be made for CIAO.

Data Collection/EDC

- Data will be collected using paper Case Report Forms provided by the CCC until the Electronic Data Capture (EDC) system is up and running
- EDC system to be used for CIAO will be ECOS. ECOS is more user friendly and intuitive than InForm
- Visit Checklists have been developed and will be posted to the ISCHEMIA website
- The Case Report Forms are based on the main trial except that they are shorter in most cases
- The CIAO Manual of Operations will be available on our website soon
- FAQs will also be available soon and will be reviewed during this webinar

What are the CIAO Inclusion Criteria?

- Enrollment in main trial using stress echocardiogram
- Core lab-verified ischemia
- No obstructive (≥50%) CAD on main ISCHEMIA study CCTA
- Ischemic symptoms
  - Timing
    - *Either before, during or after the stress echo*
    - *If symptoms are gone by the time of CIAO enrollment, the participant is still eligible*
  - Type
    - *Chest pain or discomfort*
    - *Another anginal equivalent, such as:*
      - Shortness of breath
      - Upper body discomfort other than chest (for example, arm, jaw, throat, back or abdominal discomfort)
      - Nausea, sweating or fatigue
      - Any other symptom considered by the treating physician to represent angina

What are the CIAO Exclusion Criteria?

- Prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at any time.
- That’s all!

How Can I Enroll a Participant in CIAO?

- Once you are notified that a participant you have enrolled using stress echo cannot be randomized into the main study due to the absence of obstructive CAD at angiography
  - Check eligibility (YES to symptoms, NO to prior PCI or CABG)
- Let the participant know that the stress test findings are likely correct and the reason for symptoms when the arteries are “open” is not clear – this is what CIAO is all about
- Get consent for CIAO on the IRB approved form
- Administer baseline QOL – same form you use for ISCHEMIA
- To make things easier for you, we suggest you consider asking the baseline QOL questions at time of ISCHEMIA enrollment or CCTA
  - This is OK according to the ISCHEMIA MOO
  - You can then use the questionnaire for ISCHEMIA or CIAO
- Email the CIAO team at ciaoischemia@nyumc.org to let us know you have enrolled a participant

Can I Enroll a Participant in CIAO who was Already Excluded from ISCHEMIA?

- Yes!!
- As long as the participant:
  - Meets eligibility requirements and provides consent
  - Was excluded from the main ISCHEMIA trial not more than 550 days (1.5 years) before CIAO enrollment
  - Filled in baseline QOL forms for the main trial not more than 45 days from the time of main trial exclusion
- If more than 6 months have passed since the qualifying stress echo, skip the 6-month visit
  - The participant has only 2 CIAO visits, enrollment and 12mos
  - Site will still be paid for the 6-month visit
- If more than 11 months have passed since the qualifying stress echo, schedule follow up stress testing
  - This means the participant has only one CIAO visit, the enrollment/12-month visit
  - Site will be paid for all three visits

Visit Checklists

Enrollment Visit – what is collected:

- **Participant written consent** for participation in CIAO
- **Baseline QOL Questionnaire** (same as in ISCHEMIA trial; not all questions will be entered in the CIAO EDC)
- Confidential **Patient Information Sheet** (For Site Use Only)
- **Endpoint assessment** to determine if any events between enrollment in the ISCHEMIA main trial and enrollment into CIAO
  - *If PI suspects an endpoint event has occurred, refer to MI/UA, DEATH, STROKE, RCA, HF forms*
- **Hospitalization assessment -** *Similar to main trial FACHOSP*
- **Labs** (creatinine, lipid panel, hemoglobin, HbA1c – only if done clinically within 6 months)
- **Vital signs (heart rate, blood pressure), weight, and height**
- **CCS and NYHA Class** (same as in main trial)
- **Current cardiovascular medications**
- **Physical exam (vital signs, CV and lungs)**

CCC Notification of Enrollment and Scheduling

- Send enrollment notification to the CCC:
  - Send e-mail to ciaoischemia@nyumc.org
  - Use Subject Line: CIAO Enrollment (Site xxxxxx)
  - Include the following in the e-mail
    - *Participant ID# - same ID# from the main ISCHEMIA trial*
    - *Date of Consent*
    - *Date of Baseline QOL Collection*
- Schedule participants next study visit.
  - 6m visit should be scheduled within 6 months (plus or minus 2 months) from the date of stress echo used to qualify the participant in the main study. **
    - ***If a CIAO participant is enrolled more than 6 months after the qualifying stress echo, skip the 6m visit and proceed to the 12m visit.*

6 Month Visit – can be done by phone

- **QOL** – not all questions on the IRB/EC-approved baseline QOL form will be used at this visit. Only approved questions will be asked.
- **Endpoint assessment (including cath)** - If PI suspects an endpoint event has occurred, refer to site cath, MI/UA, Death, Stroke, RCA and HF forms.
- **Hospitalization assessment -** *Similar to main trial FACHOSP*
- **Labs** (creatinine, lipid panel, hemoglobin, HbA1c – only if done clinically within 6 months)
- **Vital signs (heart rate, blood pressure), weight, and height**
- **CCS and NYHA Class** (same as in main trial)
- **Current cardiovascular medications**
- Schedule next study visit:
  - 12 month visit should be scheduled within 12 months (plus or minus 3 months) from the date of stress echo used to qualify the participant in the main study.

12 Month Visit - what data is collected:

- **QOL** – not all question on the IRB/EC-approved baseline QOL form will be used at this visit. Only approved questions will be asked.
- **Stress echo** (see next slide)
- **Endpoint assessment (including cath)** - If PI suspects an endpoint event has occurred, refer to site cath, MI/UA, Death, Stroke, RCA and HF forms.
- **Hospitalization assessment -** *Similar to main trial FACHOSP*
- **Labs** (creatinine, lipid panel, hemoglobin, HbA1c – only if done clinically within 6 months)
- **Vital signs (heart rate, blood pressure), weight, and height**
- **CCS and NYHA Class** (same as in main trial)
- **Current cardiovascular medications**
- **Physical exam (vital signs, CV and lungs)**

12 Month Visit – Stress Echo

- Schedule 12 month stress **echocardiogram**
- Schedule with the same lab used for the ISCHEMIA qualifying stress echo (whenever possible)
- Use the same type of stress (exercise or dobutamine) as for the ISCHEMIA qualifying stress. Contact the CCC if any issues
- Remind participants to take all cardiovascular medications the day of the test
- The participant name should be included during acquisition (and will be anonymized via BioClinica upload as in ISCHEMIA). Do not use the text editor to display private health information on the screen, to avoid transfer of this information to the core lab.
- Request the stress echo test images in DICOM format from your technologist (unless you are able to access directly from archival system (ex: PACS)
- Transmit the stress echo test, ECGs and Stress Echo Worksheet to the core lab via Bioclinica, using timepoint “CIAO 12 month Echo”

12 Month Stress Echo – Standard of Care or Research?

- The 12 month stress echocardiogram is done for research
- Will be paid for by the CIAO study grant
- Payment amount is based on a CPT code used in US Medicare
- The core laboratory will not provide a clinical report for the site
- The core lab interpretation will be made available in the EDC system for the site to review
- If the results of the stress echocardiogram are desired for use in clinical care, it is recommended that the site obtain a clinical interpretation. In this case, the professional fee may be billed to the participant or the participant's insurance but the technical fee may not be billed clinically. The participant must be made aware of this plan to avoid confusion about billing.

12-month visit – End of Study

- Notify the participant that their participation in CIAO has ended but he/she may be contacted in the future for assessment of events/vital status as detailed in the main ISCHEMIA trial consent, if permitted by local regulations.

Questions?

What are the expected findings of CIAO?

- It is expected that angina and ischemia will vary together over time.
- This will be taken to mean that symptoms in CIAO patients are likely due to ischemia and not, for example, altered pain sensitivity.
- This finding would provide support for design of future clinical trials in a patient group at relatively low absolute risk of major CV events, with angina relief as a surrogate outcome.
- Alternatively, CIAO results may indicate that the trajectories of angina and ischemia are not associated and in this case, treatment might be better targeted to relief of ischemia than symptoms in these patients.
- If this were the case, it would be concluded that symptoms were not due to ischemia in some or all patients and ischemia was either silent or represented a false positive finding.

Why would the investigators think that angina and ischemia may not be correlated over one year?

- Prior research has shown that many, but not all, patients with ischemic symptoms in the absence of obstructive coronary artery disease have objective evidence of ischemia.
- Some patients may have false positive tests. It is believed that the number of false positive stress echocardiograms in CIAO will be minimized by the use of core lab verification of moderate-severe ischemia before study enrollment.
- Prior research has shown that angina frequency and duration are similar among patients with and without ischemia on noninvasive testing.
- Small treatment trials have been undertaken and some showed improvement of angina that was not reflected in objective measurement of ischemia; however, those studies were markedly underpowered for that comparison.

Thank you for attending!