



Carotid Revascularization Endarterectomy and Stent Trial - **Hemodynamics** (an ancillary study to CREST-2)





CREST-H Training Slides

- Who is required to participate in CREST-H training?
 - The CREST-H site coordinator
 - The CREST-H Site PI
 - The CREST-H Imaging Co-Investigator (I-Co-I), responsible for image de-identification, image upload, and receiving any “safety reads”



CREST-H Investigators



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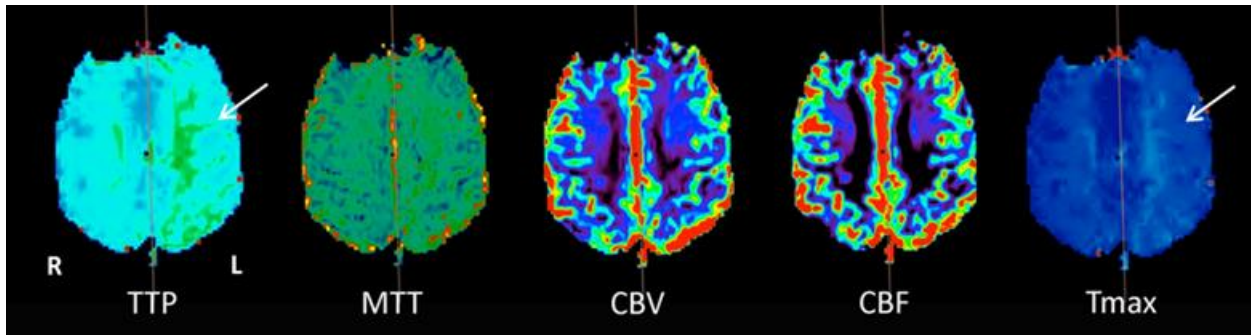
CREST-H Study Overview

- **Goal:** To determine whether the subset of CREST-2 patients with cerebral hemodynamic impairment and mild cognitive impairment benefit cognitively from revascularization.
- **Background:** Prior studies show that patients with high-grade carotid stenosis may have cognitive impairment if they have lowered cerebral blood flow on the side of carotid occlusion. Case series suggest this may be reversible with revascularization.
- **Objective:** CREST-H will assess cognitive outcomes in CREST-2 patients with cerebral hypoperfusion and mild cognitive impairment, comparing those who get revascularized (CEA or CAS) versus those who get Intensive Medical Management alone. The difference between treatment groups will be compared with a similar comparison among those without cerebral hemodynamic asymmetry.
- **Primary Endpoint:** Cognition at 1 year
- **Population:** Patients with asymptomatic high-grade carotid stenosis enrolled in the CREST-2 trial.

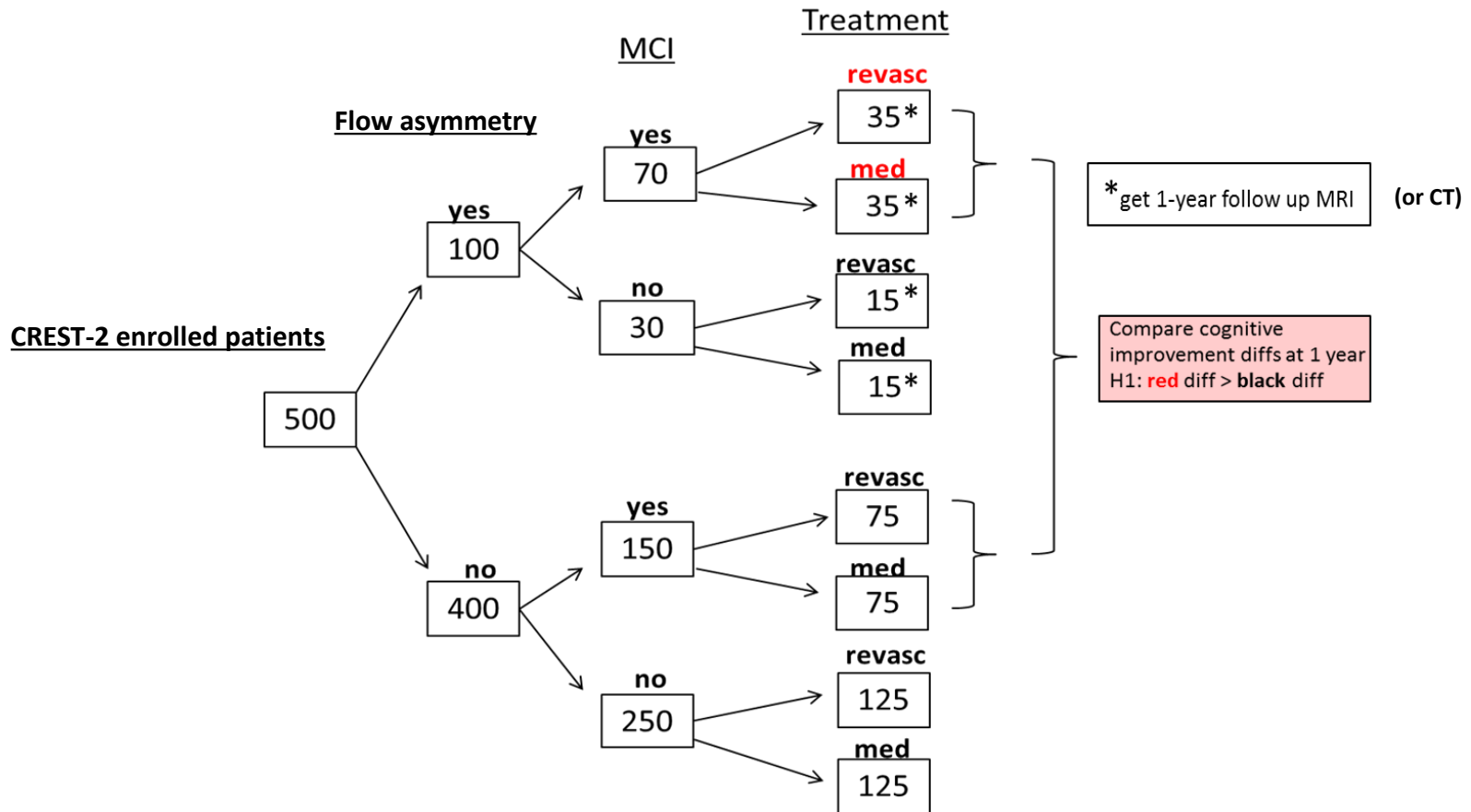


CREST-H Study Overview (cont'd)

- **Enrollment goal:** 500 patients across 75 CREST-2 sites
- **Unique testing as part of CREST-H:**
 - **MRI perfusion (MRP) or CT perfusion (CTP) scan** to look for hemodynamic asymmetry at baseline. (For MRI we also acquire DWI/ADC, FLAIR, GRE, Hi-res T1 – required for secondary aims)
 - 1.5 T or 3.0T MRI acceptable, but 3.0T preferred
 - Patients who have baseline flow alteration will receive a 1 year follow up MRI/CT scan



Study Design



Timing of CREST-H enrollment

- CREST-H enrollment and consent must take place only after the patient has been randomized in CREST-2.
- CREST-H CRFs are set up so that the enrollment date may only be the same date or later than the CREST-2 randomization date.

Who handles CREST-H Documents?

- **Regulatory:**
 - **Mayo Jacksonville** (CREST-2 Clinical Coordinating Center)
 - **MUSC** (WebDCU document uploading)
- **Data management:** Electronic Data Entry System (eDES) - **University of Alabama at Birmingham** (same as CREST-2)
- **MRI/CT image file transfer:** All study MRI and CT raw images will be sent to the CREST-2 Vascular Imaging Core Lab, **University of Maryland**, using the same link as with CREST-2. Image analysis is done centrally at **UCLA** and **Mayo Rochester**
- **IRB of record:** the central IRB (CIRB) at the **University of Cincinnati** (for StrokeNet sites), **or local IRB**, There is a separate informed consent form and a separate protocol for CREST-H

WebDCU (<https://webdcu.musc.edu>)

- This is the repository where all regulatory documents for CREST-2 and CREST-H are stored:
 1. First step is the Delegation of Authority (DOA): list the CREST-H PI, Imaging Co-I (I-Co-I) and CREST-H personnel (coordinator). This opens...
 2. Conflict of Interest form for CREST-H
 3. Human Subjects Research Document up to date
 4. CV upload for all personnel if not already there
 5. StrokeNet financial disclosure form
 6. CREST-H Webinar training certificate

What is required for the CREST-H “Green light” letter?

1. CREST-H site is in good standing with CREST-2.
2. Regulatory packet is completed (sub-contract, (c)IRB approval, WebDCU document uploads).
3. Coordinator, CREST-H PI, and I-Co-I complete CREST-H training (this webinar).
4. An MRP and CTP test image set is uploaded successfully to U Maryland, and image quality is approved by UCLA.



CREST-H Inclusion Criteria

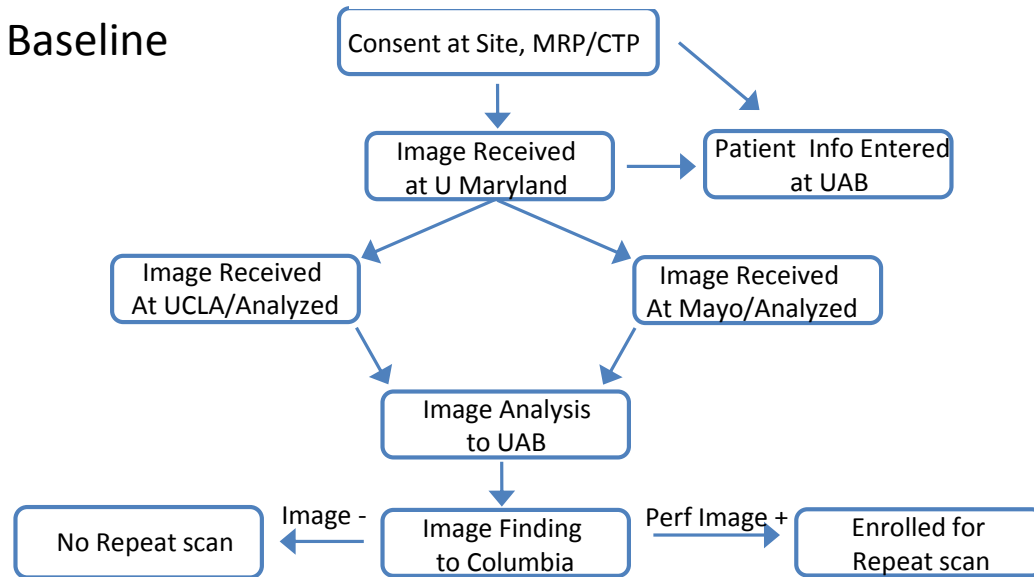
1. Randomization into CREST-2 (all CREST-2 inclusion criteria apply)
2. Additional CREST-H inclusion criteria:
 - Age 35 to 86 years (no cognitive norms are available over age 90)
 - Patient agrees to complete a baseline MRI/CT scan and another MRI/CT scan at one year if needed.

Additional CREST-H Exclusion Criteria

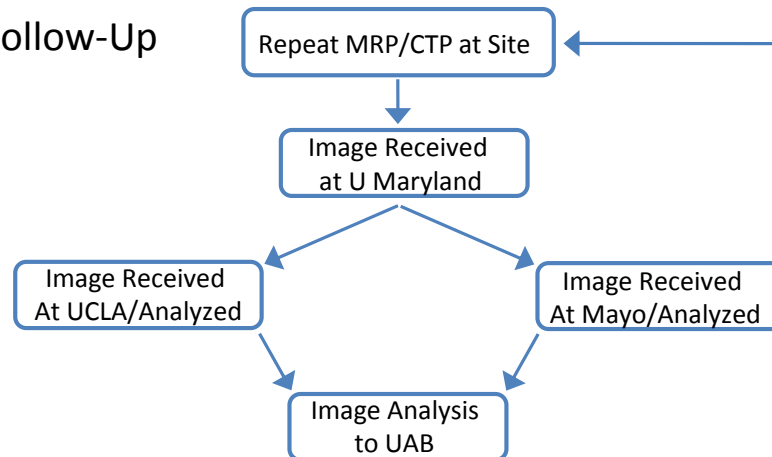
- Unable to have MRI (e.g. non-compatible metal implants, pacemaker)
- Known allergy to gadolinium contrast dye (MRI) or iodinated contrast dye (CT)
- Renal failure: either creatinine ≥ 2.5 mg/dl or GFR < 30 cc/min
- $>70\%$ stenosis on the side opposite the target vessel as assessed by MRA, CTA or Doppler ultrasound
- Pre-existing diagnosis of dementia
- History of severe head trauma (loss of consciousness >30 minutes, or seizure at the time of trauma)
- Current major depression
- Education <8 years

Data Flow

Baseline



1-Yr Follow-Up



Baseline MRI/CT scan visit

- Confirm randomization into CREST-2.
- Confirm that baseline telephone cognitive exam has been performed or scheduled through CREST-2 trial.
- MRI or CT scan and baseline cognitive exam must be done **prior to any revascularization procedure and prior to the 44-day CREST-2 follow up visit.**
- Proceed with scheduled baseline scan, de-identification, and upload to Vascular Imaging Core Lab at University of Maryland (**Note that upload must be done within 1 week of scan**)
- Once the de-identified images have been uploaded to U Maryland, **CRF H-03** will be entered by the site coordinator in eDES.
- By receipt of **CRF H-03** SDCC at UAB confirms data completion for cognitive exam, image acquisition, image upload.



CREST-H MRI Sequences

Sequence	Orientation	Time	Slice (mm)	Gap	Slices	TR	TE	TI	FOV (cm)	Frequency	Phase	Mode
High Res T1	Sagittal	7:23	1.2	0	160	NA	Full Min	900	24	192	192	3D
T2 FLAIR	Axial	4:36	4	0	36	11000	147	2460	22	256	192	2D
DWI/ADC	Axial	0:50	4	0	36	10000	Min	NA	22	128	256	2D
2D PC scout	Coronal	1:33	90	0	1	40	Min	NA	22	256	224	2D
MRA Intra	Axial	4:18	1.4 (0.7)	0	3 x 32	Min	Min	NA	18	384	224	3D
Perfusion	Axial	3:00	5	0	Max for TR	2225	60	NA	24	128	96	2D
GRE	Axial	0:09	4	0	36	1700	Full Min	NA	22	128	128	2D

Total scan time: 21:49

***FOR THE PERFUSION SEQUENCE:**

1. Antecubital vein IV catheter of 18 gauge is required.
2. A test injection will be performed with approximately 10 ml of normal saline solution.
3. Cover the indicated area with maximum number of slices for TR from the vertex inferiorly.
4. Load the power injector with 20cc contrast and 50cc saline flush.
5. Using the power injector, inject 20cc contrast at 4cc/sec and a 25cc saline flush at 4cc/sec.
6. Do an AUTOPRESCAN
7. CHOOSE SCAN
8. Inject contrast when there is 1:18 remaining in scan (11 SEC DELAY). Make sure the sequence is producing mages before you inject.



CREST-H

CT Protocol

	Non-contrast head (optional)	CT Perfusion (required)
Coverage	Top C1 lamina to vertex	Top C1 lamina to vertex
Scan type	Spiral	Dynamic Multi 4D
Rotation Time (sec)	1	0.28
Collimation	128 x 0.6	32 x 1.2
4D Range	NA	100 mm 1.5 sec
Multi Cycle time	NA	1.5/Multiple ON
Pitch	0.6	None
kVp	120	80
Effective mAs	350	200
CARE Dose 4D	Off	NA
Scan Field (mm)	300	300
Prep Delay	Min allowable	2 sec
Min. Retro (mm)	0.6	1.5
CTDI-vol (mGy)	53	8.6/scan, 1.5 sec scan time
Recon Kernel	J40	H20

1. An 18 or 20 gauge peripheral IV is inserted, preferentially within the right arm.
2. A contrast agent such as Omnipaque 350 is administered by a split does as follows: 50 mL at 7 mL/second, followed by 50 mL 0.9% NaCl at 7 mL/second.
3. The images will be processed with a semi-automated system such as the OleaSphere software platform .

Test Imaging Required Prior to CREST-H Enrollment

- Prior to site initiation, the UCLA imaging core lab will require a test set of MRP and/or CTP images to ensure adequate image quality. If a site will be performing CTP only, then only CTP test scan is required; if MRP only, then only an MRP test scan is required. (Most sites will do both.)
- These test images (clinical patients or volunteer subjects) should be de-identified and uploaded to University of Maryland, following the CREST-H study protocol.
- Approval from the UCLA Imaging lab will be required before a site is green-lighted to begin enrollment in CREST-H.

CREST- H Imaging Quality

- Throughout the study, imaging files submitted for enrolled subjects will be monitored for data quality and consistency throughout the study.
- Feedback to sites will be provided with requests for corrective action if the images are of suboptimal quality.

Scanning and Uploading Guide - 1

- The CREST-H MRI/CT scan acquisition order set should be placed on one designated MRI and CT scanner at your institution, preferably uniquely labeled as the “CREST-H” set.
- The de-identification and uploading may be performed by the site coordinator under the supervision of the I-Co-I.
- De-identification process may be different at each site. Find out how your institution de-identifies and uploads images. Some systems may allow the “patient” to be labeled from the start with the CREST-2 PID1.
- Upload scans in DICOM format for centralized processing at U Maryland via links already established as part of CREST-2: (<https://somumaryland.sharepoint.com/sites/researchcollaboration/vascularSurgery/crest2>). Note: this is a new link.

Scanning and Uploading Guide - 2

- To upload images, place all the de-identified image files in a Zip file and label the Zip file with the following nomenclature:
 - PID1_BAS/1YR_MRP/CTP_MMDDYYYY
 - For test scans use P(siteID)_TEST_MRP/CTP_MMDDYYYY
- Once on the Sharepoint website:
 1. Navigate to your site folder,
 2. Select “New File Entry”
 3. Enter the name of the Zip file in the Title field
 4. Choose the Zip file for the upload
 5. Select OK on the lower right
 6. You can enter text in the Description field if you wish
- A backup system is to mail a CD with the de-identified images (DICOM format) to Attn: John Yokemick, Vascular Imaging Core Facility, Univ Maryland, 22 S Greene St, S3B02C, Baltimore, MD 21201


Imaging Co-Investigator

- In order to minimize bias (and cross-over resulting from MR/CT perfusion information) we highly recommend that the CREST-H PI at the participating institution assign an Imaging Co-investigator (I-Co-I)* – a neurologist, surgeon or radiologist -- to perform 3 functions:
 - To facilitate/supervise the upload of de-identified scans for centralized processing at U Maryland with assistance of a coordinator if desired.
 - To receive any official safety reads from the local institution or CREST-H radiologist, and alert the site PI with any unexpected scan finding, such as brain tumor, hemorrhage, vascular malformation.
Note: If a site does not have a local safety read required, notify CREST-H and we will provide this. A radiologist reviews all structural scans centrally.
 - To remind study (treating) investigators that they are to remain blinded to any MRP/CTP information if it (mistakenly) appears on the local radiology system

*the I-Co-I may be the same as CREST-H PI as long as it is not the treating surgeon or interventionalist, so as to maintain blinding as much as possible

Electronic Data Entry System (eDES)

- The eDES used by CREST-H is the same system used by CREST-2
- It is a comprehensive data entry system that allows all study data to be entered from any site using a comprehensive, coordinated platform
- Downloaded forms allow data entry which is transferred to the online system by the coordinator



CREST-H List of CRFs

- CRF **H-01** (Inclusion-Exclusion criteria) used at time of screening and enrollment
- CRF **H-02** (Study Enrollment Form) must be entered upon enrollment and locked within 1 week of enrollment.
- CRF **H-03** (Baseline MRI/CT Form) is entered at the time of baseline MRI scan upload
- CRF **H-04** (1-Year Follow up MRI/CT Form) is entered at the time of the 1-year follow up MRI scan upload

Note: Revised CRFs are being produced for Protocol V3.0 that include CTP

H-01

CREST-2 H (Hemodynamics)		Page 1 of 2
PID1: _____ - _____ <div style="display: flex; justify-content: space-around; font-size: small;"> SITE ID </div> PID2: _____ - _____		
FORM H-01 CREST- H GENERAL INCLUSION/EXCLUSION CRITERIA		
Instructions: <ul style="list-style-type: none"> All inclusion criteria must be checked "Yes" and all exclusion criteria must be marked "No" in order for a participant to be eligible. 		
1. Date Screened: ____ / ____ / ____ <div style="display: flex; justify-content: center; font-size: x-small;"> MM DD YYYY </div>		
2. Inclusion Criteria (All must be marked "Yes" in order for the patient to be eligible.)		
2.a. Will the patient be between 35 and 86 years old on expected date of enrollment?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
2.b. Did the patient agree to complete a baseline MRI scan and at one year if needed?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3. Exclusion Criteria (All must be marked "No" for the patient to be eligible)		
3.a. Does the patient have metal in the body or a pacemaker?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.b. Does the patient have a known allergy to gadolinium contrast dye?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.c. Does the patient have a pre-existing diagnosis of dementia?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.d. Does the patient have known contralateral stenosis >70%, as defined by CREST-2 criteria?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.e. Does the patient have history of severe head trauma defined by loss of consciousness greater than 30 minutes?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.f. Does the patient have a history of seizure?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.g. Has the patient been diagnosed with major depression?	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
3.h. Does the patient have less than an 8 th grade education? <i>COORDINATOR NOTE: This should match the answer on Question 6 (Education Level) on the CREST-2 Form 5 Demographics and Social Status.</i>	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No
4. Coordinator Code: _____		

H-03

CREST-2 H (Hemodynamics)		Page 1 of 1
PID1: _____ - _____ <small style="display: inline-block; width: 100px; text-align: center;">SITE ID</small>	PID2: _____ - _____	
FORM H-03 CREST- H BASELINE MRI PERFUSION SCAN Form		
<p>Instructions:</p> <ul style="list-style-type: none"> This form is <u>required</u> for all patients who completed the CREST-H Enrollment Form, whether or not an MRI scan was done. The scan is to be done: 1) <u>prior</u> to any CREST-2 revascularization, CEA or CAS, and 2) within 44 days of randomization. If possible, the scan should be done within 14 days of CREST-H enrollment. 		
<p>1. Was the baseline MRI scan done?</p> <p>2. Date of scan: ____ / ____ / ____ <small style="display: inline-block; width: 100px; text-align: center;">MM DD YYYY</small></p> <p>3. Was a revascularization procedure of the target vessel performed prior to the MRI scan?</p> <p>4. Was the MRI scan done prior to the 44-day follow-up visit?</p> <p>5. Date scan uploaded to Vascular Imaging Core Lab at University of Maryland? ____ / ____ / ____</p> <p>NOTE: Images should be uploaded no later than 1 week after the date of the MRI. The coordinator should contact the unblinded investigator who uploaded the image to Maryland to obtain the date sent.</p> <p>6. Please indicate reason MRI scan was not done:</p> <p style="padding-left: 40px;"><input type="checkbox"/> 1 = Patient Refused</p> <p style="padding-left: 40px;"><input type="checkbox"/> 2 = Other, reason _____</p>	<p><input type="checkbox"/> 1=Yes – Continue to 2</p> <p><input type="checkbox"/> 1=Yes</p> <p><input type="checkbox"/> 1=Yes</p>	<p><input type="checkbox"/> 2=No – skip to 6</p> <p><input type="checkbox"/> 2=No</p> <p><input type="checkbox"/> 2=No</p>
<ul style="list-style-type: none"> NOTE: You will be notified via email from the SDCC to indicate whether or not the patient will be asked to return for a 1-year follow-up scan. There will be reminders sent from the SDCC to the sites 6-month, 1-month, and 2-weeks prior to the 1-year target date for patients who are to have a repeat MRI. If indicated that a 1-year scan is required please try to schedule the follow-up scan for the same day as the patient’s 1-year CREST-2 follow-up clinic visit. The acceptable time window is the same as for the 1-year CREST-2 follow-up: ± 30 days (calculated from the date of CREST-2 randomization.) 		
7. Coordinator Code: _____		

H-04

CREST-2 H (Hemodynamics)		Page 1 of 1
PID1: _____ - _____ <small style="display: inline-block; width: 100px; text-align: center;">SITE ID</small>		PID2: _____ - _____
FORM H-04 CREST- H 1-Year Follow up MRI Scan Form		
Instructions: <ul style="list-style-type: none"> To be completed only on those patients identified by the SDCC via email to your site as needing a 1-year Follow-up MRI perfusion scan. 		
<p>1. Was the 1-year follow-up scan performed?</p> <p>2. Date of scan: ____ / ____ / ____ <small style="display: inline-block; width: 100px; text-align: center;">MM DD YYYY</small></p> <p>3. Date scan uploaded to Maryland? ____ / ____ / ____</p> <p style="color: red;">Note: Images should be uploaded no later than 1 week after the date of the MRI. The coordinator should contact the unblinded investigator who uploaded the image to Maryland to obtain the date sent.</p> <p>Skip to Question 5.</p> <p>4. If scan was not completed, please indicate reason below:</p> <p><input type="checkbox"/> 1 = Missed Visit</p> <p><input type="checkbox"/> 2 = Patient Refused</p> <p><input type="checkbox"/> 3 = Patient is no longer in the CREST-2 (dead, withdrawn, etc). Confirm that the CREST-2 Form 25 Study Termination or CREST-2 Form 32 Death Form have been completed</p> <p><input type="checkbox"/> 4 = Other, Please specify _____</p> <p>5. Coordinator Code: _____</p>	<input type="checkbox"/> 1=Yes	<input type="checkbox"/> 2=No Skip to 4

How will a site know whether patient should be scheduled for a 1-year follow-up scan?

- Univ of Maryland will send baseline imaging files to UCLA to be read
- UCLA will run the image analysis and notify the SDCC and Dr. Marshall with **CRF H-05**
- PI Dr. Randy Marshall will complete **CRF H-08** that indicates whether or not the patient meets the criterion to return for a follow-up scan
- When Dr. Marshall locks the **CRF H-08**, an email notification will be sent to the site coordinator to indicate whether or not the patient is requested to have a 1-year follow-up scan.
- The site will notify the patient as to whether or not a 1-year follow-up scan is to be scheduled.

Follow-up MRI/CT scan

- Site notification about the follow up MRI/CT scan will be done *via email*
- There will be a reminder at 6 months, 1 month, and 2 weeks to facilitate scheduling of the patients.
- The follow up scan should be scheduled at the time of the patient's 1-year CREST-2 follow up visit if possible.
- **CRF H-04** is used for entering data on the 1-year follow up MRI/CT
- Follow up scanning should be done on the same scanner used for baseline
- Images should be uploaded ***no later than 1 week after image acquisition.***

Schedule of Events

	Screening/ Enrollment	Baseline	Follow up visit 1 yr	Follow up visit 2 yr	Follow up visit 3 yr	Follow up visit 4 yr / final visit
Procedures						
Medical history/exclusion criteria screen	X					
Carotid image screen to ensure no contralateral occlusion or >70% stenosis	X					
Informed consent	X					
Schedule baseline MRI/CT	X					
Confirm CREST-2 randomization completed		X				
Confirm cognitive exam completed or scheduled prior to revascularization or up to and including the 44-day visit for patients randomized to IMM only		X	X	X	X	X
MRI /CT protocol: acquisition, de-identification, file upload		X	X*			
Adverse event evaluation		X	X			

*for those with flow impairment at baseline

Site Check-list

1. Site subcontract for CREST-H in place.
2. Obtain any local IRB approvals needed.
3. Designate the I-Co-I to handle perfusion images, maintain blinding, and receive any “safety read” information
4. Confirm with your own Radiology department how de-identification and uploading of image files are done.
5. Upload a de-identified test MRP and/or CTP scan to U Maryland.



CREST-H Contact Information

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