Carotid **R**evascularization **E**ndarterectomy and **S**tent **T**rial - **H**emodynamics

(an ancillary study to CREST-2)

CREST-H Investigators

Randolph Marshall, MD, MS
Study PI

E. Sander Connelly, MD
Study PI

Ronald Lazar, PhD
Study PI

David Liebeskind, MD
Study PI

George Howard, Dr.PH
Data Management and Statistics

Brajesh Lal, MD
Image Management

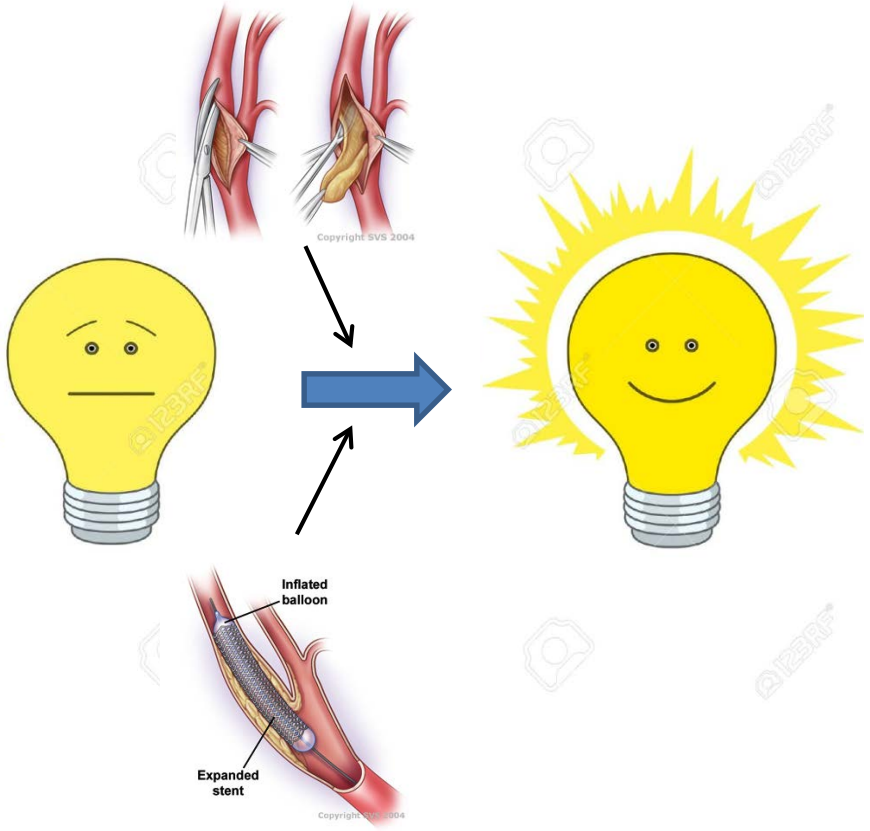
John Huston III, MD
Image Analysis

Thomas Brott, MD
CREST-2 PI

James Meschia, MD
CREST-2 Co-PI

CREST-H Study Question

- Can revascularization (CEA or CAS) improve cognitive impairment among a subset of CREST-2 patients with cerebral hemodynamic impairment?



CREST-H Study Overview

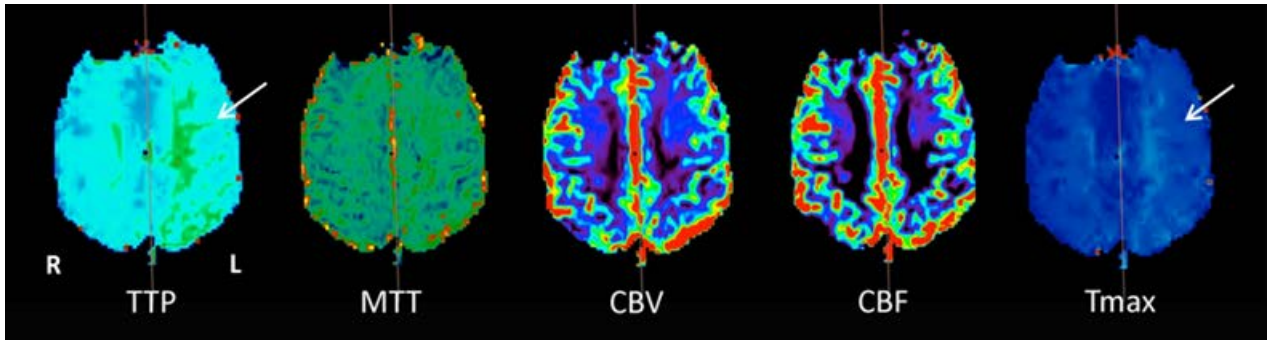
- **Goal**: To determine whether the subset of CREST-2 patients with cerebral hemodynamic impairment (“flow failure”) and mild cognitive impairment benefit cognitively from revascularization.
- **Background**: Prior studies show that patients with high-grade carotid stenosis may have cognitive impairment if they have low 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 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 hypoperfusion.
- **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 (PWI) scan to look for hemodynamic flow failure at baseline. (We also acquire DWI, MRA, GRE, FLAIR, Hi-res T1)

  - 1.5 T or 3.0T MRI acceptable, but 3.0T preferred
  - Patients who have baseline flow failure will receive a 1 year follow up MRI scan



What is so important about CREST-H?

We have a chance to identify an alternative indication for revascularization of high grade asymptomatic carotid stenosis – namely reversing cognitive decline.

"You mean even if we don't reduce the number of strokes our patients have, we might make 'em smarter?"

-interventionist at CREST2 PI meeting in Chicago

Prevalence of mild cognitive impairment in CREST-2

Table 1 . CREST-2 Baseline Cognitive Scores (n=207)

	Test	Mean Z Score	Percentage ≤ 1SD
1	CERAD Learning	0.33	2
2	Digit Span	0.12	14
3	**Animal Naming**	**-0.27**	**31**
4	**COWA**	**-0.79**	**44**
5	**CERAD Memory**	**-1.17**	**57**
	COMPOSITE Z (3 – 5)	***-0.74***	***44***

CREST-H

Other Evidence: RECON

Table 3 Multiple regression on composite neurocognitive z scores, stratified by event type (TIA as qualifying event shown here, n = 32)

Variable	Estimate	SE	95% confidence limits	Pr > |t|
Intercept	−0.973	2.120	−5.370 to 3.424	0.651
CES-D scale	−0.008	0.012	−0.033 to 0.016	0.501
PET ratio dichotomized (0 = abnormal, 1 = normal)	−1.100	0.503	−2.143 to −0.057	0.040
Age	−0.050	0.017	−0.085 to −0.014	0.008
Gender (1 for female, 0 for male)	0.196	0.307	−0.442 to 0.833	0.531
Education (0 for 8th grade, 1 for high school, 2 for college)	0.489	0.289	−0.111 to 1.089	0.105
ICA side (1 for right, 0 for left)	−0.703	0.330	−1.387 to −0.019	0.044
Previous stroke (1 for yes, 0 for no)	−0.298	0.342	−1.007 to 0.412	0.394

Abbreviations: CES-D = Center for Epidemiological Studies-Depression; ICA = internal carotid artery.

Marshall RS et al RECON baseline *Neurology* 2012; 78(4):250-5

CREST-H

More evidence: Balestrini series

- 326 pts with asymptomatic high grade carotid stenosis followed over 36 months
- MMSE declined faster in poor VMR group

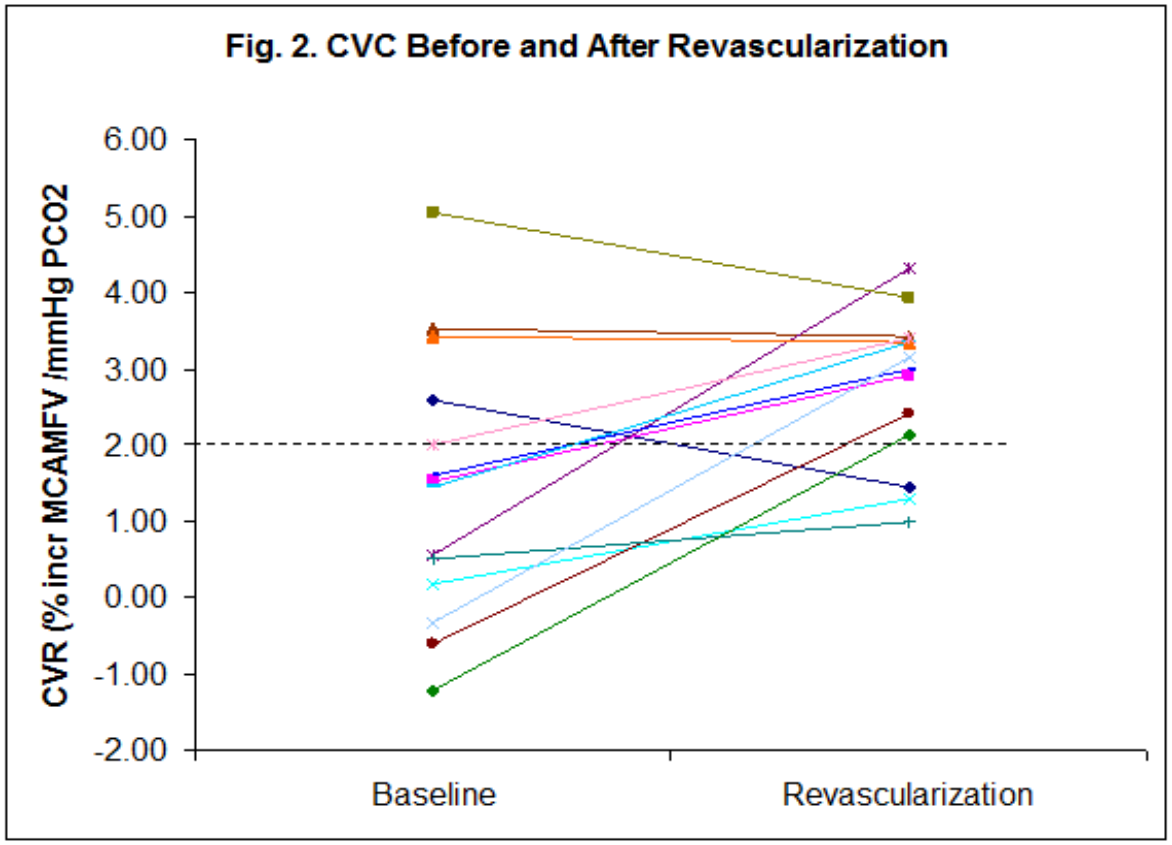
Table 2 Multiple linear regression model predicting decrease in Mini-Mental State Examination score

Variable	Coefficient	Standard error	t	p Value	95% Confidence interval
Pathologic breath-holding index	1.59	0.15	10.77	<0.001	1.29 to 1.88
Age	−0.01	0.15	−0.44	0.661	−0.04 to 0.02
Diabetes	0.13	0.16	0.82	0.410	0.18 to 0.45
Education	−0.03	0.02	−1.56	0.120	−0.07 to 0.01
Constant	2.03	1.06	1.92	0.056	−0.05 to 4.10

Belestrini S et al *Neurology* 2013;80:2145-50

CREST-H

Can we restore hemispheral flow with revascularization? **YES!!**



Marshall RS et al *Stroke* 2003;34:945-9

CREST-H

Cognitive improvement after CAS? (case series data, N=579 pts, 552 ctls)

Table 2. MMSE and MoCA scores of CLI and healthy controls.

			LCI patients					
		Controls	Before CAS	1 month	6 months	1 year	2 years	3 years
MMSE		28.67 ± 1.72	27.79 ± 1.94 a*	27.98 ± 2.15 a*	28.38 ± 2.12 a*,b**	28.55 ± 1.98 b**	28.53 ± 2.03 b**	28.61 ± 1.89 b**
MoCA		20.91 ± 2.08	19.97 ± 2.17 a*	19.91 ± 1.99 a*	20.70 ± 2.31 b**	20.82 ± 2.18 b**	20.93 ± 2.41 b**	20.89 ± 2.03 b**
	Alternating trail test	0.67 ± 0.43	0.59 ± 0.50 a*	0.60 ± 0.59 a*	0.63 ± 0.42	0.63 ± 0.61	0.65 ± 0.44 b*	0.66 ± 0.48 b*
	Cube copying	0.66 ± 0.38	0.57 ± 0.67 a*	0.59 ± 0.87	0.60 ± 0.94	0.67 ± 0.85 b*	0.65 ± 0.41 b*	0.66 ± 0.38 b**
	Clock-drawing	1.81 ± 0.57	1.64 ± 0.38 a*	1.69 ± 0.45 a*	1.70 ± 0.79 a*	1.74 ± 0.74 b**	1.75 ± 0.96 b*	1.78 ± 0.83 b**
	Naming	2.46 ± 0.61	2.39 ± 0.84	2.39 ± 0.71	2.41 ± 0.47	2.40 ± 0.53	2.41 ± 0.50	2.41 ± 0.63
	Attention	4.31 ± 1.19	4.02 ± 1.48 a*	4.15 ± 1.33 a*	4.18 ± 1.16 b*	4.28 ± 1.62 b**	4.30 ± 1.54 b**	4.34 ± 1.49 b**
	Sentence repeating	1.41 ± 0.56	1.34 ± 0.64	1.35 ± 0.65	1.34 ± 0.68	1.38 ± 0.54	1.37 ± 0.69	1.38 ± 0.66
	Verbal fluency	0.35 ± 0.48	0.31 ± 0.39	0.32 ± 0.45	0.33 ± 0.51	0.34 ± 0.40	0.33 ± 0.38	0.34 ± 0.43
	Abstraction	0.68 ± 0.54	0.61 ± 0.72	0.61 ± 0.71	0.62 ± 0.67	0.63 ± 0.48	0.63 ± 0.62	0.64 ± 0.69
	AVLT-delayed recall	3.34 ± 1.16	3.09 ± 1.22 a*	3.16 ± 1.43 a*	3.25 ± 1.29 b*	3.29 ± 1.37 b**	3.32 ± 1.51 b**	3.32 ± 1.47 b**
	Orientation	5.71 ± 0.59	5.64 ± 0.74	5.65 ± 0.65	5.64 ± 0.62	5.65 ± 0.48	5.67 ± 0.55	5.70 ± 0.41

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; AVLT, Auditory–Verbal Learning Test; CLI, cerebral lacunar infarction; CAS, carotid artery stenting.

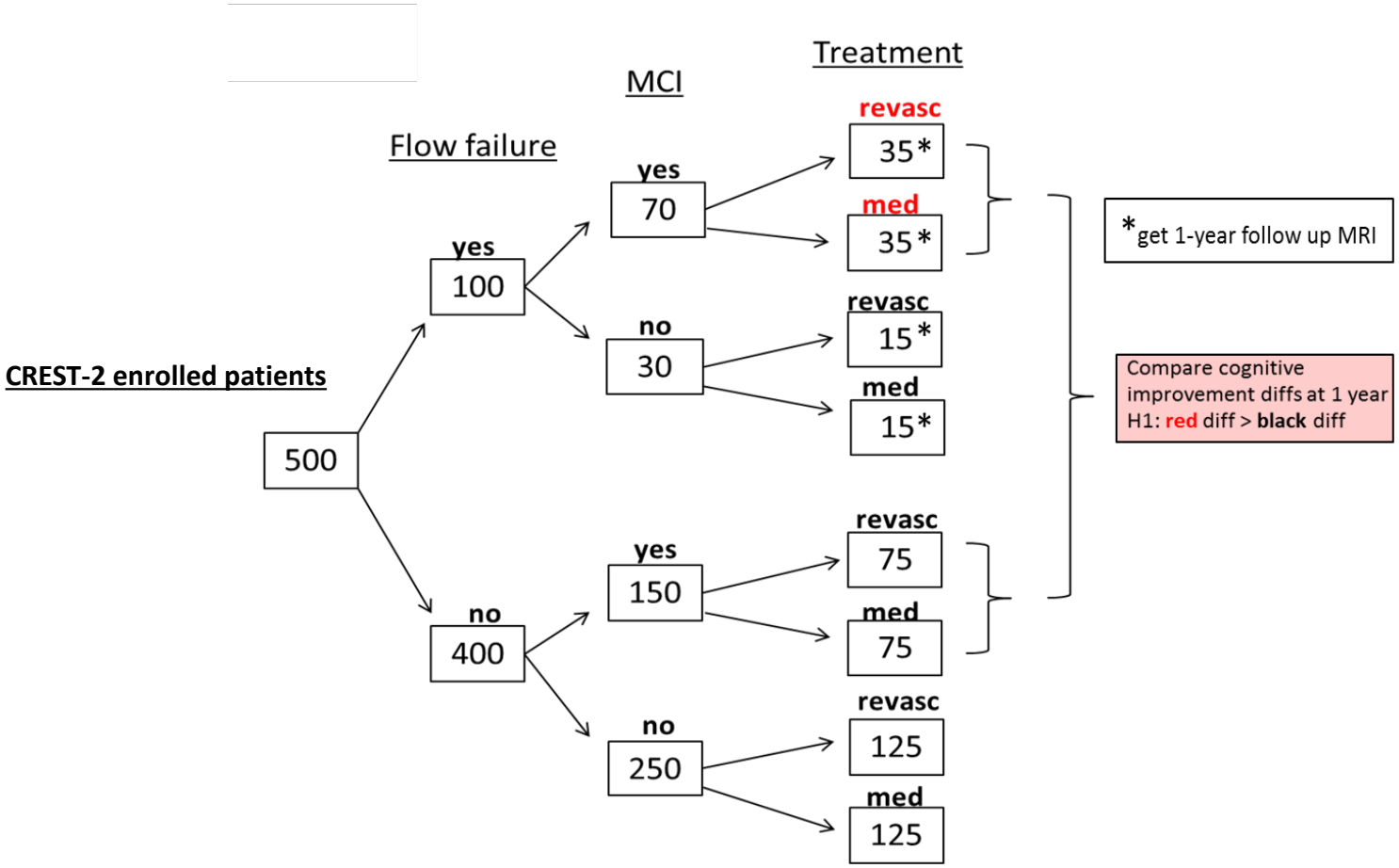
[a], Compared with the controls.

[b], Compared with the LCI patients before CAS.

*$P < 0.05$ and ** $P < 0.01$.

Zhang YX et al *PLoS One* Jun11, 2015

Study Design



CREST-H Inclusion Criteria

1. Randomization into CREST-2 (all CREST-2 inclusion criteria apply)

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

CREST-H

Unique CREST-H Exclusion Criteria

- Unable to have MRI (e.g. metal implants)
- Allergy to gadolinium contrast dye
- Renal failure: either creatinine ≥ 2.5 mg/dl or GFR < 30cc/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

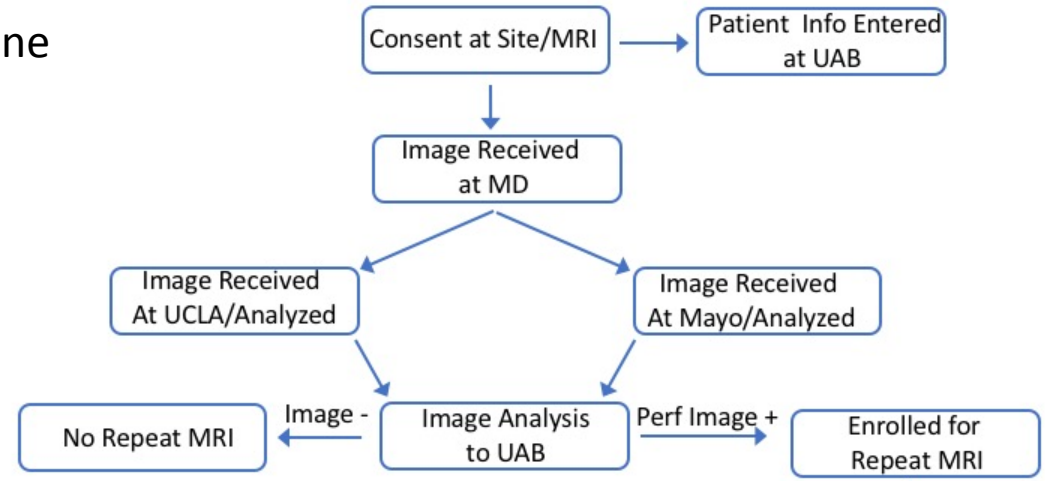
CREST-H

WHAT WE NEED:

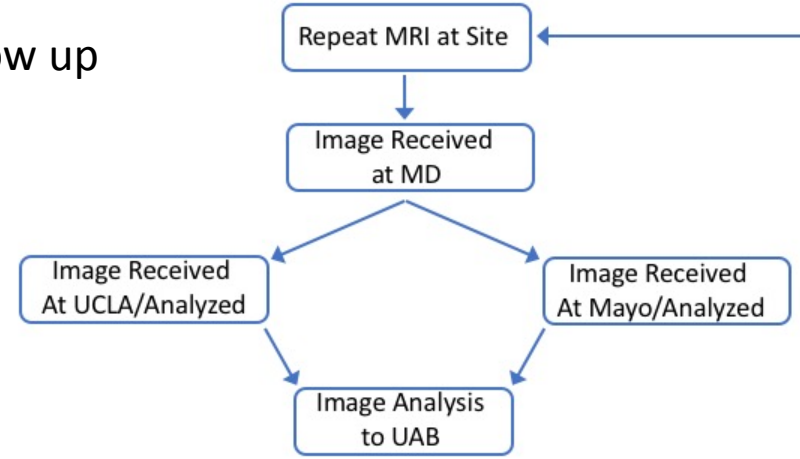
- To participate as a CREST-H site you must have:
  - 1.5T or 3T MRI scanner (3T preferred)
  - The capability to do gado-based MR perfusion on your CREST-2 patients before they get their procedure or within a week of enrollment if randomized to medical therapy alone. Other standard MRI images will also be obtained.
  - A designated, independent co-investigator who can upload de-identified images to the CREST-2 imaging site at U Maryland.

CREST-H Data Flow

Baseline



1-year follow up



CREST-H MRI Sequences

Sequence	Orientation	Slice (mm)	Gap	Slices	TR	TE	TI	FOV(cm)	Freq	Phase	Mode
High Res T1	Sagittal	1.2	0	160	NA	Full Min	900	24	192	192	3D
MRA	Axial	1.4 (0.7)	0	3 x 32	Min	Min	NA	18	384	224	3D
T2 FLAIR	Axial	4	0	36	11000	147	2460	22	256	192	2D
Perfusion*	Axial	5	0	Max for TR	2225	60	NA	24	128	96	2D
DWI/ADC	Axial	4	0	36	10000	Min	NA	22	128	256	2D
GRE	Axial	4	0	36	1700	Full Min	NA	22	128	128	2D

*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

CREST-H Image Transfer

- Images will be transferred from sites to the Vascular Imaging Core Lab at the University of Maryland (https://VIBE.umaryland.edu/VIC)

- University of Maryland will send images to:
  - UCLA (MRP, MRA) for perfusion (flow failure) analysis
  - Mayo Clinic Rochester (DWI/ADC, FLAIR, GRE, HiRes-T1) for structural analysis

Site Check-list

1. Site subcontract for CREST-H in place.
2. Confirm with your own Radiology department how de-identification and uploading of image files is done.
3. Upload a de-identified test PWI scan to U Maryland.
4. Obtain any local IRB approvals needed.
5. Decide who will be the MD designated UI to handle perfusion images and any “safety read” information
6. Make sure the treatment team remains blinded to any PWI results

CREST-H Reimbursement

In addition to CREST-2 payments, sites will receive the following:

- $1,000 in start-up to cover regulatory/IRB costs
- Up to $1,725 per patient to cover imaging and CRF completion
- **Note:** for CREST-H sites with 3.0T MRI scanners, an additional reimbursement will be provided for a “plaque imaging” MRI scan, which would be done as part of the same MRI session as the CREST-H baseline MRI (combined MRI protocol).

CREST-H Contact Information

Protocol/Eligibility/Follow-up:		
Kevin Slane (Project Manager)	(212) 342-115	kjs4@columbia.edu
Alberto Canaan	(212) 342-1491	aac23@columbia.edu
Imaging Protocol		
John Huston III (structural MRI,QA)	(507) 284-2511	jhuston@mayo.edu
David Liebeskind (perfusion MRI)	(310) 825-0703	davidliebeskind@yahoo.com
Image Transfer Protocol		
Brajesh Lal	(800) 492-5538	blal@smail.umaryland.edu
Regulatory/Contract:		
Eldina Cesko	(904) 953-3305	Cesko.Eldina@Mayo.edu
Sothear Luke	(904) 953-8521	Luke.Sothear@Mayo.edu
Sabrina Selman	(904) 953-3062	Selman.Sabrina@Mayo.edu
Recruitment/Retention/Implementation:		
Randolph Marshall	(212) 305-8389	rsm2@columbia.edu
Ronald Lazar	(205) 934-2334	rlazar@uabmc.edu
Electronic Data Entry System (eDES):		
Jason Avery	(205) 934-1780	jbird@uab.edu
Robert Caldwell	(205) 934-3395	rcaldwell@uab.edu
Lisa Irby	(205) 934-5887	lirby@uab.edu
Adverse Event Questions:		
David Rhodes	(205) 934-5842	drhodes@uab.edu
Website Questions:		
Mary Longbottom	(904) 953-7742	Longbottom.Mary@Mayo.edu