

CREST-2 Update



www.crest2trial.org

James F. Meschia, M.D.
Professor and Chair
Department of Neurology

*StrokeNet Meeting
Manhattan Beach
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CREST-2 Parallel Study Design

1 Patient Screened



Men and women who:

- > 34 years old
- > 70% carotid stenosis
- Lack other serious medical complications

2 Randomized



Stenting *

Medical Management

Endarterectomy

Medical Management

*1,240 in each Trial

3 Endpoint



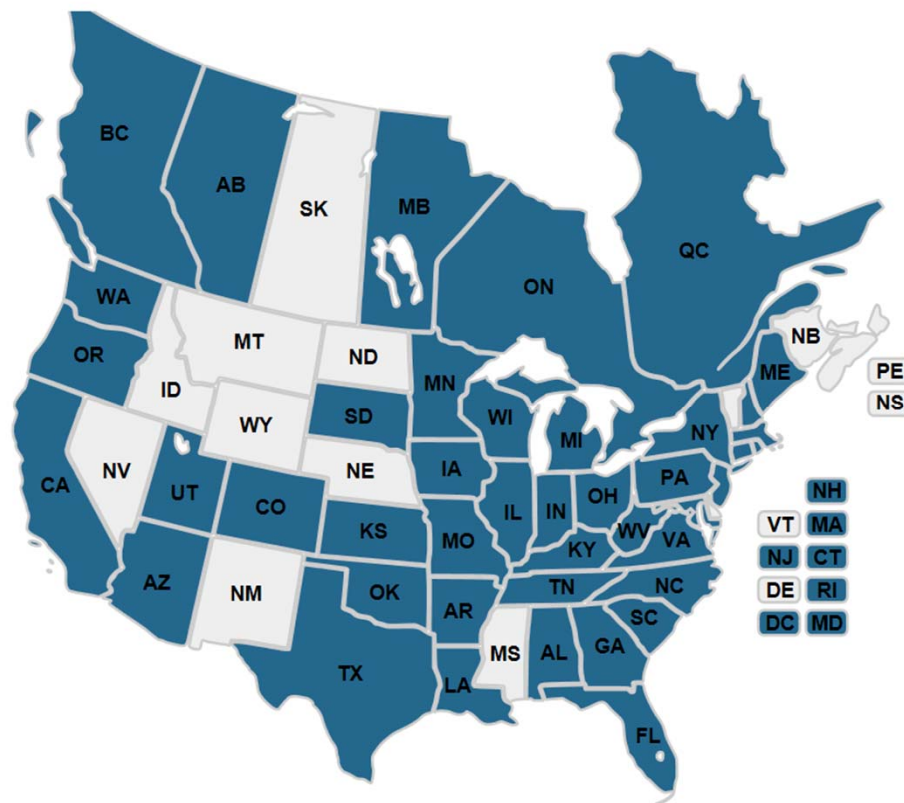
Any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.

Map of CREST-2 Study Center Locations

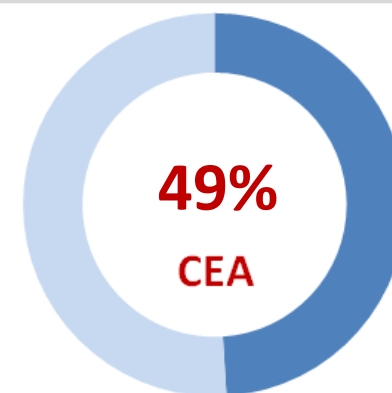
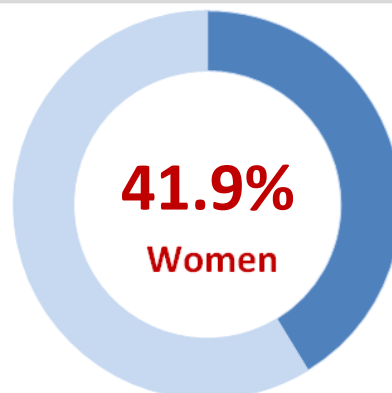
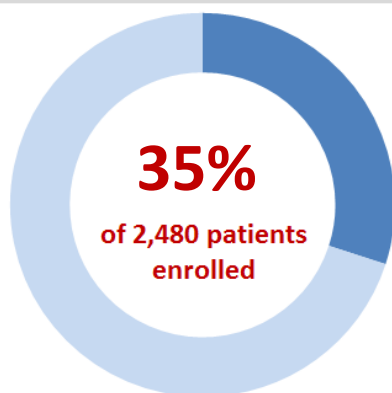
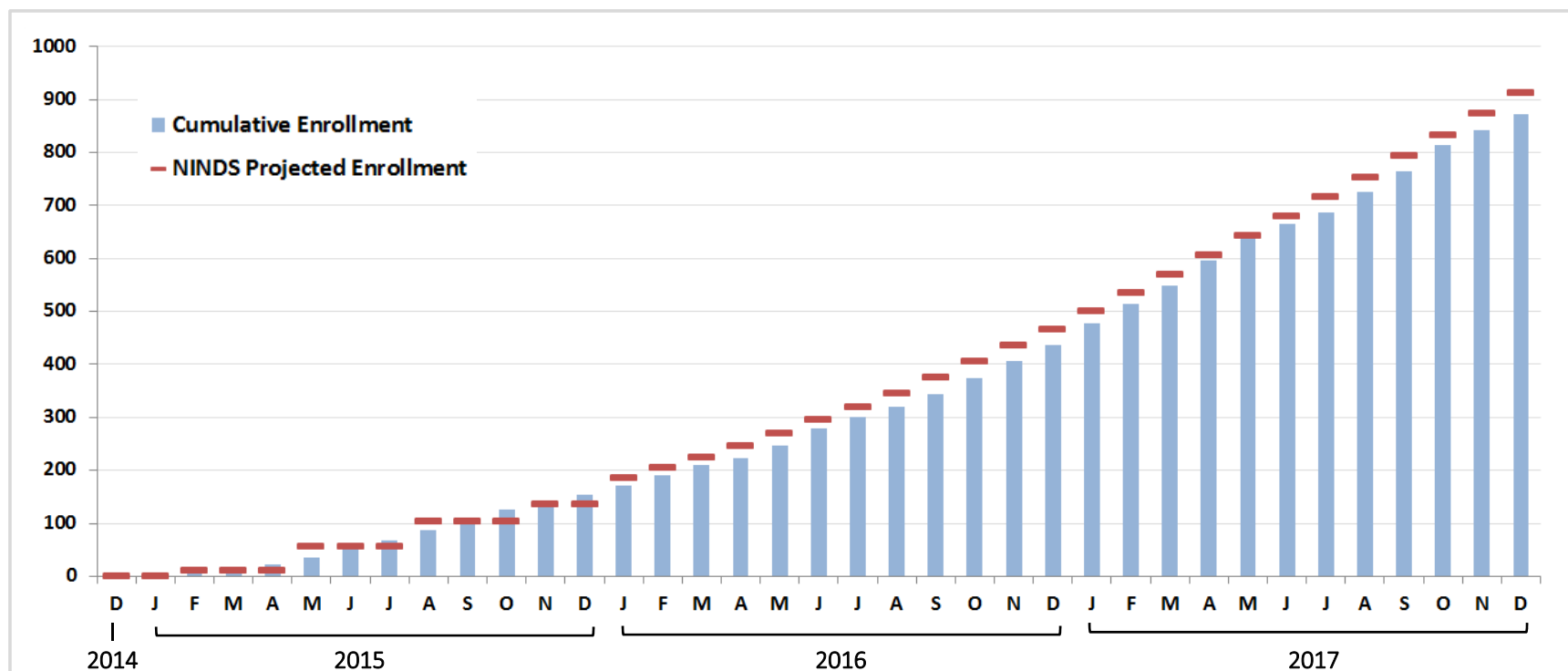
as of January 16, 2018

118 CREST-2 Centers have enrolled 895 of 2,480 CREST-2 Participants

441 CEA Trial; 454 CAS Trial



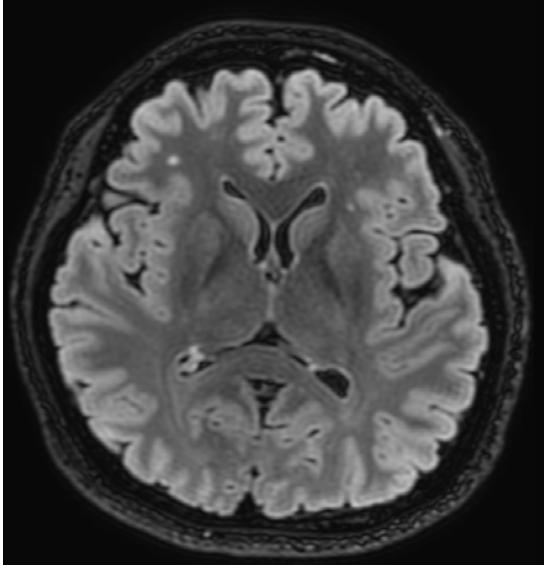
CREST-2 Enrollment



CREST-2 Protocol Version 4.4 Amendment

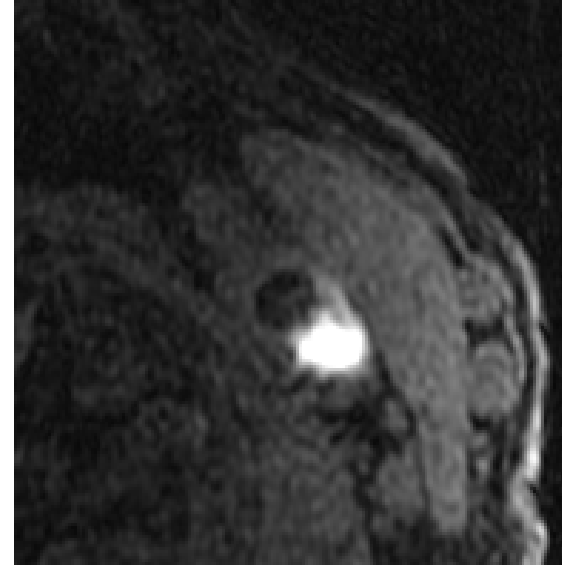
- Add 30 sites
- Add alirocumab option
- Add prasugrel option
- Add baseline plaque imaging option
- Add end of study brain MRI
- Eliminate 44-Day cognitive battery
- Remunerate patients for supplemental BP rechecks
- BP goal lowered to 130/80mmHg

CREST-2 Magnetic Resonance Imaging



Structural Brain Imaging

- High resolution sagittal T1
- Axial T2 FLAIR
- Diffusion weighted with ADC map
- 3D time-of-flight MR angiogram
- MR Perfusion for blood flow quantification
- Gradient echo imaging



Carotid Plaque Imaging

- 3D time-of-flight carotid MR angiogram
- Coronal T1 MPRAGE for carotid hemorrhage
- 3D T1 pre- and post-contrast for carotid lipid core

StrokeNet vs. Non-StrokeNet Recruitment

- StrokeNet: 168 patients have been recruited in 814 clinic months
 - average of 0.21 patients per clinic per month
- Non-StrokeNet: 574 patients have been recruited in 1,914 clinic months
 - average of 0.30 patients per clinic per month
- Recruitment in the StrokeNet sites is about 30% slower than the Non-StrokeNet sites
- In the past year, Non-StrokeNet sites have recruited 308 patients in 1,018 clinic-months (average, 0.30), while StrokeNet sites have recruited 115 patients in 490 clinic-months (average, 0.23)

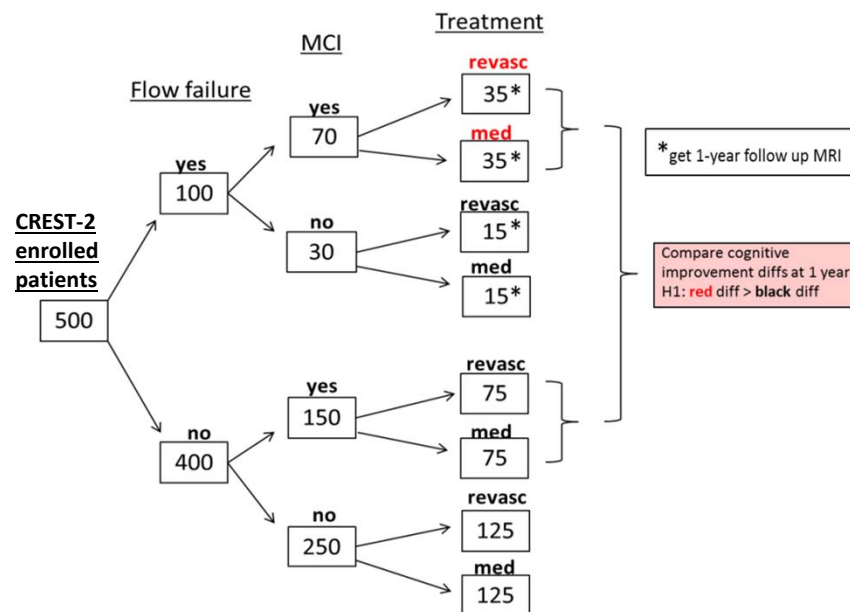
CREST-2: Enrollment by StrokeNet vs. Non-StrokeNet

	Non-StrokeNet				StrokeNet			
Month of Enrollment	# Sites Activated	# Enrolled	Cumulative # Enrolled	#/Site/Month	# Sites Activated	# Enrolled	Cumulative # Enrolled	#/Site/Month
2015-JAN	3	4	4	1.33	0	0	0	0.00
2015-JUN	31	14	48	0.45	9	1	2	0.11
2015-DEC	55	11	132	0.20	20	4	22	0.20
2016-JAN	58	14	146	0.24	22	3	25	0.14
2016-JUN	70	29	234	0.41	28	5	46	0.18
2016-DEC	79	26	355	0.33	39	5	82	0.13
2017-JAN	84	32	387	0.38	40	12	94	0.30
2017-JUN	90	18	521	0.20	45	10	145	0.22
2017-DEC	90	17	673	0.19	45	11	199	0.24

Carotid Revascularization Endarterectomy vs. Stenting Trial – Hemodynamics

- 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.

CREST-H Analysis Design



CREST-H Protocol

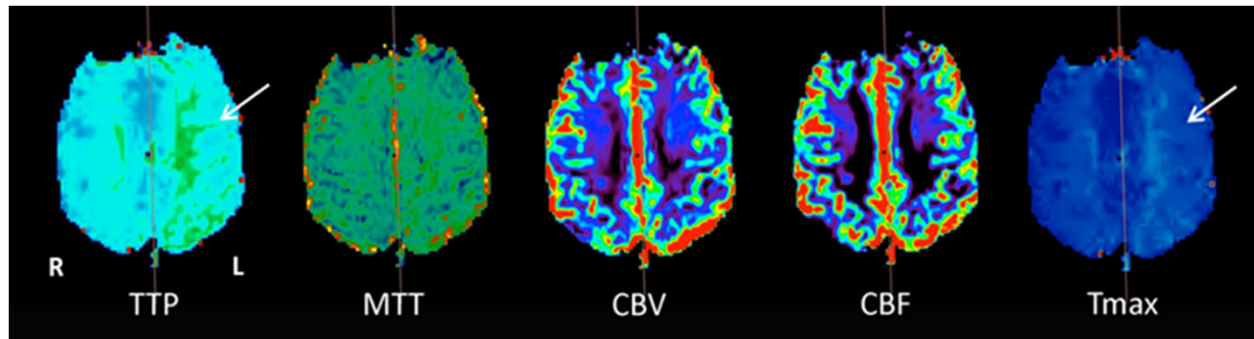
- All patients will receive cognitive testing at baseline and annually as part of the CREST-2 trial

Domain	Test	Behavior Outcome	CREST-2 Composite	CREST-H Composite
Learning	CERAD Word List Learning	Sum of 3 trials	X	
Attention	Digit Span	Number of sequences correctly repeated (forward + backward)	X	
Memory	CERAD Delayed Recall	Number correct	X	X
Executive Function	Animal Fluency	Number correct in 1 min	X	X
	Letter Fluency (Controlled Oral Word Association)	Number correct in 1 min for each of F, A, and S	X	X
	Oral Trail Making A & B	Time to complete Part B		X



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 asymmetry 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 alteration will receive a 1 year follow up MRI scan



Questions & Discussion