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

(an ancillary study to CREST-2)

CREST-H Investigators

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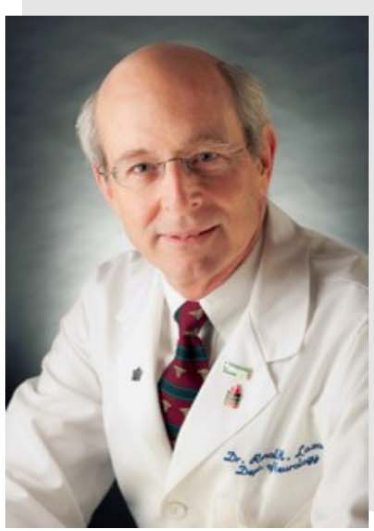

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CREST-H Progress Report

- 54 CREST-2 interested sites are undergoing the on-boarding process for CREST-H (6 dropped out); 30 are StrokeNet
  - Subaward agreements, consent form templates, and protocol documents have been sent to 52 sites
  - 187 coordinators/investigators from 40 sites have completed the training webinar
  - 11 sites are under IRB/CIRB review, 2 approved
  - Greenlighted sites: 1 (Columbia)
- 21 additional sites will be recruited over the next few months
- We are looking for actively enrolling CREST-2 sites with capability to do MR perfusion scans, and a vested interest in the investigation of cerebral blood flow and cognitive outcomes.

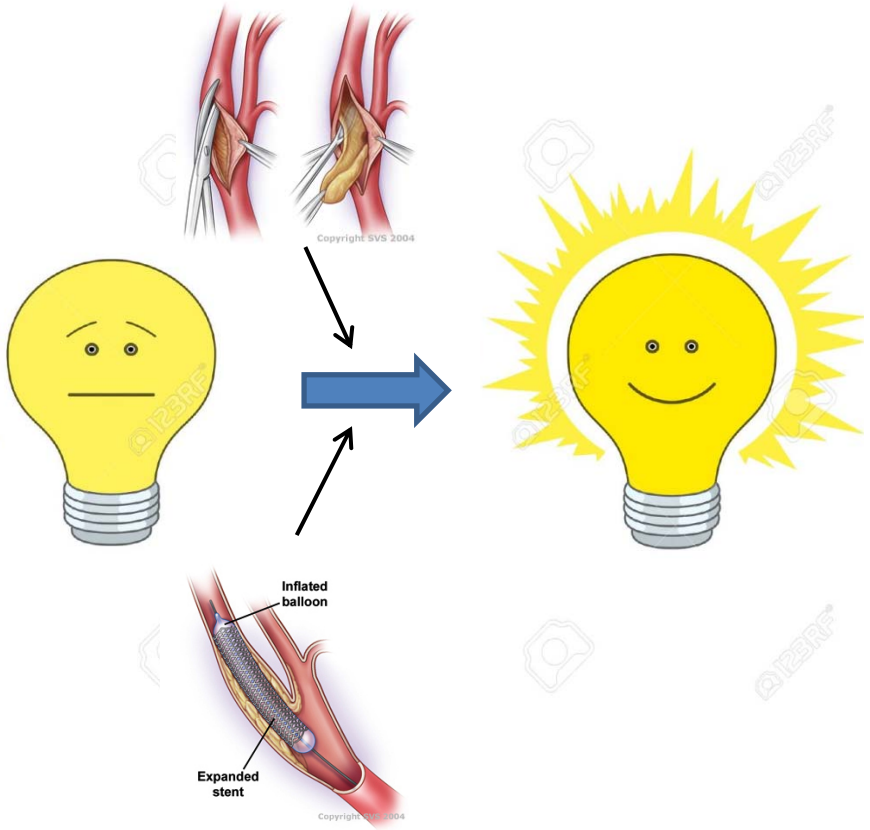
CREST-H

WHAT YOU 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 prior to their 44-day CREST-2 visit if randomized to medical therapy alone. Other standard MRI images will also be obtained.
  - A designated, unblinded, independent co-investigator who can upload de-identified images to the CREST-2 imaging site at U Maryland.

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

- **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

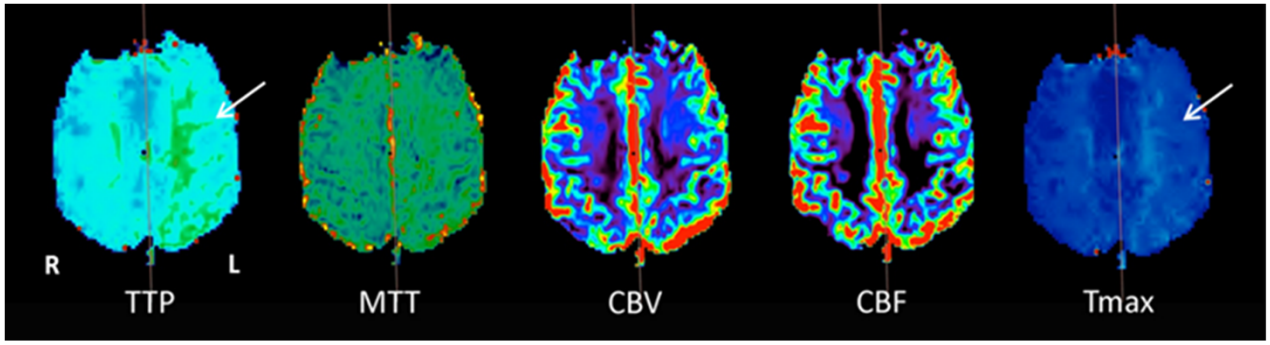
- **Population**: Patients with asymptomatic high-grade carotid stenosis enrolled in the CREST-2 trial.

CREST-H Study Overview (cont'd)

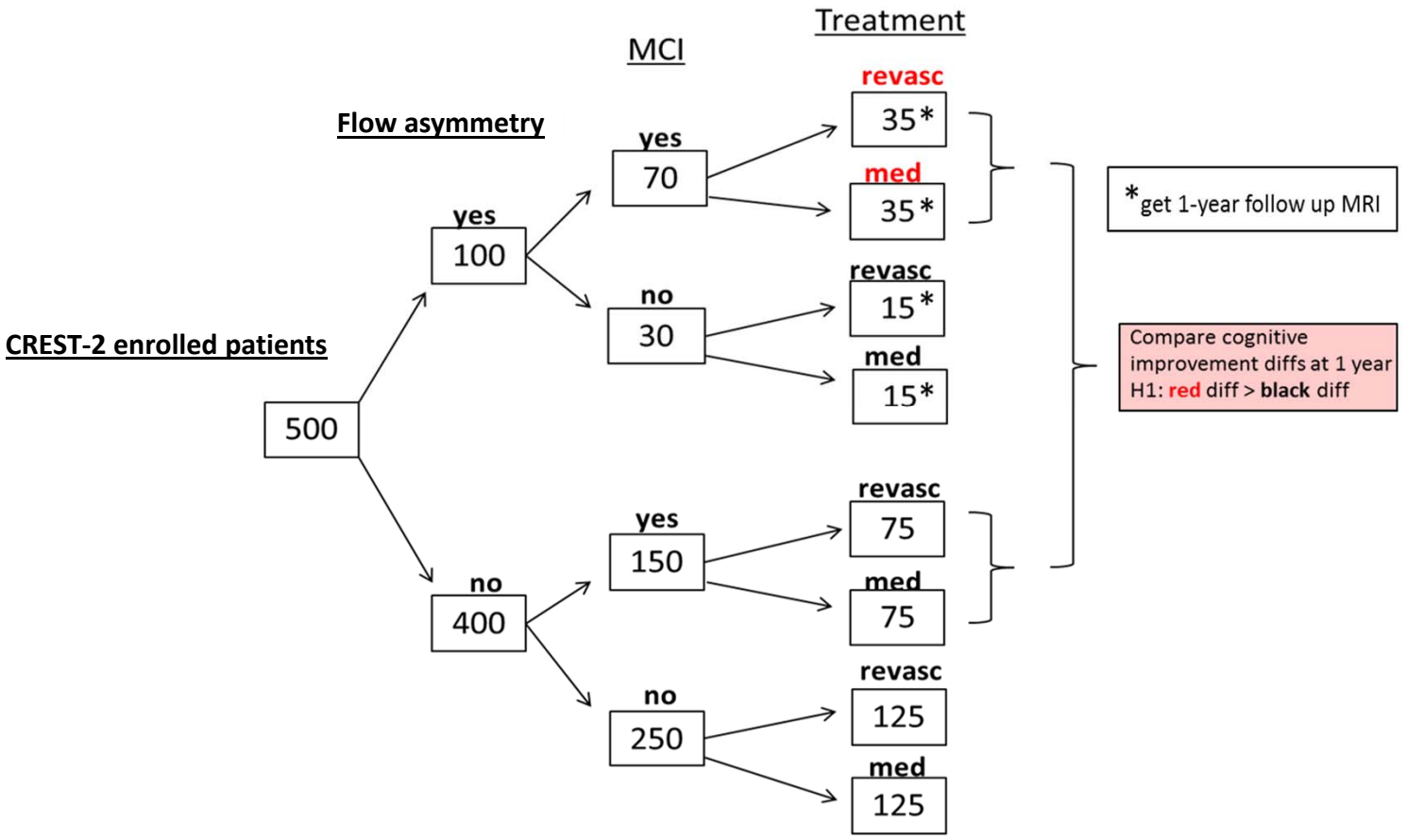
- **Enrollment goal**: 500 patients across 75 CREST-2 sites
- **Unique testing as part of CREST-H**:

  MRI perfusion (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



Study Design



CREST-H

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.

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 scan and another MRI scan at one year if needed.

CREST-H

Additional CREST-H Exclusion Criteria

- Unable to have MRI (e.g. non-compatible metal implants, pacemaker)
- Known 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 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, and protocol agreements).
3. Coordinators and investigators complete CREST-H training webinar.
4. An MRI test imaging set is uploaded successfully to U Maryland, and image quality is approved by UCLA.

CREST-H FAQs

- **Can we use CT perfusion instead of MRI?**
  - No, we are collecting additional MRI information for secondary questions about silent infarcts, WMH, and microbleeds.
- **How much time does the patient spend in the scanner?**
  - The total scanning time is 22 minutes
- **Can the CREST-2 PI be the CREST-H PI also?**
  - Yes, but there needs to be an unblinded investigator as part of the team who will be responsible for managing image files and keeping any perfusion imaging data from getting to the treating MD or patient.
- **Any chance to add on plaque imaging?**
  - Yes. This is in the works as an amendment to the CREST-2 protocol
- **How do we keep the perfusion imaging information from influencing treatment decisions?**
  - MR perfusion data is processed centrally and not released to the CREST-2 PI's or patients.
  - Protocol specifies that interventionalists remain blinded to perfusion results.

Other questions?