CREST Achieves Major Milestone

An update of new data regarding asymptomatic participants.

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The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) compares the results of carotid artery stenting (CAS) and carotid endarterectomy (CEA) in both symptomatic and, more recently, asymptomatic participants. The primary endpoints are stroke, myocardial infarction, and death during a 30-day periprocedural period, and ipsilateral stroke thereafter. CREST has an anticipated enrollment of 2,500 patients, approximately 1,400 symptomatic and 1,100 asymptomatic, making it the largest currently enrolling randomized trial comparing CAS and CEA in North America.

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It has been an exciting year for CREST. With the newest amendment to the protocol, several significant changes have been incorporated into the trial:

- The number of participating centers in the US will be increased from 70 to 110;
- Inclusion of asymptomatic participants with ≥60% stenosis by angiography or ≥70% stenosis by ultrasound;
- Inclusion of subjects with a history of paroxysmal atrial fibrillation (AF) that does not require anticoagulation therapy, and if their physician does not consider them to be at risk for cardiogenic emboli;
- Inclusion of subjects who may be sensitive to antiplatelet therapy, but who are able to tolerate a reduced daily dose of 81 mg of aspirin.

Figure 1. CREST-approved centers and randomization enrollment from 2004 to 2005.

JUSTIFICATIONS

Inclusion of the Asymptomatic Population

Nearly 75% of all stroke victims are previously asymptomatic. Approximately 70% of all CEAs in the US are currently being performed on asymptomatic patients. The Asymptomatic Carotid Surgery Trial (ACST) confirms and extends the benefits of carotid revascularization for this group. Inclusion of asymptomatic subjects in CREST is intended to add to the generalizability of the results. The CREST sample size will provide sufficient statistical power to detect a clinically significant difference between CEA and CAS in asymptomatic participants. As of August 31, 2005, more than 100 asymptomatic participants have been randomized into CREST.

Change in AF Exclusion Criteria

In previous amendments of the protocol, all participants with episodes of AF, known by history or present on entry examination, were excluded from CREST. As a result, many subjects with a history of an isolated episode of AF were ineligible for participation. Whereas chronic or intermittent AF in the presence of heart disease are major risk factors for stroke, the risk of previous AF is modest and has not been shown to exceed importance of other risk factors that are not exclusions for CREST (eg, diabetes and hypertension). Accordingly, the protocol has been amended to allow those individuals that have a history of paroxysmal AF, but have not experienced any episodes in the past 6 months, to gain entry into the trial.

CREST ALL SITE MAP

Inclusion of Subjects Who May Be Sensitive to Antiplatelet Therapy

All participants are required to be on antiplatelet therapy starting 48 hours prior to the procedure and maintained on it for at least 1 year. Previously, the preprocedural regimen consisted of aspirin 325 mg b.i.d., plus either clopidogrel or ticlopidine b.i.d. for those undergoing CAS. After the procedure, the dosage was decreased to aspirin 325 mg 1 to 2 tablets daily. Those undergoing CEA are placed on aspirin 325 mg q.d. preprocedure and maintained on that dose for at least 1 year. The current amendment allows for a lower dosage of aspirin (81 mg) for subjects who are intolerant of the higher dosage. In addition, dipyridamole 200 mg/aspirin 25 mg, clopidogrel, or ticlopidine may be substituted for aspirin after the procedure.

ENROLLMENT AND CREDENTIALING STATUS

Per the CREST protocol, each interventionist requesting credentialing and/or approval to randomize must submit case data (with the Guidant RX Acculink Carotid Stent System and the RX Accunet Embolic Protection System) for peer review by the CREST interventional management committee. As of August 31, 2005, 76 sites have been approved to randomize, a 66% increase over the number of sites approved to randomize 1 year ago. Figure 1 shows the effect these changes have had on recruitment. Since clinical sites have instituted these changes to the protocol, the average monthly recruitment has increased from approximately 20 to 50 randomizations monthly.

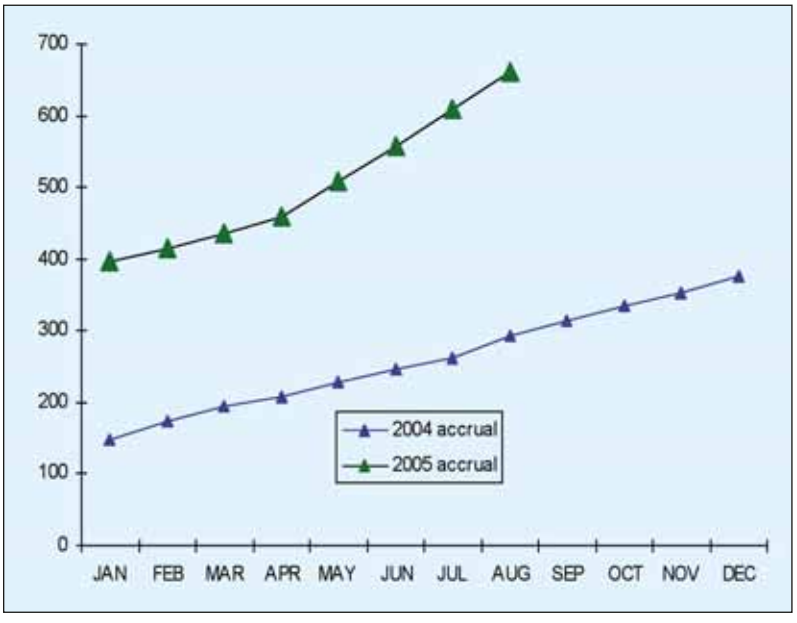

Figure 2. CREST randomization accruals from 2004 to 2005.

CREST BENCHMARKS

The first phase of the North American Symptomatic Carotid Endarterectomy Trial (NASCET I) is widely considered the benchmark trial of carotid intervention, with 659 total participants enrolled. CREST is targeted to surpass this number in September 2005. Figure 2 indicates the total number of randomizations thus far.

> " . . . the largest cohort of carotid stenting patients in North America with protocol-driven neurologic examinations."

Other Important CREST Milestones

• July 2005: 1,246 participants (symptomatic >50% stenosis and asymptomatic >70% stenosis) have been enrolled into the lead-in phase of CREST, making it the largest cohort of carotid stenting patients in North America with protocol-driven neurologic examinations.

• August 2005: Surpassed the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) total enrollment.

• August 2005: CREST is currently transitioning to a new method of data submission. The Direct Data Entry system will allow study sites to enter data collected on the case report forms directly into the computer. Data will be transmitted instantaneously, eliminating the need to copy and submit case report forms. This is truly a huge step forward in the improvement of data quality and the reduction of site queries. Currently, well over 50% of the sites have completed the conversion, with the remainder expected to be "live" in the very near future.

• Currently, there are 93 sites approved to enroll participants in CREST—88 in the US and five in Canada. There are an additional 19 sites that have been invited and are being credentialed.

• With the addition of asymptomatic participants, recent monthly recruitment has surpassed two participants for every working day. ■

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