CREST Update

Meeting the challenges of a randomized clinical trial.

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Carotid artery disease continues to be a major cause of stroke. Carotid revascularization via carotid endarterectomy (CEA) is a proven and effective therapy. For stroke prevention, no medical therapy for any other stroke risk factor has been shown to match the benefit of CEA in patients with symptomatic carotid artery disease.[1] In asymptomatic patients, the protective effect of CEA is less striking; nonetheless, the protective effect is superior to medical therapies.[2] Although CEA has been available for more than half a century, endovascular treatments for cerebrovascular disease are more recent phenomena and offer potential advantages over surgical therapies. For carotid artery disease, carotid artery stenting (CAS) is routinely performed under local anesthesia, is less invasive, is procedurally well accepted by patients, and may shorten hospital stay. Current data indicate that CAS is safe, but efficacy relative to CEA has not been established.

CREST

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is the largest enrolling randomized clinical trial (RCT) comparing the efficacy of CAS to CEA. CREST is also the largest RCT to assess carotid revascularization in both symptomatic and asymptomatic patients with carotid artery disease. CREST differs from the other recent RCTs carried out in the US (SAPPHIRE) because patients at high risk for CEA or CAS are not eligible.[3] Inclusion and exclusion criteria for CREST are similar to those of the cardinal CEA RCTs, NASCET, and ACAS, and are also similar to the eligibility criteria of the recently discontinued RCTs in Europe, EVA-3S and SPACE (Table 1).[1,2,4,5] Primary endpoints include composite of any stroke, myocardial infarction, and death during a 30-day periprocedural period and stroke ipsilateral to the study artery during the follow-up period. Sponsored primarily by the NINDS/NIH, with assistance from Abbott Vascular (Santa Clara, CA), the trial is designed to enroll 2,500 participants in the US and Canada. The investigational devices used in the CAS arm of the study are the RX Acculink stent and the RX Accunet embolic protection system, manufactured by Abbott Vascular.

Early Obstacles

During the early stages of trial development, logistical challenges had an impact on and delayed CREST enrollment. The Centers for Medicare and Medicaid Services (CMS) reimbursed CEA but did not reimburse CAS. Embolic protection became accepted as an effective adjunct of CAS and so was introduced into CREST, necessitating protocol amendments and Internal Review Board approvals. The interventionist-credentialing process was rigorous and time consuming.[6] Necessary FDA-regulatory delays occurred.

TABLE 1. SYMPTOMATIC VERSUS ASYMPTOMATIC ELIGIBILITY

	Symptomatic Eligibility (Transient ischemic attack or nondisabling stroke within 180 days)	**Asymptomatic Eligibility** (No ipsilateral neurological events within preceding 180 days)
Carotid Ultrasound - CREST-certified lab	≥70%	≥70%
Carotid Angiography - Conventional - CTA/MRA*	≥50% ≥70%*	≥60% ≥80%*

**Pending Internal Review Board/Ethics approval of CREST Protocol Amendment V.*

Enrollment and Approval

To bolster enrollment, efforts were made to prioritize trial resources to identify qualified CREST research teams at sites performing a significant number of CEA and CAS procedures.[7] As of August 1, 2007, CREST has approved 113 centers (106 in the US, seven in Canada) and more than 930 investigators to randomize into the trial (Figure 1). Among participating investigators, approximately 196 interventionists and 323 surgeons passed the stringent credentialing requirements to achieve approval to treat participants with CAS and CEA, respectively. Thirty-one investigators have the distinction of receiving approval as both a CREST randomizing interventionist and surgeon.

Figure 1. Map of North America showing locations of CREST sites.

STUDY DESIGN

After the approval of each qualified CREST center, the time-intensive process of the actual start up of the local research team ensued. As the number of centers approved to enroll increased, so did CREST's average monthly recruitment rate (39 in 2005, 58 in 2006) (Figure 2). Having now attained the FDA-mandated maximum number of centers for approval, CREST's recruitment is projected to reach completion in mid-2008.

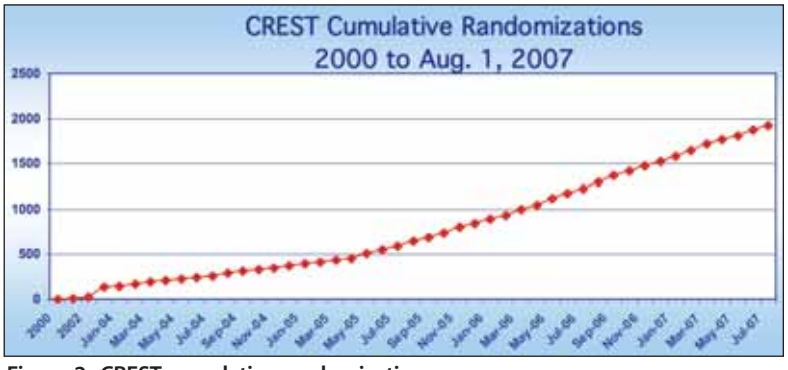

Figure 2. CREST cumulative randomizations.

As of August 1, 2007, CREST has enrolled a total of 1,925 participants (1,056 symptomatics, 869 asymptomatics, 36% female, and 9.5% nonwhite) in its randomized phase. With fewer than 600 participants needed to reach its goal of 2,500, CREST is poised to set forth several initiatives designed to improve the recruitment successes of recent years.

CTA/MRA

Because recognizing that the use of CTA/MRA to determine percent stenosis is becoming the standard of care for the majority of its approved sites, CREST recently requested and received approval by the Data Safety Monitoring Board to allow its use within the trial. Although it is still too early to determine the level of impact this change will have on recruitment, it is expected that many sites will utilize this modality as confirmation when an ultrasound result falls below the required 70% level needed to randomize into CREST. Sites wishing to use the CTA/MRA results would need to record ≥70% stenosis for symptomatic patients and ≥80% for asymptomatic patients. This 20% buffer zone for eligibility above the stenosis criteria by conventional angiography was designed to minimize the likelihood of ineligibility of participants after randomization (Table 1).

CREST Lead-In Phase

As of August 1, 2007, the nonrandomized, interventionist-credentialing phase of CREST enrolled 1,549 out of the maximum 1,800 participants allowed by the FDA. Only a few investigators continue to enroll in the lead-in phase, which will be closed in 2007.

CREST Results

The workload required to complete a multicenter RCT successfully is exceptional. The CREST centers, NIH, FDA, CMS, and the general medical community are eager for

results to demonstrate a return on the considerable resources invested. Regrettably, in an RCT, the key results can only be available after enrollment is completed (mid-2008) and after the first year follow-up of the last randomized patient (mid-2009).

WHAT CAN CREST TELL US NOW?

First, a rigorous credentialing process is likely to be a fundamental strength of CREST or of any RCT comparing a new treatment strategy to an established strategy. CREST interventionists had to demonstrate experience before being admitted into the credentialing phase. Up to 20 cases were required with use of the CREST CAS stent and protection device. Approval could only be accomplished after careful case review by a multispecialty interventionist panel that includes some of the most skilled and experienced interventionists in North America. That nearly 1,600 patients were enrolled in the lead-in phase is numerical evidence for the scrutiny applied. In the WALLSTENT trial and the EVA-3S trial, 30-day outcome results for the CAS arm were disappointing. In both of those trials, the credentialing process was truncated relative to the credentialing process employed in CREST.

Second, maxing out the number of CREST centers appears to have been crucial in navigating roadblocks to enrollment. Originally, CREST had FDA approval for approximately 40 centers, but study leadership realized early on that additional sites would be needed to meet trial enrollment goals. Randomization into a trial comparing two procedural treatments is always a challenge and is a particular challenge in a largely fee-for-service medical system. For potential CREST centers, restricted reimbursement for CAS by CMS and other carriers posed obstacles in interventionists gaining skills to allow entry into CREST. For potential CREST participants, referral patterns for carotid disease were such that the patients often were advised by referring doctors to expect either CAS or CEA before learning about the trial. For principal investigators and coordinators, the extra data requirements of an RCT and lean reimbursement stressed a work environment without extra dollars or extra hours in the day. The large numbers of centers and the highly competent research teams that are participating have been key factors in enabling CREST's enrollment to succeed despite these roadblocks.

As of August 1, 2007, 109 of the 113 approved CREST randomizing sites contributed toward the first 1,925 participants. In the top quartile of enrolling centers, several of the centers that were top enrollers during the first 2 years of CREST have struggled with low randomization rates during the last 2 years. Other centers from the lower quartiles have stepped up with accelerating randomization. The CREST leadership has been surprised by the actions of both groups—those struggling past leaders and the new leaders. If CREST had gone forward with 40 or even 60 selected centers, enrollment would have been much more vulnerable to this unpredictability. With 116 centers, CREST has, in a sense, been insulated and protected from the negative consequences of unpredictable and variable individual-center performance.

CONCLUSION

CREST is the largest randomized clinical trial in progress that compares CEA and CAS for the prevention of stroke. Enrollment in CREST should be completed in mid-2008, and follow-up should be completed in mid-2009. Accordingly, results regarding the comparative efficacy of CAS compared to CEA should become available to practitioners and the public shortly thereafter. ■

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