Commentary

Organizing the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): National Institutes of Health, Health Care Financing Administration, and industry funding

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Abstract

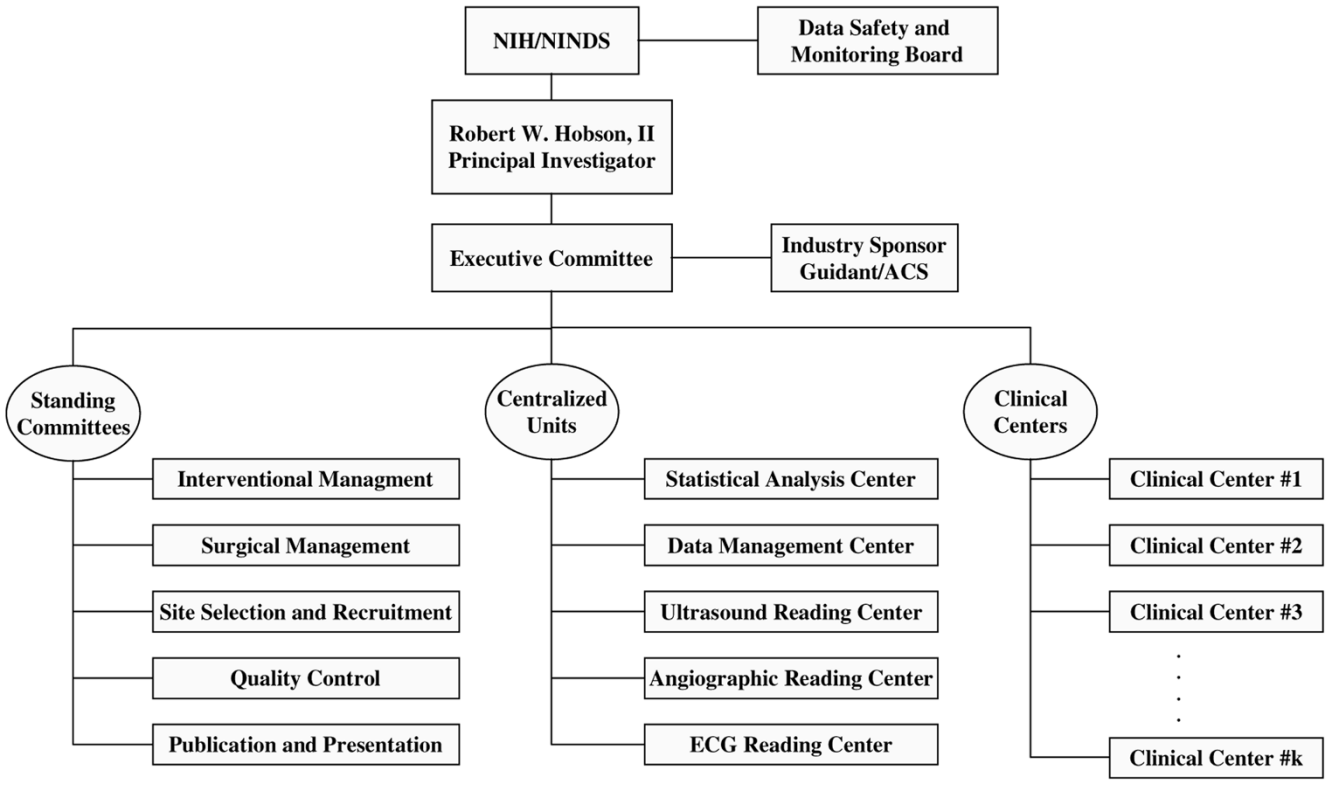
The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a prospective, randomized, multicenter clinical trial of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) as prevention for stroke in patients with symptomatic stenosis greater than or equal to 50%. CREST is sponsored by the US National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institutes of Health (NIH), with additional support by a device manufacturer, and will provide data to the US Food and Drug Administration (FDA) for evaluation of a stent device. Because of budget constraints for CREST, Health Care Financing Administration (HCFA) reimbursement for hospital costs incurred by CREST patients will be essential. The involvement of academic scientists, industry, and three separate government agencies (NIH, FDA, HCFA) has presented many challenges in conducting the trial. A review of the pathways followed to meet these challenges may be helpful to others seeking to facilitate sharing of the costs and burdens of conducting innovative clinical research.

Keywords carotid endarterectomy, carotid stent, clinical trial, government agencies

CREST is a prospective, randomized, multicenter clinical trial of CEA versus CAS for prevention of stroke in patients with symptomatic stenosis greater than or equal to 50% [1]. The study includes a lead-in phase to ensure that research participant treatment is the same for all sites, and to collect data on the outcome of procedures performed by interventionists who have previously been trained and evaluated in the use of the study stent. These data will be reviewed by the Interventional Management Committee that is responsible for approving and credentialing interventionists to perform the stent procedure in CREST. CREST is supported by US NINDS-NIH through the investigator-originated (R01) grant mechanism, and is in the process of being converted into a co-operative agreement (U01). The organizational structure for CREST is shown in Fig. 1.

CAS = carotid artery stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial; DSMB = Data and Safety Monitoring Board; FDA = Food and Drug Administration; HCFA = Health Care Financing Administration; IDE = investigational device exemption; NIH = National Institutes of Health; NINDS = National Institute of Neurological Disorders and Stroke.

Figure 1



CREST organizational structure. ACS, Advanced Cardiovascular Systems. Inc; ECG, electrocardiography.

Several other federal agencies have played major roles in the development of the study. The US FDA is interested in CAS because of its increased use, and because industry sponsors have wanted to broaden the indications for CAS in the management of extracranial carotid occlusive disease. The CREST investigators have worked closely with the FDA to meet the FDA's regulatory responsibilities and CREST's need for data that would underpin requests for regulatory approval of CAS devices.

During the late 1990s, the use of carotid angioplasty (arterial dilatation without insertion of a stent) expanded rapidly, without clinical trial data to support efficacy. In response, the HCFA issued a national noncoverage policy against reimbursement to hospitals for expenses incurred by use of carotid angioplasty in Medicare patients. (Medicare is the US federal government insurance program for people aged 65 years or older, certain young people with disabilities, and people with end-stage renal disease.) This moratorium was issued because of the lack of scientific and clinical evidence regarding the effectiveness of carotid angioplasty. Subsequently, this moratorium against carotid angioplasty was extended to cover carotid stenting as well. Because third party payers use HCFA payment as part of their guidelines for reimbursement, this decision resulted in many payers also declining to reimburse expenses incurred with carotid angioplasty, with or without stenting.

Submission of CREST proposals to the US National Institutes of Health

In 1996, a group of clinical scientists representing a number of disciplines (neurology, cardiology, interventional radiology, neuroradiology, vascular surgery, neurosurgery, and biostatistics /epidemiology) began to develop a proposal for comparing the relative efficacies of CEA and CAS (Table 1). This original submission was a 'proof of principle' trial, in which stents from a variety of manufacturers would be allowed at the discretion of the interventionist. The aim of the study was to contrast 'best' CEA versus 'best' CAS. In January 1997, as part of the preparation for this original grant application, the CREST Executive Committee had several meetings with the HCFA that resulted in written assurance that a funded NIH grant, coupled with FDA approval, would ensure coverage for the parts of the CREST protocol that dealt with 'carotid angioplasty with stents and related services'. As part of the initial application, representatives of the CREST investigative team also had a series of meetings with the FDA to review a draft protocol and to discuss procedures for

Table 1

Timeline of major CREST-related events

Date	Event
March 1996	Grant application development
Jan 1997	HCFA letter of support for CREST group
Feb 1997	1st NIH grant application submitted
Sept 1997	1st NIH grant application review
May 1998	Revised grant application submitted to NIH
May 1998	Negotiations with device companies
July 1998	2nd NIH grant application review
Jan 1999	Grant awarded
May 2000	HCFA withdraws support
June 2000	Executive order for HCFA participation in clinical trials
August 2000	HCFA support reinstated
December 2000	First patient enrolled
March 2001	HCFA decision for modification of noncoverage policy
July 2001	Effective date for HCFA reimbursement policy

the interpretation of results in order to provide 'proof of principle' for CAS in general, and for the broadening of indications for the specific devices produced by manufacturers. The resulting letter of support from the FDA was included in the initial application.

The proposal was peer reviewed for the NINDS in September 1997. The reviewers recommended restricting the study to a single stent device, clarifying the use of ultrasound and angiography in determining stenosis eligibility, further specifying the training and certification of interventionists, and modifying plans for interim analyses. The proposal was then revised and resubmitted to the NIH in May 1998. While awaiting the second NIH review, the CREST Principal Investigator began negotiations with several manufacturers that could provide carotid stents for the trial. By the time of the second peer review, in July 1998, no industry partner had been selected.

After the CREST grant was approved by the US National Institute of Neurological Disorders and Stroke

In early 1999, after approval but before the award of the CREST grant, negotiations continued with the device companies. The Guidant Corporation, the manufacturer of ACCULINK® Carotid Stent System, agreed to work with the CREST investigators to modify the peer-reviewed protocol so that the needs of the NINDS, the FDA, and the Guidant Corporation (Indianapolis, IN, USA) could all be addressed. As part of the agreement, the Guidant Corporation would provide assistance with training of the investigators and with additional site monitoring in order to comply with FDA requirements.

The industry sponsor for the trial holds the FDA investigational device exemption (IDE). An IDE is an exemption that allows an investigational device to be used in a clinical study to collect safety and effectiveness data without complying with all other FDA requirements that would apply to devices in commercial distribution. It is the policy of the NIH, when it funds all or part of a clinical study conducted under an IDE, that the 'awardee institution' and the NIH be kept informed of any significant communications with the FDA about the study. [2] This required line of communication is complicated by the statute that the FDA should communicate only with the sponsor of the IDE, in this case the Guidant Corporation, rather than the Principal Investigator. Because the Guidant Corporation was to hold the IDE, it was responsible for submission of the protocol to the FDA. Negotiations between academic and industry partners in CREST had to carefully define access to data in order to meet the needs of the NINDS, industry, and the FDA, while maintaining appropriate masking and integrity of the study.

Dual goals of the CREST protocol

For the FDA, and to meet the needs of the CREST industrial partner, the data from CREST will also be used to address an aim other than the one originally proposed by the CREST investigators to the NINDS. The CREST investigators and the NINDS are interested in establishing differences in the long-term efficacy of CEA versus that of CAS, whereas the FDA and industry are interested in establishing whether CAS is 'as effective or more effective' than CEA in preventing stroke at 1 year of follow up. These different needs for the data give rise to two 'primary' analyses for CREST, with substantial differences (Table 1). As part of the protocol approved by NINDS peer review, the CREST investigators' null hypothesis of 'no difference between two treatments in the average hazard over 4 years of follow-up' is contrasted with an alternative hypothesis that 'one treatment is better (a two-tailed test)'. These hypotheses will be addressed by contrasting the average time to event using traditional statistical methods for survival analysis.

Through a series of meetings with the FDA, it became apparent that an 'equivalency' analysis would be used by the FDA for decisions regarding the device, including revisions to the instructions for the use of the device that would broaden the categories of patients in which use of the stent would be appropriate. In this 'equivalence' approach, the null hypothesis is that 'CAS has an event rate marginally higher (by a difference of 2.6%) than CEA at the 1-year point in the follow-up'. The alternative

Table 2

Differences between the CREST and the Guidant Corporation/FDA analysis

Aspect of the trial	Superiority (CREST)	Equivalence (Guidant Corporation/FDA analysis)
Hypothesis format	Traditional	Equivalency
Primary events	Stroke, myocardial infarction, or death in 30 days; ipsilateral stroke thereafter	Stroke, myocardial infarction, or death in 30 days; ipsilateral stroke thereafter
Follow-up	Variable follow up (1–4 years)	1-year follow up
Statistical comparison	Differences in hazard of event	Event rate at 1 year

'superiority' hypothesis would be that 'the CAS event rate is as low (within a difference of 2.6%) or lower than CEA (a one-tailed test)' (Table 2). These hypotheses will be addressed by comparing Kaplan–Meier estimates of stroke-free survival at a fixed point during the patient follow up (1 year) after the procedure.

Having two groups deciding the value of CEA versus that of CAS using different hypotheses opens the possibility that 'discordant' study results may occur. For example, the CREST investigators' superiority analysis could conclude that CEA has a lower event rate than CAS, whereas the FDA analysis could conclude that CAS is as good or better than CEA. Such a result would place the scientific community at odds with a possible FDA approval to broaden the label of an already approved device. In consultation with the CREST Data and Safety Monitoring Board (DSMB), the CREST investigators considered the likelihood of discordant findings using a simulation approach that considered a wide range of study outcomes. These results suggest that there is less than a 1/1000 chance of a discordant finding [3].

Logistical Issues

As well as study design challenges introduced by the dual use of the data, many logistical issues needed to be considered. For CREST to move forward, the protocol had to be approved by both NINDS and the FDA. The NINDS would not award the grant until it was clear that a satisfactory agreement could be reached with a stent manufacturer. The final protocol (and subsequent modifications by the CREST investigators) had to be approved by the DSMB appointed by NINDS [4,5]. There was no mechanism, however, for the DSMB and the FDA to meet together, because the DSMB was only advisory to the NINDS. The NINDS program directors for CREST attended all of the FDA and the Guidant Corporation meetings to which they were invited. When subsequent protocol changes were 'suggested' by the FDA, however, the details of these changes had to first be negotiated with the CREST investigators, then with the Guidant Corporation, and then the finalized changes submitted for review by the NINDS and the DSMB. Likewise, when subsequent protocol changes were 'suggested' by the DSMB, the details of these changes had to be negotiated, and then submitted to the FDA for their review. The FDA is required by regulation to complete this review within 30-days of receipt.

Despite efforts to facilitate the communication with electronic mail, the process was made cumbersome by the formal channels of communication from CREST investigators to the NINDS, who then communicated with the DSMB, and from the CREST investigators to the Guidant Corporation, who then communicated with the FDA. The protocol development process was, however, facilitated by joint FDA, NINDS, Guidant Corporation, and CREST investigator meetings. Clearly, in order to co-ordinate research among the NIH, academic investigators, manufacturers, and the FDA, communication is greatly complicated and research may be delayed when the FDA and NINDS peer reviewers do not agree on a single study design.

An additional conflict of responsibilities arose because the FDA required Guidant Corporation (as the holder of the IDE) to be the primary depository of regulatory documents, such as Institutional Review Board approval. However, NINDS requires the office of the Principal Investigator to be the primary depository of these documents. Therefore, obtaining required documentation is a complex organizational feat that requires clear lines of communication and record keeping in order to minimize confusion from staff at the local clinical sites. For example, conflict of interest statements, approved informed consent documents, and Institutional Review Board approval documentation are independently required by the awardee institution for NINDS, and by the Guidant Corporation for the FDA. This duplication creates additional burden in the conduct of the study.

Obtaining reimbursement from the Health Care Financing Administration

As noted above, in January 1997, contingent on NIH funding and FDA approval, the HCFA committed in writing to support reimbursement for the stents placed as part of CREST. However, in May 2000, 3.5 years later, the Princi-

pal Investigator received verbal notification that the HCFA 'would be unwilling to grant [CREST] an exception to the national noncoverage policy for reimbursement for carotid angioplasty with stenting'. Changes in HCFA personnel and policies had occurred in the interim, and contributed to this reversal.

The decision of the HCFA to deny reimbursment resulted in a near shutdown of CREST start-up activities. Although 24 clinical centers had already participated in a CREST investigators' meeting and co-ordinator training session, further initiation activities were placed on hold because of the uncertainty regarding the future of the trial due to the lack of resources to pay for the hospitalization and standard care of patients randomized in CREST.

Over several months, NINDS, the Guidant Corporation, and the FDA met with the HCFA in an attempt to resolve the problem. On June 7, 2000, the President of the United States issued an Executive Order to instruct the HCFA to provide support for patients participating in clinical trials [6]. On August 3, 2000, at an additional meeting with the HCFA, the CREST investigators were informed that, as a NINDS-approved clinical trial, there would be reimbursement for the procedures performed in CREST. On March 19, 2001, the HCFA issued a final decision modifying the noncoverage policy on carotid stenting [7]. The decision was made to cover 'percutaneous transluminal angioplasty of the carotid artery concurrent with stent placement in clinical trials that receive a Category B IDE designation from the FDA' [7]. Category B devices are nonexperimental/ investigational devices.

Conclusion

Although dealing with different government agencies, industry, and an academic institution (with associated subcontracting institutions) created substantial hurdles, communication was a key component for a successful and viable grant application, and remains the key to the successful conduct and completion of CREST. Underlying this is an acknowledgment of the importance of a trial that examines carotid stenting. This is shared not only by the CREST investigators and NINDS, but also by the representatives of industry, the FDA, and the HCFA. Through this commitment by all involved, the substantial hurdles have been overcome and the study is now underway.

As of mid-June 2001, 47 centers have been selected to participate in CREST. Eight centers are approved to enroll participants in the lead-in phase, one center is approved to enroll participants in the randomization phase, and the remaining centers are in various stages of completing the regulatory and certification requirements. CREST is in an optimal position to demonstrate whether academic institutions, government agencies, and industry can work together to complete a complex clinical trial.

Competing interests

None declared.

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Appendix: CREST Executive Committee members

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