



FDA Panel Open Session: Clinical Trial Designs for CAS in Patients Not at High Risk for Adverse Events from Surgical Revascularization

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Objectives

- Provide an overview of Abbott Vascular's carotid stenting programs in the high and normal risk carotid stenting fields.
- Support use of randomized trials to determine safety and efficacy of carotid stenting versus carotid endarterectomy in the normal risk patient population

Overview: Company History

In April, 2006, Abbott Laboratories acquired Guidant Corporation's Endovascular Solutions and Vascular Intervention divisions created Abbott Vascular.

– Guidant obtained first PMA approval for the **RX Acculink® Stent** with the **RX Accunet® Embolic Protection System** for the treatment of high risk patients in August 2004.

– Abbott followed with the second approval in September 2005 for the **Xact® Stent** with the **Emboshield® Embolic Protection System**.

Overview: Company History

Acquisition brought two large normal risk randomized carotid stenting trials into Abbott Vascular.

- **CREST** physician-sponsored study, supported by NIH and Abbott Vascular.
 - **RX Acculink Stent System.**
 - Enrollment of **2,500** randomized patients expected to finish in **mid-2008.**

- **ACT I** Trial sponsored by Abbott Vascular.
 - **Xact Stent System.**
 - Enrollment of **1,658** randomized patients.

Abbott Vascular's Commitment to Carotid Therapy

High Risk Pivotal Studies		Follow - up	# of Patients
ARChER Study	(2000 – 2003)	1 year	657
SECURITY Study	(2002 – 2004)	1 year	398
High Risk Long-Term Studies			
ARChER Long-Term Study	(2000 – 2007)	2-4 years	448*
PROTECT Long-Term Study	(2006, ongoing)	2 years	121
High Risk Post-Approval Studies			
CAPTURE Study	(2004 – 2006)	30 days	4, 144
EXACT Study	(2005, ongoing)	30 days	2, 239
High Risk Post-Market Studies			
CAPTURE 2 Study	(2006, ongoing)	30 days	3,462
CHOICE Study	(2006, ongoing)	30 days	493
Total			11,512 +

* 448 patients initially enrolled in ARChER pivotal study not included in total.

CREST and ACT I Randomized Studies

	CREST Study	ACT I Study
IDE Approval	1999*	2004
Design	Randomized (1:1) comparison of CAS & CEA	Randomized (3:1) comparison of CAS & CEA
Normal Risk Population	2,500 symptomatic and asymptomatic patients	1,658 asymptomatic patients
Patients > 80 yrs	Yes**	No
Randomizing Sites	110 sites in U.S. 10 sites in Canada.	35 sites in U.S.

* Transferred from Guidant Corporation to Dr. R. Hobson in 2003

** Approximately 20% of CREST randomized patients are > 80 yrs.

Importance of Randomization in CAS Trials

- Randomization removes the potential bias in the allocation of patients to the CEA or CAS groups
 - In non-randomized concurrent or historical control, allocation bias can easily occur because the investigator or the participant may influence the choice of intervention, influence may be conscious or sub-conscious.
- Randomization tends to produce comparable groups
 - Measured and unknown prognostic factors and other characteristics of the participants at the time of randomization, will on average, be evenly balanced.
- Validity of statistical tests is guaranteed
 - If randomization is not used, further assumptions of the comparability of the groups and appropriateness of statistical models must be made before the comparisons are valid.

Potential Challenges for Randomized Trials

- Length of enrollment time
- Site availability
- Investigator and participant acceptance

History of Enrollment in CREST Randomized Trial

- Early obstacles to CREST randomized trial enrollment were:
 - CMS reimbursement for participation on an IDE study was not available at the onset of the trial
 - Embolic protection devices were not available
 - Lead-in requirements (20 patients) due to small cohort of experienced carotid interventionalists
 - Original trial design included symptomatic patients only (20% of normal risk population)
 - Slow ramp-up of clinical sites
- CREST trial enrollment increased to current levels (approximately 600 patients per year) after early trial start-up obstacles were overcome.

Contemporary Enrollment of ACT I Randomized Trial

- Current ACT I Trial enrollment:
 - CMS trial reimbursement available
 - Embolic protection devices available
 - Lead-in requirements lower (0-5) due to greater number of experienced carotid interventionists
 - Asymptomatic patients included (80% of normal risk population)
 - Sufficient number of experienced sites for participation in randomized trials
- ACT I trial enrolls approximately 250 patients per year with 35 randomizing sites

Site Availability for Normal Risk CAS Studies

- Currently, approximately 125 independent sites are enrolling CREST and ACT I
- Well over 500 sites performing CAS
- Therefore, a large number of untapped sites could be used for new randomized trials

Randomized Normal Risk Trials

- Randomized trials can enroll in a reasonable timeframe
- There is sufficient number of sites available to support randomized trial designs
- Randomized trials are the cornerstone of evidence based medicine
- Physicians and investigational sites should be encouraged to participate in normal risk carotid randomized trials

Conclusions on Randomized Studies for Normal Risk Population

- Competing non-randomized trials would undermine the completion of the enrolling randomized trials.
- For new therapy approval and reimbursement, requirements should be Level 1 evidence as provided by randomized trials. Abbott supports this position.
 - Abbott is the sole industry participant in CREST.
 - Abbott initiated the randomized ACT I study.
- Fair balance for study sponsors; FDA required randomized trials for product approvals in the normal risk population.

Conclusions on Randomized Studies for Normal Risk Population

- Abbott Vascular believes that non-randomized trials should not be allowed to initiate until the randomized trials complete enrollment:
 - Assure good science
 - Provide evidence based medicine
 - Address public health policy
- Per CMS, randomized trial evidence will likely be needed to support a positive coverage decision for normal risk carotid patients.

