To: Steve Phurrough MD, MPA cc: Rana Hogarth
Marcel Salive MD, MPH

From: Brian G. Firth MD, PhD, FACC

Date: January 6, 2004

Subject: **Carotid Artery Stenting with Embolic Protection:**
A Formal Request for Revision of the Coverage Issues Manual (Revised)

Effective July 1, 2001, Section 50-32 of the Coverage Issues Manual was revised to provide Medicare coverage of percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with carotid stent placement when furnished in accordance with the Food and Drug Administration (FDA) approved protocols governing Category B Investigational Device Exemption (IDE) clinical trials. The manual states that "PTA of the carotid artery, when provided solely for the purpose of carotid artery dilation concurrent with carotid stent placement, is considered to be a reasonable and necessary service only when provided in the context of such a clinical trial, and therefore is considered a covered service for the purposes of these trials. Performance of PTA in the carotid artery when used to treat obstructive lesions outside of approved protocols governing Category B IDE clinical trials remains a noncovered service."

I am writing to formally request a revision of the Coverage Issues Manual to cover carotid artery stents and embolic protection devices for use in the treatment of carotid artery disease in high risk patients if they have received approval from the Food and Drug Administration (FDA) for that purpose, and if they are used according to the FDA-approved labeling instructions. The effective date of coverage should be the first day of the quarter following FDA approval. Cordis submitted the final module, including the one-year primary clinical end-point from the SAPPHIRE trial, to the FDA on October 7, 2003. These data support the safety and efficacy of the Carotid Stenting System (PRECISE™ Stent and AngioGuard™ Embolic Capture Guidewire) for treating high-risk patients with carotid artery disease.

Attached is the supporting documentation for this request. I would be pleased to provide you any additional information that would be of assistance during your review and will keep you informed of the FDA review process.

If you have any questions about this submission, please contact Paul Marshall (908) 412-7130 or Dr. Brian Firth (908) 412-3099.

Carotid Artery Stenting with Embolic Protection: A Formal Request for Revision of the Coverage Issues Manual

Background

An estimated 730,000 people in the United States have a new or recurrent stroke each year. Twenty – thirty percent of strokes are believed to be due to carotid artery atherosclerosis with 25% of stroke victims dying and 60% becoming permanently disabled. More than 70% of stroke victims are over 65 years of age and an estimated 4.5 million stroke victims are alive today. Stroke is the third leading cause of death and according to the American Heart Association Fact Book, in 1999 the societal cost for the care of stroke victims was $45 billion dollars. An estimated 180-200,000 carotid endarterectomy procedures are performed annually in the USA, 20-25% on patients that are considered to be at high risk due to coexisting medical or surgical conditions.

Carotid Endarterectomy (CEA)

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) (Stroke, 1991: 22: 711-720) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) (JAMA. 1995 May 10;273(18):1421-8) demonstrated the benefits of surgical carotid endarterectomy (CEA) and contributed to the widespread adoption of CEA as a means of preventing stroke. However, these studies specifically excluded patients at high medical or surgical risk. In high-risk patients, the results of CEA appear to be substantially less satisfactory, with 30-day mortality rates that are 3 - 20 times higher than reported in ACAS and NASCET, respectively (Wennberg, JAMA, 1998:16:279:1278). Furthermore, the procedure usually requires general anesthesia and is largely confined to treating lesions at or below the carotid bifurcation. In addition, it can result in cranial nerve palsies.

Stenting

Carotid artery stenting is a promising alternative to CEA for the treatment of extra-cranial cerebrovascular disease. Compared with endarterectomy, carotid stenting could offer the following advantages:

- Morbidity and mortality could be reduced in patients who have severe coexisting disease (e.g. coronary artery disease, pulmonary disease, prior radiation or surgery to the head and neck).
- The procedure does not need to be restricted to the cervical segment of the carotid artery; lesions above the jaw and below the clavicle can be readily treated.
- The procedure can be safely performed on restenotic lesions, and simultaneous procedures can be done on carotid, vertebral, and coronary arteries.
- General anesthesia is not required.
- The risk of cranial nerve palsies is virtually eliminated.

Several FDA approved clinical trials are currently being conducted in the United States, the majority of which are registries of procedures performed on high-risk patients. A notable exception is the NHLBI-sponsored randomized trial (CREST) that is focusing on low-moderate risk patients, similar to those patients treated in the NASCET and ACAS surgical carotid endarterectomy trials.

Another important exception is the SAPPHIRE multicenter study (Cordis sponsored) that randomized high-risk patients to either surgery or carotid stenting with embolic protection. This

study also included parallel registries of patients who met the inclusion criteria but were determined by the surgeon (or interventionalist) at each study site to be at too high a risk for carotid endarterectomy (or stenting) and, therefore, inappropriate for randomization. These patients had the opportunity to be treated by the alternate method. A manuscript describing the results of the SAPPHIRE trial will be submitted shortly to the New England Journal of Medicine. We will let you know when it has been accepted and will provide you with an accepted copy at that time.

Device Name and Description

The devices used in the SAPPHIRE trial were the Carotid Stenting System (Cordis PRECISE™ Nitinol Stent and AngioGuard™ XP Embolic Protection System) These are the brand names of the two devices that are used in combination to perform the procedure.

The 5.5F and 6F Cordis PRECISE™ Nitinol Stent Systems are designed to deliver a flexible, self-expanding endoluminal nitinol stent to the carotid vasculature via 5.5F or 6F maximum profile sheathed delivery systems. The systems consist of a nitinol self-expanding stent and a delivery system comprised of an inner shaft, an outer sheath, and a Tuohy Borst valve.

A copy of the proposed *Instructions for Use* submitted to the FDA is attached. (Appendix A).

The AngioGuard XP ™ Emboli Capture Guidewire is designed to be used in a standard fashion to cross the lesion and support placement of the Cordis PRECISE™ Nitinol Stent System. Once the guidewire is across the lesion, the filter basket is expanded in an umbrella-like fashion in the vessel lumen. During the carotid stenting procedure, emboli are collected in the filter basket as the blood passes through it. At the completion of the procedure, the filter is collapsed, capturing the emboli so it can be removed through the guide catheter or sheath introducer and out of the body.

A copy of the proposed *Instructions for Use* submitted to the FDA is attached. (Appendix B).

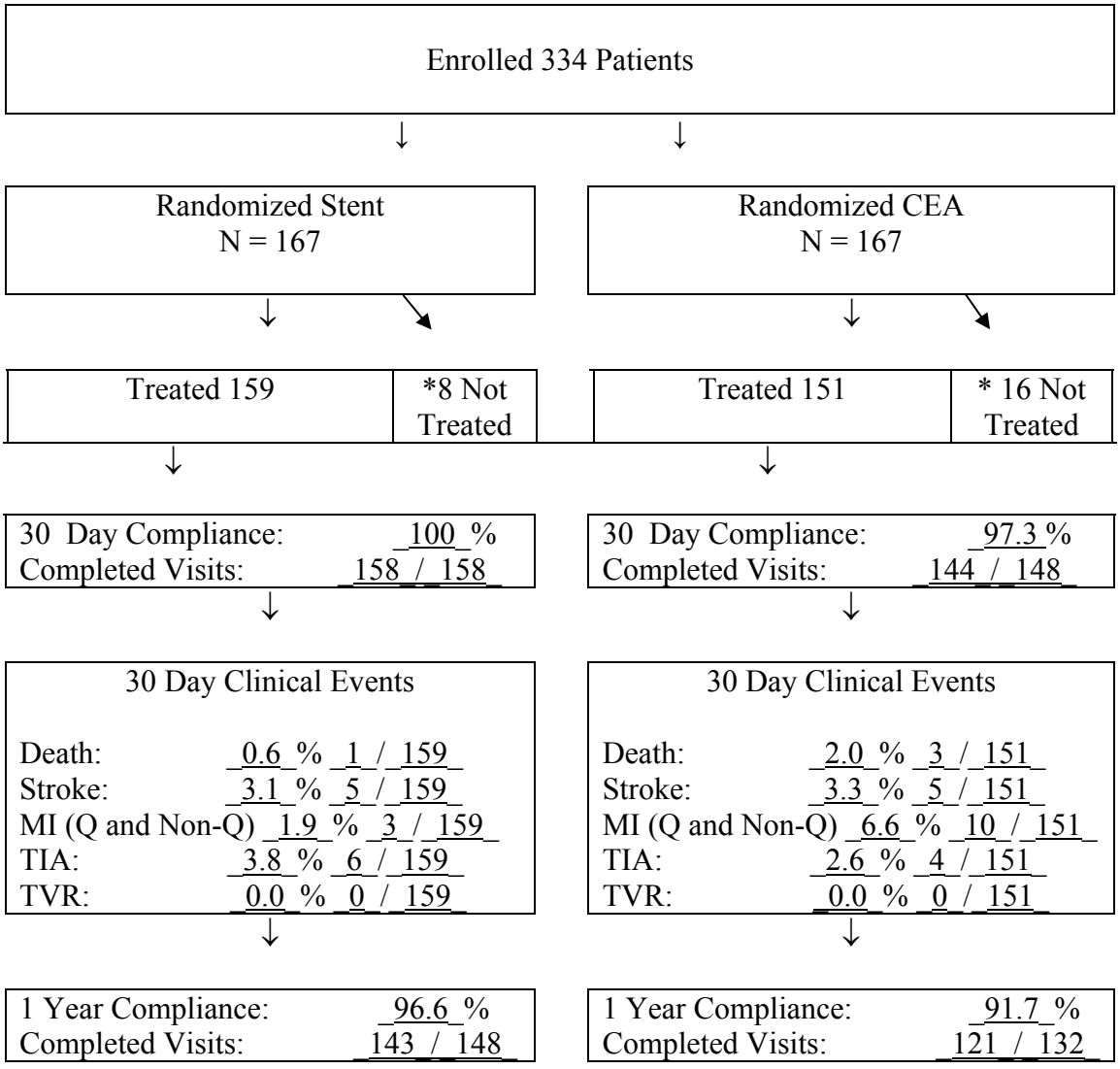
CLINICAL TRIAL DATA SUMMARY:

The details from various SAPPHIRE related trials and studies are attached. Appendix C is a summary of the SAPPHIRE randomized trial (Intention to Treat Analysis) and the SAPPHIRE registry. Appendix D is a summary of the SAPPHIRE randomized population (Per Protocol Analysis). Appendix E is a summary of the carotid stent feasibility study and site-sponsored IDE clinical studies. The SAPPHIRE trial data are repeated in the *Instructions for Use* (IFU) for the devices. Rather than removing them from the IFUs, we would just point out that this information is redundant.

A brief perspective on the clinical trial data is presented below.

At the request of the FDA, a true Intention to Treat Analysis (ITT) was performed of all patients randomized in the SAPPHIRE Randomized Trial, whether or not they ultimately received any treatment at all, to determine whether the Primary End-Point of the trial, namely Non-Inferiority of Carotid Stenting with Embolic Protection to Carotid Endarterectomy at 1 year, was met. In addition, an Evaluable Patient (per Protocol Treatment) analysis was also performed and reported. There were 167 patients randomized to carotid endarterectomy and 167 randomized to carotid stenting. Of these, 16 patients randomized to carotid endarterectomy and 8 patients randomized to carotid stenting were not treated, as shown on the flow diagram and for reasons listed below. Thus, 151 randomized patients were actually treated with carotid endarterectomy and 159 with carotid stenting and form the basis of the Evaluable Patient Analysis. The two major reasons for randomized patients not being treated were 1) patient withdrawal of consent following randomization and 2) patient not meeting inclusion criteria at the time of angiography.

Flow Diagram of Randomized Evaluable Patients



1 Year Clinical Events	
Death:	_6.9_% _11_/_159_
Stroke:	_5.7_% _9_/_159_
TIA:	_6.9_% _11_/_159_
TVR:	_0.6_% _1_/_159_

1 Year Clinical Events	
Death:	_12.6_% _19_/_151_
Stroke:	_7.3_% _11_/_151_
TIA:	_3.3_% _5_/_151_
TVR:	_4.0_% _6_/_151_

Listing of Patients Not Treated and Reasons for Not Treating

Site	Patient	Randomized	Description
3	5	CEA	Diagnostic angio showed patient <60% stenosed and decision made that surgery was not necessary.
3	25	CEA	Patient/family withdrew consent prior to treatment.
3	59	Stent	After sheath insertion patient experienced hypertension followed by aphasia, hemiparesis, and unresponsiveness. Reported as massive stroke. Course complicated by MI and patient died 13 days post-procedure. Narrative notes that neither the AngioGuard nor the Precise Stent were used or attempted.
53	4	CEA	Patient Withdrew Consent prior to Rx.
53	10	CEA	Patient randomized to surgery but not performed. Referred for stenting on 1/8/2001. Died from refractory arrhythmia on 1/11/2001.
53	11	CEA	Patient Withdrew Consent prior to Rx.
53	13	CEA	Patient Withdrew Consent prior to Rx.
67	1	CEA	Disease not meeting I/E criteria; 100% occlusion by ultrasound.
111	2	CEA	Patient Withdrew Consent prior to Rx.
111	4	CEA	Patient Withdrew Consent prior to Rx.
111	12	Stent	Disease not meeting I/E criteria; 40% stenosis at procedural angiography.
113	2	Stent	Disease not meeting I/E criteria.
113	9	Stent	Withdrawn by physician after multiple cancellations; subsequently patient withdrew consent.
113	11	CEA	Patient Withdrew Consent prior to Rx.
219	5	Stent	Patient Withdrew Consent prior to Rx.
236	1	Stent	Patient condition deteriorated prior to Rx.
236	22	Stent	Patient Withdrew Consent prior to Rx.
237	1	CEA	Randomized treatment not performed. Narrative supports finding that Angio revealed involvement of External Carotids Only - Contrary to Ultrasound screen failure
237	2	CEA	Randomized treatment not performed. Ultra sound velocities did not meet Inclusion criteria, but coordinator not informed of this by lab until after she randomized patient.
251	8	CEA	Patient Withdrew Consent prior to Rx. The patient was not treated based on Angiographic Data that did not support ultrasound findings.
263	4	Stent	Day of randomization admitted to hospital with major stroke. Randomized treatment not performed.
268	19	CEA	Patient condition deteriorated prior to Rx. Narrative states that patient was subsequently determined to be at too high risk for any procedure.
307	4	CEA	Patient was found to have highly abnormal blood test results on screening, and PI wanted him to have consult with hematologist prior to procedure. While awaiting appointment with hematologist, the final date for study procedures to be done lapsed, and the patient was cancelled.
307	5	CEA	Patient was randomized, but there were signs and symptom of cardiac anomalies that the PI wanted to work up prior to procedure. Cardiac cath reveal severe aortic stenosis which PI determined made pt too high risk for randomized treatment.

SAPPHIRE Trial: Summary of One-year Results (Intention to Treat Analysis)

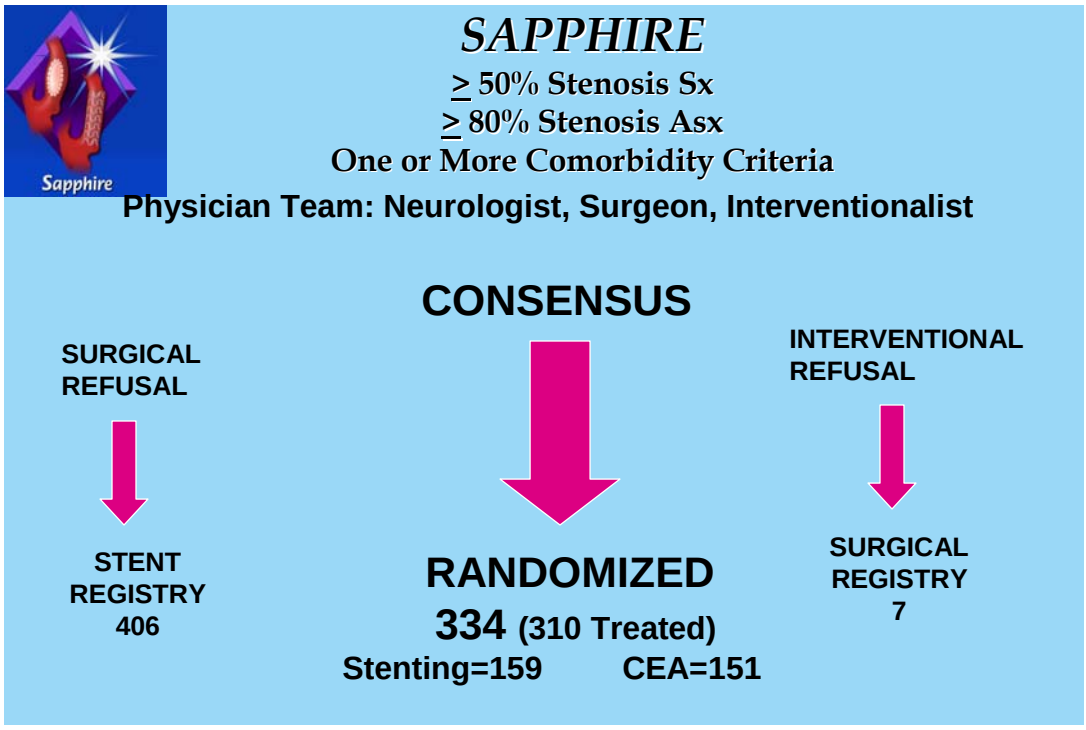
The Intention to Treat Analysis of the primary end-point (a composite of all major events at 1 year) including all randomized patients demonstrated that carotid stenting with embolic protection is not inferior to carotid endarterectomy and is a viable alternative to carotid endarterectomy in high risk patients with symptomatic and asymptomatic carotid artery stenosis. Thus, the primary end-point of the trial was met. Please see Appendix C for an extract from the ITT analysis submitted to the FDA.

In the SAPPHIRE Randomized Trial:

- The composite rate of death, stroke and MI was 12.0% in the stent group vs 19.2 % in the CEA group (P =0.10).
- The composite rate of death and stroke (ACAS definition) at 1 year was 5.4% in the stent group and 7.8% in the carotid endarterectomy group (P=0.51).
- The incidence of major ipsilateral stroke was 0.6% for patients randomized to the stent group and 3.0% for patients that were treated with surgery (P=0.21).
- Cranial nerve injury occurred in none of the stented patients but 4.2% of the surgery patients (P=0.001).
- Target vessel revascularization at 360 days was 0.6% for patients randomized to stenting and 3.6% in those randomized to carotid endarterectomy (P=0.12).

In the SAPPHIRE Registry:

- The preliminary results from the SAPPHIRE Registry patients who were treated by stenting after being turned down for revascularization by the surgeon show that the one-year major adverse event (MAE) rate was 15.8%, a very encouraging result in this very high risk group. The 406 patients in this Registry met the inclusion criteria and did not meet the exclusion criteria for randomization (as determined by the site panel comprising an interventionalist, a neurologist and a surgeon) but were formally turned down for surgery by the surgeon at the site and then entered the stent registry.



- Successful delivery and retrieval of the AngioGuard™ device, was 95.6% (152/159) in the randomized stent arm and 91.6% (372/406) in the stent registry arm.

Appendix C summarizes the clinical results.

SAPPHIRE Trial: Summary of 30-day Results (Intention to Treat Analysis)

The results in the Randomized portion of the SAPPHIRE trial at 30 days are as follows:

MAE (all deaths, strokes and MIs):	Stent: 4.2%; Surgery: 7.2% (p=0.35)
Death or stroke:	Stent: 4.2%; Surgery: 4.8% (p=1.00)

The results in the Registry portion of the SAPPHIRE trial at 30 days are as follows:

MAE (all deaths, strokes and MIs):	Stent: 6.9%;
Death or stroke:	Stent: 5.9%;

SAPPHIRE Trial: Randomized Patients Per Protocol (Evaluable Patients) Analysis

Summary of 1-year and 30-day results:

Statistical Analysis of the Evaluable Patients in terms of the Primary End-Point (composite of Major Adverse Events [MAE]) at 1 year again demonstrated that carotid stenting with emboli protection is NOT inferior to carotid endarterectomy, with a strong trend toward superiority (P=0.053) --- see Appendix D.

The key results in the Randomized portion of the SAPPHIRE trial in the Evaluable Patients are as follows:

1-year follow-up:

MAE (all deaths, strokes and MIs): Stent: 11.9%; Surgery: 19.9%
(P=0.45 by Wilcoxon; P=0.48 by Log Rank; and P= 0.06 by student t-test).
Death or stroke: Stent : 5.0%; Surgery: 7.3% (P=0.48)
Major ipsilateral stroke: Stent: 0.0%; Surgery 3.3% (P=0.03)
Myocardial infarction: Stent: 2.5%; Surgery: 7.9% (P=0.04)

30-day follow-up:

MAE (all deaths, strokes and MIs): Stent: 4.4%; Surgery: 9.9% (P=0.08)
Death or stroke: Stent: 3.8%: Surgery 4.6% (P=0.78)

Comparison of Stenting to Major Surgical Trials

The 30-day and 1-year death or stroke rate should be compared to the results reported in the classic NASCET (symptomatic carotid stenosis) and ACAS (asymptomatic patients) studies. At the same time, it should be noted that :

1) In both the NASCET and ACAS studies co-morbid conditions that are known to increase the risk of major adverse events, criteria that were explicitly used to EXCLUDE patients from these trials, actually form the central basis for INCLUSION in the SAPPHIRE trial. The results in these patients who were excluded from the ACAS and NASCET trials have been reported in the literature (see attached references) to be considerably worse than patients without these co-morbid medical and/or surgical conditions.
2) Since the pre-defined end-points in the SAPPHIRE trial are much more comprehensive than in ACAS or NASCET, and include all-cause mortality and myocardial infarctions at all time-points, we have re-stated the 30-day and 1-year results using the ACAS definition (all deaths and strokes to 30 days [30-day endpoint); PLUS neurological deaths and ipsilateral strokes between 31 days and 1 year [1-year endpoint])

3) It is also worth noting that the ACAS study included asymptomatic patients with >60% diameter stenosis whereas the SAPPHIRE trial only included asymptomatic patients with >80% diameter stenosis. The risk of stroke has been demonstrated to *increase* with increasing severity of obstruction. In asymptomatic patients with stenosis *less than 75%,* one year or annual incidence of stroke was determined to be 1.3-1.7%; conversely, in patients with severe carotid-artery stenosis (*greater than 75 %*) the incidence of stroke was 5.5 percent and the incidence of combined transient ischemic attack and stroke was 10.5% per year, in the absence of surgical treatment. (References: New England Journal of Medicine. 315(14):860-5, 1986 Oct 2; Stroke. 22(12):1485-90, 1991 Dec).
   Therefore, it seems that the asymptomatic patients included in SAPPHIRE were at an increased risk of both stroke (due to severity of stenosis) and other adverse events (due to co-morbid conditions) as compared to the ACAS population. This is important to recognize since approximately 2/3 of patients in SAPPHIRE were asymptomatic.
4) It was not possible to re-state the results using the NASCET definition because their definition apparently counted strokes at 30 days only if they persisted at 90 days. Our data were not collected in such a way as to allow such an adjustment to be made. However, it seems reasonable to conclude that if we could analyze and present our data using the even more restricted death and stroke endpoint used in NASCET, the resulting percentages would be equal to or lower than using the ACAS definition.
5) Against this background of increased risk in both the symptomatic and asymptomatic patients enrolled in the SAPPHIRE Randomized trial, the higher rate of adverse events in the surgical group appears well within what would be expected with carotid endarterectomy. Furthermore, carotid stenting with embolic protection, is clearly and statistically NOT INFERIOR to carotid endarterectomy and has a generally LOWER complication rate in this study than carotid endarterectomy. In fact, when the analysis is done on an evaluable patient basis, stenting is significantly superior to carotid endarterectomy in terms of the primary end-point (MAE at 1 year), major ipsilateral stroke and myocardial infarctions (all $p<0.05$).
6) The results in the SAPPHIRE Stent Registry represent the results in an even higher risk cohort than the randomized trial who were refused surgery by the surgeon after the panel (surgeon, interventionalist and neurologist) at the site had determined that the patient satisfied the inclusion and did not meet the exclusion criteria. The results of this registry should be interpreted in this light.

Feasibility Trial and Site IDEs

These data are supplied as supplemental information (Appendix E).

The Feasibility Trial was conducted at sites as training before they entered the SAPPHIRE trial in order to familiarize the operators with both the Cordis PRECISE™ Nitinol Stent and the AngioGuard™ XP Emboli Capture Guidewire System. Since the AngioGuard ™ System was only rolled into the study part way through the trial, only

one-third (85/260) of the patients had the benefit of an emboli protection system. This accounts for the slightly higher ipsilateral stroke rate seen in this registry as compared to the SAPPHIRE trial. As can be seen in appendix E, in patients who had AngioGuard™ Emboli Capture System the major and minor ipsilateral stroke rates were 0.0% and 3.5%, respectively, at one-year. These data strongly suggest that the AngioGuard™ Emboli Capture System reduces the incidence of cerebral embolic events and the resulting stroke rate. These data were monitored and managed in the same manner as the SAPPHIRE trial in terms of data management and independent adjudication of adverse events.

The site IDE data were requested by the FDA and are included for the sake of completeness. These studies were not designed, sponsored, or monitored by Cordis. The data were provided to Cordis by the individual sites who all used the PRECISE™ Stent and AngioGuard™ System. Twenty-five of the thirty sites had not been involved in the SAPPHIRE trial and thus largely represent the experience at different centers from those involved in the SAPPHIRE trial.

Physician and Hospital Staff Training Program

Cordis submitted to the FDA a proposal for an extensive physician and hospital staff training program to make certain that physicians and hospital staff involved in the implantation and post-operative care of patients receiving the Cordis PRECISE™ Stent and utilizing the AngioGuard™ Emboli Capture Guidewire are well qualified to perform this procedure and are familiar with the products and post-operative patient management. Approval of this well-defined, detailed training program is an integral part of the PMA application and required element for approval of the carotid stening by the FDA. Institutions that are not currently performing non-coronary endovascular interventions would first be required to demonstrate competency in vessels other than the carotid before they could be eligible for training to do carotid stenting procedures.

Upon completion of the Cordis training program, participants should be able to demonstrate competency in the following areas:

- Clinical evaluation of carotid artery disease and the medical, surgical and interventional treatment options.
- Symptomatic and asymptomatic patient screening for carotid artery disease through interpretation of duplex ultrasound, Magnetic Resonance Angiography, and other angiographic information.
- Clinical and anatomic indications for carotid stenting based on the FDA-approved clinical indication.
- Equipment selection and use, preparation and deployment of the PRECISE Systems in conjunction with ANGIOGUARD Systems.
- Post procedure management and patient follow up.
- Procedure and equipment troubleshooting.

Please see Appendix F.

Hospital Qualifications

As noted above, physicians and hospital staff are both essential to quality patient outcomes. Therefore, the Cordis training program includes physicians and hospital staff that are responsible for patient management.

Status of FDA Approval

Cordis Corporation submitted a PMA application to the FDA on October 7, 2003. An FDA Advisory Panel is expected, but a date for the Panel has not been selected.

Draft Labeling (Cordis PMA Submission)

Indications for Use

Carotid artery stenting with embolic protection is indicated for use in the treatment of carotid artery disease in high-risk patients. High-risk is defined as patients with neurological symptoms (one or more TIA's or one or more completed strokes) and ≥50% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram;

OR

Patients without neurological symptoms and ≥80% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram.

Symptomatic or asymptomatic patients must also have one or more condition(s) that place them at high-risk for carotid endarterectomy.

(See appendices A & B for the complete instructions for use)

Suggested Coverage Language

Cordis recommends the following coverage language:

CMS is withdrawing the current non-coverage instructions for carotid artery stenting procedures and replacing it with the following instruction.

Effective [enter the date of the first day of the quarter following FDA approval] Medicare covers carotid artery stents and embolic protection devices for use in the treatment of carotid artery disease in high risk patients if these specific devices have received approval from the Food and Drug Administration (FDA) for that purpose, and if they are used according to the FDA-approved labeling instructions.

Site of Service

Medicare has identified this service as inpatient only. Cordis agrees with this decision because of the need to monitor patients for any sign of neurological changes for a minimum of 24 hours post-procedure.

"PTA of the carotid artery concurrent with carotid stent placement may not be performed in a hospital outpatient setting". (Program Memorandum: Intermediaries/Carriers, Transmittal AB-01-74, dated May 3, 2001).

Coding and Payment

Diagnosis code:	433.01 Occlusion and stenosis of precerebral arteries; carotid artery
Procedure codes:	39.50 Angioplasty or atherectomy of non-coronary vessel Percutaneous transluminal angioplasty (PTA) of non-coronary vessels and 39.90 Insertion of non-drug-eluting, non-coronary artery stent(s)
DRG Assignment:	DRG 533 - Extracranial procedures with complication or co-morbidity (cc) or DRG 534 - Extracranial procedures without complication or co-morbidity (cc)

CPT Code Application

On October 6, 2003, the American College of Cardiology submitted an application to the American Medical Association CPT Editorial Panel requesting two new CPT codes for carotid artery stenting procedures. This application was co-sponsored by the following 10 medical societies: American Academy of Neurology, American Association of Neurological Surgeons, American College of Cardiology, American College of Radiology, American Society of Interventional & Therapeutic Neuroradiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society for Cardiovascular Angiography and Interventions Society of Interventional Radiology and the Society for Vascular Surgery.
See Appendix H.

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(Highlighted references are included as attachments)

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Listing of Appendices

Instructions for use

- PRECISE™ Carotid Stent (Appendix A)
- AngioGuard™ Embolic Protection System (Appendix B)

Summary of Clinical Results

- SAPPHIRE Randomized Trial -Intention to Treat Analysis (Appendix C)
- SAPPHIRE Registry (Appendix C)
- SAPPHIRE Randomized Trial -Evaluable Patients: Per Protocol Analysis (Appendix D)
- Feasibility Study (Appendix E)
- Site-Sponsored IDEs (Appendix E)

Physician training program (Appendix F)
Overview of non-Cordis sponsored clinical trials (Appendix G)
CPT code application (Appendix H)
Nine selected publications