

## **Appendix A: General Methodological Principles of Study Design**

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

### **1. Assessing Individual Studies**

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological

strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

## **2. Generalizability of Clinical Evidence to the Medicare Population**

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

### **3. Assessing the Relative Magnitude of Risks and Benefits**

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

## **Appendix B: National Coverage Determination**

### **National Coverage Determination Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting**

Effective xxx xx, 2007, Medicare covers PTA of the carotid artery concurrent with the placement of an FDA-approved carotid stent with embolic protection for the following:

- Patients who are at high risk for carotid endarterectomy (CEA) and who also have symptomatic carotid artery stenosis  $\geq 70\%$ . Coverage is limited to procedures performed using FDA-approved carotid artery stenting systems and embolic protection devices;
- Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the NCD on carotid artery stenting (CAS) post-approval studies (Medicare NCD Manual 20.7);
- Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis  $\geq 80\%$ , in accordance with the Category B IDE clinical trials regulation (42 CFR 405.201), as a routine cost under the clinical trials policy (Medicare NCD Manual 310.1), or in accordance with the NCD on CAS post-approval studies (Medicare NCD Manual 20.7).

*Coverage is limited to procedures performed using FDA approved carotid artery stents and embolic protection devices.*

*The use of a distal embolic protection device is required. If deployment of the distal embolic protection device is not technically possible, then the procedure should be aborted given the risks of CAS without distal embolic protection.*

Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA.

Significant comorbid conditions include but are not limited to:

- congestive heart failure (CHF) class III/IV;
- left ventricular ejection fraction (LVEF)  $< 30\%$ ;
- unstable angina;
- contralateral carotid occlusion;
- recent myocardial infarction (MI);
- previous CEA with recurrent stenosis;
- prior radiation treatment to the neck; and

- other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II.

Symptoms of carotid artery stenosis include carotid transient ischemic attack (distinct focal neurological dysfunction persisting less than 24 hours), focal cerebral ischemia producing a nondisabling stroke (modified Rankin scale < 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax). Patients who have had a disabling stroke (modified Rankin scale  $\geq$  3) shall be excluded from coverage.

The determination that a patient is at high risk for CEA and the patient's symptoms of carotid artery stenosis shall be available in the patient medical records prior to performing any procedure.

The degree of carotid artery stenosis shall be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient's medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis must be confirmed by angiography at the start of the procedure. If the stenosis is determined to be less than 70% by angiography, then CAS should not proceed.

In addition, CMS has determined that CAS with embolic protection is reasonable and necessary only if performed in facilities that have been determined to be competent in performing the evaluation, procedure and follow-up necessary to ensure optimal patient outcomes. Standards to determine competency include specific physician training standards, facility support requirements and data collection to evaluate outcomes during a required reevaluation.

CMS has created a list of minimum standards modeled in part on professional society statements on competency. All facilities must at least meet CMS's standards in order to receive coverage for carotid artery stenting for high risk patients.

- Facilities must have necessary imaging equipment, device inventory, staffing, and infrastructure to support a dedicated carotid stent program. Specifically, high-quality X-ray imaging equipment is a critical component of any carotid interventional suite, such as high resolution digital imaging systems with the capability of subtraction, magnification, road mapping, and orthogonal angulation.
- Advanced physiologic monitoring must be available in the interventional suite. This includes real time and archived physiologic, hemodynamic, and cardiac rhythm monitoring equipment, as well as support staff who are capable of interpreting the findings and responding appropriately.
- Emergency management equipment and systems must be readily available in the interventional suite such as resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.

- Each institution shall have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program shall be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties to determine appropriate physician qualifications. Examples of standards and clinical competence guidelines include those published in the December 2004 edition of the American Journal of Neuroradiology, and those published in the August 18, 2004 Journal of the American College of Cardiology.
- To continue to receive Medicare payment for CAS under this decision, the facility or a contractor to the facility must collect data on all carotid artery stenting procedures done at that particular facility. This data must be analyzed routinely to ensure patient safety. This data must be made available to CMS upon request. The interval for data analysis will be determined by the facility but shall not be less frequent than every 6 months.

Since there currently is no recognized entity that evaluates CAS facilities, CMS has established a mechanism for evaluating facilities. Facilities must provide written documentation to CMS that the facility meets one of the following:

1. The facility was an FDA approved site that enrolled patients in prior CAS IDE trials, such as SAPPHIRE, and ARCHER;
2. The facility is an FDA approved site that is participating and enrolling patients in ongoing CAS IDE trials, such as CREST;
3. The facility is an FDA approved site for one or more FDA post approval studies; or
4. The facility has provided a written affidavit to CMS attesting that the facility has met the minimum facility standards. This should be sent to:

Director, Coverage and Analysis Group  
7500 Security Boulevard, Mailstop C1-09-06  
Baltimore, MD 21244.

The letter must include the following information:

Facility's name and complete address;

Facility's Medicare provider number;

Point-of-contact for questions with telephone number;

*Discussion of how each standard has been met by the hospital;*

Mechanism of data collection of CAS procedures; **and**

Signature of a senior facility administrative official.

A list of certified facilities will be made available and viewable at:

<http://www.cms.hhs.gov/coverage/carotid-stent-facilities.asp>. In addition, CMS will publish a list of approved facilities in the Federal Register.

*Facilities must recertify every two (2) years in order to maintain Medicare coverage of CAS procedures. Recertification will occur when the facility documents that and describes how it continues to meet the CMS standards.*

*The process for recertification is as follows:*

*At 23 months after initial certification:*

- *Submission of a letter to CMS stating how the facility continues to meet the minimum facility standards as listed above.*

*At 27 months after initial certification:*

- *Submission of required data elements for all CAS procedures performed on patients during the previous two (2) years of certification.*
- *Data elements:*

*Patients' Medicare identification number if a Medicare beneficiary;*

*Patients' date of birth;*

*Date of procedure;*

*Does the patient meet high surgical risk criteria (defined below)?*

- *Age  $\geq 80$ ;*
- *Recent (< 30 days) Myocardial Infarction (MI);*
- *Left Ventricle Ejection Fraction (LVEF) < 30%;*
- *Contralateral carotid occlusion;*
- *New York Heart Association (NYHA) Class III or IV congestive heart failure;*
- *Unstable angina: Canadian Cardiovascular Society (CCS) Class III/IV;*
- *Renal failure: end stage renal disease on dialysis;*
- *Common Carotid Artery (CCA) lesion(s) below clavicle;*
- *Severe chronic lung disease;*
- *Previous neck radiation;*
- *High cervical Internal Carotid Artery (ICA) lesion(s);*
- *Restenosis of prior carotid endarterectomy (CEA);*
- *Tracheostomy;*
- *Contralateral laryngeal nerve palsy.*

*Is the patient symptomatic (defined below)?*

- *Carotid Transient Ischemic Attack (TIA): distinct focal neurologic dysfunction persisting less than 24 hours;*
- *Non-disabling stroke: Modified Rankin Scale < 3 with symptoms for 24 hours or more;*
- *Transient monocular blindness: amaurosis fugax.*

*Modified Rankin Scale score if the patient experienced a stroke;*

*% stenosis of stented lesion(s) by angiography;*

*Was embolic protection used?*

*Were there any complications during hospitalization (defined below)?*

- *All stroke: an ischemic neurologic deficit that persisted more than 24 hours;*
- *MI;*
- *All death.*

*Recertification is effective for two (2) additional years during which facilities will be required to submit the requested data every April 1 and October 1.*

*CMS will consider the approval of national carotid artery stenting registries that provide CMS with a comprehensive overview of the registry and its capabilities, and the manner in which the registry meets CMS data collection and evaluation requirements. Specific standards for CMS approval are listed below. Facilities enrolled in a CMS approved national carotid artery stenting registry will automatically meet the data collection standards required for initial and continued facility certification. Hospitals' contracts with an approved registry may include authority for the registry to submit required data to CMS for the hospital. A list of approved registries will be available on the CMS coverage website.*

### *National Registries*

*As noted above, CMS will approve national registries developed by professional societies and other organizations and allow these entities to collect and submit data to CMS on behalf of participating facilities to meet facility certification and recertification requirements. To be eligible to perform these functions and become a CMS approved registry, the national registry, at a minimum, must be able to:*

- 1. Enroll facilities in every US state and territory;*
- 2. Assure data confidentiality and compliance with HIPAA;*
- 3. Collect the required CMS data elements as listed in the above section;*
- 4. Assure data quality and data completeness;*
- 5. Address deficiencies in the facility data collection, quality and submission;*
- 6. Validate the data submitted by facilities as needed;*
- 7. Track long term outcomes such as stroke and death;*
- 8. Conduct data analyses and produce facility specific data reports and summaries;*
- 9. Submit data to CMS on behalf of the individual facilities;*
- 10. Provide quarterly reports to CMS on facilities that do not meet or no longer meet the CMS facility certification and recertification requirements pertaining to data collection and analysis.*

*Registries wishing to receive this designation from CMS must submit evidence that they meet or exceed our standards. Though the registry requirements pertain to CAS, CMS strongly encourages all national registries to establish a similar mechanism to collect comparable data on CEA. Having both CAS and CEA data will help answer questions about carotid revascularization, in general, in the Medicare population.*

*CAS for patients who are not at high risk for CEA remains covered only in FDA-approved Category B IDE clinical trials under 42 CFR 405.201.*

*CMS has determined that PTA of the carotid artery concurrent with the placement of an FDA-approved carotid stent is not reasonable and necessary for all other patients.*

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