# Appendix I

Table 1. Carotid Artery Stenting Trials

| Author/ Year | Study Design | Demographics | Results | |
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| | | | CAS | CEA |
| Brooks et al., 2001. | Rand. Trial n=104.<br>Inclusion: symptoms/signs cerebral ischemia ipsilateral ICA, events within 3 months of eval., >70% stenosis, life expect. 5 yrs., willingness, sign informed consent.<br>Exclusion: vertebral-basilar insuff., intracranial occlusive disease, NIH stroke scale >4, arrhythmia, allergy aspirin, heparin, ticlopidine, clopidogrel, bleeding or coagulopathy, h/o ICH.<br>Patients received aspirin and clopidogrel. | Mean age=66 yrs CAS group.<br>Mean age=70 yrs CEA group.<br>Male/female not reported.<br>Presenting symptoms= stroke, TIA, amaurosis fugax.<br>Mean follow-up not reported. | N=53.<br>Death=0.<br>Stroke=0.<br>Transient cerebral ischemia=1. | N=51.<br>Death=1.<br>Stroke=0.<br>Transient cerebral ischemia=0. |
| Brooks et al., 2004. | Randomized trial n=85.<br>Inclusion: >80% internal carotid stenosis by angiography, life expect. 5 yrs., willingness, sign informed consent.<br>Exclusion: any symptom cerebrovascular ischemia, arrhythmia, allergy aspirin, heparin, clopidogrel, bleeding or coagulopathy.<br>Patients received aspirin and clopidogrel. | Mean age=67 yrs CAS group.<br>Mean age=70 yrs CEA group.<br>Male/female not reported.<br>Mean follow-up not reported. | N=43.<br>Stroke/TIA=0. | N=42.<br>Stroke/TIA=0. |
| CAVATAS, 2001. | Randomized trial n=504.<br>Inclusion: stenosis of the common carotid artery, carotid bifurcation, or internal carotid artery that investigators believed needed treatment and was suitable for both carotid endarterectomy and endovascular treatment.<br>Exclusion: unsuitable for surgery because of medical or surgical risk factors (eg, recent myocardial infarction, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis), unwilling to undergo either procedure, unable to give informed consent, or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery, if angiography showed thrombus in the carotid artery, severe intracranial carotid artery stenosis beyond the skull base, or a stenosis unsuitable for endovascular treatment—eg, because of tortuous vascular anatomy. | Mean age=67 yrs endovascular group.<br>Mean age=67 yrs CEA group.<br>Male=69% endovascular group.<br>Malee=70% CEA group.<br>Mean follow-up=1.95 yrs. | N=251 for endovascular treatment.<br>Deaths=7.<br>Disabling stroke=9.<br>Non-disabling stroke=9.<br>Death or any stroke=25.<br><br>Subgroup N=55 stenting.<br>Stroke=3.<br>Cerebral hem =2. | N=253.<br>Deaths=4.<br>Disabling stroke=11.<br>Non-disabling stroke=10.<br>Death or any stroke=25. |
| Yadav et al., 2004. | Randomized trial n=334.<br>Patients were randomly assigned to a procedure only if all members of the team were in agreement that the patient was a suitable candidate for either endarterectomy or stenting.<br>Inclusion: Age ≥18 yr, unilateral or bilateral atherosclerotic or restenotic lesions in native carotid arteries, symptoms plus stenosis of more than 50% of the luminal diameter, no symptoms plus stenosis of more than 80% of the luminal diameter, criteria for high risk (at least one factor required) | Mean age=72.5 yrs CAS group.<br>Mean age=72.6 yrs CEA group.<br>Male=66.9% CAS group.<br>Male=67.1% CEA group.<br>Mean follow-up | Death=2.<br>Stroke=6.<br>MI=4.<br>Death, stroke or MI=8. | Death=4.<br>Stroke=5.<br>MI=10.<br>Death, stroke or MI=16. |

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| | -clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, previous radical neck surgery or radiation therapy to the neck, recurrent stenosis after endarterectomy, age >80 yr. Exclusion: Ischemic stroke within previous 48 hr., intraluminal thrombus, total occlusion of target vessel, vascular disease precluding use of catheter-based techniques, intracranial aneurysm >9 mm in diameter, need > 2 stents, h/o bleeding disorder, percutaneous or surgical intervention planned within next 30 days, life expectancy <1 yr., ostial lesion of common carotid artery or brachiocephalic artery. | not reported. | | |

## Appendix II

## General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability 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 potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its 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 systematical assessment of factors related to outcomes.
- Larger sample sizes in studies 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 (performance bias).
- 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, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. 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 selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider 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 determinations 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. One of the goals of our determination process is to assess net health outcomes. 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

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.