Supplementary Online Content


eMethods 1. COSS protocol amendments

eMethods 2. Initial clinical and vascular imaging criteria to determine PET eligibility

This supplementary material has been provided by the authors to give readers additional information about their work.
COSS Protocol Amendments

Five protocol amendments have been approved by the COSS DSMB and instituted.

**Amendment I (1-07-03)**
Amendment I changed the PET eligibility from > 1.160 to > 1.130.

The original PET eligibility criterion for COSS was an ipsilateral-to-contralateral ratio of > 1.160. Based on data from the St. Louis Carotid Occlusion Study sample of 45 subjects who had hemispheric symptoms within the previous 120 days, the expected 2 year ipsilateral stroke rate in the medical group in COSS would be 50%. However, in calculating the sample size, we used a conservative estimate of 40%. Of the first 10 subjects enrolled into COSS, only one met this PET eligibility criterion of 1.160. The protocol was amended with approval of the DSMB to lower that PET eligibility criterion to 1.130. Based on the St. Louis Carotid Occlusion Study data, this threshold identifies 22 subjects including 9 of the 12 who went on to have ipsilateral strokes within the next two years yielding an estimated 2-year ipsilateral stroke rate of 41%. Lowering the criterion to 1.130 did not require a change in the sample size because the estimated 2-year stroke rate in the non-surgical group will remain 40%.

**Amendment II (11-01-03)**
Amendment II modified the Analysis Plan

After considerable discussion with the COSS DSMB, it became apparent that the original monitoring and analysis plans with two interim analyses when 1/3 and 2/3 of participants had completed two years of follow-up would not work. This was deemed important because the first interim analysis would probably not occur until most participants had already been randomized. The Committee requested that a new plan be prepared that would allow for more frequent interim monitoring when fewer participants had completed the two-year follow-up. In order to accommodate this request it was necessary to modify the overall analysis plan to include participants with only partial follow-up (less than two years) in all interim analyses. Rather than comparing life table estimates of the rates of the primary event at two-years, we plan to use Poisson regression to compare the current rates whenever an analysis is run. The advantage is that it allows the DSMB to view the current event history regardless of the timing of the analysis while accounting for the varying follow-up experience on individual patients. Any clinic or surgeon whose surgical morbidity or mortality significantly exceeds 12% will be counseled and if satisfactory improvements are not observed the clinic or surgeon will not be allowed to continue participation in the study. Therefore, the question of whether surgery is worse than medical care is being answered in another way. We therefore plan to use a one-sided 2.5% level test rather than a one-side 5% level test for the primary outcome. The analysis plan for the primary endpoint now reads as follows:

The primary analysis will use Poisson regression to compare the rates of primary events in the two treatment groups. All participants will be included in the analysis and each participant will be analyzed in the treatment to which s/he was randomized. Each participant’s days at risk will be computed as the difference between the day of randomization and the day of last follow-up (for those who do not have a primary event) or the day of the event (for participants who experience a primary event). All participants will be included in the analysis up to their two-year follow-up visit or until their last quarterly follow-up visit if they are lost to follow-up before two-years. The primary model will include terms for treatment assignment and center. We will use a one-sided, 2.5% level test for a relative risk in favor of the surgical group. The alternative will be that the rate of primary events is lower in the surgical group than in the non-surgical group. We will also use one-sided alternatives for all interim analyses.

**Amendment III (12-31-03)**
Amendment III changed Eligibility Criteria.

At the suggestion of the DSMB, eligibility criteria were reviewed for modifications that could be made to improve recruitment without compromising the scientific integrity of the study.

**Inclusion Criterion Change**

1. Currently Inclusion Criterion #2 reads:
2. Vascular imaging demonstrating less than 50% stenosis of the contralateral extracranial internal carotid artery

Changed to: eliminate clinical inclusion criterion # 2.

Patients with contralateral occlusion are limited to 37 (10%) randomized participants. Contralateral endarterectomy is permitted only with development of symptomatic contralateral carotid stenosis of greater than 50% which in the judgment of the local investigators requires surgery.

Exclusion Criteria Changes

1. Currently Exclusion Criterion #3 reads as follows:
   3. Known heart disease likely to cause cerebral ischemia (Echocardiography is not required.)
      This includes the following conditions ONLY:
      - Atrial fibrillation
      - Prosthetic valve(s)
      - Infective endocarditis
      - Left atrial or ventricular thrombus
      - Sick sinus syndrome
      - Myxoma
      - Cardiomyopathy with ejection fraction <25%

      This is an all-inclusive list. The following conditions are NOT EXCLUSIONS: patent foramen ovale, atrial septal aneurysm.

   Changed to: atrial fibrillation is no longer an exclusion.

2. Currently Exclusion Criterion #5 reads as follows:
   5. The following medical conditions:
      - Cancer (other than skin)
      - Renal Failure (BUN and/or creatinine > twice normal upper limit)
      - Congestive Heart Failure
      - Myocardial Infarction within 6 months
      - Liver disease
      - Pulmonary disease constituting an anesthetic risk

   Changed to: eliminate exclusion criterion #5

3. Exclusion # 14 currently reads:
   14. Allergy to iodine or x-ray contrast media if supplemental arteriography is required

   Changed to: If supplemental arteriography is required, allergy to iodine or x-ray contrast media, serum creatinine > 3.0 mg/dl or other contraindication to arteriography.

4. Exclusion Criterion #16 currently reads:
   16. Medical indication for treatment with anticoagulant drugs, ticlopidine, clopidogrel or persantine such that these medications cannot be replaced with aspirin for one month after enrollment

   Changed to: Medical indication for treatment with anticoagulant drugs, ticlopidine, clopidogrel or other antithrombotic medications such that these medications cannot be replaced with aspirin in the perioperative period as deemed necessary by the COSS neurosurgeon if the participant is randomized to surgical treatment.

Amendment IV (2-01-07)

Amendment IV:
1. Reduced bias in ascertainment of the primary endpoint
2. Stopped follow-up at two years.

1. Change Ascertainment of the Primary Endpoint

Currently the primary endpoint is specified as follows (MOP 8.3.2):

“The primary endpoint in the surgical group will be the combination of the following: (1) the occurrence of all stroke and death from randomization through 30 days post operation and (2) the occurrence of ipsilateral ischemic stroke within two
years of randomization. The primary endpoint in the non-surgical group will be the combination of the following: (1) the occurrence of all stroke and death from randomization through a period equivalent to surgery plus 30 days and (2) the occurrence of ipsilateral ischemic stroke within two years of randomization. For the non-surgery group, we will define “surgery plus 30 days” as 30 days plus the average number of days from randomization to surgery observed in the surgery group.”

Changed to: The primary endpoint in the surgical group will be the combination of the following: (1) the occurrence of ipsilateral ischemic stroke from randomization to surgery, (2) the occurrence of all stroke and death from surgery through 30 days post operation and (3) the occurrence of ipsilateral ischemic stroke within two years of randomization. Those in the surgery group who are never operated by the end of the trial would be evaluated in the same way as the non-surgical group. The primary endpoint in the non-surgical group will be the combination of the following: (1) the occurrence of all stroke and death from randomization through 30 days post randomization and (2) the occurrence of ipsilateral ischemic stroke within two years of randomization.

Comment:
This aspect of trial design is similar to that used in the original EC/IC bypass trial. However, since this is an intent-to-treat trial, there will be some patients assigned to surgery who will never be operated. Under the original definition of the primary endpoint, they would have had the primary endpoint of all stroke and death for the entire two years. Similarly, for those with greatly delayed surgery the primary endpoint would have been all stroke and death until they are operated. This clearly biases against surgery.

2. Termination of Follow-up at 2 years post-randomization
Currently, the schedule for follow-up visits is as follows (MOP 7.12.2.3):

“All participants will be followed at three-month intervals (plus or minus 10 days) after randomization for the duration of the study.”

Changed to: All participants will be followed at three-month intervals (plus or minus 10 days) after randomization until the 24 month time point

Comment:
The primary analysis is based on the occurrence of the primary endpoint at two years after randomization. All participants would be followed every three months for the duration of the trial, which would be for a maximum duration of six years. The reason for this prolonged follow-up beyond that necessary for the primary efficacy analysis was to collect data on the longer-term outcome of both un-operated and operated patients. At this point, it is clear that recruitment will take much longer so some participants would need to be followed for many years. As time goes on, the enthusiasm of the participants and coordinators wanes and the complete follow-up necessary to make the data valid becomes logistically harder and harder to obtain. Already, of 30 participants in COSS for over two years, 9 have modified consent to only have more infrequent follow-up and 5 have withdrawn altogether.

Amendment V (12-29-09)

- The number of participants that will need to be enrolled for PET has been increased from 930 to 1400. The new value of 1400 is based on the actual 27% of enrolled subjects who go on to be randomized.
- The 10% limit on participants with contralateral stenosis or occlusion has been removed.
- Appendix D is updated with the most recent AHA recommendations for stroke prevention.
- Revised Statistical Analysis Plan 4.02 as approved by the COSS DSMB (MOP 3.0 Appendix G)
- Protocol Violations List defining major and minor violations. (MOP Appendix H)
- Additional edits are made to the text of the Protocol document to incorporate minor corrections and add details to current study practices as well as to update Case Report Forms completion instructions.
eMethods 2

Initial Clinical and Vascular Imaging Criteria to Determine PET Eligibility

**Inclusion Criteria**

1. Vascular imaging demonstrating occlusion of an internal carotid artery.
   NOTE: Inclusion criterion 1 may be demonstrated by any vascular imaging modality (e.g. Doppler ultrasound, magnetic resonance angiography, CT angiography or intra-arterial catheter arteriography). Validation of sensitivity and specificity of non-arteriographic modalities versus arteriography is not required since all participants must have catheter arteriography to determine final eligibility. Subjects with contralateral stenosis or occlusion are eligible.
2. [Criterion Eliminated]
3. Transient ischemic attack (TIA) or ischemic stroke in the hemispheric carotid territory of an occluded internal carotid artery
   a. This is a clinical diagnosis based on all available data that does not require confirmation by neuroimaging. Participants with TIA or infarction restricted to the retina only are not eligible, but those with combined retinal and hemispheric carotid territory syndromes will be eligible. In participants with hemisensory or hemimotor signs or symptoms, including single limb, specific hemispheric signs or symptoms (e.g. aphasia) will not be required for inclusion but absence of cerebellar and brainstem signs or symptoms will be required.
   b. Participants who have previously undergone endarterectomy for stenosis of the ipsilateral external carotid or contralateral internal carotid artery are eligible whether or not they have had recurrent symptoms.
   c. Participants who have undergone carotid endarterectomy (CEA) for symptomatic carotid stenosis who develop a post-operative carotid occlusion but experience no further symptoms after the time of surgery are not eligible unless further symptoms occur.
4. Most recent qualifying TIA or stroke occurring within 120 days prior to performance date of PET
5. Modified Barthel Index \( \geq 12/20 \)
6. Language comprehension intact, motor aphasia mild or absent such that effective communication with the participant is possible
7. Age 18-85 years inclusive
8. Competent to give informed consent
9. Legally an adult
10. Geographically accessible and reliable for follow-up

**Exclusion Criteria**

1. Non-atherosclerotic carotid vascular disease
   The intent is to include only atherosclerotic carotid occlusion. All other non-atherosclerotic conditions (for example, moya-moya disease, fibromuscular dysplasia, carotid dissection, arteritis, radiation-induced vasculopathy such as that following irradiation for neck cancer) are excluded. These entities are given as examples, not as an all-inclusive list.
2. Blood dyscrasias
   This includes the following conditions ONLY:
   - Polycythemia vera
   - Essential thrombocytosis
   - Sickle cell disease (SS or SC)
   This is an all-inclusive list. The following conditions are NOT EXCLUSIONS: anticardiolipin antibodies, lupus anticoagulant, protein S, C, or antithrombin III deficiency, Factor V Leiden or other causes of activated protein C resistance, prothrombin gene mutations.
3. Known Cardio embolic heart disease (Echocardiography is not required.)
   This includes the following conditions ONLY:
   - Prosthetic valve(s)
   - Infective endocarditis
   - Left atrial or ventricular thrombus
   - Sick sinus syndrome
   - Myxoma
   - Cardiomyopathy with ejection fraction <25%
   This is an all-inclusive list. The following conditions are NOT EXCLUSIONS: atrial fibrillation, patent foramen ovale, atrial septal aneurysm.
4. Other non-atherosclerotic condition likely to cause focal cerebral ischemia

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5. [Criterion Eliminated]
6. Any condition likely to lead to death within 2 years
7. Other neurological disease that would confound follow-up assessment
8. Pregnancy
9. Subsequent cerebrovascular surgery planned which might alter cerebral hemodynamics or stroke risk
   This includes contralateral internal or common carotid endarterectomy or angioplasty, ipsilateral external carotid artery
   endarterectomy or angioplasty, carotid stump closure, vertebral or basilar artery angioplasty, any arterial grafting
   procedures to the carotid or vertebral arteries.
10. Any condition which in the participating surgeon’s judgment makes the participant an unsuitable surgical candidate
11. Concurrent participation in any other experimental treatment trial
12. Participation within the previous 12 months in any experimental study that included exposure to ionizing radiation
13. Acute, progressing or unstable neurological deficit
    Neurological deficit must be stable for 72 hours prior to the performance of PET.
14. If supplemental arteriography is required, allergy to iodine or x-ray contrast media, serum creatinine > 3.0 mg/dl or
    other contraindication to arteriography.
15. If aspirin is to be used as antithrombotic therapy in the perioperative period, those with allergy or contraindication to
    aspirin are ineligible
16. Medical indication for treatment with anticoagulant drugs, ticlopidine, clopidogrel or other antithrombotic medications such
    that these medications cannot be replaced with aspirin in the perioperative period as deemed necessary by the COSS
    neurosurgeon if the participant is randomized to surgical treatment.

NOTE: Participants with any of the medical conditions specified in exclusion criteria 17 through 20 can become eligible if
the exclusion criterion no longer applies within 120 days of onset of the most recent qualifying event.
17. Uncontrolled diabetes mellitus (FBS > 300 mg%/16.7 mmol/L)
18. Uncontrolled hypertension (systolic BP>180, diastolic BP >110)
19. Uncontrolled hypotension (diastolic BP <65)
20. Unstable angina