

QUESTIONS & ANSWERS

1. NASCET Patients: *Can NASCET patients participate in the ACE trial?*

No. Patients can only enter one trial, not both. Also, patients must not be participating in any other drug trials. This is a requirement of most hospital IRBs and was included in the ACE grant application.

2. NASCET vs ACE: *How do we decide whether to enter a patient into NASCET or ACE?*

NASCET takes precedence. This will still leave many patient eligible for ACE including: (1) those not eligible for NASCET, e.g. patients scheduled for carotid endarterectomy who are asymptomatic or who have severe (70-99%) stenosis (2) patients who refuse to be randomized in NASCET but who are willing to participate in ACE, and (3) patients of non-NASCET surgeons at your center (provided the NASCET surgeons at your center agree that these surgeons would meet the same criteria of surgical skill applied to the NASCET surgeons).

3. Number of Patients: *Can we enter more patients than we committed to on the ACE center registration form? Is there any restriction on the number of patients that an individual center can enter into the ACE trial?*

Each center can enter as many patients as they can find. We asked for an estimate of entry rate only to help us plan the trial. The faster we enroll patients the faster we will answer the research question.

4. Ideal Entry Time: *How long before surgery should patients be randomized and started on study ASA?*

Patients should be entered into the ACE trial as soon as possible once surgery has been scheduled so that they can be started on study ASA before surgery. Ideally we would like patients to be on study ASA for 2 or 3 days, or more, before surgery, but we will accept patients up to 8 hours before surgery provided they have not taken ASA (325 mg/day or more) in the past 48 hours, and are able to take the first days dose of study medication (all 5 pills) at least 8 hours before surgery.

5. Short Lead Time: *Can patients we entered into the ACE trial even if there isn't time to start them on study medication before surgery?*

No. All patients entered into the ACE trial must receive at least one full days dose of study medication (all 5 pills) at least 8 hours before surgery. Do not enter patients if this is impossible or in doubt.

6. Long Lead Time: *Can a patient be randomized if surgery will not take place for quite some time, e.g. if the date of surgery is more than a week away?*

Yes. Such patients should be provided with a single 1 week blister pac of study ASA and asked to start taking it 1 week before surgery. The scheduled start date should be printed on the cover of the blister pac. Please call the patient on the start date to confirm that they have started taking it.

7. ASA Before Surgery: *It is standard practice in our setting to give all carotid endarterectomy patients 1300 mg of ASA before surgery. Is this allowed.?*

No. The objective of the ACE trial is to determine whether the risk of perioperative events is influenced by aspirin dose, started before surgery. Patients who participate in the ACE trial must start the study medication before surgery and not receive ASA from any source other than their randomly assigned study medication blister pacs. Physicians who believe that they already know the answer to the study question and are convinced that this (or some other) dose of ASA should be given to patients pre-operatively should not participate in the ACE trial.

8. ASA Before Surgery: *It is standard practice in our setting to take all patients off ASA before surgery. Is this allowed.?*

No. The objective of the ACE trial is to determine whether the risk of perioperative events is influenced by aspirin dose, started before surgery. Thus patients who participate in the ACE trial must start and remain on their randomly assigned study medication before surgery. Physicians who believe that they already know the answer to the study question and believe that ASA should not be given to patients pre-operatively should not participate in the ACE trial.

9. Prior ASA: *Can patients enter the trial if they are already taking ASA?*

Patients who are already taking ASA (325 mg or more per day over the past 2 days) must stop it at least 48 hours before surgery and agree not to take ASA from any source other than the study medication blister packs (5 tablets per day as directed) until the end of the trial (90 days post-surgery).

10. Drugs Containing ASA:*Can patients enter the trial if they are on a medication which contains ASA?*

Many medications which contain ASA, contain a dose of 325 mg or more and thus are equivalent to taking this much pure ASA. Patients who are taking ASA in any form must stop it at least 48 hours before surgery and not resume taking it until the end of the trial (90 days post-surgery). A list of common medications containing ASA, and analgesics which do not contain ASA is included at the end of this section.

11. Antiplatelet Drugs: *Can patients enter the trial if they are on antiplatelet drugs?*

Antiplatelet drugs such as: ticlopidine (ticlid), sulfinpyrazone (anturane), and dipyridamole (persantine) must be discontinued prior to surgery and not resumed until the end of the trial (90 days post-surgery).

12. N.S.A.I.D.s: *Can patients enter the trial if they are on Non-Steroidal Anti-Inflammatory Drugs?*

Yes. There are no restrictions on the use of N.S.A.I.Ds (other than ASA) before, during or after surgery.

13. Heparin: *What restrictions, if any, are placed on the use of heparin, before, during and after surgery?*

Both Heparin and ASA increase bleeding time and thus care must be taken when using them together. However, the ACE protocol does not place any restrictions on the use of heparin.

14. Dextran: *Can dextran be used during surgery?*

Yes. There are no restrictions on the use of volume expanders like dextran.

15. Rescheduled Surgery: *What if surgery is cancelled and rescheduled after the patient has been randomized and started on study ASA?*

If surgery is rescheduled within the next week have the patient continue taking study ASA. Provide them with another blister pac if necessary to keep them on study ASA up to and including the day of surgery.

If surgery will be delayed longer than a week provide the patient with a new blister pac of study ASA and ask them to start taking it 1 week before surgery.

16. Cancelled Surgery: *What if surgery is cancelled and not rescheduled after the patient has been randomized and started on study ASA?*

If surgery is completely cancelled report the circumstances to the ACE coordinating center. If the patient has suffered a stroke, heart attack or death complete and fax the appropriate ACE event report forms.

It is important that we are able to report on the status of all randomized patients at the end of the trial, regardless of the treatments actually received. Thus, if surgery is cancelled for any reason other than death we request that you complete Form 5.1 to report on the patients status 3 months after randomization. This one page form can be completed by telephone interview if necessary. Other than this final follow-up report, the baseline forms (1.0-1.8), and any applicable event reports, no other ACE study forms need to be completed or faxed.

17. Repeat Surgery: *What if surgery is repeated on the same patient during the 3 years of the ACE trial (same or other side)? Can a patient be entered into the trial again and get a new study kit?*

No. A patient can only participate in the ACE trial once.

18. Who Can Operate: *Can patients only be entered if they are seeing a NASCET surgeon, or can non-NASCET surgeons participate in the ACE trial?*

Non-NASCET surgeons can participate in the ACE trial provided

they have been approved by the NASCET surgeons at their center. All surgeons, NASCET and non-NASCET, who have agreed to participate in the ACE trial, should be named on the ACE study registration form which is to be faxed to the coordinating center before the trial begins. This form, can be updated and refaxed if new surgeons or neurologists join the trial, or if there is a change in study coordinator. No other documentation is required.

19. Neurological Exam: *Must the neurologist see each patient, or can the study coordinator perform the neurological exam and only require the neurologist to see patients in whom abnormalities are encountered?*

As in the NASCET trial, the ACE study coordinator may perform the neurological exam provided he/she is a nurse practitioner with neurological experience, who is accustomed to working with and supporting the study neurologist in this way. However, the neurologist is ultimately responsible for the neurological assessment.

20. CT Scans: *CT scans are requested for patients who suffer a stroke following surgery. How should they be sent?*

CT scans should be sent by mail to the ACE Coordinating Center, at the following address:

ACE Trial Coordinating Center
McMaster University
Department of Clinical Epidemiology & Biostatistics
Chedoke Division, Building 74
1200 Main Street West
Hamilton, Ontario, Canada L8N-3Z5

21. Angiography: *Is an angiogram required before entering patients into ACE?*

No, an angiogram is not required.

22. Ultrasound: *What is meant by “peak velocity” measurements?*

This refers to peak systolic velocity at maximal stenosis on the artery being operated on. The same applies for frequency changes in peak velocity.

23. Patient Consent Form: *The first paragraph of the consent form states “...serious risks associated with this operation, namely stroke and death, which occur in about 5 percent of patients receiving this operation in North America.” Can a center add a line which states the risk at their particular hospital?*

Yes, the consent form can be modified to suit local needs. The form which was included in the protocol and sent to all study centers is simply a model.

24. Patient Consent Form: *Should the patient consent form include a general release of medical record information?*

Yes, this is a good idea. You may modify the consent form to suit local standards. Including a general release statement may make it easier to retrieve information if the patient should suffer a stroke or die.

25. Used Blister Pacs: *After collecting used medication blister pacs from patients should they be returned to the ACE coordinating center?*

No. Used blister pacs are collected to allow you to complete the ACE compliance forms to show the amount of medication remaining in each pac. Once these forms have been completed the blister pac and any unused medication can be disposed of at your center.

26. 13 Blister Pacs: *What if 13 blister pacs are not enough to last to the final 3 month follow-up for some patients?*

The critical period for this study runs from the day before surgery to the 30th day following surgery. This is when it is most important for patients to be on the study dose of ASA as almost all of the strokes and deaths which we will observe in the ACE trial will occur on the day of surgery or shortly thereafter. Thus we will not be concerned if patients run out of study medication a week or two before their final 90 day post-operative assessment.

27. Extra Study ASA: *What if a patient vomits their study ASA shortly after taking it during the post-operative recovery period?*

The 13th blister pac in each patient medication kit can be used as a spare, if necessary, to replace the dose which has been lost in this or

any other way. Using a blister pac in this way will reduce the total length of time that a patient can be on study ASA to 12 weeks. As noted in the previous point the critical period for study treatment is before and immediately following surgery. Twelve weeks of treatment are quite adequate to answer the study question.

28. ASA After Study: *What dose of ASA should be patients be given after they have completed the study?*

Once the patient has completed their study medication you are free to put the patient on whatever dose of ASA, or other antiplatelet medication you would have normally recommended to such patients. The research time horizon for the ACE trial is very short. We are only investigating the risk of stroke in the first 3 months following carotid endarterectomy. Patients will not be followed in the study beyond this point.

29. Hospital Discharge: *What if a patient is discharged on a weekend or in the evening? How should the discharge forms (3.1-3.3) be completed and how should used blister pacs be collected and new ones dispensed?*

In such cases please visit the patient as close to the time of discharge as possible to complete the 3 page discharge report forms, and to make arrangements to collect used blister pacs and dispense new ones. For example, you might provide the patient with a self addressed intra-hospital return envelope into which he/she can place used blister pacs, and also provide the patient with an envelope containing the new blister pacs needed to last until the 30 day follow-up assessment. Alternatively, such arrangements might be made with the nursing staff. We leave it to each center coordinator to identify the solution which will work best in your particular setting.

30. Data Forms:

When a patient has completed the trial what should we do with the ACE study case report forms (CRFs)?

Please fax completed CRFs to the ACE coordinating center as soon as possible after each patient assessment, and keep the originals on file during the trial. Because of recent concerns about the reliability of the data reported in clinical trials it will be necessary to perform random site visits during the trial to verify study data against medical records. Also we will be collecting original CRFs, or a Xerox copy, near the end of the trial to confirm that no changes have been made since the forms were faxed.