

ASA & CAROTID ENDARTERECTOMY (ACE) INVESTIGATOR INFORMATION

This document provides a guide to the logistics of the ACE Trial and should be referenced in conjunction with the ACE study protocol.

1. Research Objectives and Design
2. Enrolling Patients
3. Organization of Study Medication and Case Report Forms (CRFs)
4. How to Complete CRFs
5. Dispensing and Collecting Study Medication
6. Data Collection and Management
7. Important Information

1. RESEARCH OBJECTIVES AND DESIGN

The ACE Trial was designed to investigate the means of reducing the perioperative risk of stroke and death following carotid endarterectomy in patients with symptomatic high grade carotid stenosis. Specifically, the primary research question asked by this study is “Among patients who undergo carotid endarterectomy, is the risk of stroke and death in the 30 day perioperative period, and in the first 3 months after surgery, influenced by the prescription of high doses of ASA (≥ 650 mg/day) versus low doses of ASA (≤ 325 mg/day), started prior to surgery, and continued for 3 months?”.

The ACE Trial will involve 2,800 patients from 75 NASCET centres in the USA and Canada. Patients scheduled for carotid endarterectomy surgery at centres currently participating in the NASCET collaborative study group, will be assigned randomly before surgery, to one of 4 drug treatment groups consisting of an ASA daily dose of 81 mg, 325 mg, 650 mg, or 1300 mg. Patients will begin taking study medication 7 days prior to surgery and continue on this same dose for 90 days after surgery. Patient assessments will occur at baseline, surgery, hospital discharge, 30 days and 3 months. During the 3 month follow-up period, the outcome events of stroke, death and change in functional status will be recorded for each patient and used as a basis for comparison of the 4 ASA dosage groups.

2. ENROLLING PATIENTS

The ACE Research Coordinator for each centre will be responsible for recruiting patients. All patients who are scheduled for carotid endarterectomy surgery at a participating NASCET centre within 7 days during the period April ?, 1994 to ???, are eligible to participate in the ACE Trial provided they meet the appropriate criteria set out below.

Inclusion Criteria:

- a) Patient is scheduled for carotid endarterectomy at a NASCET centre

- b) Patient can tolerate a possible maximum dose of 1300 mg ASA daily for 3 months
- c) The study medication will be the patient's only source of ASA during the trial
- d) Patient will not take any other antiplatelet drugs during the study
- e) Patient agrees to return for the 30-day and 3-month follow-up assessments
- f) Both neurologist and surgeon agree that the patient is suitable for the trial
- g) Patient has signed a consent form to enter this trial
- h) Total dose of ASA consumed in the past 48 hours does not exceed 325 mg OR surgery is scheduled for 48 hours or more since the last dose of ASA was taken

Exclusion Criteria:

- a) One or more of the above "Inclusion Criteria" are not met
- b) Patients who have suffered a devastating stroke in the distribution of the carotid stenosis considered for carotid endarterectomy are not eligible

Entering and Randomizing Patients

Patients will be recruited for the ACE Trial as soon as possible once carotid endarterectomy surgery is scheduled. The following constitute entry and randomization of the patient into the ACE Trial and will be performed by the Research Coordinator(?) at each centre.

1. Check that the patient meets all study criteria
2. Check that the patient has agreed to the trial and signed a study consent form
3. Print the patient's full name and date of randomization on the outside of the patient randomization envelope
4. Open the envelope and check to be sure there is a complete set of patient case report forms inside
5. Locate the study medication kit for this patient by matching the randomization number found on the CRFs with that on one of the medication cartons. For the duration of the trial, all study medication for this patient is contained in this carton.

Registering Randomized Patients with the ACE Data Management Office

The randomization package for each patient contains a one-page "PATIENT ENTRY FORM". It is the responsibility of the Research Coordinator at each centre to complete and fax this form immediately to (905) 574-4755, the ACE Data Man-

agement Office, to register the patient into the trial.

3. ORGANIZATION OF STUDY MEDICATION AND CASE REPORT FORMS (CRFs)

Each centre participating in the ACE Trial shall receive enough ACE Patient Kits (includes study medication and case report forms), to enroll and follow patients in the ACE study for the next 6 months. After 6 months, more kits will be sent as required for an additional 6 month period. The number of patients enrolled in each centre is based on the estimate provided to the ACE Coordinating Centre by each centre's study investigator. The documents and medication for your centre will arrive as follows:

- 1 or more boxes containing study medication. Within these box(es) medication will be found in small cartons containing 13 blister pacs each of ASA. These cartons will be labelled with a Patient ID # which is to be matched with an identical ID # on one of the envelopes containing the study forms.
- 1 or more large envelopes containing smaller envelopes each labelled with a Patient ID #. Each of these smaller envelopes hold a complete set of study forms for each patient and the Patient ID # on each should be matched to the identical ID # on a medication carton. Also in these envelopes are a patient information sheet and consent form.
- An envelope addressed to the ACE study coordinator containing Investigator instructions and information.

Study Medication

The ASA being used in this study has a shelf life of 18 months only, therefore centres will not receive all patient kits in one shipment at the beginning of the study, but in several shipments during the study. Use of the patient kits will be monitored centrally by the ACE Data Management office, through the receipt of the 1-page "Patient Entry Form" which is faxed for each patient. It is therefore critical that this 1-page form be faxed immediately upon randomization.

Medication will be packaged in small cartons each labelled with a patient identification number and containing 13 blister pacs of ASA. Each pac contains 5 tablets per day for 7 days for one of the 4 treatment regimes, (81mg, 325mg, 650mg, 1300mg).

Study Case Report Forms (CRFs)

Study data forms are organized by patient folders. There will be one folder per patient, each having the patient identification number labelled on the outside and containing a complete set of CRFs.

A complete set of CRFs should contain the following:

- Form 1.0 Patient Entry Form

This should be completed and faxed immediately at the patient's entry visit, and serves to register the patient at the ACE Coordinating Centre.

- Forms 1.1-1.10 Initial Assessment (Baseline)
These 10 forms are to be completed and faxed upon entry into the trial, and will include: brief medical history, neurological assessment, functional status, current medications, doppler and angiographic imaging results.
- Forms 2.1-2.2 Surgical Report
This 2-page report is used to describe the operation and is to be completed and faxed after surgery but prior to hospital discharge.
- Forms 3.1-3.3 Hospital Discharge
This 3-page summary includes minor and major post-operative complications and a functional status assessment.
- Forms 4.1-4.2 30 Day Follow-up
Blister packs of study medication will be collected at this visit to measure patient compliance. Assessments include functional status, intercurrent cerebrovascular events, changes in medical, neurological status, medication history.
- Forms 5.1-5.4 3 Month Follow-up
Same as 30 Day Follow-up visit.
- Forms 5.5-5.7 Patient Compliance Report
This 3-page report is completed at both the 30 Day and 3 Month Follow-up visits.
- Form 6.1 Stroke Report Form
A stroke report should be completed each time the patient suffers a stroke, and faxed immediately to the ACE Coordinating Centre.
- Form 7.1 Death Report Form
This one-page form is completed upon a patient's death and faxed immediately to the ACE Coordinating Centre.

4. HOW TO COMPLETE CRFs

Please follow the DataFax Instructions on page 5 of this document. If further information is required, please contact the ACE Data Management office by telephone at (905) 574-4755 or by fax at (905) 574-2837.

DataFax Instructions

A: What is DataFax?

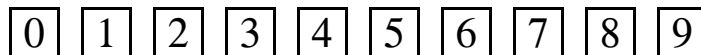
DataFax is a direct fax to computer data management system for collecting study case report forms (CRFs). It includes optical character recognition (OCR) and an automated quality control system.

B: Why are We Using DataFax For This Study?

1. To increase the speed and efficiency of data collection from clinical sites.
2. To improve data quality through continuous monitoring and Quality Control Reports.

C: What is Expected of Clinical Investigators?

1. Complete CRFs as follows:
 - work through the book in sequence.
 - use a black ball point pen.
 - enter Patient Number (same as assigned on the ACE Patient Kit), Patient Initials and Date in the fields provided at the top of each CRF page.
 - all dates are to be completed in the order **month/day/year**.
 - please **print** all text.
 - mark choice fields with an **X** inside the appropriate box.
 - to maximize OCR accuracy please print numbers **inside** the boxes as shown below:



- if data is not available print "NA" (beside, not inside, the boxes), and provide an explanation.
 - do not erase or "white out" errors. Draw a line through the error and make the correction above it.
 - initial and date all corrections.
 - designated pages must be signed and dated by an investigator.
2. Immediately Following Each Patient Visit
 - check CRFs for completeness and accuracy.
 - then fax CRFs to the DataFax computer at the ACE Data Management Centre at (905) 574-4755.
 3. Respond to DataFax Quality Control Reports.

At one week intervals you will receive a Quality Control Report by fax, identifying any items on the CRFs which are incomplete or unclear. Respond by making the necessary corrections and refaxing the updated CRF page(s) as soon as possible.
 4. CRF Updates & Corrections

If you make changes to a CRF page which has already been faxed, fax it again, immediately after making the change. Remember to initial and date all changes.
 5. Event Reports

Complete and fax Event forms as required.

D: Faxing Guidelines

- set your fax machine to transmit standard 8.5 x 11 inch pages.
- send faxes in standard mode (fine mode works but costs more and is unnecessary).
- do not fax the instruction pages.
- place pages face down on the fax input paper tray.
- don't overload the paper tray or your fax machines memory limitations.
- transmit the pages to the DataFax computer at (905) 574-4755.
- check that the fax was transmitted successfully.
- put the pages back into the patients case record file.

5. DISPENSING AND COLLECTING STUDY MEDICATION

Upon entry and prior to surgery, patient will be randomly assigned to one of 4 treatment groups which will differ only in the dose of ASA prescribed (81mg, 325mg, 650mg, 1300mg ASA). Randomization packages will be used in sequence by patient identification number, which will be printed on the outside of each envelope containing the CRFs and each of the medication cartons. The patient will begin taking one of the 4 doses of study medication on the day of randomization and will continue on this same dose throughout the study until the final 3 month assessment. A patient has completed the study once they have gone for their 3 month assessment. At this final visit, the physician may change the ASA dose to whatever they consider appropriate, or switch to another antiplatelet regimen.

Dispensing Study Medication

It is the study coordinator's responsibility to ensure that the patient be given sufficient medication to last through to the next study assessment. The patient begins taking study medication on the day of randomization and should be instructed to take 5 pills every day until the day of the 3-month follow-up visit. 3 pills should be taken in the morning after the patient awakes or with breakfast. 2 pills should be taken with dinner or before bedtime. If a patient forgets to take the morning dose (3 pills), they should be instructed to take the morning and evening dose together, but never to take more than 1 days worth of pills on any given day. The patient should also be reminded to bring their study medication to the hospital on the day of surgery so the medication may continue while the patient remains in the hospital.

Collecting Study Medication

The patient should be reminded to bring all blister pacs (used and unused) to all study assessments and in particular both their 30-day and 3-month follow-up visits. Compliance will be measured by counting and recording the number of pills remaining in each blister pac. If a patient should forget their medication, ask them to provide a mental picture of their weekly medication pacs with the location of the unused portion of their medication. Remind them to bring their forgotten blister pacs to their next assessment.

6. DATA COLLECTION AND MANAGEMENT

The ACE Data Management office is located at McMaster University in Hamilton, Ontario. All data will be collected and managed by a computerized data management system called DataFax.

DataFax

With DataFax, case report forms (CRFs) are faxed from the participating centres to a central data management office where they are received by computer. DataFax's intelligent character recognition (ICR) software reads the fax and extracts the data which has been written on the CRF and enters it into the study database. The central research staff then use DataFax on-screen to review the CRFs, complete data entry and flag problems which are then faxed back to the participating centre in the form of a Quality Control (QC) Report. The participating centre will always have the original CRFs on site to aid in resolving data clarification requests.

Quality Control (QC) Reports

QC Reports will be faxed to each centre on a weekly basis and consist of 3 parts:

1. Status Summary:
Provides a summary of the status of all patients enrolled to date from your centre.
2. Fax/Refax List:
Lists problems or requests for clarification for patients in your centre. You are asked to correct or resolve the problems from this section on your original CRFs and fax back the corrected CRFs to the Data Management office.
3. Question/Answer List:
This section also lists problems flagged by the research staff, but rather than refaxing the corrected CRFs, you are asked to simply write the correction in the space provided below each question and fax this part of the QC report back to the Data Management office.

An example of a QC Report has been included on page XX of this document.

If at any time you have questions regarding the contents of a particular QC report, contact the Data Management office. Please be sure to quote to QC Report number (9 digit number - 3 digit centre number + 6 digit report date).

Other Reports

In addition to weekly QC Reports, each centre will receive by fax a monthly study status report. This report will show for each centre the number of:

1. patients entered into the trial
2. completed follow-up visits
3. outstanding data clarification requests
4. overdue assessments.

Centres will be identified by a 3-digit number to preserve their anonymity, but will be able to compare their performance with that of other centres.

7. IMPORTANT INFORMATION

ACE Data Management Office
McMaster University
Department of Clinical Epidemiology & Biostatistics
Chedoke Division, Building 74
1200 Main Street West
Hamilton, Ontario
L8N 3Z5
Telephone: (905) 521-2100 X4090
Fax (general correspondence only): (905) 574-2837
Fax (DataFax computer): (905) 574-4755

What to Do If

1. A patient fails to return for a scheduled follow-up visit.
This will probably not occur very often as patients who are recovering from surgery are expected to keep follow-up appointments. However, in the event that a patient fails to return, a follow-up assessment should be determined by telephone contact with the patient and/or the patient's family physician. The CRFs for the missed follow-up visit should be filled out as accurately as possible, based on telephone contact, and faxed to the Data Management office. Be sure to write "Telephone contact" below the Patient No. on all CRFs for this visit.
2. A patient forgets to bring all empty blister pacs and unused study medication to their next follow-up visit.
Give the patient a diagram of a study medication pac and ask them to indicate by memory which of the blisters contain unused medication for each week that they should have taken study medication. Remind them to bring the forgotten medication pacs to their next follow-up visit. Once you receive these pacs, check compliance against that previously indicated from memory by the patient.
3. Study CRFs are incomplete because data is unavailable.
Write "NA" beside each missing data field and fax the CRFs to the Data Management office. If the data becomes available at a later date, simply correct the CRF(s), initial and date the change, and refax the appropriate pages. The research staff will note this and make corrections to the database accordingly.

If you do not indicate that missing data is "NA", DataFax will assume that the data has been forgotten and repeatedly ask you to complete the missing data fields on the CRF(s).

4. Investigator needs to know what dose of ASA the patient is taking due to the occurrence of a serious adverse event.

In the event that this occurs, the ACE Data Management office should be notified immediately. The data management office does not have access to the coded randomization schedule containing the ASA dosage levels, but will contact the Safety and Efficacy Monitoring Committee (SEMC). You will be informed of the decision by telephone.