Major Ongoing Stroke Trials

The following is a list of major ongoing studies about stroke. Information about other multicenter studies that might be included in this list should be submitted to the Stroke Editorial Office by the Principal Investigator. The list will appear online in the February, June and October issues of Stroke.

Aortic Arch Related Cerebral Hazard (ARCH)
This study is designed to compare the efficacy of warfarin (target INR 2.0 to 3.0) with that of aspirin (75 to 150 mg per day) in combination with clopidogrel (75 mg per day) in the secondary prevention of vascular events in patients with stroke or systemic arterial embolism who are found to have significant atheroma of the aortic arch. Patients will be followed by 4 monthly reviews from randomization to the end of the study. The primary end point is time to one of a composite of recurrent ischemic stroke, intracranial hemorrhage, myocardial infarction, peripheral embolism or vascular death.


Contact: Australia: Prof Geoffrey Donnan, Coordination Centre, NSRI, Level 1, Neurosciences Building, Austin Health, 300 Waterdale Road, Heidelberg Heights, Vic 3081, Australia. Phone 61-3-9496-2699. Fax 61-3-9457-2650. E-mail donnan@unimelb.edu.au Europe: Prof Pierre Amarenco, Department of Neurology and Stroke Centre, Bichat - Claude Bernard University Hospital and Medical School Denis Diderot University - Paris VII 46 rue Henri Huchard, 75018 Paris, France. Phone 33-1-40258726. Fax 33-1-4025-7198. E-mail pierre.amarenco@bch.ap-hop-paris.fr

Location: Australia: Coordination Centre, National Stroke Research Centre, Austin Health, Heidelberg Heights Vic 3081, Australia. Europe: Coordination Centre, Department of Neurology and Stroke Centre, Bichat - Claude Bernard University Hospital and Medical School Denis Diderot University - Paris VII, 75018 Paris, France.

Number of Centers: Australia: 20; Europe: 40.

Sponsors: The National Health and Medical Research Council of Australia; The National Heart Foundation; The Medical Research Council of France; and the Sanofi-Aventis Company.


Asymptomatic Carotid Emboli Study (ACES)
Better ways are required to identify high risk patients with asymptomatic carotid stenosis who may be suitable for endarterectomy. Previous small studies have suggested that the presence of asymptomatic embolic signals detected using transcranial Doppler ultrasound may identify a high risk group. ACES is a large multicentre international prospective study which will determine whether asymptomatic emboli detected in the middle cerebral artery are an independent predictor of stroke and TIA risk in patients with asymptomatic carotid stenosis (≥70%). Carotid stenosis is identified by duplex ultrasound. Unilateral middle cerebral artery transcranial Doppler recordings are made for one hour on each of two occasions at study entry. Recordings are made onto digital audiotape and are analysed by the coordinating centre, blinded to subject identity. Subjects are then followed for two years, at six monthly intervals with repeat 1 hour Doppler recordings at 6, 12, and 18 months and repeat carotid duplex at 12 months. There is also an option to perform cerebrovascular reactivity measurements at study entry. Recruitment began in 2000. 482 patients are enrolled in the study. Enrollment is now complete. Follow-up will be completed in 2009.

Principal Investigator: Hugh Markus, FRCP
Contact: Jennifer Siegel, ACES Study Coordinator, Centre for Clinical Neuroscience, St. George’s University London, SW17 ORE, Phone 020 8725 1369, Fax 020 8725 2950, E-mail acestrial@sglu.ac.uk

Location: Austria, China, Croatia, France, Georgia, Germany, Hong-Kong, Ireland, Israel, Italy, Lithuania, Netherlands, Poland, Singapore, Slovenia, Spain, United Kingdom (coordinating center location), United States.

Number of Centers: 29.

Sponsor: British Heart Foundation.


Asymptomatic Carotid Surgery Trial (ACST)
This is an international, multicenter trial to assess the place of carotid endarterectomy (CEA) in the management of patients with severe carotid stenosis that are currently asymptomatic. Patients were randomized either to best medical treatment (BMT) alone or to BMT plus CEA. Recruitment is now complete, and 5-year results were published in The Lancet in May 2004, but follow-up continues.

Principal Investigators: A.W. Halliday, FRCS; A.O. Mansfield, FRCS; and D.J. Thomas, MD, FRCP
Contact: Steven Robertson, Trial Manager. Phone +44(0) 20 8725-3746. Fax +44(0)20 8725-3782. E-mail acst@sglu.ac.uk

Location: The ACST Office, Department of Cardiac and Vascular Sciences, St. Georges University of London, Cranmer Terrace, London SW17 0RE.

Number of Centers: 120+

Sponsor: Stroke Association and Medical Research Council (UK).


Blood Pressure in Acute Stroke Collaboration (BASC)
Hypertension and hypotension in the acute phase of stroke are associated with a poor outcome; paradoxically, lowering blood pressure may also worsen outcome. BASC is performing a systematic review of blood pressure change versus outcome in acute stroke trials that involve vasoactive agents. Both group and individual patient data are being analyzed to assess whether therapeutic alteration of blood pressure is safe and effective in improving outcome, and if so, with which agent. Authors of such trials who are willing to share their trial data are invited to contact the investigators.

Principal Investigator: Philip Bath, FRCP
Contact: P.M.W. Bath, FRCP; Division of Stroke Medicine, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, UK. Phone 44-115-823-1768. Fax 44-115-823-1767. E-mail philip.bath@nottingham.ac.uk

Location: University of Nottingham, Nottingham, UK.

Number of Centers: Those centers that have organized a randomized controlled trial in acute stroke involving a vasoactive drug which lowers or raises blood pressure.

Sponsor: South Thames & Trent Regional Health Authority National Health Service Research and Development Executives. The study is being performed under the auspices of the Cochrane Collaboration Stroke Group and is published in the Cochrane Library.

Dates of Study: November 1995 (continuing).
Carotid Occlusion Surgery Study (COSS)

COSS is a randomized, partially blinded, controlled trial to test whether extracranial-intracranial arterial bypass surgery, when added to best medical therapy, can reduce by 40% subsequent ipsilateral ischemic stroke at 2 years in subjects with recently symptomatic internal carotid artery occlusion and ipsilateral increased oxygen extraction fraction measured by PET. PET scans will be performed within 120 days of the qualifying TIA or stroke on 1400 clinically eligible subjects to identify 372 with increased oxygen extraction fraction distal to an occluded carotid who will be randomized to receive surgery or no surgery. Study participants will be followed for a 2-year period. Follow-up includes clinic visits at 1 month, and every 3 months after randomization for 2 years. All participants will receive best medical management, which includes management of hypertension and other medical risk factors.

Principal Investigators: William J. Powers, MD (Clinical Coordinating Center), William R. Clarke, PhD (Data Management Center)

Contact: Carol Papps, RN, Carotid Occlusion Surgery Study, Box 8111, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110. Phone 314-362-4299, Fax 314-362-4521. E-mail carol@npw.wustl.edu Website: www.cosstrial.org

Location: University of North Carolina, Chapel Hill, NC (Clinical Coordinating Center) University of Iowa, Iowa City, IA (Data Management Center).

Number of Centers: 40 to 50.

Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health.


Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)

CREST is a prospective, randomized, multicenter, clinical trial to assess the relative efficacy of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) using the RX ACCULINK Carotid Stent System and RX ACCUNET Embolic Protection Device in preventing stroke, myocardial infarction and death during the 30-day periprocedural period and ipsilateral stroke thereafter in subjects with symptomatic and asymptomatic extracranial carotid stenosis.

The study includes a lead-in phase for credentialing of interventionists, beyond their initial training and certification requirements. Approximately 2500 subjects with transient ischemic attack, amaurosis fugax, or nondisabling stroke within 180 days of randomization will be enrolled and followed. Patients undergo a routine Doppler ultrasound of both legs at 7, and wherever possible, 30 days postrandomization. The primary outcomes are the presence of DVT in the popliteal vein or more proximal vein detected on either Doppler ultrasound or venography within 7 and 30 days of randomization. Patients are followed-up at 6 months to identify late events, survival and functional status.

Chief Investigator: Professor Martin Dennis, Neurosciences Trials Unit, Western General Hospital, Crewe Road, Edinburgh UK. EH4 2XU. Phone 44 (0)131 537 1082. Fax 44 (0)131 332 5150. E-mail clots@skull.dcn.ed.ac.uk Website: www.clotstrial.com

Location: Europe, Argentina, Australia, India, Canada, Mexico, Poland, Singapore.

Number of Centers: 126 centers to date.

Sponsor: Medical Research Council (UK).


The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)

Summary: Up to 40% of acute stroke patients on hospital admission are already taking antihypertensive therapy, and most will develop elevated blood pressure levels as an acute complication of the stroke. However, no guidelines exist as to whether antihypertensive therapy should be continued or discontinued after acute stroke. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) is a multicenter, prospective, randomized, open, blinded-end point study to assess whether existing antihypertensive therapy should be continued or discontinued within 48 hours of stroke onset and for the subsequent 2 weeks. A study population of 2900 patients with both cerebral infarction and hemorrhage on antihypertensive treatment at hospital admission will be recruited giving the study a 90% power at the 5% significance level to detect a relative reduction of 10% (absolute risk reduction of 6%) in death and dependency between continuation and discontinuation groups at 2 weeks. Nondysphagic, hospital-admitted stroke patients will be
recruited within 48 hours of stroke onset and also within 48 hours of last dose of pre-existing antihypertensive therapy. Baseline investigations will include blood pressure measurement using UA-767 monitor, modified Rankin Scale score, Barthel Index, National Institutes of Health Stroke Score and Oxfordshire Community Stroke Project Classification. Patients will be centrally randomized by secure website to continue or discontinue pre-existing antihypertensive treatment for a 2-week period. Blood pressure, modified Rankin Scale score, Barthel Index and National Institutes of Health Stroke Score will be repeated at 2 weeks by an observer blinded to the randomized group. Mortality and health-related quality of life outcomes will be centrally recorded at 6 months. The primary outcome will be death or dependency (modified Rankin Scale score >3) at 2 weeks postrandomization. Early secondary outcomes of neurological deterioration, functional status, blood pressure changes from admission and discharge destination will be recorded at 2 weeks. Late secondary outcome measures of death and dependency, fatal and nonfatal stroke recurrence, functional status, health-related quality of life and discharge destination will be recorded at 6 months.

**Principal Investigators:** Professor T.G. Robinson and Professor J.F. Potter

**Contact Details:** Department of Cardiovascular Sciences, Leicester Medical School, University Hospitals of Leicester NHS Trust, Gwendolen Road, Leicester LE5 4PW, Phone +44 (0)116 258 4223. Fax 0 +44 (0)116 258 4187. E-mail cossacs@le.ac.uk

**Location:** United Kingdom.

**Sponsor:** The Health Foundation.

**Date of Study:** December 2002 (ongoing).

*Efficacy of Nitric Oxide in Stroke (ENOS) trial*

Nitric oxide is a multimodal molecule, which is a candidate treatment for acute ischemic and hemorrhagic stroke, as based on preclinical and clinical data from 3 phase II trials. Potential mechanisms of action include lowering blood pressure, improving cerebral perfusion, and neuroprotection. ENOS is a large collaborative international academic randomized controlled trial, designed to test the safety and efficacy of transdermal glyceryl trinitrate (a nitric oxide donor) in 5000 patients when given within 48 hours of stroke onset. Patients who are taking antihypertensive therapy at the time of their stroke will also be randomized to continue or temporarily stop this. The primary end point is combined death or dependency (modified Rankin Scale 3 to 6) at 3 months, to be assessed centrally by telephone. Subgroup analyses will include efficacy in patients with: ischemic stroke, high blood pressure (systolic blood pressure >160 mm Hg), and treatment <12 hours. Randomization and data registration are performed over the Internet. Centers are invited to join the collaborative group. 988 patients had been recruited by August 2008.

**Principal Investigator:** Philip M.W. Bath, MD, FRCP

**Contact:** P.M.W. Bath, ENOS Trial Centre, Division of Stroke Medicine, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, UK. Phone 44-115-823-1768. Fax 44-115-823-1767. E-mail enos@nottingham.ac.uk Internet: http://www.enos.ac.uk/

**Location:** Global.

**Number of Centers:** 66 (looking for 200) from 13 countries.

**Sponsor:** UK Medical Research Council (previously BUPA Foundation, The Hypertension Trust, University of Nottingham).

**Dates of Study:** July 2001 to October 2011.

**Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO (CLOSURE)**

CLOSURE is a prospective, multicenter, randomized controlled trial to evaluate the safety and efficacy of the STAR-flex Septal Closure System versus aspirin and/or warfarin therapy for the prevention of stroke, TIA and mortality in patients with an initial stroke or TIA due to a presumed paradoxical embolism through a patent foramen ovale (PFO). The goal is to determine whether device closure of a PFO is superior to best medical therapy for preventing recurrent stroke or TIA in patients with an initial cryptogenic stroke/TIA and a PFO. Sixteen hundred patients (800 in each group) at up to 100 sites nationally will be randomized within 180 days of the entry event. Study patients will be followed for 2 years. All strokes and TIs will be adjudicated by a blinded Clinical Events Committee using prespecified clinical and MR imaging definitions. The primary end point of incidence of 24-month stroke or TIA, all cause mortality for the first 30 days of follow-up or hospital discharge, whichever is longer, and neurological mortality from ≥31 days of follow-up will be analyzed on an intent-to-treat basis using the χ² test and logistic regression adjusting for study center and demographic characteristics deemed related to the primary end point. Safety analyses will focus on the incidence of severe adverse events related to either device insertion or major bleeding complications on medical therapy.

**Principal Investigator:** Anthony J. Furlan, MD

**Co-Principal Investigator:** Marc Reisman, MD

**Executive Committee:** A.J. Furlan, M. Reisman, H. Adams, L. Wechsler, Gregory Albers, Robert Felberg, M. Landzberg, H. Hermann, Al Raizner, Saibal Kar

**Data Safety Monitoring Board:** J.P. Mohr, Chairman

**Clinical Events Committee:** Marc Fisher, Chairman

**Data Management:** Harvard Clinical Research Institute.

**Contact:** A.J. Furlan, Cleveland Clinic Department of Neurology, S91, 9500 Euclid Avenue, Cleveland, Ohio 44195. Fax 216 444 0232. Phone 216 444 5535. E-mail furlana@ccf.org

**Sponsor:** NMT Medical, 27 Wormwood St., Boston MA 02210-1625.

**Dates of Study:** July 2003 to July 2006.

**The Field Administration of Stroke Therapy - Magnesium (FAST-MAG) Phase 3 Trial**

Magnesium is neuroprotective in preclinical models of stroke and has been safe and shown signals of potential efficacy when administered early after onset in initial human stroke clinical trials. Delayed initiation of neuroprotective agents has hindered past phase 3 neuroprotective agent trials. The purpose of the FAST-MAG phase 3 trial is to demonstrate that paramedic initiation of intravenous magnesium sulfate within 2 hours of symptom onset improves the long-term functional outcome of hyperacute stroke patients.

FAST-MAG is a multicenter, randomized, double-blind, placebo-controlled phase 3 trial that will enroll 1298 patients (649 in each arm). The study population consists of prehospital patients with acute stroke, including both cerebral infarction and intracerebral hemorrhage patients. Inclusion criteria: (1) likely stroke as identified by the Los Angeles Prehospital Stroke Screen (LAPSS), (2) age 40

+ indicates centers that are currently recruiting.
to 95, (3) symptom onset within 2 hours of treatment initiation, (4) deficit present \(\geq 15\) minutes. Study agent will be started within 1 hour of onset in \(\approx 1/2\) of enrolled patients and between 1 to 2 hours after onset in the remainder. Study sites are up to 80 ambulance-receiving hospitals in Los Angeles County, serviced by the LA County EMS Agency. In the study intervention, paramedics administer a loading dose of magnesium sulfate (Mg) or matched placebo in the field, 4 grams over 15 minutes. In the ED, a maintenance infusion follows, 16 grams Mg or matched placebo over 24 hours. Explicit informed consent is obtained in the field by phone physician contact, either from competent patients or on scene legally authorized representatives, using an in-vehicle FAST-MAG cellular phone.

The primary end point is the distribution of scores across all 7 strata of the modified Rankin Scale global measure of functional outcome, assessed 90 days after treatment. Secondary end points include NIHSS (neurologic deficit), Barthel Index (disability), and Stroke Impact Scale (quality of life).

**Principal Investigator:** Jeffrey L. Saver, MD  
**Co-Principal Investigators:** Sidney Starkman, MD; Sam Stratton, MD; Chelsea Kidwell, MD; Marc Eckstein, MD  
**Contact:** Jeffrey L. Saver, MD, Professor of Neurology, UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095. Phone 310-794-6379. Fax 310-267-2063. E-mail jsaver@ucla.edu  
**Location:** Los Angeles County.  
**Number of Centers:** Up to 80.  
**Sponsor:** National Institute of Neurologic Disorders and Stroke - National Institutes of Health.  
**Dates of Study:** 2003–2008.

### Increasing Stroke treatment through Interventional Behavior Change Tactis (INSTINCT)

The Increasing Stroke Treatment through Interactive behavioral Change Tactic (INSTINCT) trial is a multicenter, randomized, controlled study designed to evaluate the effectiveness of a standardized, system-based, barrier assessment and interactive educational intervention (BA-IEI) approach to increase appropriate tPA use in stroke. The intervention is based on adult education and behavior change theory, targets emergency departments and hospital systems, and is designed for replication in community health initiatives. It incorporates local stroke champion development, hospital-specific barrier evaluation, mixed CME modules targeting identified barriers, performance feedback, protocol development, and academic detailing. The primary end point will be the increase in appropriate use of tPA in stroke with evaluations of change in emergency physician knowledge on tPA use.

**Principal Investigator:** Phillip A. Scott, MD  
**Contact:** Shirley Frederiksen, MS, RN, Project Manager, 24 Frank Lloyd Wright Dr, Lobby H Box 381, Ann Arbor, MI 48106. Phone 734-232-2142.  
**Location:** University of Michigan Department of Emergency Medicine.  
**Number of Centers:** 24.  
**Sponsor:** National Institute for Neurological Disorders and Stroke, National Institutes of Health.  
**Dates of Study:** July 2005 to July 2010.

### International Citicoline Trial on acUte Stroke (ICTUS)

Citicoline is a safe drug approved in some countries for the treatment of acute ischemic stroke. The drug has shown some evidence of efficacy given within 24 hours from symptoms onset in a pooled analysis, based on 4 clinical trials done in the United States with oral citicoline. We aim to study the effects on recovery at 3 months of oral citicoline 2000 mg a day for 6 weeks in patients with moderate-to-severe acute ischemic stroke compared with placebo.

ICTUS is a randomized (under minimization) double-blind placebo-controlled trial. Patients aged 18 years or older, without previous disability, with a measurable focal neurological deficit referable to the middle cerebral artery and lasting for a minimum of 60 minutes, baseline National Institute of Health Stroke Scale (NIHSS) score of 8 or higher, a neuroimaging compatible with the diagnosis of acute ischemic stroke, and able to be treated within 24 hours of symptoms onset will receive citicoline or placebo (1000 mg every 12 hours intravenously during the first 3 days and orally from the fourth day until the end of the 6 weeks treatment period).

The study follows a sequential analysis (triangular model), with the first approach to test efficacy in 1000 patients. If the study is continued at this point, further analyses will take place when data are available on 1533, 2067 and 2600 patients respectively. This strategy (design) has 80% power to establish a treatment effect of 1.26 (common odds ratio).

Each comparison on the basis of intention-to-treat criteria will consist of a global score test combining 3 measures of success evaluated 12 weeks after treatment: NIHSS \(\leq 1\), modified Rankin Scale (mRS) \(\leq 1\), and Barthel Index \(\geq 95\). A patient who dies before 12 weeks will be considered to have failed on all 3 measures. Secondary end points are single scales at week 12, with the same cut-off points. Formal training and certification of the investigators in the use of mRS and NIHSS is required. Safety end points include: vital signs, adverse events, symptomatic hemorrhagic transformation in patients treated with alteplase (European Cooperative Acute Stroke Study [ECASS] criteria), neurological deterioration, and mortality.

**Principal Investigator:** Antoni Dávalos, MD, PhD  
**Contact:** Antoni Dávalos, E (Chairman); José Alvarez-Sabín, E; José Castilho, E; Erik Cobo, E (Statistician); Exuperio Díez-Tejedor, E; Jose Ferro, P; Savion Gropper, E; Eduardo Martínez-Vila, E; Julió J Secades, E.  
**Data Safety Monitoring Board:** Kenneth R. Lees, UK (Chairman); Werner Hacke, D; Steve Warach, USA; John Whitehead UK (Statistician).  
**Contact:** Dr. Antoni Dávalos, Department of Neurosciences. Hospital Germans Trias i Pujol, Crta. de Canyet, s/n, 08916 Badalona (Spain). Phone: +34 934 978 911. Fax: +34 934 978 742. E-mail: adavalos.germanstrias@genca.cat. Dr. Julio J Secades, Medical Department, Ferrer Group S.A., Avda. Diagonal 549 5th, 08029.
Barcelona (Spain). Phone: +34 936 003 837. Fax: +34 934 907 078. E-mail: jscadets@ferrergrup.com

Location: Spain and Portugal.

Centers: 34 centers in Spain, 10 in Portugal, and in the near future 10 in Germany.

Sponsor: Ferrer Group S.A.

Registers: EudraCT N° 2005-004825-25; ClinicalTrials.gov NCT00331890; Stroke Trials Registry; ww.thelancet.com/journals/lancet/misc/protocol06PRT-3005.

Dates of Study: 2006 to 2010. 471 patients were included by March 31, 2008.

*Intra-Arterial Versus Intravenous Thrombolysis In Acute Ischemic Stroke (SYNTHESIS EXPANSION)

The trial has entered a new phase with a grant from the Italian Agency for Drugs (AIFA Agenzia Italiana del Farmaco) now financing it. In this new phase, the name has turned into SYNTHESIS EXPANSION; a web-based data collection and randomization system has been implemented and the protocol has undergone refinements as far as the intraarterial procedure. SYNTHESIS EXPANSION remains a multicenter RCT, open-label, with blinded follow-up aiming to determine whether locoregional intra-arterial (IA) alteplase (in the new protocol, “alone, associated to, or substituted by mechanical recanalization manoeuvres”), as compared with systemic intravenous (IV) infusion of the same drug within 3 hours of ischemic stroke, increases the proportion of independent survivors at 3 months. Eligibility still applies to patients with symptomatic, CT verified, acute ischemic strokes being able to initiate IV alteplase within 3 hours and IA procedure within 6 hours of stroke onset when uncertainty about appropriateness of the 2 approaches exists as established by the treating physician. Eligible patients are randomized to receive either 0.9 mg/kg (max 90 mg) IV alteplase (control arm) or to receive up to 0.9 mg/kg IA alteplase (max 90 mg) over 60 minutes into the thrombus and/or to undergo a mechanical recanalization procedure (clot mechanical disruption and/or retrieval, PTA stenting of the occluded artery or of disclosed underlying stenotic lesion). The study remains designed to detect or disprove (α=5% and power probability=80%) a 15% absolute difference between the treatment groups in the percentage of patients with a favourable outcome (modified Rankin Scale score 0 to 1). Enrollment will still be completed with 350 randomized patients.

Principal Investigator: A. Ciccone
Safety and Monitoring Committee: L. Candelise, G. Del Zoppo, P. Sandlercock.
Monitor: E. Botto
Follow-Up: T. Cantisani

Contact: Alfonso Ciccone, Stroke Unit, Ospedale “Niguarda Ca’ Granda”, Piazza Ospedale Maggiore 3, 21064 Milano, Italy (E-mail alfonso.ciccone@ospedaleniguarda.it). Phone +39-02-64442348. Fax +39-02-64442819.

Location: Italy.

Number of Centers: 14 centers are currently authorized for recruitment; 4 centers have expressed interest or are in the process of application to local ethical committees; investigators from other centers are invited to participate.

Sponsor: Grant from AIFA (Agenzia Italiana del Farmaco).

Dates of Study: SYNTHESIS ended in January 2008 with 54 recruited patients (15% of the total). Its results are in the process of being published. Recruitment for SYNTHESIS EXPANSION has started February 1st 2008 and 11 patients (over 22 considered eligible) have been randomized up to now.

*Locomotor Experience Applied Post-Stroke (LEAPS)

Locomotor training using body weight support and a treadmill as a therapeutic modality for the rehabilitation of walking poststroke is being rapidly adopted into clinical practice. A 2005 Cochrane review highlighted the urgent need for a well-designed trial to determine the effectiveness of this intervention.

The objective of the LEAPS trial is to determine whether there is a difference in the proportion of participants who successfully recover walking ability at 1 year poststroke when individuals are randomized to a specialized locomotor training program (LTP) conducted at 2 or 6 months poststroke, or those randomized to a home-based nonspecific, low intensity exercise intervention (HEP) provided at 2 months poststroke.

The LTP program includes use of body weight support on a treadmill and overground training. The LTP and HEP interventions are delivered for 36 sessions over 12 weeks. Successful walking recovery is defined as the achievement of a 0.4 m/s gait speed or greater by persons with initial severe gait impairment (<0.4 m/s), or the achievement of a 0.8 m/s gait speed or greater by persons with initial moderate gait impairment (≥0.4 m/s to <0.8 m/s). We will also determine whether the timing of LTP delivery (early vs late) affects the improvement in gait speed at 1 year and whether initial locomotor impairment severity interacts with the timing of LTP delivery. The effect of number of treatment sessions will be determined by changes in gait speed taken pretreatment, post-12, post-24, and post-36 sessions.

We will recruit 400 adults, with moderate or severe walking limitations, within 45 days of their stroke onset. Participants are followed until 2 months poststroke to establish eligibility. At 2 months, participants who continue to be eligible undergo baseline assessment. After baseline assessment, participants are stratified by locomotor impairment severity as determined by overground walking speed and randomly assigned to 1 of 3 groups: (a) LTP-Early; (b) LTP-Late or (c) Home-based Exercise Program—Early.

Principal Investigator: Pamela W. Duncan, PhD, FAPTA LEAPS Data Management and Analysis Center: Stanley Azen, PhD
Steering Committee: Pamela W. Duncan, PhD, FAPTA; Andrea Behrman, PhD, PT (Co-PI); Katherine Sullivan, PhD (Co-PI); Steven Nadeau, MD; Bruce Dobkin, MD; Samuel S. Wu, PhD; and Sarah Hayden

Data Safety Monitoring Board: Bruce Coull, MD (Chair); Elizabeth A. Noser, MD; Michael Parides, PhD; and Steven Wolf, PhD, PT

Medical Safety Monitor: Alexander Dromerick, MD

Contact: Pamela W. Duncan, PhD; LEAPS Administrative Coordinating Center, Duke University, 2200 West Main Street, Suite 220, Durham, NC 27705. Phone 919-286-3399 ext 235. Fax 919-286-5601.

Location: LEAPS Administrative Coordinating Center: Duke University, Durham, NC; Data Management and Analysis Center: University of Southern California, Los Angeles, CA; Clinical Coordinating Centers: University of Florida, Gainesville, FL and University of Southern California, Los Angeles, CA; Clinical Intervention Sites: Brooks Rehabilitation Hospital, Jacksonville, FL; Florida Hospital, Orlando, FL, long Beach Memorial Hospital, Long Beach, CA; Sharp Rehabilitation Center, San Diego, CA; and USC PT Associates, Los Angeles, CA.

* indicates centers that are currently recruiting.
Number of Centers: 5 clinical intervention sites currently enrolling participants.
Sponsors: National Institute of Neurological Disorders and Stroke and the National Center for Medical Rehabilitation Research.
Web address: http://leaps.usc.edu/
Clinical Trial Registration: ClinicalTrials.gov NCT00243919.

*Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH-II)*

The MASH-II study is a phase III randomized, international multicenter trial to determine whether magnesium reduces the frequency of poor outcome (death or dependence) in patients admitted within 4 days after aneurysmal subarachnoid hemorrhage. Magnesium sulfate 64 mmol/day (equals 16 grams/day) or placebo intravenously is started as soon as possible after informed consent and continued until 20 days after the hemorrhage. We plan to include 1200 patients in 5 years. Outcome will be assessed after 3 months by means of the modified Rankin score.

Principal Investigators: Walter M. van den Bergh; Gabriel J.E. Rinkel
Steering Committee: S.M. Dorhout Mees, MD, WM. van den Bergh, MD; A. Algra, MD; G.J.F. Brekelmans, MD; J. van Gijn, MD; F. van Kooten, MD; P.M. Lavados, MD; R.J. van Oostenbrugge, MD; G.J.E. Rinkel, MD; R. Al-Shahi Salman, MD; W.P. Vandertop, MD; M. Vermeulen, MD (New members may be added if more (international) centers join the study).

Data Monitoring Committee: J.G. van der Bom (chair); W.P. Th.M. Mali; P.M. Rothwell; R.S.C. Kerr

Contact: Sanne M. Dorhout Mees, MD, Department of Neurology Go3.224, University Medical Center Utrecht, PO Box 8550, 3508 GA Utrecht, The Netherlands. Phone +31-30-2508350. Fax +31-30-2522782. E-mail S.M.Dorhoutmees@umcutrecht.nl

Number of Randomizing Centers: 8.
Number of Randomized Patients: 575.
Sponsor: The Netherlands Heart Foundation (grant number: 2005B016).
Dates of Study: Randomization was started in January 2004. Analysis of the results is planned in 2010.
ISRCTN#: 68742385.
EudraCT#: 2006-003523-36.

*Optimizing the Analysis of Stroke Trials (OAST)*

Most trials in acute stroke have been neutral (or even negative). One possible explanation is that they may have been analyzed suboptimally. Functional outcome is usually scored using ordinal scales (eg, modified Rankin Scale [mRS], Barthel Index) and yet analyses are often based on dichotomization of the data (eg, mRS 0 to 2 vs 3 to 6), a process that would be expected to reduce statistical power. We are comparing a variety of ordinal and nominal statistical approaches using individual patient data from interventions which modify outcome (either positively or negatively) in acute stroke or stroke rehabilitation; neutral trial data from neutral interventions will not be included. The aim is to identify one (or more) optimal approach(es) for use in future stroke trials. Authors of relevant trials who are willing to share their trial data are invited to contact the investigators.

Contact: Philip M.W. Bath, FRCP; Division of Stroke Medicine, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK. Phone 44-115-823-1768. Fax 44-115-823-1767. E-mail Philip.bath@nottingham.ac.uk

Location: University of Nottingham, Nottingham, UK.

Number of Centers: Those that have organized a positive or negative randomized controlled trial in acute stroke or stroke rehabilitation.

Sponsor: The Stroke Association (UK).

Dates of Study: October 2004 (continuing).

Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard-of-Care Treatment (RESPECT) Trial

PURPOSE: To investigate whether percutaneous PFO closure is superior to current standard-of-care medical treatment in the prevention of recurrent embolic stroke. DESIGN: Multicenter, randomized, active control, blinded adjudicated outcome, clinical trial. SAMPLE SIZE: 710 patients (355 per study arm). POPULATION STUDIED: Patients aged 18 to 60 years with patent foramen ovale (PFO) who have had a cryptogenic stroke due to presumed paradoxical embolism within the last 270 days. INTERVENTIONS: Patients are randomly assigned to medical therapy or PFO closure with the AMPLATZER PFO Occluder. Medical therapy options include aspirin alone, coumadin alone, clopidogrel alone, or aspirin combined with extended-release dipyridamole. OUTCOME MEASURES: The primary end point is recurrent nonfatal stroke, all-cause post-randomization death within 45 days of randomization or 30 days after implant, whichever occurs last, or fatal ischemic stroke. The secondary efficacy end points are complete closure of the defect at the 6-month follow-up, time to recurrent symptomatic cryptogenic nonfatal stroke or cardiovascular death, and transient ischemic attack. The primary safety end point is all major adverse events.

STATISTICAL ANALYSIS: The superiority of the device will be tested by using an exact binomial test of the proportion of device primary end point events to primary end point events across both arms of the study, conditioned on the total number of events.

Steering Committee Members: John Carroll, MD, University of Colorado School of Medicine, Denver, Colo; Jeffrey Saver, MD, UCLA, Los Angeles, Calif; Richard Smalling, University of Texas Houston, Houston, Tex; David Thaler, TUFTS – NEMC, Boston, Mass.

Contact: Jeffrey L. Saver, MD, Professor of Neurology, UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095. Phone 310-794-6379 Fax 310-267-2063. E-mail jsaver@ucla.edu

Number of Centers: 60 sites in the United States.
Sponsor: AGA Medical Corporation, 5050 Nathan Lane North, Plymouth, MN 55442.

Dates of Study: August 2003–Ongoing.

Scandinavian Candesartan Acute Stroke Trial (SCAST)

SCAST is an international randomizing, placebo-controlled, double-blind trial of candesartan (an angiotensin receptor blocker) in acute stroke. Patients presenting within 30 hours of stroke (ischemic or hemorrhagic) and with systolic blood pressure ≥140 mm Hg are randomly assigned to candesartan or placebo for 7 days (doses increasing from 4 to 16 mg once daily). The follow-up period is 6 months. Primary effect variables: (1) death or major disability at 6 months; (2) vascular death, myocardial infarction or stroke during the first 6 months. Target recruitment: 2500 patients by mid-2009.

Coordinating Investigator: Eivind Berge, MD, PhD

* indicates centers that are currently recruiting.
Stent-protected Percutaneous Angioplasty of the Carotid versus Endarterectomy (SPACE)

SPACE is a multicenter, prospective, randomized trial to determine whether carotid endarterectomy (CEA) and percutaneous angioplasty (PTA) are equivalent with respect to ipsilateral stroke, a restenosis degree of ≥70% ECST criteria or ≥50% NASCET criteria, respectively, and technical success in patients with transient cerebral ischemia (TIA) or nondisabling stroke because of severe carotid stenosis. This study will include 950 patients per group. Interim analysis is planned after 450 patients per group have been treated or 3 years. Inclusion criterion is symptomatic, high-grade carotid stenosis (≥70% ECST or ≥50% NASCET) within 180 days before randomization (TIA or nondisabling stroke). Primary end point is ipsilateral stroke or death within 30 days after intervention. Secondary end points are: Ipsilateral stroke or death within 24 months after randomization; restenosis ≥70% of treated carotid artery within 6, 12, and 24 months after randomization; technical complications (ME, vascular occlusion, residual stenosis ≥70%) within 6 and 30 days after intervention; stroke of any localization within 30 days and 24 months after intervention. Each study center consists of 3 departments (Neurology, Vascular Surgery, and Interventional Radiology). Certification for each of the 3 specialties has to be given by a quality standards committee, with documentation of 25 CEA per vascular surgeon, 25 PTA per interventional radiologist, and ultrasound expertise for neurologists. An external data monitoring strategy is in place. This trial is now complete.

Steering Committee: Neurology: Werner Hacke; Heidelberg, Germany (Chair), Michael Hennerici; Mannheim, Germany; Vascular Surgery: Jens R. Allenberg; Heidelberg, Germany; Henning Eckstein, Munich, Germany; Interventional Radiology: Hermann Zeumer; Hamburg, Germany; Olav Jansen; Kiel, Germany.

Contact: Alexandra K. Kunze, MD; Department of Neurology, University of Heidelberg. Im Neuenheimer Feld 400; D-69 120 Heidelberg; Phone +49/6221 5682211. Fax +49/6221 565348. E-mail alexandra_kunze@med.uni-heidelberg.de. Website: www.space.stroke-trial.com

Location: Europe.

Number of Centers: 37.

Sponsors: BMBF (German Ministry of Science), DFG (German Research Council), Guidant, Boston Scientific.


*Surgical Trial in Lobar Intracerebral Haemorrhage (STICH II)

This is an international multicenter trial to determine whether a policy of “early surgical evacuation” of the hematoma in patients with spontaneous supratentorial lobar intracerebral hemorrhage only will improve outcome compared with a policy of “initial conservative treatment.” Primary outcome is mortality and morbidity at 6 months as measured by the Glasgow Outcome Scale. Secondary outcome instruments include the modified Rankin Scale, EuroQol and the Barthel Index. The trial will also help to better define the indications for surgery. In total 600 patients, for whom the surgeon is in equipoise about the need for surgical evacuation, will be randomized to receive “early surgery” (within 12 hours of randomization), preferably using craniotomy, or “initial conservative treatment.” Patient status is recorded 2 weeks after randomization and then outcome is assessed at 6 months using a structured postal questionnaire to the subject or subject’s relative to ensure assessor blindness. Funding for this trial was activated in September 2006, and as of March 31, 2008, 42 patients and 40 centers had been recruited. Center recruitment is ongoing. Please visit the website if you would like to take part.

Principal Investigators: Prof A.D. Mendelow, Dr B.A. Gregson, Mr P.M. Mitchell, Prof G.D. Murray and Dr A.R. Gholkar

Contact: Dr Barbara Gregson, Trial Director. Phone: 44-191-256-3139. Fax: 44-191-256-3268. E-mail: stich@ncl.ac.uk
**Third International Stroke Trial (IST-3)**

**Background:** For every 1000 patients with acute stroke treated with intravenous recombinant tissue plasminogen activator (IV rt-PA) within 6 hours of stroke onset, 55 avoid death or dependence, yet few patients are being treated worldwide. The third International Stroke Trial (IST-3) aims to provide more reliable evidence on which categories of patients benefit most from IV rt-PA and how it could be more widely used. **Study Design:** IST-3 is an international, multicenter, randomized, controlled, postlicensing trial of IV rt-PA (0.9 mg/kg) for acute ischemic stroke, with a PROBE (Prospective, Randomized, Open, Blinded Endpoint) design. **Patient Eligibility:** Eligible patients must be assessed and able to start treatment within 6 hours of onset, and a CT (or MR) scan must have excluded intracranial haemorrhage. Details of inclusion/exclusion criteria are given in the trial protocol. **Center Eligibility:** To join the study, centers must have an established acute stroke service which meets predefined criteria. **Trial Procedures:** are very efficient and aim to ensure trial treatment is started with minimal delay. Patient inclusion is by telephone call to a rapid centralized randomization system which balances on key prognostic factors. Trial treatment is only allocated by the system after the baseline data have been successfully recorded and cross-checked. Brain imaging (CT or MR) must be repeated after treatment (at 24 to 48 hours). An international expert panel reviews ‘blinded’ all baseline and follow-up CT/MR images by means of an innovative centralized web-based image-reading system (see ACCESS study for details). In all centers, follow-up is conducted by centralized (blinded) postal or telephone questionnaire, conducted independently of the clinician treating the patient. **Trial Outcome Measures:** The primary measure of outcome is death or dependence at 6 months (poor functional outcome). A number of secondary outcomes are specified in the protocol. Planned subgroup analyses will include an assessment of the effect of: age, stroke severity, time to randomization, CT appearances, blood pressure and other factors on the risks and benefits of treatment. **Sample Size:** With 1000 patients the trial is powered to detect a 7% absolute difference in the primary outcome. With 3500 patients, the trial could detect a 4% absolute difference in the primary outcome, and with 6000 patients, mostly treated between 3 and 6 hours of onset, the trial could detect a 3% absolute difference in the primary outcome. **Study Progress:** A total of 1225 patients had been recruited by July 29, 2008. **Trial Coprincipal Investigators:** Richard Lindley and Peter Sandercock. **Imaging Principal Investigator:** Joanna Wardlaw **Contact:** Professor Peter Sandercock, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, United Kingdom. Fax ++ 44 (0)131 332 5150. E-mail IST3@skull.dcn.ed.ac.uk **Location:** UK, Italy, Norway, Belgium, Sweden, Australia, New Zealand, Canada, Poland, Austria, Portugal, Mexico, India. **Number of Centers:** Currently 85; new centers are welcome to join.

**Trial on Endovascular Aneurysm Management (TEAM)**

The management of patients with unruptured aneurysms remains controversial. Patients with unruptured aneurysms may experience intracranial haemorrhage, but the incidence of this event is still debated. Endovascular treatment can prevent rupture but involves immediate risks. Furthermore, successful treatment does not eliminate all risks. Hence, the balance of the risks and benefits is uncertain. TEAM (for Trial on Endovascular Aneurysm Management) is an international, randomized, multicenter, controlled trial comparing the combined mortality and morbidity (modified Rankin Scale [mRS] ≥3) from intracranial hemorrhage in patients with unruptured aneurysms treated by conservative management (or deferral for 10 years or until definite indications are thought to have arisen) as compared to endovascular coiling. Secondary end points will include the incidence of hemorrhagic events in both groups, the morbidity related to endovascular coiling, morphological results at 5 and 10 years, overall clinical outcome at 5 and 10 years, quality of life assessment, and the level of distress caused by the knowledge of the hemorrhagic risk. To take into account ease of recruitment, feasibility, generalizability, and ethical considerations, entry criteria will be minimized. The analyses will be performed on 2 populations: intent-to-treat and per protocol. The main statistical tests will involve comparisons between the 5- and 10-year probabilities of poor outcomes (mRS ≥3): (1) from hemorrhage related to the lesion, excluding per operative complications, (2) the 5/10-year probabilities of mortality from hemorrhage or from complications of treatment, or (3) comparisons of the 5- and 10-year probabilities of combined disease or treatment-related mortality and morbidity, in the absence of other causes of death or disability. Other analyses will involve Kaplan-Meier life-table methods to assess the 5- and 10-year mortality from intracranial bleeding or from treatment among all those allocated immediate coiling (including the few who did not undergo it) and all those allocated deferral of any intervention (including the few who will eventually be operated on) as well as overall mortality. The study will be conducted in 60 international centers. The entire study will enroll ~2002 patients equally divided between the 2 groups, a size sufficient to achieve 80% power at a 0.0167 significance to detect differences in (1) disease or treatment-related poor outcomes from 7%–9% to 3%–5%; (2) overall mortality from 16% to 11%. The duration forecast of the study is 14 years, the first 3 years being for patient recruitment plus a minimum of 10 years of follow-up. **Principal Investigator:** Dr Jean Raymond, MD
Steering Committee: Dr Andrew Molyneux, MD, UK; Professeur Jacques Moret, MD, France; Dr Herman Zeumer, MD, Germany; Dr Alejandro Berenstein, MD, USA; In Sup Choi, MD, USA; Cameron McDougall, MD, USA; Gabriel Rinkel, MD, The Netherlands; Claiborne Johnston, MD, PhD, USA; Dr Jean Raymond, MD, Canada; Dr Isabelle Rouleau, PhD, Canada; Dr Allan J. Fox, MD, Canada; Dr Jean-Paul Collet, MD, PhD, Canada; Dr Yves Lepage, PhD, Canada.

Contact: Guylaine Gevry, Interventional Neuroradiology Clinical Research Unit (NRI-CRU), 1560 Sherbrooke East, Suite Z-12909, Montreal, QC, Canada, H2L 4M1. Phone 514-890-8000 Ext 27235. Fax 514-412-7621. E-mail guylaine.gevry@crchum.qc.ca. Trial website: http://www.teamstudy.org

Location: Canada, USA, Europe, Turkey, China.

Number of Centers: 60 in total. 33 are already active. Interested centers may still join in.

Sponsor: Canadian Institutes of Health Research (CIHR).


*VITAmins TO Prevent Stroke (VITATOPS)

The VITATOPS study is a multicenter, randomized, double blind, placebo-controlled secondary stroke prevention trial to determine whether the addition of vitamin supplements (B12 500 µg, B6 25 mg, Folate 2 mg) to best medical/surgical management (including modification of risk factors) will reduce the combined incidence of recurrent vascular events (stroke, myocardial infarction) and vascular death in patients with recent stroke or transient ischemic attack (TIA). All patients presenting to one of the participating neurologists or general physicians within 7 months of stroke (ischemic or hemorrhagic) or TIA (eye or brain) are eligible for this trial. Eligible patients will be randomized in a double-blind fashion to receive multivitamins or placebo, 1 tablet daily. The primary outcome event is the composite event “stroke, myocardial infarction, or death from any vascular cause”, whichever occurs first. Our target is to recruit a total of 8000 patients with a median follow-up of 2.5 years. Recruitment to the trial began in November 1998 and is planned to continue until 2008. We aim to complete final follow-up by 2009. However, the Steering Committee will be flexible in dictating the need for ongoing recruitment and continuing follow-up, depending on the overall rate of the primary outcome event in the entire cohort at each interim analysis.

Steering Committee (alphabetically): Dr Ross Baker, Dr John Eikelboom, Ms Anna Gelavis, Prof Graeme Hankey (chairman), Mrs Siobhan Hickling, Prof Konrad Jamrozik, A/Prof Francesco van Bockxmeer.

Contact: VITATOPS Trial Office, Stroke Unit, Royal Perth Hospital, Wellington St Perth 6001, Australia. Phone +61 8 9224 7004. Fax +61 8 9224 8424. E-mail VITATOPS@health.wa.gov.au Website: http://vitatops.highway1.com.au

Centers: Australia (16), Austria (1), Belgium (1), Brazil (1), Hong Kong (2), India (23), Italy (8), Malaysia (2), Moldova (1), Netherlands (3), New Zealand (5), Pakistan (3), Philippines (8), Portugal (4), Republic of Georgia (1), Serbia & Monte Negro (2), Singapore (1), Sri Lanka (2), United Kingdom (29) and United States (5) and actively seeking centers worldwide.


* indicates centers that are currently recruiting.