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.

Steering Committee: P. Amarenco, G.A. Donnan, S.M. Davis, B.R. Chambers, A. Cohen, G.J. Hankey, E. Jones, C.R. Levi and P. Ravaud.

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.

Dates of Study: Oct 2002 to Dec 2008

***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. 455 patients are currently enrolled in the study and we aim to recruit a total of 480 patients. Recruitment is planned to finish in 2007, with follow-up complete in 2009.

Principal Investigator: Hugh Markus, FRCP

Contact: Sheila Reihill, ACES Study Coordinator, Centre for Clinical Neuroscience, St. George's University London, SW17 ORE, Phone 020 8725 5374, Fax 020 8725 2950, E-mail s.reihill@sgul.ac.uk

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

Number of Centers: 29 (still recruiting)

Sponsor: British Heart Foundation

Dates of Study: 2000-2008

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@sgul.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)

Dates of Study: Commenced April 1993 (follow-up ongoing for publication of 10-year results in 2007/2008, but recruitment closed in 2003)

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)

*Indicates centers that are currently recruiting.

Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

CAVATAS is a randomized, multicenter trial to determine the benefits and risks of percutaneous transluminal angioplasty of the carotid and/or vertebral arteries in patients with symptomatic and asymptomatic cerebrovascular disease. The study includes a randomized comparison between carotid angioplasty and carotid endarterectomy.

Principal Investigator: Martin M. Brown, MD

Contact: Martin M. Brown, MD, FRCP, Professor of Stroke Medicine, Institute of Neurology, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK. Phone 44-20-7829-8753. Fax 44-20-7833-8613

Location: Europe, North America, and Australia

Number of Centers: 24. Total number of patients recruited=562.

Sponsor: British Heart Foundation, National Health Service Research and Development Programme, The Stroke Association

Dates of Study: April 1992 to July 2007. Recruitment stopped on July 31, 1997. Follow-up is now complete.

***Web Address*:** www.cavatas.com

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 930 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 2 years. Follow-up includes clinic visits at 1 month, 3 months and every 3 months 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 Hess, 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@npg.wustl.edu Website: www.cosstrial.org

Location: Washington University School of Medicine, St. Louis, MO (Clinical Coordinating Center) University of Iowa, Iowa City, IA (Data Management Center)

Number of Centers: 20 to 40

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

Dates of Study: July 2002–July 2008

***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 peri-procedural period and ipsilateral stroke thereafter in subjects with symptomatic and asymptomatic extracranial carotid stenosis. The study includes a lead-in phase for credentialing of interventionalists, beyond their initial training and certification requirements. Approximately 2500 subjects with transient ischemic attack, amaurosis fugax, or nondisabling stroke within 180 days of randomization and ipsilateral carotid stenosis ≥50% (defined as ≥70% by ultrasound or ≥50% by angiography) for symptomatic patients and >60% (defined as >70% by ultrasound or >60% by angiography) for asymptomatic patients will be followed for up to 4 years. Follow-up includes clinic visits at 1, 6, and 12 months, then every 6 months for study duration with phone contact every 3 months. All patients will receive best medical management, which includes treatment with aspirin, management of hypertension and medical risk factors. Recruitment of patients began in December 2000, but the start-up date will vary across centers depending upon their completion of certification and regulatory requirements. Currently 1545 lead-in participants and 1885 randomized subjects have been enrolled. CREST is approved for renewal and continuation from 2007 through 2011.

Principal Investigator: Robert W. Hobson II, MD

Contact: Alice Sheffet, PhD, CREST-Administrative Center, UMDNJ-New Jersey Medical School, 30 Bergen Street, ADMC 617, Newark, New Jersey 07017, USA. Phone 973-972-7718. Fax 973-972-8383. E-mail sheffeaj@umdnj.edu

Location: North America

Number of Centers: 124

Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health; Abbott Vascular, Inc

Dates of Study: 2000 to 2011

***CLOTS Trial (Clots in Legs or sTockings after Stroke): A randomized trial to establish the effectiveness of graduated compression stockings to prevent poststroke deep-vein thrombosis.**

The CLOTS Trial is a family of 2 multicenter, international, partially blinded, randomized controlled trials which aim to establish the effectiveness of graduated compression stockings (GCS) to prevent poststroke deep-vein thrombosis (DVT). Trial 1 is comparing full-length GCS with no GCS, whilst Trial 2 is comparing full-length and below-knee GCS. Centers randomize consenting patients into either Trial 1 or 2 depending on their current practice and beliefs with respect to GCS after stroke. Patients who are admitted to hospital within 1 week of an acute stroke and are immobile can be randomized into CLOTS. The allocated type of GCS is applied to both legs as soon as possible after randomization and worn until the patient is independently mobile around the ward or until they are discharged from hospital or until the patient declines to wear them. 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, Singapore

***Number of Centers*:** 104. We estimate we will need to enroll at least 1500 patients in Trial 1 and 2500 in Trial 2, and are actively seeking collaborating centers.

***Sponsor*:** Medical Research Council (UK)

***Dates of Study*:** 2001–2009

***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. 700 patients had been recruited by June 2007.

***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: 46, looking for 200

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 STARflex 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 TIAs 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 χ^2 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 to 95, (3) symptom onset within 2 hours of treatment initiation, (4) deficit present ≥15 minutes. Study agent will be started within 1 hour of onset in ≈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

***Global Carotid Artery Stent Registry**

This registry is an expanding multicenter, retrospective study to determine the benefits and risks of percutaneous transluminal angioplasty with stent placement of the cervical carotid arteries in patients with cerebrovascular disease. The basic intent of the survey is to evaluate the growth of carotid stent placement and obtain an early review of its results, including stent procedures, technical success, and types of stems placed. In addition, complications such as TIAs, minor and major strokes, and deaths for symptomatic and asymptomatic patients will be studied. Long-term follow-up involving restenosis rates and neurological events will be monitored.

Principal Investigator: Michael H. Wholey, MD, MBA
Contact: Michael H. Wholey, MD, MBA, Department of Radiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78284. Phone 210-567-6433. Fax 210-567-5541. E-mail wholey@uthscsa.edu
Location: Global
Number of Centers: Currently 30, looking for l00+. Recruitment criteria is a minimum of 15 carotid stent procedures performed to date. Open to all interventional specialists.
Sponsor: None
Dates of Study: June 1997 (continuing)

Increasing Stroke treatment through Interventional Behavior Change Tactics (INSTINCT)

The **IN**creasing **S**troke **T**reatment through **I**nteractive behavioral **C**hange **T**actic (**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 Carotid Stenting Study (ICSS)**

ICSS is a randomized, multicenter trial to compare the risks of treatment and benefits in the prevention of stroke of primary carotid stenting in comparison with conventional carotid endarterectomy.

Principal Investigator: M.M. Brown, MD
Contact: Martin M. Brown, MD, FRCP, Professor of Stroke Medicine, Institute of Neurology, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. Phone 44-20-7829-8753. Fax 44-20-7833-8613
Location: Europe, North America, Australia and New Zealand
Number of Centers: 50. New centers welcome
Sponsor: University College London
Dates of Study: Recruitment started in 2001.
Web Address: www.cavatas.com

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

SYNTHESIS is a multicenter RCT, open-label, with blinded follow-up aiming to determine whether locoregional intra-arterial (IA) alteplase, 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 applies to patients with symptomatic, CT verified, acute ischemic strokes being able to initiate IV alteplase within 3 hours and IA alteplase 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 up to 0.9 mg/kg IA alteplase (max 90 mg) over 60 minutes into the thrombus eventually associated with clot mechanical disruption and/or retrieval. The study is 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 be completed with 350 randomized patients.

Principal Investigator: A. Ciccone
Steering Committee: *Neurology:* A. Ciccone, A. Gatti, A. Guccione, M. Magoni, I. Santilli, M. Sessa, R. Sterzi. *Interventional Neuroradiology:* L. Valvassori, F. Scomazzoni, R. Gasparotti, E. Boccardi

Safety and Monitoring Committee: L. Candelise, G. Del Zoppo, P. Sandercock.
Monitor: E. Ballabio.
Follow-Up: T. Cantisani
Randomization: C. Coppola
Contact: Alfonso Ciccone, Stroke Unit, Ospedale 'Niguarda Ca' Granda', Piazza Ospedale Maggiore 3, 20164 Milano, Italy (E-mail alfonso.ciccone@ospedaleniguarda.it). Phone +39-02-64442348. Fax +39-02-64442819
Location: Italy.
Number of Centers: 4 centers are currently authorized for the start-up phase; 15 centers in Italy have applied for an expansion phase of the study, with financial support from AIFA (see below); investigators from other centers are invited to participate.
Sponsor: Spontaneous study. The study has just been financed by a grant from AIFA, the Italian National Agency for Drugs.
Dates of Study: Recruitment started in January 2004 and about 14% of it has been completed.

***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 ($<$0.4 m/s), or the achievement of a 0.8 m/s gait speed or greater by persons with initial moderate gait impairment ($\geq$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 30 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: David G. Sherman, 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 242; 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; Centinela Freeman Regional Medical Center, Inglewood, CA, Florida Hospital, Orlando, FL, Long Beach Memorial Hospital, Long Beach, CA, and Sharp Rehabilitation Center, San Diego, CA.
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
Dates of Study: September 2005 through June 2010.
Web address: www.leaps-study.org
Clinical Trial Registration: ClinicalTrials.gov NCT00243919

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

The MASH-II study is a prospective randomized, placebo-controlled, 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; W.M. van den Bergh, MD; A. Algra, MD; G.J.E. Rinkel; G. Brekelmans, MD; C. Dirven, MD; J.van Gijn, MD; F. van Kooten, MD; R.J. van Oostenbrugge, MD; M. Vermeulen, MD (New members may be added if more (international) centers join the study)
Contact: Sanne M. Dorhout Mees, MD, Department of Neurology G03.224, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. Phone +31-30-2508350. Fax +31-30-2522782. E-mail S.M.Dorhoutmees@umcutrecht.nl
Number of Randomizing Centers: 5
Number of Randomized Patients: 397
Sponsor: The Netherlands Heart Foundation (grant number: 2005B016)
Dates of Study: Randomization was started in January 2004
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 centers 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)

***PAIS: Paracetamol (Acetaminophen) In Stroke**

A randomized, placebo-controlled, double-blind clinical trial.

Subfebrile temperature and fever are strong predictors of poor functional outcome in acute stroke. Two pilot studies showed that high-dose paracetamol lowers body temperature by 0.3°C to 0.4°C in patients with acute ischemic stroke, even when they are normothermic. This effect was noted within 4 hours after the start of treatment. The purpose of PAIS is to assess whether this decrease in body temperature translates into better clinical outcomes. The study is designed as a multicenter, randomized, double-blind, placebo controlled trial. In total, 2500 patients with an acute ischemic or hemorrhagic stroke will be included. Treatment with high-dose paracetamol (6 g/day) or placebo will be started within 12 hours after the onset of symptoms, and continued for 3 days. Exclusion criteria are a body temperature <36°C or >39°C, a history of liver disease, alcohol abuse, liver enzymes increased above twice the upper limit of normal, allergy to paracetamol and significant prestroke impairment (a score of 3 or more on the modified Rankin Scale [mRS]). Follow-up at 3 months is done by telephone, by the central study office. The primary outcome measure is dichotomized score on the mRS (0 to 2: good outcome, 3 to 6: poor outcome) at 3 months. Secondary end points are the score on the Barthel Index after 2 weeks, the EuroQol at 3 months, and body temperature after 24 hours of treatment.

Steering Committee: M.H. den Hertog (study-coordinator), D.W.J. Dippel (principal investigator), H.B. van der Worp (co-principal investigator), H.M.A. van Gemert, A. Algra, J. van Gijn, L.J. Kappelle, P.J. Koudstaal.

Contact: M.H. den Hertog, Erasmus Medical Center Rotterdam, Dr. Molewaterplein 40, Suite 22-40, PO Box 2040, 3000 CA, Rotterdam, The Netherlands, Phone 31-10-4088206, Fax 31-10-4089446, E-mail m.denhertog@erasmusmc.nl, Website: www.pais-study.org

Number of Centers: Currently 26, other centers are invited to participate.

Sponsor: Netherlands Heart Foundation NHF grant 2002 B148

***Dates of the Study*:** Randomization and follow-up May 30, 2003 through May 2008; 1200 patients have been randomized until June 2007.

Prevention of Poststroke Depression after Acute Ischemic Stroke Using the Selective Serotonine Reuptake-Inhibitor Sertraline (PreDIS-Study)

The development of persistent depressive symptoms is a severe and frequent complication of ischemic stroke (i.e., poststroke depression, PSD). The reported prevalences of depressive symptoms in stroke patients varied from 20% to 50% and from 12% to 26% for major depressive symptoms in previous studies. Several follow-up studies revealed a higher overall mortality and a less beneficial functional outcome in stroke patients with major depression. Data from interventional studies treating or preventing PSD are rare. In most trials tri- or tetracyclic antidepressive agents were used, which are often accompanied by therapy limiting adverse events, especially in elderly patients with cardiovascular disease. The PreDIS-Study was designed to limit such adverse events by the use of a selective serotonine reuptake inhibitor for which safety, tolerability, and efficacy has been shown in depressive patients with stroke or myocardial infarction. The primary end point of the study is to demonstrate a preventive effect of sertraline on the incidence of PSD. Secondary end points are improvement of functional outcome and quality of life. The PreDIS-Study was a double-blind, randomized, placebo-controlled trial that enrolled 300 patients from 10 neurological stroke units in Germany. Interim analysis was performed after 180 patients completed their follow-up. Inclusion criterion is a unilateral ischemic cerebral infarction within 3 days before hospital admission. Major exclusion criteria are early and complete recovery of neurological symptoms, mechanical ventilation for >2 days, severe aphasia, dementia, pre-existing antidepressive medication, or depressive symptoms at study entry. Patients were randomized to 50 mg/d sertraline or placebo within the first 6 days after hospital admission. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale, the Montgomery-Asberg-Depression-Scale, and the International Diagnosis Checklist for ICD-10 at baseline, 4, 12, and 24 weeks. Functional outcome was determined by the European Stroke Scale, the modified Rankin Scale, and the Barthel Index. Cognitive performance was assessed by the Mini-Mental-State Examination and the Digit-Span Test. Quality of life was determined at 12 and 24 weeks using the SF36. This trial has been finished and we will try to publish the results soon.

Principal Investigators: Dr W. Huff, PD; Dr M. Sitzer; Prof Dr H. Steinmetz

Contact: PD Dr M. Sitzer, Zentrum der Neurologie und Neurochirurgie, J.W. Goethe-Universitat Frankfurt/Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany. Phone 49-6301-5942. Fax 49-6301-4498. E-mail sitzer@em.uni-frankfurt.de

***Location*:** Germany

Number of Centers: 10

Sponsor: Pfizer Inc

Dates of Study: Randomization and follow-ups August 2001 through January 2005

Safety of Tirofiban in Acute Ischemic Stroke (SaTIS)

The administration of highly selective glycoprotein IIb/IIIa-receptor-antagonists has been shown to improve the treatment of acute coronary and experimental cerebral ischemia. Results of pilot studies in the setting of acute ischemic stroke with tirofiban, a nonpeptide substance with fast acting and deactivating properties, led to the initiation of a multicenter, prospective, randomized and placebo-controlled trial, targeting the frequency of cerebral hemorrhages as primary end point. 240 stroke patients with a symptom onset <22 hours and NIHSS Score of 4 to18, admitted outside the 3- to 6-hour time window, will receive either tirofiban or placebo, in addition to the centers' respective standard therapy. Study drug administration of tirofiban will be performed according to the concentration described in the PRISM-Plus study. A preliminary interim analysis will be due after inclusion of 30 patients per group. Patients' CCT-scans at the time of admission and 4 to 6 days after symptom onset will be subject to central, blinded evaluation. Secondary end point is the neurological outcome within 3 to 5

months after enrollment as judged by clinical disability scales: Barthel Index and modified Rankin Scale.

The results of this study could be a rationale for a subsequent phase III-study to examine the efficacy of tirofiban in acute ischemic stroke.

Principal Investigators: M. Siebler MD
Steering Committee: G. F. Hamann MD, M. Hennerici MD, Fiebach MD; U. Junghans MD, G.-M. van Reutern MD, J. Röther MD, R.J. Seitz MB, A. Villringer MD, O.W. Witte MD
Safety Committee: M. Bähr MD, Chr. Hamm, R. von Kummer MD,
Contact: Verica Jovanovic, Clinical Trial Coordinator, Department of Neurology, University of Duesseldorf, Moorenstrasse 5, D-40225 Duesseldorf. Phone 49-211-8119148. Fax 49-211-8116635. E-mail jovanovv@uni-duesseldorf.de
Location: Germany
Number of Centers: 9
Sponsor: Investigator driven, supported by BMBF/Competence network stroke
Dates of Study: August 2002 through August 2005

***Siblings With Ischemic Stroke Study (SWISS)**

Cohort and twins studies suggest that there is an important genetic component to the overall risk of acquiring ischemic stroke. SWISS is a prospective, multicentered clinical investigation to search for chromosomal regions of interest that harbor stroke susceptibility genes. A microsatellite genome-wide screen will be carried out using DNA collected in this study from sibships consisting of a proband with ischemic stroke and one or more concordant sibling with or without discordant siblings. Three hundred concordant sibling pairs and 200 discordant siblings (800 total study subjects) will be enrolled. A genotype-blinded central committee adjudicates concordance and discordance for ischemic stroke in siblings. Probands are enrolled at participating clinical centers. Probands are potentially eligible for SWISS if they are diagnosed by a study neurologist as having had a CT- or MRI-confirmed ischemic stroke, have at least 1 living sibling with a history of stroke, and are at least 18 years old. Probands are excluded if the index stroke occurred within 48 hours after an invasive cerebrovascular or cardiovascular procedure or within 60 days after a nontraumatic subarachnoid hemorrhage. Also excluded are subjects with brain biopsy-proven CNS vasculitis, mechanical aortic valve, mechanical mitral valve, bacterial endocarditis, CADASIL, Fabry's disease, homocystinuria, MELAS, or sickle cell disease. As of June 15, 2007, 254 stroke-affected sibling pairs had been enrolled.

Principal Investigator: James F. Meschia, MD
Contact: Alexa Richie, Clinical Research Coordinator, Mayo Clinic, 4500 San Pablo Road, 2 East Cannaday Bldg, Jacksonville, FL 32224. Phone 904-296-3815. Fax 904-953-6036. E-mail Richie.alexa@mayo.edu
***Location*:** Stroke Verification Committee: Department of Neurology, Mayo Clinic, Jacksonville, Fla
Statistical Coordinating Center: Department of Biostatistics, Wake Forest University School of Medicine, Winston-Salem, NC
DNA Banking: Coriell Cell Repository, Camden, NJ
Core Genetics Laboratory: National Institute on Aging (Bethesda, MD). Data Management: Mayo Clinic, Jacksonville, Fla.
Number of Centers: 53
Sponsor: National Institute of Neurological Disorders and Stroke, National Institutes of Health
Dates of Study: Ongoing

Stent-protected Percutanous 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 specialities 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 +49/622 l/568211; Fax +49/622 I/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
Dates of Study: 2000–2005

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

A number of large randomized trials have shown that statin treatment of patients with coronary heart disease (CHD) not only reduces the incidence of myocardial infarction (MI) and death, but also the occurrence of stroke. However, data on the effect of statins in the secondary prevention of stroke in patients with previous stroke or TIA are lacking. The SPARCL trial evaluated the benefits of aggressive lipid lowering in this patient population by comparing the effects of atorvastatin versus placebo on specified cerebrovascular end points. The SPARCL study was a double-blind, randomized, placebo-controlled trial that enrolled over 4200 patients from >200 centers worldwide. Inclusion criteria was previous stroke or TIA and low-density lipoprotein cholesterol >100 mg/dL (2.6 mmol/L) and <l90 mg/dL (4.9 mmol/L). Patients with evidence of CHD were excluded. Patients were randomized to 80 mg/day atorvastatin or placebo. The primary efficacy parameter was the time from randomization to the first occurrence of a primary end point, defined as a fatal or nonfatal stroke. Secondary efficacy parameters included the occurrence of at least 1 primary end point, the time from randomization to the first occurrence of a secondary end point (cardiac death, nonfatal MI, resuscitated cardiac arrest, unstable angina) and the occurrence of at least 1 secondary end point. Treatment and follow-up was planned until 540 primary end points had occurred. This trial is now finished.

Steering Committee: K.M.A. Welch, USA (Chairman); P. Amarenco, France; J. Bogousslavsky, Switzerland; A. Callahan, USA; L. Goldstein, USA; M. Hennerici, Germany; H. Sillesen, Denmark; J. Zivin, USA.
Contact: Henirk Sillesen, MD, DMSc, Department of Vascular Surgery, Gentofte University Hospital, DK-2900 Hellerup (Denmark) Phone 45 3977 3402 Fax 45 3977 7674 E-mail hens@gentoftehosp.kbhamt.dk
Location: Worldwide
Number of Centers: >200
Sponsor: Pfizer Inc
Study Dates: Recruitment started November 1998. Enrollment of 4732 patients was completed in March 2001. Patient follow-up was for an average of 5 years. The study has been completed.

***Study of Efficacy of Tirofiban in Acute Ischemic Stroke (SETIS)**

Study Design: double-blind randomized trial of IV tirofiban versus IV ASA. Patients with acute ischemic stroke presented within 6 hours will be randomized to treatment with tirofiban (0.6 μg/kg/min for 30 minutes followed by 0.15 μg/kg/ min infusion for 72 hours) or acetylsalicilic acid (ASA, 300 mg IV daily bolus for 3 days), following a 1-way, matched pair, randomization list. Matching will be performed according to gender, age ≤70 or >70 years, NIHSS score ≤14 or >14. Treatment will be administered on a double-blind basis, using undistinguishable vials both for bolus infusion and continuous infusion. Serious adverse events will be reported to an unassociated physician of the safety committee. The choice of ASA and not placebo for the nontreatment group, is due to the evidence that early treatment with ASA has some beneficial effect, though limited, in short-term mortality.

Study Objectives: Assess the efficacy of tirofiban in terms of short-term neurological improvement (NIHSS score reduction of at least 4 points), and absence or minimal long-term disability (NIHSS score and mRS score at 3 months decreased to 0 or 1).

Sample Size: Sample size was based on an expected percentage of favorable outcomes on primary variables (short-term neurological improvement and absence of long-term disability) at least 15% greater in patients treated with tirofiban than those treated with ASA, and considering in the latter treatment group a favorable outcome in at least 40% of the patients. Considering the short-term primary variable, the total number of patients, increased by estimating a 10% total drop-out rate, is 150 for each treatment group. Sample size computed on long-term primary variables, under the same conditions, would require 120 patients for each treatment group, so that a series of 300 patients would be adequate for analysis of the protocol-specified primary variables. Variables will be analyzed on the basis of either the 'intention-to-treat' or the 'per-protocol' criteria. Prespecified causes of treatment withdrawal are intracranial hemorrhage, severe uncontrolled hypertension, allergic reactions, extracranial hemorrhage, severe thrombocytopenia.

Patients: main inclusion criteria are the following: onset of symptoms within 6 hours, absence of hemorrhage at CT scan, absence of severe anemia, thrombocytopenia, major trauma or recent surgery, prolonged PT.

In the Dates of the Study we previously reported an expected length of recruitment of 2 years. However, due to our recruitment the study will last at least 4 years.
Principal Investigators: G. Torgano, C. Mandelli, B. Zecca
Contact: Dr Giuseppe Torgano, Dipartimento di Medicina d'Urgenza, Ospedale Policlinico, Via F. Sforza, 20122 Milano, Italy. Phone 0039-02-55033620, Fax 0039-02-55033600, E-mail setis@policlinico.mi.it.
Location: Northern Italy
Number of Centers: 3 centers currently authorized; investigators from other centers are invited to participate.
Sponsor: spontaneous study.
Dates of Study: Randomization started by the end of 2003; recruitment up to obtaining computed sample size; interim analysis for sample size correct estimation has been scheduled; expected length of recruitment at least 4 years.

***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 Barthe1 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 July 27, 2007, 13 patients and 19 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: 44-19l-256-3268. E-mail: stich@ncl.ac.uk
Location: STICH Office, Ward 31, North Wing, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK.
Website: www.ncl.ac.uk/stich
Number of Centers: 19
Funder: Medical Research Council (UK)
Sponsor: Newcastle upon Tyne Hospitals NHS Trust
ISRCTN: ISRCTN22153967
Dates of Study: 2006 to 2010

***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. ***Study Progress:*** the randomized start-up study began cautiously in 2001 and was completed successfully on December 31, 2002. Following a review of the safety and efficacy data by the independent Data Monitoring Committee (Chair Professor Rory Collins), recruitment continued without interruption into the expansion phase (2003 to 2005), and again, after review, into the main Medical Research Council funded phase which began in May 2005 and will continue until 2009, with trial reporting in 2009. The trial will involve up to 6000 patients recruited from 250 to 400 centers in up to 40 countries worldwide. A total of 828 patients had been recruited by June 19, 2007.

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 with additional countries due to join

***Number of Centers*:** Currently 76, but up to 400 may join the main phase

Sponsor: The study is an investigator led trial. The University of Edinburgh and the Lothian Health Board are cosponsors. The start-up phase was supported by a grant from the Stroke Association, UK. The expansion phase was funded by The Health Foundation UK. The main phase of the trial is supported by: UK MRC, Norwegian Research Council, AFA Insurances (Sweden); the Swedish Heart Lung Fund, the Government of Poland, the Australian Heart Foundation, Australian NHMRC, the Dalhousie University Internal Medicine Research Fund. Drug and placebo for the 300 patients in the double-blind component of the start-up phase were supplied by Boehringer-Ingelheim. The study is being designed, conducted, analysed and reported independently of all of the sponsors and funding agencies.

ISRCTN: ISRCTN25765518

***Dates of Study*:** 2001-2009.

***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] $\geq$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 $\geq$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 $\approx$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 M-8203, 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. Actively seeking collaborating centers

Sponsor: Canadian Institutes of Health Research (CIHR)

Dates of study: Recruitment 2006-2010; follow-up until 2020

***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 (B_{12} 500 μg, B_6 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 over the next 2 years 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, Clin 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 (9), 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 (18) and United States (5) and actively seeking centers worldwide.

Dates of Study: 1998 – 2009

Stroke
Journal of the American Heart Association

Major Ongoing Stroke Trials

Stroke. 2007;38:e116-e125
doi: 10.1161/STROKEAHA.107.111222
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628