

Ongoing Clinical Trials Posters II

Thursday, February 2, 2012 6:15:00 PM - 6:45:00 PM

Presentation Number: CT P1

Trial Abbreviation: IMS III Trial

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Trial Name: The Interventional Management of Stroke (IMS) III Trial: An Ongoing Phase III Trial

Trial Registry Number ID: NCT00359424

Trial Sponsor: NIH/NINDS

Trial Web Site: <http://www.ims3.org/>

Publishing Title: The Interventional Management of Stroke (IMS) III Trial

Author Block: Thomas A Tomsick, **Joseph P Broderick**, Univ of Cincinnati, Cincinnati, OH

Abstract Body:

BACKGROUND AND PURPOSE: The IMS I and II pilot trials showed that the combined intravenous (IV) and intra-arterial (IA) approach to recanalization may be more effective than standard IV rt-PA (Activase®) alone for moderate-to-large (NIHSS ≥ 10 or 8-9 with positive CTA) strokes, and with a similar safety profile. Therefore, the primary objective of this NIH-funded, Phase III, randomized, multi-center, open-label clinical trial is to determine whether a combined IV/IA approach to recanalization is superior to standard IV rt-PA alone when initiated within three hours of acute ischemic stroke onset.

METHODS: A projected 900 subjects with moderate-to-large ischemic strokes between ages 18-82 will be enrolled at 50+ centers in the United States, Canada, Australia and Europe. All subjects must have IV treatment initiated within three hours of stroke onset. Subjects will be randomized in a 2:1 ratio with more subjects enrolled in the combined IV/IA group. Both treatment arms will receive the full standard dose (0.9 mg/kg, 90 mg max [10% as bolus]) of rt-PA intravenously over one hour. Randomization must occur within 40 minutes of starting the infusion. The combined IV/IA group will be sent immediately for angiography. If a treatable thrombus is not demonstrated, no IA therapy will be administered. If an appropriate thrombus is identified, treatment will continue with either the Concentric Merci® Retriever, the Penumbra System™ thrombus-removal device, the ev3 Solitaire™ FR Revascularization device, infusion of rt-PA and delivery of low-intensity ultrasound at the site of the occlusion via the EKOS® Micro-Infusion Catheter (in US only), or infusion of rt-PA via a standard microcatheter. New devices will be evaluated as they become clinically available. The choice of IA strategy will be made by the treating neurointerventionalist. IA treatment must begin within 5 hours and be completed within 7 hours of stroke onset. The primary outcome measure is a favorable clinical outcome, defined as a modified Rankin Score (mRS) of 0-2 at 3 months. The primary safety measure is mortality at 3 months and symptomatic ICH within the first 36 hours after onset. Finally, a secondary objective of the IMS III Trial is to determine the cost-effectiveness of the combined IV/IA approach as compared to standard IV rt-PA.

CONCLUSIONS: The IMS III Trial will develop and maintain a network of interventional centers to test the safety, feasibility, and potential efficacy of a combined IV/IA approach to recanalization using intra-arterial infusion of rt-PA and/or FDA-approved catheter devices. As of November 1, 2011, 570 subjects had been randomized. This abstract reflects the current Amendment 5 protocol, sites are currently seeking approval for Amendment 5.

Author Disclosure Block: T.A. Tomsick: Research Grant; Significant; Co-Principal Investigator of NINDS-funded IMS III Trial. Other Research Support; Modest; EKOS Corporation supplies catheter devices for ongoing IMS III clinical trial. Other Research Support; Significant; Genentech Inc. - Supplier of (IA) alteplase for NINDS-funded IMS III trials.. Consultant/Advisory Board; Modest; Genentech 2008 - Fee paid to UC Radiology Department. Consultant/Advisory Board; Significant; ev3 image review - Fee paid to UC Radiology Department. **J.P. Broderick:** Research Grant; Modest; NINDS-funded Genetic and Environmental Risk Factors for Hemorrhagic Stroke, NINDS-funded Comparison of Hemorrhagic and Ischemic Strokes Among Blacks and Whites, NINDS-funded IRIS Trial, CREST, COSS, and SWISS Studies. Research Grant; Significant; NINDS-funded IMS III Trial, NINDS-funded UC Spotrias, NINDS-funded FIA Study, NINDS-funded T-32 Cerebrovascular Fellowship Program. Other Research Support; Modest; EKOS Corporation supplies catheter devices for ongoing IMS III clinical trial. Other Research Support; Significant; Genentech Inc. (Supplier of alteplase for NINDS-funded CLEARER, IMS III trials). Honoraria; Modest; PhotoThera - \$1,050.00 honorarium received for participation in DSMB on 2/25/10., PhotoThera - \$4,400.00 honorarium received for participation in DSMB on 7/26/10., Genentech Inc. - \$1,500.00 honorarium received on 4/24/10 for participation in stroke advisory board., Oakstone Medical Publishing – \$1,000.00 honorarium received on 3/11/10 for a talk.. Other; Modest; Consulting fees and honoraria are placed in an educational/research stroke fund in the University of Cincinnati, Department of Neurology.

Presentation Number: CT P2

Trial Abbreviation: The CLEAR-ER Stroke Trial

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Trial Name: The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke Enhanced Regimen

Trial Registry Number ID: P50-NS044283

Trial Sponsor: NINDS

Trial Web Site: www.clear-er.org

Publishing Title: The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke Enhanced Regimen (The CLEAR-ER Stroke Trial): An Ongoing Phase IIb Trial

Author Block: Arthur M. Pancioli, U CINCINNATI MEDICAL CTR, Cincinnati, OH

Abstract Body:

INTRODUCTION AND HYPOTHESIS:

The CLEAR-ER trial is a NIH-funded, Phase IIb, randomized, multi-center, double-blind, controlled trial of the combination of medium dose rt-PA plus eptifibatide versus standard dose rt-PA in acute ischemic stroke patients that can have rt-PA treatment begun within 3 hours of symptom onset.

METHODS:

A total of 126 subjects with a NIHSS > 5 will be enrolled over the next 2 years at 9 centers in the United States. Patients are randomized to a combined intravenous medium-dose rt-PA (0.6mg/kg, 60 mg max) and eptifibatide (135 mcg/kg IV bolus and a 2 hour infusion of 0.75 mcg/kg/min) or standard dose (0.9 mg/kg, 90 mg max, 10% as bolus) rt-PA in a 5 to 1 ratio. This will result in a total of 105 patients treated with the combined regimen, and 21 patients treated with standard dose IV rt-PA alone. The primary safety outcome measure is symptomatic ICH within 36 hours of initiation of therapy. The study will determine if there is a signal of efficacy such that a Phase III Trial of this combination is warranted. The primary measure of clinical outcome is the percentage of patients meeting a modified Rankin Scale score of 0 or 1 or return to their baseline at 90 days post treatment.

CONCLUSIONS: The CLEAR-ER Trial will obtain reliable estimates of the safety of an enhanced dosing regimen of eptifibatide in combination with medium-dose rt-PA in acute stroke patients in whom treatment is begun within three hours of onset. As of October 7, 2011, 80 subjects have been randomized into the trial.

Author Disclosure Block: A.M. Pancioli: Research Grant; Significant; NINDS. Other Research Support; Significant; Genentech, Schering Plough/ Merck. Consultant/Advisory Board; Modest; Banyan Medical.

Presentation Number: CT P3

Trial Abbreviation: MR RESCUE

Trial Contact Information: Megan Miles, mrm273@georgetown.edu, 202-687-5396

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Trial Name: Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy

Trial Registry Number ID: NCT00389467

Trial Sponsor: NIH-NINDS

Trial Web Site: No Website

Publishing Title: Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy

Author Block: **Chelsea Kidwell**, Georgetown Univ, Washington DC, DC; Reza Jahan, Sidney Starkman, Jeffrey R. Alger, Judy Guzy, UCLA Stroke Ctr, Los Angeles, CA; Megan Miles, Georgetown Univ, Washington DC, DC; James Norman, Jeffrey L Saver, UCLA Stroke Ctr, Los Angeles, CA; MR RESCUE Investigators

Abstract Body:

Background and Objective: The general aim of the MR RESCUE Trial is to investigate whether multimodal imaging can identify patients who will benefit substantially from mechanical embolectomy with the Concentric Clot Retriever device or the Penumbra System for the treatment of acute ischemic stroke up to 8 hours from symptom onset.

Design: MR RESCUE is a randomized, controlled, blinded-outcome phase IIB clinical trial.

Population Studied: Acute ischemic stroke patients with large vessel ICA or MCA occlusion enrolled within 8 hours of symptom onset. 120 patients will be enrolled.

Intervention: Patients are randomized to embolectomy (employing the Concentric Retriever or Penumbra System) or standard medical care, with randomization stratified by penumbral pattern.

Outcome Measures: The primary outcome measure is the day 90 modified Rankin Score. Additional clinical, angiographic and MRI/CT radiographic outcome measures will also be assessed.

Analysis: The primary hypothesis is that the presence of substantial ischemic penumbral tissue on multimodal imaging identifies patients most likely to respond to mechanical embolectomy for acute ischemic stroke. The primary endpoint analyzed will be the distribution of scores on the modified Rankin Scale of global handicap at 90 days. Nested hypotheses test for 1) treatment efficacy in patients with penumbral regions pretreatment, and 2) absence of treatment benefit (equivalency) in patients without penumbral regions pretreatment.

Trial Status: Actively recruiting. 115 patients have been enrolled and 25 total sites are participating.

Author Disclosure Block: **C. Kidwell:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **R. Jahan:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **S. Starkman:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **J.R. Alger:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **J. Guzy:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **M. Miles:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **J. Norman:** Research Grant; Significant; NINDS Grant Number P50 NS44378. **J.L. Saver:** Research Grant; Significant; NINDS Grant Number P50 NS44378.

Presentation Number: CT P4

Trial Abbreviation: FAST-MAG

Trial Contact Information: Jeffrey Saver, MD / jsaver@ucla.edu

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Trial Name: Field Administration of Stroke Therapy - Magnesium Phase 3 Clinical Trial

Trial Registry Number ID: NCT00059332

Trial Sponsor: NIH-NINDS

Trial Web Site: www.fastmag.info

Publishing Title: The Field Administration of Stroke Therapy - Magnesium (FAST-MAG) Phase 3 Clinical Trial

Author Block: Jeffrey L Saver, Geffen Sch of Med at UCLA, Los Angeles, CA; Marc Eckstein, LAFD EMS, Los Angeles, CA; Sam Stratton, LA EMS Agency, Los Angeles, CA; Frank Pratt, Geffen Sch of Med at UCLA, Los Angeles, CA; Scott Hamilton, Stanford Univ, Palo Alto, CA; Robin Conwit, NIH-NINDS, Bethesda, MD; David Liebeskind, Geffen Sch of Med at UCLA, Los Angeles, CA; Gene Sung, Nerses Sanossian, Univ of Southern California, Los Angeles, CA; Sidney Starkman, Geffen Sch of Med at UCLA, Los Angeles, CA; for the FAST-MAG Investigators and Coordinators

Abstract Body:

BACKGROUND: Magnesium is neuroprotective in preclinical models of stroke and has been safe and shown signals of potential efficacy when delivered early after onset of human cerebral ischemia. Delayed initiation of neuroprotective agents has hindered past phase 3 neuroprotective agent trials.

OBJECTIVE: To demonstrate that paramedic initiation of intravenous magnesium sulfate within 2 hours of symptom onset improves the longterm functional outcome of hyperacute stroke patients.

DESIGN: Multicenter, randomized, double-blind, placebo-controlled phase 3 trial. **POPULATION STUDIED:** 1700 patients (850 in each arm) 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 40-95, 3) symptom onset within 2 hours of treatment initiation, 4) deficit present \geq 15 minutes. **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. **OUTCOME MEASURE(S):** The primary endpoint is the modified Rankin Scale measure of global disability, assessed using the Rankin Focused Assessment (RFA) 90 days after treatment. Secondary endpoints include NIHSS (neurologic deficit), Barthel Index (activities of daily living), and Stroke Impact Scale (quality of life). **ANALYSIS:** The primary analysis will assess the difference in the distribution of mRS scores between treated and placebo groups, employing the Cochran-Mantel-Haenszel test statistic (shift analysis). **TRIAL SITES:** Through 11/1/11, 308 ambulances, 42 EMS agencies, and 59 receiving hospitals throughout Los Angeles and Orange Counties are actively recruiting patients, and 2900 paramedics have been trained in study procedures. Site investigators include over 400 emergency physicians and over 125 neurologists, neurosurgeons, and hospitalists. **TRIAL STATUS:** Through 11/1/11, 1401 patients had been enrolled. Median pretreatment stroke severity on the Los Angeles Motor Scale (LAMS) is 4. Adjudicated final diagnoses are acute cerebral ischemia in 72%, intracerebral hemorrhage in 24%, and stroke mimic in 4%. Treatment was initiated within 1 hour of onset in 74% and between 1-2 hours in 25%. Median interval from last known well to start of study agent is 46 minutes.

Author Disclosure Block: J.L. Saver: None. M. Eckstein: None. S. Stratton: None. F. Pratt: None. S. Hamilton: None. R. Conwit: None. D. Liebeskind: None. G. Sung: None. N. Sanossian: None. S. Starkman: None.

Presentation Number: CT P5

Trial Abbreviation: CREST

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Trial Name: Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): Long Term Follow-up

Trial Registry Number ID: R01 NS038384

Trial Sponsor: NINDS/NIH

Trial Web Site: www.cresttrial.org

Publishing Title: Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): Update On Long Term Follow-up (Up to 10 Years)

Author Block: Alice J Sheffet, Susan E Hughes, MeeLee Tom, UMDNJ-New Jersey Medical Sch, Newark, NJ; Ariane Mackey, CHA Hop de L'Enfant-Jesus, Quebec, QC,, QC, Canada; William Brooks, Central Baptist Hosp, Lexington, KY; Wayne Clark, Oregon Health and Science Univ, Portland, OR; Michael D Hill, Univ of Calgary, Calgary, AB, Canada; Pierre Leimgruber, Spokane Cardiology/NWCRI, Spokane, WA; Jenifer H Voeks, Univ of Alabama at Birmingham, Birmingham, AL; Mary E Longbottom, Thomas G Brott, for the CREST Investigators, Mayo Clinic Florida, Jacksonville, FL

Abstract Body:

BACKGROUND: Multi-site international clinical trials currently support guidelines for carotid treatment based on 2-4 years of follow-up for patients living decades after revascularization. Designed to establish the relative efficacy of carotid endarterectomy (CEA) versus carotid stenting (CAS), CREST published its primary results July 1, 2010 for peri-procedural and mid-term outcomes with a median follow-up of 2.5 years. The risk of the composite primary outcome of stroke, myocardial infarction or death did not differ significantly for CEA and CAS.

OBJECTIVE: To extend CREST follow-up (maximum of 10 years) to evaluate the long term clinical and anatomical durability of CAS versus CEA (as assessed by ipsilateral stroke and recurrent stenosis \geq 50%).

DESIGN: CREST (ClinicalTrials.gov NCT00004732) is an NINDS-funded, randomized, two-arm, multi-site trial with blinded endpoint adjudication. Extended follow-up of CREST CAS and CEA subjects includes annual clinic visits and mid-point telephone contacts (up to 10 years of follow-up; average 7.5 years).

POPULATION: Active post-procedure symptomatic and asymptomatic CREST subjects (n=2000) re-consented for up to 10 years of follow-up.

OUTCOMES: The primary aim is to assess CEA versus CAS in the prevention of ipsilateral stroke. Secondary aims will 1) assess if there are effect modifiers of the long term durability of the two procedures, such as age, sex, pre-procedural degree of stenosis and symptomatic status, 2) assess if there is a temporal change or pattern in the relative efficacy of the two procedures, 3) assess differences between groups in the rates of restenosis or revascularization, 4) link Medicare-eligible CREST participants with inpatient and outpatient CMS data files to assess patient outcomes and utilization of healthcare services.

ANALYSIS: Statistical analysis of the primary aim (time-to-event modeling with adjustment for major baseline covariates) will assess post-procedural treatment differences from Day 31 up to 10 years, providing 90% power to detect a hazard ratio of 1.67.

TRIAL PROGRESS:

Publication of primary results (*N Eng J Med* Jul 2010) was followed by the publication of protocol-specified secondary aims: Safety of CAS and CEA by Symptomatic Status (*Stroke* Mar 2011); Myocardial Infarction following CAS and CEA (*Circulation* Jun 2011); Influence of sex on outcomes of CAS and CEA (*Lancet Neurology* Jun 2011); Health Related Quality of Life after CAS versus CEA (*JACC* Oct 2011); Age and Outcomes after CAS and CEA (*Stroke* Oct 2011). The FDA approved expanded use of trial devices on May 6, 2011 after a review of CREST data, and audits of the Administrative Center, Statistical and Data Management Center, and 10 clinical sites.

NINDS approved CREST follow-up through 2016. Visits and forms are streamlined for efficient reporting of events and data necessary for the assessment of the long term effectiveness of CAS versus CEA and reduce patient/clinic burden and cost. To date, 108 US and Canadian sites are participating in CREST long term follow-up; 76 have signed contracts through 2016 and 1562 CREST subjects are re-consented for extended follow-up. **Top re-consenting sites are: CHA Hopital de L'Enfant-Jesus, Quebec City, QC, Canada; Central Baptist Hospital, Lexington, KY; Oregon Health and Science University, Portland, OR; University of Calgary, Calgary, AB, Canada; and Spokane Cardiology/NWCRI, Spokane, WA.**

Continuing CREST follow-up will allow comparison of clinical and anatomical durability of CAS and CEA in symptomatic and asymptomatic subjects for the longest period in any carotid trial.

Author Disclosure Block: A.J. Sheffet: None. **S.E. Hughes:** None. **M. Tom:** None. **A. Mackey:** None. **W. Brooks:** None. **W. Clark:** None. **M.D. Hill:** None. **P. Leimgruber:** None. **J.H. Voeks:** None. **M.E. Longbottom:** None. **T.G. Brott, for the CREST Investigators:** None.

Presentation Number: CT P6

Trial Abbreviation: SPS3

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Trial Email: Oscar. Benavente@ubc.ca

Trial Name: Secondary Prevention of Small Subcortical Strokes

Trial Registry Number ID: NCT00059306

Trial Sponsor: NIH/NINDS

Trial Web Site: <http://www.sps3.org>

Publishing Title: Secondary Prevention of Small Subcortical Strokes

Author Block: Ana Roldan, Marie Benavente, Univ of British Columbia, Vancouver, BC, Canada; Leslie McClure, Univ of Alabama, Birmingham, AL; Christopher Coffey, Univ of Iowa, Iowa City, IA; Jeff Szychowski, Univ of Alabama, Birmingham, AL; Pablo Pergola, Univ of British Columbia, Vancouver, BC, Canada; Robin Conwit, NIH/NINDS, Bethesda, MD; Robert Hart, McMaster Univ, Hamilton, ON, Canada; **Oscar Benavente**, Univ of British Columbia, Vancouver, BC, Canada

Abstract Body:

Background Small subcortical strokes(S3) account for about 25% of all brain infarcts, are very frequent among Hispanic Americans(HA) and are usually due to cerebral small artery disease which predisposes to vascular dementia. Over 2 million S3 survivors are at high risk of stroke recurrence and subsequently vascular dementia; millions more suffer subclinical S3 and cognitive decline caused by the intrinsic disease of the small penetrating cerebral arteries. No previous randomized trials have focused on secondary prevention after S3 or subcortical TIA, optimal target levels of BP control after stroke and their relationship to cognitive decline, or prevention of stroke and dementia in HA. **Objectives** Determine: if the combination of Aspirin 325 mg/d+Clopidogrel 75 mg/d is more efficacious than Aspirin 325 mg/d alone **AND** whether intensive BP lowering (systolic <130 mmHg) is superior to usual hypertension management (systolic between 130-149 mmHg) in reducing stroke recurrence, cognitive decline and major vascular events in patients with symptomatic S3 or subcortical Transit Ischemic Attack (TIA). **Methods** SPS3 is a randomized multicenter clinical trial preceded by a 3 year pilot study. Patients are assigned in a factorial design to 2 interventions: a. Aspirin 325 mg/d vs. Aspirin 325 mg/d+Clopidogrel 75 mg/d. (double-blinded). b. Two targets of systolic BP, "usual" (130-149 mmHg) vs."intensive" (<130 mmHg). (open-label with blinded event assessment). Will include 3000 participants (20% HA) with symptomatic, MRI documented S3/subcortical TIA within the prior 6 months and without carotid stenosis or major cardiac sources of embolism. Follow-up every 3 months for a mean of 2.9 yrs. **Outcomes** Recurrent stroke (primary), cognitive decline, major vascular events and death. **Trial Status** 3020 patients from 8 countries were randomized. The study recruitment was completed on April 4, 2011 and Follow up will be completed on April 2012. **Sponsorship** NIH/NINDS. **Registry #** NCT00059306. **Grant #** U01 NS38529. <http://www.sps3.org> **PI** Oscar Benavente, MD. Professor of Neurology, University of British Columbia, Vancouver, Canada. **Contacts** Oscar.Benavente@ubc.ca; Robert.Hart@phri.ca

Author Disclosure Block: **A. Roldan:** None. **M. Benavente:** None. **L. McClure:** None. **C. Coffey:** None. **J. Szychowski:** None. **P. Pergola:** None. **R. Conwit:** None. **R. Hart:** None. **O. Benavente:** None.

Presentation Number: CT P7

Trial Abbreviation: MR WITNESS

Trial Contact Information: Brenda Thornell, bthornell@partners.org, 617-724-1538, 617-643-3939

Trial Email: mrwitness@partners.org

Trial Name: MR WITNESS: A Phase IIa Safety Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients

Trial Registry Number ID: NCT01282242

Trial Sponsor: Massachusetts General Hospital

Trial Web Site: <http://www.mrwitness.org>

Publishing Title: MR WITNESS: A Phase IIa Safety Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients

Author Block: Ona Wu, Massachusetts General Hosp, Boston, MA; Lawrence L Latour, Natl Inst of Neurological Diseases and Stroke, Natl Insts of Health, Bethesda, MD; Shlee S Song, Cedar Sinai Medical Ctr, Los Angeles, CA; Karen L. Furie, Massachusetts General Hosp, Boston, MA; Steven Warach, Natl Inst of Neurological Diseases and Stroke, Natl Insts of Health, Bethesda, MD; Lee H. Schwamm, Massachusetts General Hosp, Boston, MA; MR WITNESS investigators

Abstract Body:

Rationale: Many patients are discovered with acute stroke symptoms whose onset is unwitnessed. Current FDA indications exclude them from intravenous (IV) alteplase or rt-PA therapy because it has been more than 3 h since the patient was last known to be well. We propose to use advanced MR imaging as the “witness” to testify when the stroke actually started in patients who do not have a human witness.

Background: Many acute ischemic stroke patients are not eligible for intravenous (IV) thrombolytic treatment with alteplase because the time of stroke onset cannot be determined or the patient is outside the treatment time window on initial presentation based on last seen well (LSW) time. For many patients, their LSW time is when they went to sleep the night before and this puts potentially eligible patients out of treatment windows for thrombolytics even if the stroke occurred within the hour upon waking. Fluid-Attenuated Inversion Recovery (FLAIR) signal intensity changes become conspicuous at subacute time points (> 3h). Using diffusion-weighted MRI (DWI), where changes are evident within minutes of ischemia onset, in conjunction with normal FLAIR has been reported to identify acute ischemic strokes at three hours or less. Our goal is to determine if MRI can be used as a surrogate “witness” when no human witness of stroke onset is available, to safely administer IV rt-PA in acute stroke patients who would otherwise not qualify for standard IV rt-PA therapy. If our study is successful, we can potentially expand the use of lytics to a stroke patient population for whom little acute intervention is currently offered.

Objectives:

- (1) To determine the safety of IV alteplase therapy in subjects with unwitnessed stroke onset with LSW time greater than 3 h, who otherwise meet thrombolysis therapy guidelines, and exhibit MRI evidence consistent with early stroke.
- (2) To validate novel MRI profiles to improve the sensitivity while maintaining high specificity for detecting subjects with stroke duration less than or equal to 3.5 h.
- (3) To explore imaging surrogates of clinical efficacy in subjects with unwitnessed stroke onset who are treated with thrombolysis

Design

MR WITNESS is an open-label, single-arm, multi-center Phase IIa safety study of IV alteplase in MRI-selected ischemic stroke subjects who currently have no standard therapeutic intervention, subjects with unwitnessed stroke onsets. We propose to extend IV rt-PA treatment to a sub-population of these patients, namely those

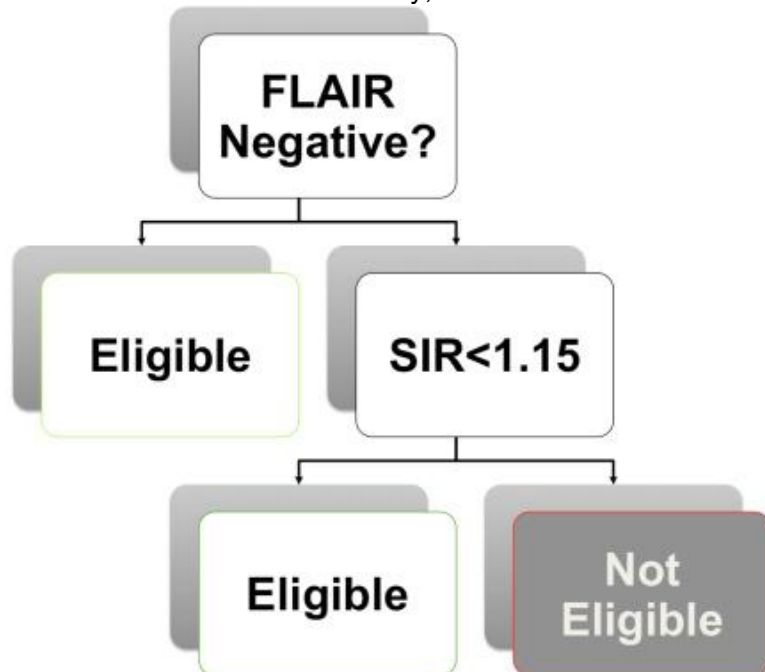
who are seen within 3 h of symptom discovery, with a LSW time between 3 h and 24 h, and most importantly, whose admission MRI would classify them as being an early stage stroke. The algorithm is shown in the figure, where SIR represents the signal intensity ratio (SIR) of FLAIR signal intensity in lesion region of interest to normal contralateral tissue. (See Figure.)

Outcome Measures: The primary outcome for this study is safety as evidenced by no significant increase in symptomatic intracranial hemorrhage (SICH) rates at 24 hours using ECASS 2 definition (any hemorrhage with neurologic deterioration as indicated by an NIH Stroke Scale (NIHSS) score that increased by 4 or more points over baseline value). SICH rates and all serious adverse events (SAE) is monitored by an Independent Medical Monitor and Data and Safety Monitoring Board (DSMB). Only subjects who receive rt-PA are included in the safety analysis; intention to treat subjects who for any reason do not receive alteplase will be excluded. For secondary safety outcomes, other SAE are monitored, such as symptomatic edema or mortality, to investigate whether our rates are significantly higher than those reported by ECASS 3. For secondary outcomes, we will also examine rates of early reperfusion and lesion growth in alteplase treated patients when evaluating for potential benefit.

Study Population: Eighty adult subjects 18-80 years of age with acute ischemic stroke who arrive between 4.5 h and 24 h since last known well and be able to receive rt-PA within 4.5 h of symptom discovery. Subjects must be eligible to receive rt-PA using ECASS 3 criteria, excluding last seen well criterion.

Intervention: Enrolled subjects will receive standard dose IV alteplase (0.9 mg/kg with maximum dose \leq 90 mg) according to AHA guidelines.

Procedures: Non-research baseline MRI and 24h post-treatment non-contrast CT. Research MRI will be obtained post-drug infusion and at 30 days. NIHSS scores will be recorded at baseline, post-drug, and prior to 24 h CT. At 5-days or discharge and at 30 days, NIH SS, Barthel Index (BI), and modified Rankin Scale (mRS) scores will be obtained. At 90 day, mRS and BI will be obtained.



Author Disclosure Block: **O. Wu:** Research Grant; Significant; P50NS051343, R01NS059775, R01NS063925. **L.L. Latour:** None. **S.S. Song:** None. **K.L. Furie:** Research Grant; Significant; P50NS051343. **S. Warach:** None. **L.H. Schwamm:** Research Grant; Significant; P50NS051343.

Presentation Number: CT P8

Trial Abbreviation: PROTECT DC

Trial Contact Information: Deeonna Farr MPH, Deeonna.E.Farr@medstar.net

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Trial Name: Preventing Recurrence of Thromboembolic Events through Coordinated Treatment in the District of Columbia

Trial Registry Number ID: NCT00703274

Trial Sponsor: NINDS U54 057405

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT00703274?term=protect+dc&rank=1>

Publishing Title: A Phase II RCT of Stroke Navigators to Improve Compliance with Secondary Stroke Prevention: PROTECT DC

Author Block: Alexander W Dromerick, Natl Rehabilitation Hosp, Washington, DC; M. Christopher Gibbons, Johns Hopkins Sch of Med, Baltimore, MD; Dorothy F Edwards, Univ of Wisconsin, Madison, WI; Deeonna Farr, Natl Rehabilitation Hosp, Washington, DC; Annapurni Jayam-Trouth, Howard Univ Sch of Med, Washington, DC; Nawar M Shara, Georgetown Univ/Medstar Health Res Inst, Washington, DC; Brisa M Sanchez, Univ of Michigan, Ann Arbor, MI; Stephen J Fernandez, Medstar Health Res Inst, Hyattsville, MD; Regina Coles, Georgetown Univ, Washington, DC; Judson D Richardson, Natl Rehabilitation Hosp, Washington, DC; Bruce Ovbiagele, Univ of California, San Diego, CA; Chelsea S Kidwell, Georgetown Univ, Washington, DC

Abstract Body:

Trial Abbreviation: PROTECT DC

Trial Registry Number: NCT00703274

Background: Despite significant advances in the prevention and treatment of cerebrovascular disease, stroke remains the third leading cause of death and a leading cause of adult disability. The initiation of effective secondary prevention strategies is most effective when implemented early (before disabling stroke occurs), monitored frequently, and maintained long-term after a cerebrovascular event. PROTECT DC facilitates the initiation of secondary prevention behaviors in an attempt to prevent the recurrence of stroke among participants. The program trains a lay person, called a stroke navigator, to provide participants with education on secondary prevention behavior and to navigate the health and human service system, which will assist participants in obtaining the necessary services and programs to engage in secondary prevention behaviors.

Population (n=230):

1. Age \geq 18 years
2. Hospitalized due to ischemic stroke or intercurrent ischemic stroke event within the past 30 days
3. Large vessel, small vessel, or cryptogenic with stroke risk factor etiologies as defined by TOAST criteria
4. Community dwelling prior to stroke
5. Resides within the District of Columbia or closely in its suburbs
6. Expected to reside after hospital discharge within the District of Columbia or closely in its suburbs
7. Caregiver or interested party available, if moderately or severely disabled (not required to actually reside with participant)
8. Sufficient number of collateral contacts to assure follow-up.
9. NIHSS \leq 20

Objective: To determine whether stroke navigators can improve compliance with secondary stroke prevention measures in an urban underserved population with atherogenic ischemic stroke.

Design: Phase II, single-blind, randomized controlled trial

Interventions:

Experimental: Stroke navigation for a one year period.

Control: Usual and customary care for one year

Outcome Measures:

Primary: Composite score of compliance with objective measures of risk factor control (e.g. systolic blood pressure, HbA_{1c}, LDL, INR, antithrombotic pill count) at one year after stroke onset.

Secondary: Stroke knowledge, exercise, dietary modification, smoking cessation at one year.

Analysis: Intention to treat

Trial status: Actively enrolling since July 1, 2008; as of October 24, 2011, 222 of the target 230 participants have been enrolled, with 112 randomized to the experimental condition and 110 randomized to the control condition. Thus far, 129 participants have completed the primary 1-year time point. Mean age of the enrolled participants is 62 years (SD=12, range 33 - 90), 87% are African-American, 46% are male and the median NIHSS score is 2 (range 0 - 20).

PI/Coordinator Name: Alexander W. Dromerick MD/Chelsea S. Kidwell MD/Deeonna E. Farr MPH

PI/Coordinator Affiliation: Georgetown University/National Rehabilitation Hospital

Trial Sponsor: National Institute of Neurological Disorders and Stroke

Contact Information: Deeonna.E.Farr@Medstar.net; Voice: 202-877-1931

Author Disclosure Block: **A.W. Dromerick:** None. **M.C. Gibbons:** None. **D.F. Edwards:** None. **D. Farr:** None. **A. Jayam-Trouth:** None. **N.M. Shara:** None. **B.M. Sanchez:** None. **S.J. Fernandez:** None. **R. Coles:** None. **J.D. Richardson:** None. **B. Ovbiagele:** None. **C.S. Kidwell:** None.

Presentation Number: CT P9

Trial Abbreviation: STOP-IT Study

Trial Contact Information: Project Manager: Janice Carrozzella, RN, CCRA; carrozj@uc.edu; PH: 513-475-8793; Fax: 513-475-8797

Trial Email: carrozj@uc.edu

Trial Name: The Spot Sign for Predicting and Treating ICH Growth Trial

Trial Registry Number ID: NCT00810888

Trial Sponsor: NIH / NINDS

Trial Web Site: www.STOPITSTUDY.org

Publishing Title: STOP-IT Study

Author Block: Matthew Flaherty on Behalf of STOP-IT Study Investigators, Univ of Cincinnati, Cincinnati, OH

Abstract Body:

Title: The Spot Sign for Predicting and Treating ICH Growth (STOP-IT) Study

Trial Registry Number: NCT00810888

Background:

Intracerebral hemorrhage (ICH) is estimated to affect 67,000 persons in the United States and 5,000 persons in Canada annually and is associated with a 40-50% case-fatality rate. There are no proven treatments for ICH. The demonstration that hematoma growth after ictus is common and associated with neurological decline has spurred research into early hemostatic therapy to potentially improve patient outcomes.

Recombinant activated factor VII (rFVIIa) was proven to significantly reduce hematoma growth when administered within four hours of symptom onset in two placebo-controlled, blinded, randomized clinical trials. Because rFVIIa works to stop bleeding but should not otherwise affect the natural history of ICH, only patients destined to have hematoma growth will benefit from this therapy. Ideally, clinicians will be able to identify patients who will have significant hematoma growth regardless of their time of presentation and administer hemostatic therapy to this group.

CT angiography (CTA) is a widely available, fast, non-invasive tool that has shown promise for predicting hematoma growth. In multiple, recent retrospective case series patients with contrast extravasation within their hematomas (the spot sign) had greater risk of subsequent hematoma growth and worse outcomes than patients without extravasation.

The next step in this treatment paradigm is to confirm the ability of CTA to predict hematoma growth and to explore the role CTA may play in the administration of hemostatic therapy.

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- Objectives:

Objectives:

•

Determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

o

Working hypothesis: For patients scanned within five hours of stroke onset, the spot sign will have a high sensitivity and specificity for hematoma growth.

•

Determine the feasibility of using CTA to identify ICH patients at high risk of hematoma growth and to select

patients for randomization to treatment with rFVIIa or placebo.

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Working Hypothesis #1: Site investigators will determine the presence or absence of a spot sign in the acute setting with a high degree of accuracy as compared to blinded over-read by a study neuroradiologist.

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Working Hypothesis #2: Use of CTA to identify candidates for randomization to rFVIIa versus placebo can be done in a time-efficient manner

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Randomize ICH patients who present within five hours of symptom onset and have a spot sign to treatment with rFVIIa versus placebo, in order to (a) determine if rFVIIa is effective at reducing hematoma growth among patients with a spot sign and (b) provide preliminary efficacy data for this treatment paradigm.

o

Working Hypothesis: Spot-positive patients treated with rFVIIa will have less hematoma growth than spot-positive patients treated with placebo.

Design:

STOP-IT will enroll patients with acute ICH less than five hours from symptom onset. Patients will be included in one of two study arms. The first arm will be a multicenter, randomized, double-blind, placebo-controlled trial comparing rFVIIa to placebo for treatment of patients with acute ICH and a spot sign on CTA. The second arm will be a multicenter, prospective observational study of hematoma growth among patients without a spot sign on CTA. Comparisons will be made between 1) patients with a spot sign randomized to placebo and patients without a spot sign, in order to determine the value of the spot sign for predicting hematoma growth and 2) patients who have a spot sign and are randomized to rFVIIa or placebo in order to determine the effect of study drug upon hematoma growth.

Population:

Approximately 184 subjects with intracerebral hemorrhage fulfilling inclusion and failing no exclusion criteria will be enrolled into one of two study arms at thirteen clinical sites across the United States and Canada.

Interventions:

Eligible, consented subjects presenting within five hours of ICH onset will be qualified for enrollment into one of two study arms in this multicenter phase II study. Patients who have a spot sign present on CTA will be randomized 1:1 to treatment with either rFVIIa (80 mcg/kg - maximum dose volume 10.0 mL, equivalent to maximum weight of 125 kg) or placebo. Patients without a spot sign will be enrolled in a prospective observational arm and their data will be compared to spot-positive patients treated with placebo to determine the sensitivity and specificity of the CTA spot sign for hematoma growth.

Outcome Measures:

Primary Outcome: Clinical

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Safety: Life-threatening thromboembolic complications defined as development of (1) acute myocardial ischemia; (2) acute cerebral ischemia; and (3) acute pulmonary embolism through day 4 following completion of study drug administration.

•

The rate of hematoma growth among spot sign positive subjects at 24 hours, comparing subjects treated with rFVIIa to those treated with placebo. Hematoma growth will be defined as a > 33% or > 6 cc increase in volume.

Secondary Outcome: Clinical

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Incidence of other potentially study drug related thromboembolic complications such as deep venous thrombosis and elevations in troponin not associated with ECG evidence of acute coronary syndrome through day 90 following completion of study drug administration.

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The rate of total hemorrhage volume growth (hematoma plus IVH) among spot-positive subjects and ninety day outcomes among spot positive subjects, dichotomized as modified Rankin Scale score of 0-4 versus 5-6, comparing subjects treated with rFVIIa to those treated with placebo

Primary Outcome: Test Performance:

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The sensitivity and specificity of the spot sign for predicting hematoma growth.

Secondary Outcome: Test Performance:

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The positive and negative predictive values of the spot sign and the accuracy of the site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist.

Analysis (Imaging):

The local investigator will use the baseline CT as part of the screening process for eligibility. Baseline hematoma volume for study screening will be calculated by the ABC/2 method. De-identified baseline and 24-hour CTs will be provided to the University of Calgary via the Clinical Coordinating Center for subsequent interpretation by a blinded clinician. Hematoma volumes for study endpoints will be calculated by volumetric analysis. Scans will also be analyzed for the location of hemorrhage, the presence and volume of IVH, the presence or absence of hydrocephalus, edema volume, mass effect, prior infarction(s) (baseline CT) and acute infarction(s).

Local investigators will interpret the CTA for the presence or absence of the spot sign in the acute setting. Digital, de-identified copies of the CTAs will be provided to Sunnybrook Health Sciences Centre via the Clinical Coordinating Center for subsequent interpretation by a blinded neuroradiologist. All CTAs will also be subsequently reviewed for the presence or absence of the spot sign by a blinded study neurologist and a blinded study emergency medicine physician. Measures of inter-rater reliability will be determined among the evaluators, with the neuroradiologist's reading considered the gold-standard.

Trial Status:

Eight clinical sites actively recruiting: 23 subjects enrolled as of November 1, 2011

Principal Investigator:

Matthew L. Flaherty, MD - University of Cincinnati

Trial Sponsor:

National Institute of Health / National Institute of Neurological Disorders and Stroke

Trial Contact Information:

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Trial website: www.STOPITSTUDY.org

Author Disclosure Block: M. Flaherty on Behalf of STOP-IT Study Investigators: Other Research Support; Significant; Novo Nordisk is supplying study drug for this trial.

Presentation Number: CT P10

Trial Abbreviation: TIPS

Trial Contact Information: Catherine Amlie-Lefond MD

Trial Email: pending

Trial Name: Thrombolysis in Pediatric Stroke

Trial Registry Number ID: N/a

Trial Sponsor: NIH

Trial Web Site: pending

Publishing Title: Thrombolysis in Pediatric Stroke (TIPS)

Author Block: Anthony K Chan, McMaster's Univ, Hamilton, ON, Canada; Gabrielle A deVeber, Hosp for Sick Children, Toronto, ON, Canada; Joan C Gill MD, Medical Coll of Wisconsin, Milwaukee, WI; Collin A Hovinga, Dell Children's Medical Ctr, Austin, TX; Adam Kirton, Univ of Calgary, Calgary, AB, Canada; Rebecca N Ichord, The Children's Hosp of Philadelphia, Philadelphia, PA; Michael Rivkin, Children's Hosp of Boston, Boston, MA; Aniko Szabo, Osama O Zaidat, Medical Coll of Wisconsin, Milwaukee, WI; **Catherine Amlie-Lefond**, Seattle Children's Hosp, Seattle, WA

Abstract Body:

Thrombolysis in Pediatric Stroke (TIPS) is a five-year multi-center international safety and dose-finding study of intravenous (IV) tPA in children with acute AIS to determine the maximal safe dose of intravenous (IV) tPA among three doses (0.75, 0.9, 1.0 mg/kg) for children age 2-17 years within 4.5 hours from onset of acute arterial ischemic stroke (AIS). It represents the first study of acute intervention for pediatric stroke.

An adaptive dose finding method will be applied to escalate across the three dose levels within two age groups: 2-10 years (prepubertal) and 11-17 years. Dose will be escalated based on safety (absence of excess toxicity) with at least 3 children treated at each dose level.

Toxicity for the purpose of this study is defined as:

1. PH2 (parenchymal hemorrhage involving > 30% of the infarcted area), regardless of whether or not it is associated with clinical deterioration, OR,
2. PH1 (parenchymal hemorrhage involving \leq 30% of the infarcted area with some slight space-occupying effect OR an intraventricular, subarachnoid, or parenchymal hemorrhage outside the infarct seen on neuroimaging, AND an increase in Pediatric NIHSS of \geq 4 from baseline (pre-tPA value). The hemorrhage should be considered to be the cause of deterioration.

The secondary outcomes will include other hemorrhagic or nonhemorrhagic complications of tPA administration.

Children enrolled in TIPS will have PedNIHSS score of \geq 6 and \leq 25 that is not improving at the time of initiation of tPA administration. Baseline neuroimaging must have no evidence of intracranial hemorrhage (including HI-1, HI-2, PH-1 or PH-2). Patients with an acute infarct on MRI involving 1/3 or more of the complete MCA territory involvement will be excluded.

TIPS will also determine the pharmacokinetics of tPA and its inhibitor, plasminogen activator inhibitor, including free tPA, PAI-1, and tPA antigen in children receiving IV tPA for acute AIS. In addition, TIPS will measure the 3-month neurological outcome in children treated with IV tPA.

TIPS was designed and has been instituted through the infrastructure of the International Pediatric Stroke Study. This multinational research collaboration of child neurologists, hematologists, and pharmacologists dedicated to the prevention and treatment of stroke in childhood permits pooling of patients data and resources and ensures a larger and more ethnically diverse cohort for clinical trials than would be possible at any one center or in any single country.

TIPS has been funded by the National Institutes of Health and has study start-up in January, 2011. Initial enrolling sites include 21 sites in 4 countries. This phase 1 study is a critical step to allowing children to benefit

from two evidence-based acute stroke treatments that save lives and improve neurological outcome in adults: the use of tPA, and the development of dedicated stroke units that provide standardized best practice acute care.

Author Disclosure Block: **A.K. Chan:** None. **G.A. deVeber:** None. **J.C. Gill:** None. **C.A. Hovinga:** None. **A. Kirton:** None. **R.N. Ichord:** None. **M. Rivkin:** None. **A. Szabo:** None. **O.O. Zaidat:** None. **C. Amlie-Lefond:** None.

Presentation Number: CT P11

Trial Abbreviation: ICTUS Trial

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Trial Name: CITICOLINE IN THE TREATMENT OF ACUTE ISCHEMIC STROKE. AN INTERNATIONAL

Trial Registry Number ID: NCT00331890

Trial Sponsor: Ferrer Group

Trial Web Site: www.ferrergrupo.com

Publishing Title: ICTUS Study: International Citicoline Trial on acUte Stroke (update 2012)

Author Block: Julio Secades, FERRER GROUP, Barcelona, Spain; **Antoni Dávalos**, Hosp German Tries i Pujol, Badalona, Spain; José Alvarez-Sabín, Hosp de la Vall d'Hebron, Barcelona, Spain; José Castillo, Hosp Clínico Univrio de Santiago, Santiago de Compostela, Spain; Erik Cobo, Univ Plitecnica de Catalunya, Barcelona, Spain; Exuperio Díez-Tejedor, Hosp Univrio La Paz, Madrid, Spain; Jose Ferro, Hosp Santa Maria, Lisboa, Portugal; Eduardo Martínez-Vila, Clínica Univria de Navarra, Pamplona, Spain; for the ICTUS Trial Investigators

Abstract Body:

Background: Citicoline is a safe drug approved in some countries for the treatment of acute ischemic stroke. The drug has shown some evidence of efficacy in a data pooled analysis, based on four clinical trials performed in USA with oral citicoline given within 24 hours from symptoms onset.

Trial Steering Committee: Antoni Dávalos (Chairman), José Alvarez-Sabín, José Castillo, Erik Cobo (Statistician), Exuperio Díez-Tejedor, Jose Ferro, Savion Gropper, Eduardo Martínez-Vila, Julio J Secades.

Data Safety Monitoring Board: Kennedy R Lees (Chairman), Steve Warach, John Whitehead (Statistician).

Purpose: To confirm the results obtained in the data pooled analysis.

Design: Multicenter, randomized (under minimization), double-blind, placebo-controlled trial, based on a sequential analysis (triangular model).

Sample Size: The study will follow a sequential analysis, with interim analysis planned with 1000, 1533, 2067, and 2600 patients. The upper limit has been established in 3350 patients. This design has 80% power to establish a treatment effect of 1.26 (common odds ratio).

Centers: 24 centers in Spain, 8 in Portugal and 9 in Germany

Study Population: Male or female, ≥ 18 years old, treated within 24 hours of symptoms onset, with a measurable focal neurological deficit lasting for a minimum of 60 minutes. Baseline NIHSS score ≥ 8 , with a neuroimage compatible with the diagnosis of acute ischemic stroke and symptoms referable to MCA territory. Pre-stroke mRS ≤ 1 . Signed informed consent is mandatory.

Interventions: Patients will be randomized in a 1:1 ratio to receive either citicoline or placebo. Citicoline forms: 1000 mg ampoules (4 cc) and 500 mg tablets. Daily dosage: 1000 mg/12 h i.v. during the first three days and orally from the fourth day until the end of the 6 weeks treatment period.

Outcome Endpoints: Primary end-point will consist in a global score test combining three measures of success evaluated 12 weeks after treatment on the basis of intention-to-treat criteria: neurological (NIHSS) ≤ 1 , disability (MRS ≤ 1), and activities of daily life (BI ≥ 95), averaged using a Global Test. Secondary endpoints: Results of the single scales at week 12. Formal training and certification in the use of mRS and NIHSS are mandatory.

Safety Endpoints: Vital signs, adverse events, symptomatic hemorrhagic transformation in patients treated with rTPA (ECASS criteria), neurological deterioration, mortality, and concomitant medication records

Statistical Analysis: The main analysis will consist of a Global Test combining the three measures of success on the basis of intention-to-treat criteria applying LOCF. A patient who dies before 12 weeks will be considered to have failed on all three measures.

Trial Status: All the centers are open. Close to 2400 patients are expected to be included by February 2012. The third interim analysis on 2067 patients will be completed before the conference.

Registers: EudraCT N° 2005-004825-25; ClinicalTrials.gov NCT00331890; Stroke Trials Registry.

Author Disclosure Block: **J. Secades:** Employment; Significant; Full time employee. **A. Dávalos:** Honoraria; Significant; As PI of ICTUS Trial. **J. Alvarez-Sabín:** Consultant/Advisory Board; Modest; TSC ICTUS trial. **J. Castillo:** Consultant/Advisory Board; Modest; TSC ICTUS Trial. **E. Cobo:** Consultant/Advisory Board; Modest; TSC ICTUS Trial. **E. Díez-Tejedor:** Consultant/Advisory Board; Modest; TSC ICTUS Trial. **J. Ferro:** Consultant/Advisory Board; Modest; TSC ICTUS Trial. **E. Martínez-Vila:** Consultant/Advisory Board; Modest; TSC ICTUS Trial.

Presentation Number: CT P12

Trial Abbreviation: CRYSTAL-AF

Trial Contact Information: Frank Beckers, frank.beckers@medtronic.com

Trial Email: Frank Beckers

Trial Name: Cryptogenic Stroke and Underlying Atrial Fibrillation

Trial Registry Number ID: NCT00924638

Trial Sponsor: Medtronic, Inc.

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT00924638>

Publishing Title: Cryptogenic Stroke And Underlying Atrial Fibrillation Trial (CRYSTAL-AF): Design, Clinical Significance And Status

Author Block: Richard A Bernstein, Northwestern Univ, Glenview, IL; Johannes Brachmann, Klinikum Coburg and Essen, Coburg, Germany; Hans-Christoph Diener, Univ Hosp Essen, Essen, Germany; Carlos A. Morillo, McMaster Univ, Hamilton, ON, Canada; Tommaso Sanna, Vincenzo Di Lazzaro, Catholic Univ of the Sacred Heart, Roma, Italy; Rod Passman, Northwestern Univ, Glenview, IL; Marilyn M. Rymer, St. Lukes Hosp, Kansas City, KS

Abstract Body:

Stroke is the third leading cause of mortality in the US and the leading cause of long-term disability. Stroke of undetermined cause (cryptogenic) accounts for approximately 25-30% of ischemic strokes. Paroxysmal atrial fibrillation (AF) may be an important underlying cause. Patients with cryptogenic stroke are usually treated with antiplatelet agents. However, when AF is detected, guidelines recommend anticoagulation due to its superior efficacy in this population. The optimum method for detecting paroxysmal AF in patients with stroke is not known.

The CRYSTAL AF study seeks determine if long term monitoring using the Reveal XT insertable cardiac is superior to routine monitoring for detecting AF in patients with cryptogenic stroke.

Study design:

CRYSTAL AF is a 1:1 randomized, prospective, multicenter study in which approximately 450 patients will be included at about 60 active sites in Europe and North America. Patients are eligible for inclusion after diagnosis of cryptogenic stroke, with minimum testing specified by the study. Each patient will be followed until study closure with a minimum of 12 months. Half of the enrolled patients will have a REVEAL-XT implanted, the other half will undergo standard monitoring.

Objectives: The primary objective is the time to first documented AF by 6 months of continuous rhythm monitoring versus standard. The primary secondary objective is the time to first documented AF event by 12 months. Other secondary objectives are:

- To compare the incidence of recurrent stroke or TIA between the two study groups.
- To compare the change, and reasons for change, in use of oral anticoagulation and anti-arrhythmic drugs over time in both arms.
- To compare the number and duration of cardiovascular related hospitalizations in both arms
- To describe health outcomes, economic and clinical disease burden and the care pathways of enrolled patients
- To evaluate the role of the Patient Assistant device in time to diagnosis in patients implanted with the Reveal XT. The patient follow-up in the Reveal implanted arm will use CareLink remote monitoring system.

Current status:

As of 12 October 2011, 316 patients had been enrolled in the study.

Study milestone schedule:

Data collection will be closed 12 months after enrollment of the last patient. The study enrolled the first patient on 17 June 2009; and a publication is expected in early 2013.

Author Disclosure Block: **R.A. Bernstein:** Speakers' Bureau; Significant; Medtronic. Consultant/Advisory Board; Modest; Medtronic. **J. Brachmann:** Consultant/Advisory Board; Modest; Medtronic. **H. Diener:** Consultant/Advisory Board; Modest; Medtronic. **C.A. Morillo:** Consultant/Advisory Board; Modest; Medtronic. **T. Sanna:** Consultant/Advisory Board; Modest; Medtronic. **V. Di Lazzaro:** Consultant/Advisory Board; Modest; Medtronic. **R. Passman:** Consultant/Advisory Board; Modest; Medtronic. **M.M. Rymer:** Consultant/Advisory Board; Modest; Medtronic.

Presentation Number: CT P13

Trial Abbreviation: ENOS

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Trial Name: Efficacy of Nitric Oxide in Stroke

Trial Registry Number ID: ISRCTN99414122

Trial Sponsor: University of Nottingham, United Kingdom

Trial Web Site: www.enos.ac.uk

Publishing Title: Efficacy of Nitric Oxide in Stroke (ENOS) Trial - A Prospective Randomised Controlled Trial in Acute Stroke

Author Block: Sandeep Ankolekar, Cheryl Hogg, Sally Utton, **Philip M Bath**, Univ of Nottingham, Nottingham, United Kingdom

Abstract Body:

Rationale: Acute hypertension is associated with a poor outcome after stroke. No large trials have assessed the effect of altering BP during the acute phase of stroke on outcome. We are testing whether nitric oxide, a multimodal molecule given as glyceryl trinitrate (GTN), is safe and effective in improving outcome after acute stroke. Furthermore, around half of all patients admitted with acute stroke are taking antihypertensive therapy immediately prior to the stroke. No data exist as to whether it is beneficial or safe to stop or continue this treatment during the acute phase.

Design: ENOS is a prospective, international, multicentre, randomised, parallel-group, blinded, controlled trial. 3,500 - 5,000 ischaemic or haemorrhagic stroke patients with systolic BP 140-220 mmHg, and within 48 hours of onset will be included. Subjects will be randomised to 7 days of single-blind treatment with transdermal GTN or control. Those patients taking prior antihypertensive therapy will also be randomised to continue or temporarily stop this for 7 days. ENOS is conducted over a secure internet site. The primary outcome is modified Rankin Scale at 90 days which is carried out by a blinded assessor. The analysis will be by intention to treat.

Trial status: As at 24th October, 2011, 2584 patients had been recruited from 137 centres (Australia, Canada, China, Denmark, Egypt, Hong Kong, India, Italy, Malaysia, New Zealand, Philippines, Poland, Republic of Ireland, Romania, Singapore, Spain, Sri Lanka and UK). More centres welcome to join.

Contact information: <http://www.enos.ac.uk> , E-mail: enos@nottingham.ac.uk, Telephone: +44 (0)115 823 1770

Author Disclosure Block: **S. Ankolekar:** None. **C. Hogg:** None. **S. Utton:** None. **P.M.W. Bath:** None.

Presentation Number: CT P14

Trial Abbreviation: SHINE Trial

Trial Contact Information: Karen C. Johnston, kj4v@virginia.edu, phone - 434 924-5323, Fax- 434 982-1726

Trial Email: kj4v@virginia.edu

Trial Name: Stroke Hyperglycemia Insulin Network Effort Trial

Trial Registry Number ID: NCT01369069

Trial Sponsor: NIH-NINDS

Trial Web Site: <http://www.nett.umich.edu/nett/shine>

Publishing Title: Stroke Hyperglycemia Insulin Network Effort Trial

Author Block: **Karen C Johnston**, Univ of Virginia, Charlottesville, VA; Askiel Bruno, Georgia Health Sciences Univ, Augusta, GA; Christiana E. Hall, Univ of Texas, Southwestern, Dallas, TX

Abstract Body:

Trial Name: Stroke Hyperglycemia Insulin Network Effort Trial

Trial Abbreviation: SHINE Trial

Trial Registry ID: NCT01369069 (clinicaltrials.gov)

Background: Hyperglycemia is common in acute stroke patients. Ischemic stroke patients with hyperglycemia have worse outcomes than those with euglycemia. There is clinical equipoise regarding how hyperglycemia should be managed in acute ischemic stroke patients.

Objective: To assess the safety and efficacy of glucose control (80 - 130 mg/dL) using insulin infusion versus standard sliding scale insulin with target glucose <180 mg/dL.

Design: SHINE is a multicenter, randomized, controlled trial with 2 treatment arms. Randomization is stratified by NIHSS score and IV thrombolysis.

Population: Adult acute ischemic stroke patients with diabetes mellitus and hyperglycemia at the time of enrollment (glucose >110 mg/dL) or admission glucose of ≥ 150 mg/dL if not diabetic. Patients must be enrolled within 12 hours of stroke symptom onset and within 3 hours of hospital arrival. Patients will be recruited from approximately 45 NETT sites (hubs and spokes) and 10 non NETT sites.

Sample Size: 1400 subjects

Intervention: Patients will be randomized to intervention (IV insulin drip with target glucose 80-130 mg/dL) or control treatment (subcutaneous sliding scale insulin with target <180 mg/dL). Patients in the intervention group will utilize the GlucoStabilizer computerized decision support tool to guide therapy. Patients will receive up to 72 hours of treatment.

Outcome Measures: The primary efficacy outcome is modified Rankin Scale with favorable outcome dependent on baseline stroke severity (sliding dichotomy). The primary safety outcome is severe hypoglycemia (<40 mg/dL).

Statistical Analysis: The efficacy analysis using a two sided alpha = 0.05, will have 80% power to demonstrate a clinically relevant treatment effect, defined as an absolute increase in favorable outcome of 7% or higher. Safety will be declared if the absolute rate of hypoglycemia in the intervention group does not exceed that of the control group by more than 4%.

Trial Status: Funding was received in August 2011. The investigator meeting was held in January 2012, and enrollment is expected to begin in spring 2012. A 4 year period of enrollment is expected.

Sponsor: NIH-NINDS (U01 NS069498)

Trial Web Site: www.SHINETrial.com or <http://www.nett.umich.edu/nett/shine>

Author Disclosure Block: **K.C. Johnston:** Research Grant; Significant; NIH-NINDS U01 NS069498. **A. Bruno:** Research Grant; Significant; NIH-NINDS U01 NS069498. **C.E. Hall:** Research Grant; Significant; NIH-NINDS U01 NS069498.

Presentation Number: CT P15

Trial Abbreviation: ARUBA

Trial Contact Information: JP Mohr MD MD jpm10@columbia.edu 212 305 5796 212 305 8033

Trial Email: jpm10@columbia.edu

Trial Name: A Randomized Trial of Unruptured Brain Arteriovenous Malformations

Trial Registry Number ID: NCT00389181

Trial Sponsor: NINDS/NIH

Trial Web Site: www.arubastudy.org

Publishing Title: The Aruba Trial

Author Block: C. Stapf, APHP Hop Lariboisiere, Univ of Paris, Paris, France; J. P Mohr, Neurological Inst, New York, NY; A J Moskowitz, InCHOIR, Mount Sinai Medical Sch, New York, NY; M K Parides, E Moquete, InCHOIR, Mount Sinai Medical Sch, New York, NY; W L Young, Univ of California at San Francisco, Sa Francisco, CA; C S Moy, NINDS, NIH, Bethesda, MD; E Vicaut, APHP Hop Lariboisiere, Univ of Paris, Paris, France

Abstract Body:

RATIONALE: Current invasive treatment for brain arteriovenous malformations (BAVMs) is varied and includes endovascular procedures, neurosurgery, and radiotherapy. However, conspicuously absent from the literature are controlled treatment data for any comparison of treatments, immediate or deferred, on the benefit of preventive therapy for unruptured BAVMs .

DESIGN: ARUBA is an international, multicenter, randomized, controlled, open, prospective clinical trial sponsored by the NINDS (<http://clinicaltrials.gov/ct/show/NCT00389181>)

SAMPLE SIZE: 400 patients (1:1 random assignment).

POPULATION STUDIED: Patients aged ≥ 18 years, diagnosed with an unruptured BAVM considered by the local investigators to be suitable for attempted eradication.

Outcome measures: The primary outcome is the composite event of death from any cause or stroke (hemorrhage or infarction confirmed by imaging). Clinical outcome status will be measured by the Rankin Scale, NIHSS, SF-36, and EuroQol.

INTERVENTIONS: Patients are randomly assigned to best possible invasive therapy (medical management plus endovascular, surgical, and/or radiation therapy) versus medical management alone. Patients will be followed for 5-10 years from randomization.

PRIMARY AIM: To determine whether medical management alone is superior, or not inferior, to invasive therapy in averting death (any cause) or stroke (symptomatic hemorrhage or infarction).

SECONDARY AIM: To determine whether treatment of unruptured BAVMs by medical management alone offers a lower risk of death or clinical impairment (Rankin Score ≥ 2) at 5 years post-randomization compared to invasive therapy.

TRIAL STATUS: More than 170 patients have been enrolled worldwide as of October 2011. Interested multidisciplinary treatment teams are welcome to join.

SPONSOR: NIH/NINDS (NCT00389181)

CONTACT: jpm10@columbia.edu (www.arubastudy.org)

Author Disclosure Block: C. Stapf: None. J.P. Mohr: None. A.J. Moskowitz: None. M.K. Parides: None. E. Moquete: None. W.L. Young: None. C.S. Moy: None. E. Vicaut: None.

Presentation Number: CT P16

Trial Abbreviation: PODCAST

Trial Contact Information: Mrs Lynn Stokes/Lynn.stokes@nottingham.ac.uk/Tel: +44 (0)115 82 31671/Fax:0115 82 30273

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Trial Name: Prevention Of Decline in Cognition After Stroke Trial

Trial Registry Number ID: ISRCTN85562386

Trial Sponsor: University of Nottingham, United Kingdom

Trial Web Site: www.podcast-trial.org

Publishing Title: Podcast: Prevention Of Decline In Cognition After Stroke Trial: A Factorial Randomised Trial Of Blood Pressure And Lipid Lowering

Author Block: Sandeep Ankolekar, Lynn Stokes, **Philip M Bath**, Univ of Nottingham, Nottingham, United Kingdom

Abstract Body:

Rationale: Stroke and dementia are common, economically costly to society, and devastating to patients and their family. Elevated BP and cholesterol are common after stroke and may be associated with increasing cognitive decline. Although BP-lowering post-stroke may reduce cognitive decline, there is little evidence to date that lipid lowering is effective in preventing cognitive decline. Critically, it is unknown whether BP and cholesterol should be lowered intensively, or moderately as per current guidelines. The aim of the proposed trial is to determine if intensive BP and/or lipid lowering therapy after stroke is better in preventing cognitive decline, compared to current guideline treatment.

Design: PODCAST is a prospective, randomised, open-label, blinded end-point, controlled, partial factorial, phase IV trial. The start up phase will assess feasibility of the study over 3 years in 600 patients. The main phase will then assess the efficacy of intensive treatment in a further 2,800 patients over 8 years in total. The target Systolic Blood Pressure (SBP) is <125 mm Hg for the intensive BP lowering group and <140 mm Hg for the guideline group. For the intensive lipid lowering group the target Low Density Lipoprotein-Cholesterol (LDL-C) is <2 mmol/L and <3 mmol/L for the guideline group. The primary outcome is Addenbrooke's Cognitive Examination. Secondary outcomes include vascular events, quality of life, functional outcome, depression and death.

Trial Status: The trial has UK Ethics and NHS RD approvals and has recruited 12 patients to date.

Contact Information:

Website: <http://www.podcast-trial.org/>

E-mail: podcast@nottingham.ac.uk

Telephone: +44 (0) 115 8231671

Author Disclosure Block: **S. Ankolekar:** None. **L. Stokes:** None. **P.M.W. Bath:** None.

Presentation Number: CT P17

Trial Abbreviation: The Gore REDUCE Study

Trial Contact Information: reduce@wlgore.com

Trial Email: reduce@wlgore.com

Trial Name: GORE HELEX™ Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO)

Trial Registry Number ID: NCT00738894

Trial Sponsor: W.L. Gore & Associates, Inc

Trial Web Site: <http://www.clinical.goremedical.com/REDUCE/>

Publishing Title: GORE HELEX™ Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO) - The Gore REDUCE Study

Author Block: **Scott E Kasner**, Univ of Pennsylvania, Philadelphia, PA; on behalf of the Gore REDUCE Study Investigators

Abstract Body:

Rationale: The relationships between cryptogenic stroke and patent foramen ovale (PFO) are complex, and the role of percutaneous closure for prevention for recurrent stroke remains promising but uncertain.

Objective: The REDUCE Study is designed to demonstrate that PFO closure with the GORE HELEX Septal Occluder plus antiplatelet medical management is safe and effective and reduces the risk of recurrent stroke or imaging-confirmed transient ischemic attack (TIA) when compared to antiplatelet medical management alone in patients with a PFO and history of cryptogenic stroke or imaging-confirmed TIA.

Design: Multicenter, multinational, randomized clinical trial.

Population:

- 664 men and Women, age 18 - 60 years
- Cryptogenic ischemic stroke or imaging-confirmed TIA
- Presence of Patent Foramen Ovale (PFO) confirmed by transesophageal echocardiography (TEE)
- No evidence of an alternative etiology for stroke

Intervention: Participants will be randomized 2:1 to PFO closure with the GORE HELEX Septal Occluder plus antiplatelet medical management vs. antiplatelet medical management alone. Patients will be followed to 2 years for the primary endpoint, and up to 5 years for secondary endpoints.

Primary Outcome: Time to recurrent stroke or imaging-confirmed TIA, or death due to stroke through 24 months post-randomization. All events will be adjudicated by a blinded clinical events committee.

Secondary Outcomes: Proportion of participants with new ischemic lesions on MRI at 2 years compared to MRI obtained at baseline; systemic embolic events; PFO closure in device-arm subjects by transthoracic echocardiography (TTE); device- and procedure-related adverse events; time to recurrent stroke or imaging-confirmed TIA, or death due to stroke through 60 months post-randomization.

Statistical Analysis: Time to recurrent stroke or imaging-confirmed TIA will be compared using an unadjusted log-rank test and presented using Kaplan-Meier methods. The primary analysis will be by intention-to-treat.

Trial Status: Enrollment is ongoing at a maximum of 50 investigational sites in the United States, Denmark, Finland, Sweden, Norway, and the United Kingdom with no per-site subject limit.

Author Disclosure Block: **S.E. Kasner:** Research Grant; Significant; Principal Investigator grant to University of Pennsylvania.

Presentation Number: CT P18

Trial Abbreviation: Wake-Up Stroke

Trial Contact Information: Jennifer Garrett, RN, 713-500-7183, jennifer.m.garrett@uth.tmc.edu

Trial Email: jennifer.m.garrett@uth.tmc.edu

Trial Name: Safety of Intravenous Thrombolysis for Wake-up Stroke

Trial Registry Number ID: NCT01183533

Trial Sponsor: University of Texas Health Science Center at Houston and Genentech

Trial Web Site: <http://www.clinicaltrials.gov/ct2/show/NCT01183533>

Publishing Title: Safety of Intravenous Thrombolysis for Wake-up Stroke

Author Block: Claude Nguyen, Navdeep Sangha, William Hicks II, Osman Mir, Yazan Alderazi, Andrew Bursaw, Jennifer Garrett, Andrew Barreto, Sean Savitz, Univ of Texas Health Science Ctr at Houston, Houston, TX

Abstract Body:

Background

The only proven effective therapy for acute ischemic stroke remains intravenous (IV) tissue plasminogen activator (t-PA), which can only be used within 4.5 hours of symptom onset. Up to 25% of ischemic stroke patients wake up with their stroke. These patients are largely excluded from receiving acute thrombolytic therapy, as their time of onset is unknown. Recent studies suggest that patients with wake-up stroke (WUS) may benefit from receiving IV t-PA; a recent retrospective study of WUS patients found no significant increase in intracerebral hemorrhage or neurological deterioration, supporting the safety of administering IV t-PA to WUS patients. Therefore, we now conduct a prospective study to more definitively assess safety of thrombolysis in WUS patients.

Objective

We aim to assess the safety of administering IV t-PA to patients with WUS. We hypothesize that patients with WUS who are treated with IV t-PA will not have significantly increased proportion of symptomatic hemorrhage compared with those treated with IV t-PA by standard of care.

Design

This is an open label, multi-center, safety study of acute treatment with IV t-PA in patients with ischemic stroke who wake up with their symptoms.

Population Studied (including sample size)

Those with suspected acute ischemic stroke occurring during sleep or who woke up with focal neurological symptoms will be considered. This includes all patients last known to be neurologically normal the night before, who were found with stroke deficits upon awakening. Patients must be 18-80 years old and have baseline NIHSS ≤ 25 . Blood pressure must be ≤ 185 mmHg systolic and ≤ 110 mmHg diastolic at enrollment. Treatment of higher systolic BP is permitted prior to enrollment. Patients with the following will be excluded: hypodensities $> 1/3$ of the MCA territory on noncontrast CT head, prior ischemic stroke within the last 3 months, prior intracranial hemorrhage, known cerebral aneurysm or AVM, coagulopathy, surgical procedures within 14 days of event, GI/GU bleeding within 14 days of event, treatment with oral anticoagulants and having INR > 1.7 , platelet count < 100000 , glucose < 50 or > 450 , or those who may undergo intraarterial therapy. A total of 40 patients will be enrolled.

Intervention

Qualifying patients will be consented to receive t-PA within 3 hours of awakening. 0.9 mg/kg (maximum of 90

mg) IV t-PA will be administered with 10% bolus given over 1 minute, and the rest given as an infusion over the remaining hour. We will use standard post t-PA medication restrictions within the first 24 hrs of t-PA, including no antiplatelets or anticoagulants.

Outcome Measures

Primary outcome measure is the frequency of symptomatic hemorrhagic transformation within 24 hours of treatment, defined as any intracerebral hemorrhage associated with a ≥ 4 point increase in NIHSS. Secondary outcome is the NIHSS score at 24 hours, 3 days, and 90 days, and modified Rankin Score at 3 days and 90 days.

Analysis

This is a safety study, with no control group. We aim to determine whether patients with WUS can be safely treated with IV t-PA. In secondary analysis, we also aim to measure the frequency of reperfusion or recanalization post-treatment in all patients that receive perfusion and angiography studies pre-treatment.

Trial Status

The trial is currently ongoing at Memorial Hermann-Texas Medical Center and Memorial Hermann-Southwest Medical Centers. Currently 14 patients have been enrolled.

Author Disclosure Block: **C. Nguyen:** None. **N. Sangha:** None. **W. Hicks:** None. **O. Mir:** None. **Y. Alderazi:** None. **A. Bursaw:** None. **J. Garrett:** None. **A. Barreto:** None. **S. Savitz:** Research Grant; Significant; Genentech.

Presentation Number: CT P19

Trial Abbreviation: StELLAR

Trial Contact Information: Julie Jurf, RN, MSN, jjurf@ucsd.edu, 858-657-7185

Trial Email: jjurf@ucsd.edu

Trial Name: Safety of tPA + Transcranial Emission of Low-Energy Lasers for Acute Stroke Recovery

Trial Registry Number ID: NCT01220739

Trial Sponsor: NIH/NINDS, University of California, San Diego, and Photothera

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT01220739?term=stellar&rank=2>

Publishing Title: Safety of tPA + Transcranial Emission of Low-Energy Lasers for Acute Stroke Recovery

Author Block: Justin Zivin, Rema Raman, Univ of California, San Diego, La Jolla, CA; Christopher Fanale, Swedish Medical Ctr, Englewood, CO; Souvik Sen, Univ of South Carolina, Columbia, SC; Scott Kasner, Hosp of the Univ of PA, Philadelphia, PA; Arbi G. Ohanian, Huntington Memorial Hosp, Pasadena, CA; Philip Delio, Santa Barbara Cottage Hosp, Santa Barbara, CA; **Karen Rapp**, Julie Jurf, Brett Meyer, Thomas M. Hemmen, Univ of California, San Diego, La Jolla, CA

Abstract Body:

Background: Neuroprotection with Transcranial Laser Therapy (TLT) has shown promise in preliminary clinical trials without thrombolysis. The Safety of tPA + Transcranial Emission of Low-Energy Lasers for Acute Stroke Recovery (StELLAR) study aims to assess the safety and preliminary efficacy of combining intravenous tPA with TLT using the NeuroThera® Laser System in subjects treated for acute ischemic stroke.

Design: This is a phase II (N = 200), prospective, double-blind, randomized, sham-controlled, multi-center, safety and preliminary efficacy study of intravenous (IV) tissue plasminogen activator (tPA) versus IV tPA plus transcranial laser therapy (TLT) at approximately 10 investigational sites. Patients are randomized (1:1) to receive sham TLT procedure or active TLT procedure (TLTG). The randomization is stratified by baseline National Institute of Health Stroke Scale (NIHSS) (7-9, 10-13, 14-17) and Study Site. Treatment with IV tPA must begin within 3 hours of symptom onset, and the initiation of the TLT procedure must begin no sooner than 12 hours after the initiation of tPA treatment, and no greater than 24 hours from stroke onset. To monitor for asymptomatic intracranial hemorrhages (aICH), a head CT must be negative for ICH \geq 12 hours post IV tPA bolus.

Population studied (including sample size): Patients with acute stroke, age 40 - 80, baseline NIHSS 7 - 17, who received IV tPA within 3 hours from stroke onset. The study will enroll 200 subjects.

Intervention(s): The transcranial laser therapy (TLT) is provided in a laser safe environment after all individuals, including the subject, don protective eyewear. After the subject's scalp hair is removed, and fitted with a TheraCap™, the TLT is implemented. The TheraCap™ guides personnel to twenty treatment site openings over the patients scalp. Each site is treated for two minutes. Allowing for time between each site, the total procedure time is approximately 60 minutes. The treatment is double-blind, and neither the site personnel nor the subject know whether they receive active or sham therapy.

Outcome Measure(s): The primary safety endpoint for this study is the occurrence of symptomatic intracranial hemorrhages at 36 hours from tPA initiation. The primary effectiveness endpoint for this study is the mRS score dichotomized as 0-1 versus a mRS score of 2-6 at 90 days.

Analysis: For the primary safety endpoint, the power calculations were based on a 2-sided chi-square test for detecting a difference between two proportions, assuming a Type 1 error of 0.05. With a sample size of 100 patients in each group (200 patients overall) and assuming an sICH rate of 6.4% in the sham therapy group, we have 80% power to detect a rate as low as 20.4% in the TLT treatment arm (an absolute difference in sICH

rates of 14% or higher). That is, the ICH rate could reach 20.4% before we have sufficient power to detect a significant result. For the primary effectiveness endpoint, with a sample size of 100 in each of the two groups and assuming a success rate (defined as a score of 0-1) in Day 90 mRS of 39% in the sham therapy arm (NINDS rt-PA trial), we have 80% power to detect a success rate as high as 60% (an absolute difference in good outcome rates of 21% or higher) in the active treatment group.

Trial Status: Trial recruitment commenced June 2011. After the first 20 subjects DSMB and FDA will review the data for any overt signs of safety concerns, particularly focusing on the incidence of symptomatic hemorrhage within the first 36 hours after tPA. As of November 1, 2011, three sites are open for recruitment, and two sites are in the startup phase. Five patients are enrolled. We are seeking additional study sites.

Author Disclosure Block: **J. Zivin:** None. **R. Raman:** None. **C. Fanale:** None. **S. Sen:** None. **S. Kasner:** Consultant/Advisory Board; Modest; Photothera NEST 3 Steering Committee. **A.G. Ohanian:** None. **P. Delio:** None. **K. Rapp:** Consultant/Advisory Board; Modest; ZZ Biotech. **J. Jurf:** None. **B. Meyer:** Consultant/Advisory Board; Modest; Genentech Advisory Board, The Medicines Company - Consultant. **T.M. Hemmen:** None.

Presentation Number: CT P20

Trial Abbreviation: VERITAS Study

Trial Contact Information: Linda Rose-Finnell, lfinnell@uic.edu, 312-355-2050

Trial Email: lfinnell@uic.edu

Trial Name: Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERITAS) Study

Trial Registry Number ID: NCT00590980

Trial Sponsor: NIH/NINDS

Trial Web Site: <http://veritas.neur.uic.edu>

Publishing Title: Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERITAS) Study

Author Block: **Sepideh Amin-Hanjani**, Keith Thulborn, Sean Ruland, Dilip Pandey, DeJuran Richardson, Univ of Illinois at Chicago, Chicago, IL; Gregory J. Zipfel, Washington Univ Sch of Med at St. Louis, St. Louis, MO; Mitchell S. Elkind, Columbia Univ, New York, NY; David S. Liebeskind, Univ of California at Los Angeles, Los Angeles, CA; Jeffrey Kramer, Mercy Hosp and Medical Ctr, Chicago, IL; Frank Silver, Univ of Toronto-Toronto Western Hosp, Toronto, ON, Canada; Scott E. Kasner, Univ of Pennsylvania, Philadelphia, PA; Colin Derdeyn, Washington Univ Sch of Med in St. Louis, St. Louis, MO; Philip B. Gorelick, Fady T. Charbel, Univ of Illinois at Chicago, Chicago, IL

Abstract Body:

Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERITAS) Study

Sepideh Amin-Hanjani, Keith Thulborn, Sean Ruland, Dilip Pandey, DeJuran Richardson, Gregory J. Zipfel, Mitchell S. Elkind, David S. Liebeskind, Frank Silver, Jeffrey Kramer, Scott Kasner, Colin Derdeyn, Philip B. Gorelick, Fady T. Charbel.

Background: Over one third of ischemic strokes occur in the posterior circulation, a leading cause of which is vertebrobasilar occlusive disease secondary to atherosclerosis. Symptomatic vertebrobasilar disease (VBD) carries a high annual risk of stroke, averaging 10-15% per year. Advances in endovascular angioplasty and stenting have created new treatment options, but these interventions carry significant risks, and the selection criteria for appropriate candidates remain uncertain. Determining predictors of stroke in this population is an important step toward identifying those high risk patients most suitable for consideration of intervention. Preliminary studies suggest that the risk of stroke in VBD is strongly related to the extent to which intracranial blood flow is compromised.

Objective: To test the hypothesis that among patients with symptomatic VBD, those with distal blood flow compromise, as determined by magnetic resonance (MR) blood flow imaging, are at higher risk of subsequent posterior circulation stroke than those with normal flow.

Design: VERITAS is a 5 year multicenter, prospective, observational cohort study, with a recruitment goal of 80 patients.

Population Studied: The target population is patients with symptomatic VBD. Inclusion criteria: stroke or transient ischemic attack (TIA) in the vertebrobasilar territory; $\geq 50\%$ stenosis or occlusion of extracranial or intracranial vertebral or basilar arteries; symptoms within 60 days of enrollment; ≥ 18 years of age and ability to provide informed consent. Exclusion criteria: major disabling stroke prohibiting the ability to return for follow-up assessment; limited life expectancy; known cardiac disease associated with cardioembolic risk (e.g. atrial fibrillation and prosthetic valves); blood dyscrasias; non-atherosclerotic vertebrobasilar disease (e.g. dissection); unilateral vertebral stenosis or occlusion; inability to undergo MRI or cerebral angiography.

Study Procedures: Patients will undergo blinded hemodynamic assessment with MR based imaging, consisting of quantitative MR angiography and MR perfusion, at enrollment and at 6 month intervals for at least

one year. Clinical assessments to identify recurrent ischemic events will be performed at routine intervals up to two years maximum.

Outcome Measures: The primary endpoint is fatal and nonfatal ischemic stroke in the vertebrobasilar territory.

Analysis: Analysis of the primary endpoint will consist of time-to-event comparison using the log-rank test between patients designated as 'low flow' versus 'normal flow' based upon the enrollment MR imaging.

Trial status: The study is open for enrollment at 6 sites (UIC, UCLA, Washington University, Columbia, Mercy, UHN-Toronto Western Hospital). As of October 24, 2011, 57 subjects have been enrolled.

PI/Coordinator name: Sepideh Amin-Hanjani, MD

PI/Coordinator Affiliation(s): University of Illinois at Chicago

Trial Sponsor: NIH/NINDS

Trial Contact information: Linda Finnell, MPA, CCRA; 312-355-2050; lfinnell@uic.edu

Trial Email: lfinnell@uic.edu

Trial web site: <http://veritas.neur.uic.edu>

Author Disclosure Information:

Trial Name: Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke

Trial Abbreviation: VERITAS Study

Trial Registry Number or 10: NCT00590980

PI/Coordinator Name(s): Sepideh Amin-Hanjani, MD

PI/Coord. Affiliation(s): University of Illinois at Chicago

Trial Sponsor(s): NINDS

Trial E-mail: lfinnell@uic.edu

Trial Web Site: <http://veritas.neur.uic.edu>

Trial Contact Information: Linda Rose-Finnell, lfinnell@uic.edu, 312 355-2050

Author Disclosure Block: **S. Amin-Hanjani:** Research Grant; Significant; NIH/NINDS. Other Research Support; Modest; GE Healthcare, VasSol Inc. **K. Thulborn:** Ownership Interest; Significant; Thulburn Associates, Inc. (owner). **S. Ruland:** None. **D. Pandey:** None. **D. Richardson:** None. **G. Zipfel:** Research Grant; Significant; NIH. Other Research Support; Modest; AHA, American Health Assistance Foundation, McDonald Center for Systems Neuroscience, Washington University Institute of Clinical and Translational Sciences. **M. Elkind:** None. **D. Liebeskind:** None. **J. Kramer:** None. **F. Silver:** None. **S. Kasner:** None. **C. Derdeyn:** Research Grant; Significant; NIH/NINDS. Ownership Interest; Modest; Modest, nFocus, Inc.. Consultant/Advisory Board; Modest; Pulse Therapeutics. Consultant/Advisory Board; Significant; W.L.Gore and Associates. **P. Gorelick:** Other Research Support; Significant; Lundbeck Inc. **F. Charbel:** Ownership Interest; Significant; VasSol, Inc..

Presentation Number: CT P21

Trial Abbreviation: DIAS-3 and DIAS-4

Trial Contact Information: H. Lundbeck A/S, Valby, Denmark

Trial Email: LundbeckClinicalTrials@lundbeck.com

Trial Name: Desmoteplase in Acute Ischemic Stroke

Trial Registry Number ID: NCT00790920 and NCT0085661

Trial Sponsor: H. Lundbeck A/S, Valby, Denmark

Trial Web Site: www.lundbeck-dias.com

Publishing Title: Desmoteplase 3-9 hours after Acute Ischemic Stroke: the Ongoing DIAS-3 and DIAS-4 Clinical Trials

Author Block: **Gregory W Albers**, Stanford Univ Stroke Ctr, Palo Alto, CA; Rüdiger von Kummer, Univ of Technology, Dresden, Germany; on behalf of the DIAS-3 and DIAS-4 Study Group

Abstract Body:

Desmoteplase is a novel, highly fibrin-specific thrombolytic agent in phase III of clinical development. In comparison to alteplase, it has high fibrin selectivity, no apparent neurotoxicity or negative effect on the blood-brain barrier. The safety and efficacy of desmoteplase is being studied in the DIAS Clinical Trial Program. Three studies (DEDAS, DIAS and DIAS-2) have been completed, two large randomized, double-blind, placebo-controlled, phase III trials are ongoing worldwide (DIAS-3 and DIAS-4, n=800 in total). The objective of DIAS-3 and DIAS-4 is to evaluate the safety and efficacy of a single IV bolus injection of 90 µg/kg desmoteplase given 3-9 hours after onset of ischaemic stroke (NIHSS 4-24, age 18-85 years). Patients are selected with occlusion or high-grade stenosis (TIMI 0-1) in proximal cerebral arteries, assessed by CT or MR angiography. The selection is based on the results of post-hoc analyses on data from DEDAS, DIAS and DIAS-2 showing that desmoteplase was clinically beneficial in patients presenting with TIMI 0-1 at baseline. The primary efficacy outcome is the modified Ranking Scale score at Day 90. Other outcomes include NIHSS score at Day 90, recanalization in patients with follow-up angiography, clinical outcome in patients with core-lesion <25 mL, and clinical outcome in patients with perfusion/diffusion mismatch. Safety outcomes comprise mortality, symptomatic intracranial hemorrhage, symptomatic ischemic edema, and other major hemorrhagic events.

An independent data review by the Data Monitoring Committee (DMC) in October 2011, revealed no safety issues. The DMC encouraged investigators in both trials to continue to enroll suitable patients.

In the USA, to support patient recruitment and retention, a DIAS trial network (hub-spoke model) has been implemented that consists of both tertiary and community-based acute stroke centers managed by regional hub directors.

Desmoteplase is the only thrombolytic agent in late stage development for acute ischemic stroke, despite the fact that there is a high unmet need. Therefore, the results of the DIAS clinical trial program will be important for physicians and patients in need of a safe and effective treatment in a time-window of up to 9 hours.

Author Disclosure Block: **G.W. Albers:** Honoraria; Modest; H. Lundbeck A/S; Boehringer Ingelheim. **R. von Kummer:** Honoraria; Modest; H. Lundbeck A/S.

Presentation Number: CT P22

Trial Abbreviation: ARTSS-2

Trial Contact Information: Loren Shen 713.500.7084 loren.shen@uth.tmc.edu

Trial Email: loren.shen@uth.tmc.edu

Trial Name: ARTSS-2: A pilot, phase IIb, randomized, multi-center trial of Argatroban in combination with recombinant tissue plasminogen activator for acute stroke.

Trial Registry Number ID: NCT01464788

Trial Sponsor: NIH; The University of Texas Health Science Center, Houston

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT01464788?term=argatroban&rank=7>

Publishing Title: ARTSS-2: A Pilot, Phase IIb, Randomized, Multi-center Trial Of Argatroban In Combination With Recombinant Tissue Plasminogen Activator For Acute Stroke

Author Block: Andrew D. Barreto, UNIV OF TEXAS-HOUSTON, Houston, TX; Andrei V Alexandrov, Univ of Alabama-Birmingham, Birmingham, AL; Loren Shen, Tiffany C Roper, UNIV OF TEXAS-HOUSTON, Houston, TX; April Sisson, Univ of Alabama-Birmingham, Birmingham, AL; Yazan Alderazi, UNIV OF TEXAS-HOUSTON, Houston, TX; Clotilde Balucani, Steven R. Levine, SUNY Downstate, Brooklyn, NY; Claudia Pedroza, Mohammad H. Rahbar, James C. Grotta, UNIV OF TEXAS-HOUSTON, Houston, TX

Abstract Body:

Background: Recombinant tissue plasminogen activator (rt-PA), the only **proven treatment for acute ischemic stroke, fails to reperfuse brain in most patients with large thrombi. In our Phase IIa low-dose safety study (n=65), the two drugs appear safe when delivered concomitantly and recanalization rates were greater than with historical controls. This study will provide evidence-based hypotheses and data needed to design a larger definitive trial.**

Study Purposes: Primary Objective: To estimate overall treatment benefit (improvement in disability) among stroke patients treated with rt-PA who are randomized to also receive either low-dose Argatroban, high-dose Argatroban or neither. **Secondary Objectives:** 1) To help verify the safety (as measured by incidence of intracranial hemorrhage) of low-dose combination Argatroban and rt-PA and test the safety of high-dose combination treatment; 2) To assess rates of early recanalization for use in assessing mechanisms of treatment effect and in predicting outcome of the drug combination.

Study Population: 105 total ischemic stroke patients all treated with rt-PA (0-3 hour or 0-4.5 hour according to each site's local standard); age ≥ 18 years; proximal (intracranial) artery occlusion as imaged by either transcranial Doppler ultrasound (TCD) or CT-angiogram (CTA), or clinically suspected occlusion with NIHSS ≥ 10 .

Treatment: Three treatment arms (n=35 each) will be enrolled:

- 1) Low-dose Argatroban* (1.0 μ g/kg/min continuous infusion of Argatroban, preceded by a 100 μ g/kg bolus administered over 3-5 minutes Infusion will be titrated to achieve an aPTT of 1.75 times baseline - not to exceed 10 μ g/kg/min) + usual care IV-rt-PA;
- 2) High-dose Argatroban* 3.0 μ g/kg/min continuous infusion of Argatroban, preceded by a 100 μ g/kg bolus administered over 3-5 minutes Infusion will be titrated to achieve an aPTT of 2.25 times baseline - not to exceed 10 μ g/kg/min) + usual care IV-rt-PA;
- 3) Intravenous-rt-PA alone (usual care). *Argatroban infusions will continue for a maximum of 48 hours.

Primary Outcome: Excellent functional outcome as measured by the percentage of patients with a 0 or 1 on the

modified Rankin Scale (mRS) at day 90 as assessed by study personnel blinded to treatment.

Secondary Outcomes:

- 1) Safety as measured by the incidence of:
 - a) Symptomatic intracranial hemorrhage (sICH);
 - b) Parenchymal Hemorrhage 2 (PH-2);
 - c) Major systemic hemorrhage.
- 2) Rates and completeness of arterial recanalization assessed at baseline and 2-3 hours by Transcranial Doppler ultrasound (TCD) or CT-Angiogram (CTA).
- 3) Neurological deficits improvement from baseline to 2 hours, 24 hours, end of Argatroban infusion, Day 7/discharge and day 90 as measured by NIHSS.
- 4) Quality of Life - obtained by standard gamble, time-trade-off method and visual analogue scale (VAS).
- 5) Cost and cost-effectiveness analysis

Significance:

Data generated will be used to:

- 1) Compare with Phase IIa study safety and recanalization results.
- 2) Design a Phase 3 efficacy study of 1 or 2 doses of Argatroban + rt-PA compared to usual care (rt-PA alone).

Author Disclosure Block: **A.D. Barreto:** None. **A.V. Alexandrov:** None. **L. Shen:** None. **T.C. Roper:** None. **A. Sisson:** None. **Y. Alderazi:** None. **C. Balucani:** None. **S.R. Levine:** None. **C. Pedroza:** None. **M.H. Rahbar:** None. **J.C. Grotta:** None.

Presentation Number: CT P23

Trial Abbreviation: STICH II

Trial Contact Information: Dr B A Gregson, stich@ncl.ac.uk, Fax:+44 191 222 5762, Tel: +44 191 222 5761

Trial Email: stich@ncl.ac.uk

Trial Name: Surgical Trial in Lobar Intracerebral Haemorrhage

Trial Registry Number ID: ISRCTN22153967

Trial Sponsor: newcastle upon Tyne Hospitals NHS Foundation Trust

Trial Web Site: www.research.ncl.ac.uk/stich

Publishing Title: Surgical Trial in Lobar Intracerebral Haemorrhage

Author Block: Barbara Gregson, **A David Mendelow**, Newcastle Univ, Newcastle Upon Tyne, United Kingdom; STICH II Investigators

Abstract Body:

Background

Spontaneous superficial intracerebral haemorrhage (ICH) accounts for 20% of all stroke-related sudden neurological deficits and has the highest morbidity and mortality of all strokes. The role of surgery remains controversial following the report of the international STICH trial which was neutral. Further analyses and meta-analysis have suggested that patients with lobar haemorrhage may benefit from early surgery.

Objective

STICH II aims to establish whether a policy of earlier surgical evacuation of haematomas in selected patients with spontaneous lobar ICH will improve outcome compared to a policy of initial conservative treatment.

Design

STICH II is an international multicentre randomised parallel group trial.

Population

Patients for whom the treating neurosurgeon is in equipoise about the benefits and risks of early craniotomy are eligible for the trial. Inclusion criteria include superficial, spontaneous lobar ICH on CT scan, best motor score on the Glasgow Coma Score (GCS) of 5 or 6 and best eye score on the GCS of 2 or more, and volume of haematoma between 10 and 100m. Patients are ineligible if the haemorrhage is due to an aneurysm or angiographically proven arteriovenous malformation, is secondary to tumour or trauma or extends into the basal ganglia, thalamic, cerebellar or brain stem. Patients are also ineligible if there is any Intraventricular haemorrhage or hydrocephalus or if there is severe, pre-existing physical or mental disability or severe co-morbidity which might interfere with assessment of outcome.

Six hundred patients will be recruited to the trial.

Intervention

The trial intervention is early evacuation of the haematoma, by craniotomy, within 12 hours of randomisation combined with appropriate best medical treatment versus best medical treatment, combined with delayed evacuation only if it becomes necessary later.

Outcome measures

Outcome is measured at six months via a structured postal questionnaire including the Glasgow Outcome scale, Modified Rankin Scale and EuroQol.

Analysis

Analysis will be on an "intention to treat" basis. The primary analysis will be a simple categorical frequency comparison using the chi-squared test for prognosis based favourable and unfavourable outcome at six months.

Trial status

The STICH II trial is funded by the UK MRC and NIHR EME and sponsored by Newcastle upon Tyne Hospitals NHS Trust. (ISRCTN22153967) Patient recruitment is ongoing. At 31 October 119 centres from 38 countries had been recruited and 496 patients recruited from 68 of those centres. Current details at 31 December 2011 of recruiting centres and recruited patients will be presented.

Author Disclosure Block: **B. Gregson:** Employment; Significant; NIHR - MRC and HTA. Research Grant; Significant; NIHR-HTA and MRC. **A.D. Mendelow:** Research Grant; Significant; NIHR-HTA and MRC. Other; Modest; Codman, NovoNordisk, Newcastle Neurosurgical Foundation.

Presentation Number: CT P24

Trial Abbreviation: TARDIS

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Trial Email: tardis@nottingham.ac.uk

Trial Name: Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke

Trial Registry Number ID: ISRCTN47823388

Trial Sponsor: University of Nottingham, United Kingdom

Trial Web Site: www.tardistrial.org

Publishing Title: Triple Antiplatelets For Reducing Dependency After Ischaemic Stroke (tardis). Safety And Tolerability Of Intensive Antiplatelet Therapy With Combined Aspirin And Clopidogrel In High Risk Patients With Recent Ischaemic Stroke: A Randomised Controlled Trial

Author Block: Sandeep Ankolekar, Margaret J Adrian, **Philip M Bath**, Univ of Nottingham, Nottingham, United Kingdom

Abstract Body:

Rationale: The risk of recurrence is greatest immediately after stroke or TIA. Existing prevention strategies (antithrombotic, lipid/blood pressure lowering, endarterectomy) reduce, not abolish, further events. Dual antiplatelet therapy - aspirin & clopidogrel (AC) for ischaemic heart disease, aspirin & dipyridamole (AD) for stroke, is superior to aspirin monotherapy. We hypothesise that triple antiplatelet therapy (ACD) will be superior to current guideline therapy (AD or C) in patients at high-risk of recurrence, providing bleeding does not become excessive.

Design: TARDIS is a multicentre, parallel-group, prospective, randomised, open-label, blinded-endpoint, controlled trial. In the start-up phase, we will assess over 3 years the safety, tolerability and feasibility of intensive antiplatelet therapy (ACD) versus guideline therapy (AD or C) given for 1 month in up to 750 patients with acute stroke/TIA. The main phase will then assess the safety and efficacy of intensive therapy in up to 3,500 patients. The primary outcome is ordinal stroke severity(fatal/severe non-fatal/mild/TIA/none) at 90 days. Secondary outcomes include death, myocardial infarction (MI), vascular events, function, bleeding, serious adverse events; sub-studies will assess cerebral emboli and platelet function.

Trial status: The trial started in April 2009. As of 27 October 2011, 573 patients have been recruited from 55 centres within the UK Stroke Research Network.

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Author Disclosure Block: S. Ankolekar: None. M.J. Adrian: None. P.M.W. Bath: None.

Presentation Number: CT P25

Trial Abbreviation: Stroke tDCS

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Trial Name: Enhancement of Rehabilitative Treatment-Dependent Functional Recovery After

Trial Registry Number ID: NCT00085657

Trial Sponsor: NIH/NICHHD/NINDS

Trial Web Site:

<http://www8.utsouthwestern.edu/patientcare/dallas/clinicaltrials/medical/advertisement.html?formId=58382>

Publishing Title: Transcranial Direct Current Stimulation (tDCS) Enhanced Stroke Recovery and Cortical Reorganization

Author Block: Timea M Hodics, UNIVERSITY OF TEXAS SOUTHWESTERN, Dallas, TX; Alexander W Dromerick, Natl Rehabilitation Hosp, Washington, DC; John C Pezzullo, Georgetown Univ, Washington, DC; Benjamin Xu, Natl Insts of Health,, Bethesda, MD; Joseph Hidler, Natl Rehabilitation Hosp, Washington, DC; John Hart, Karen Kowalske, Bhim Upreti, Arun Alex, UNIVERSITY OF TEXAS SOUTHWESTERN, Dallas, TX; Leonardo G Cohen, Natl Insts of Health, Bethesda, MD

Abstract Body:

Trial Abbreviation: Stroke tDCS

Trial Registry Number or ID: NCT00085657

Background:

There is no accepted strategy to enhance the effects of motor training on functional recovery after stroke, the most common cause of adult long-term disability. There is emerging evidence that suggests that novel noninvasive intervention, tDCS enhances aspects of cortical plasticity and motor behavior in healthy volunteers and chronic stroke patients. It is desirable to develop strategies to enhance the effectiveness of rehabilitative therapy on motor recovery particularly in the early phase after stroke, as the speed of recovery is fastest at this early stage.

Objectives:

1. To determine whether tDCS application will improve motor recovery of the upper extremity after stroke beyond what is achievable with standard rehabilitative treatment (SRT) alone.
2. To collect preliminary data on the neural substrates underlying recovery of motor function after SRT alone (sham condition) and with additional brain stimulation. (tDCS condition)

Design:

We are enrolling patients from University of Texas Southwestern Medical Center (UTSW) who had a single ischemic stroke and have moderate to severe hand weakness but are able to activate their wrist flexors are included within 5-15 days of the stroke onset. We added a separate subgroup of patients with no hand movement. Eligible patients are randomized in one of the two study arms: SRT + tDCS or in SRT + sham stimulation. Patients receive 20 minutes of tDCS or sham of the affected motor cortex simultaneously with SRT Monday-Friday for a total of ten sessions. Outcome measures are collected at discharge, 3months and at 12 months.

We perform functional MRI in volunteers and in a subgroup of patients before and after the stimulation and follow-up and TMS studies.

Population Studied:

We will consent 160 eligible subjects aged 18-80 years old.

Intervention:

tDCS is a noninvasive form of cortical stimulation that uses a battery-powered device. Weak current (1mA) is delivered for 20 minutes through surface electrodes which are positioned above the motor cortical representational field of the affected hand (anodal stimulation) and over the contralesional forehead.

Outcome Measures:

The upper extremity component of Fugl-Meyer test (uFM), the Wolf Motor Function Test (WMFT), Jebsen-Taylor Test (JTT), Motor Activity log (Uswatte, Taub et al. 2005), Medical Research Council Scale (MRC), Modified Ashworth-Spasticity scale (ASS), Abilhand scale (AHS), Barthel Index (BI), NIH stroke scale (NIHSS).

Analysis:

Two way analysis of variance (ANOVA) involving two factors: treatment group (tDCS or Sham) and stratum (uFM over or less than 30).

Trial Status: Total 35 subjects have been enrolled so far. (24 acute stroke patients and 11 volunteers for the imaging component of the study)

PI/Coordinator Name(s): Timea Hodics/Bhim Upreti

PI/Coord. Affiliation(s): University of Texas Southwestern

Trial Sponsor(s): NIH/NICHHD/NINDS

Trial Contact Information(name,e-mail,web, fax and/or phone): Timea

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Trial Web Site:

<http://www8.utsouthwestern.edu/patientcare/dallas/clinicaltrials/medical/advertisement.html?formId=58382>

Author Disclosure Block: **T.M. Hodics:** Research Grant; Significant; NIH/NICHHD K23 grant #5K23HD050267, S,B;. **A.W. Dromerick:** None. **J.C. Pezzullo:** None. **B. Xu:** None. **J. Hidler:** None. **J. Hart:** None. **K. Kowalske:** None. **B. Upreti:** Employment; Significant; NIH/NICHHD K23 grant #5K23HD050267, S,A. **A. Alex:** Employment; Modest; NIH/NICHHD K23 grant #5K23HD050267, S,A. **L.G. Cohen:** None.

Presentation Number: CT P26

Trial Abbreviation: SUSTAIN (Systematic Use of STroke Averting INterventions)

Trial Contact Information: Project Manager: Monica Ayala-Rivera, mayala@labiomed.org, Phone: (877) 715-9791

Trial Email: mayala@labiomed.org

Trial Name: Randomized Controlled Trial of an Intervention to Enable Stroke Survivors Throughout the Los Angeles County Safety Net to

Trial Registry Number ID: NCT00861081

Trial Sponsor: American Heart Association

Trial Web Site: <http://clinicaltrials.gov/ct2/show/study/NCT00861081?term=NCT00861081&rank=1>

Publishing Title: Randomized, Controlled Trial of an Intervention to Enable Stroke Survivors Throughout the Los Angeles County Safety Net to "Stay With the Guidelines

Author Block: Eric M. Cheng, William Cunningham, David Geffen Sch of Med, Univ of California, Los Angeles, Los Angeles, CA; Amytis Towfighi, Rancho Los Amigos Rehabilitation Ctr, Downey, CA; Nerses Sanossian, Univ of Southern California, Los Angeles, CA; Robert J. Bryg, Olive View-UCLA Medical Ctr, Sylmar, CA; Tom L. Anderson, Harbor-UCLA Medical Ctr, Torrance, CA; Jeff J. Guterman, David Geffen Sch of Med, Univ of California, Los Angeles, Los Angeles, CA; Sandra G. Gross-Schulman, Los Angeles County Dept of Health Services, Olive View-UCLA Medical Ctr, Sylmar, CA; Sylvia Beanes, American Heart Association, Los Angeles, CA; Andrea S. Jones, Healthy African American Families, Los Angeles, CA; Honghu H. Liu, Susan L. Ettner, Jeffrey L. Saver, Barbara G. Vickrey, David Geffen Sch of Med, Univ of California, Los Angeles, Los Angeles, CA

Abstract Body:

Trial Abbreviation:

SUSTAIN (Systematic Use of STroke Averting INterventions)

Registry Trial Number: NCT00861081

Background:

Better control of risk factors, especially hypertension, could substantially decrease the incidence of stroke. Effective stroke prevention care is lacking, especially among minority populations.

Objective:

To determine whether a chronic care model-based care intervention called SUSTAIN (Systematic Use of Stroke Averting Interventions) reduces the risk of stroke in a county system serving a predominantly minority population, and if so, at what cost.

Design:

Randomized-controlled trial.

Population Studied:

Patients who have developed a new ischemic stroke or TIA within the past 6 months and possess a systolic blood pressure greater than 120 mm Hg. An inclusion criteria is that subjects expect to obtain health care within the Los Angeles county health care system in the following year.

Interventions:

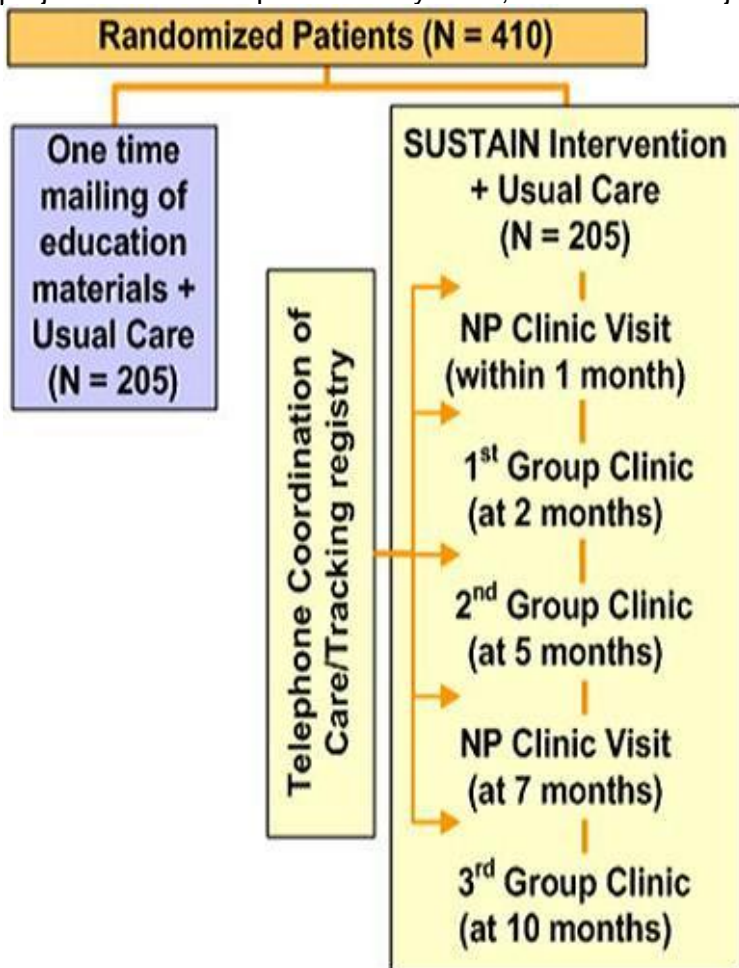
Subjects randomized to the intervention arm will be managed by a care manager - nurse practitioner or physician assistant - following protocols jointly developed by the research team, physicians working in the county system, and directors of community resource programs (see Figure). Subjects are scheduled for three group clinics and two individual clinics. Subjects also receive telephone calls between face-to-face visits to further coordinate their care. Subjects are trained to use self-management tools, including report cards and home blood pressure monitors. The care managers use database systems that provide decision support and

track tasks for each subject. The care managers have clinical privileges to adjust medications relevant to risk factor control. Subjects randomized to the control arm receive a pamphlet on controlling stroke risk factors. Outcomes Measurements: The primary outcome is control of systolic blood pressure. Secondary outcomes include control of other risk factors, stroke knowledge, and adoption of healthy lifestyle habits and medication adherence.

Analysis:

An intention-to-treat analysis will be used to determine whether persons randomized to the intervention arm achieve better outcomes than persons randomized to the control arm at 12 months after randomization. Further analyses will determine whether variables such as socioeconomic status, stroke severity, medication adherence are predictive of outcomes. In order to perform a cost analysis, direct costs will be calculated with the start-up costs and maintenance costs, including clinic room charges, materials, telephone costs, and intervention care management. Utilization costs will also be calculated using a query of county administrative database.

Trial Status: The study has enrolled more than half of its anticipated target enrollment of 410. Enrollment is projected to be completed in July 2012, and the last subject is projected to exit the study in July 2013.



Author Disclosure Block: E.M. Cheng: None. W. Cunningham: None. A. Towfighi: None. N. Sanossian: None. R.J. Bryg: None. T.L. Anderson: None. J.J. Guterman: None. S.G. Gross-Schulman: None. S. Beanes: None. A.S. Jones: None. H.H. Liu: None. S.L. Ettner: None. J.L. Saver: None. B.G. Vickrey: None.

Presentation Number: CT P27

Trial Abbreviation: J-STARS

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Trial Email: jstars-office@umin.ac.jp

Trial Name: Japan Statin Treatment Against Recurrent Stroke

Trial Registry Number ID: NCT00221104

Trial Sponsor: Translational Research Informatics Center, Kobe, Hyogo, Japan; The Japanese Ministry of Health, Labour and Welfare

Trial Web Site: <http://jstars.umin.ne.jp>

Publishing Title: Present Status of J-STARS and Substudies

Author Block: Masayasu Matsumoto, Takemori Yamawaki, Toshiho Ohtsuki, Naohisa Hosomi, Hiroshima Univ Grad Sch Biomed Sci, Hiroshima, Japan; Masanori Fukushima, Yoji Nagai, Translational Res Informatics Ctr, Kobe, Japan; Kazuo Minematsu, Chiaki Yokota, Natl Cerebral and Cardiovascular Ctr, Osaka, Japan; Hideki Origasa, Dept of Biostatistics and Clinical Epidemiology, Univ of Toyama Graduate Sch of Med and Pharmaceutical Sciences, Toyama, Japan; Shinichiro Uchiyama, Dept of Neurology, Neurological Inst, Tokyo Women's Medical Univ Sch of Med, Tokyo, Japan; Setsuro Ibayashi, Dept of Med and Clinical Science, Graduate Sch of Medical Sciences, Kyushu Univ, Fukuoka, Japan

Abstract Body:

Background: In Japan, it is still unclear if hyperlipidemia is a risk factor of recurrent stroke or not in the ischemic stroke patients, though inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase could decrease the incidence of coronary heart disease and first occurrence of stroke in Japanese patients with hypercholesterolaemia (MEGA study). The neuroprotective mechanism beyond cholesterol-lowering effects could be expected to attenuate cerebrovascular inflammation and atherosclerosis.

Objective: This study hypothesizes if the treatment with a low-dose pravastatin (10mg/ day) prevents recurrent stroke in Japanese patients with ischemic stroke with safety.

Design: J-STARS is a multicenter, prospective, randomized, open label, blinded-endpoint, active controlled, parallel group trial.

Population studied: Eligibility includes, 1) ischemic stroke from 1 month to 3 years after the onset, except for cardiogenic embolism, 2) 45-80 years old, and 3) total cholesterol level of 180-240mg/dl without the prescription of statin. Exclusion criteria includes, 1) ischemic stroke of other determined cause according to the TOAST classification, 2) ischemic heart disease necessary to require statin, and 3) hemorrhagic disorders.

Interventions: Patients will be randomized into the group receiving pravastatin 10mg/day or that having no statin.

Outcome Measures: The primary outcome for this study is cerebrovascular events. The secondary outcomes include the events of ischemic stroke (subtype analysis according to the TOAST classification) or hemorrhagic stroke, cardiovascular events including myocardial infarction, all the cerebrovascular and cardiovascular events, death of stroke, vascular events, and all causes, hospital admission, activity of daily living, modified Rankin Scale, dementia and cognitive impairment.

Statistical Analysis: We are scheduled to conduct an interim analysis in 2011. Based on the results, the independent data monitoring committee will recommend continuation or discontinuation of this study. The final analysis will be performed by employing Kaplan-Meier survival method, log-rank test and Cox proportional hazard model.

Trial Status: A total of 1578 patients were recruited from 123 centers by 2009, and have been in the process of the mean duration of follow-up for 3.9 years. Mean age 66.2 years; 25.4% atherothrombotic infarction, 64.2% lacunar infarction. We have 10 participating centers in disaster area of Tohoku Earthquake. They are continuing follow-up of the patients. We deeply appreciate your supporting us. The latest status including substudies will be presented at the conference.

Author Disclosure Block: **M. Matsumoto:** None. **T. Yamawaki:** None. **T. Ohtsuki:** None. **N. Hosomi:** None. **M. Fukushima:** None. **Y. Nagai:** None. **K. Minematsu:** None. **C. Yokota:** None. **H. Origasa:** None. **S. Uchiyama:** None. **S. Ibayashi:** None.

Presentation Number: CT P28

Trial Abbreviation: ICTuS2/3

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Trial Email: jjurf@ucsd.edu

Trial Name: The Intravascular Cooling in the Treatment of Stroke 2/3 Trial

Trial Registry Number ID: NCT01123161

Trial Sponsor: NINDS SPOTRIAS 3P50NS044227 and 5P50NS044148

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT01123161>

Publishing Title: Phase 2/3 Study of Intravenous Thrombolysis and Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS 2/3)

Author Block: **Thomas M Hemmen**, Karen S Rapp, Rema Raman, UCSD MEDICAL CENTER, San Diego, CA; Mauricio Concha, Sarasota Memorial Hosp, Sarasota, FL; Gregor Brössner, Univ Hosp Innsbruck, Innsbruck, Austria; Gilda Tafreshi, Scripps Mercy Hosp, San Diego, CA; Vivek Misra, Univ of Texas, Houston, TX; Salvador Cruz-Flores, St Louis Univ, St Louis, MO; Rainer Kollmar, Univ of Erlangen, Erlangen, Germany; David Brown, Hoag Hosp, Newport Beach, CA; Irfan Altafullah, North Memorial Hosp, Robbinsdale, MN; Patrik Michel, Univ of Lausanne, Lausanne, Switzerland; Sven Poli, Univ of Heidelberg, Heidelberg, Germany; Fen-Lei Chang, Parkview Hosp, Fort Wayne, IN; Andrei V Alexandrov, Univ of Alabama, Birmingham, AL; Carlos Smith, St. Joseph Hosp, Tampa, FL; Julie Jurf, UCSD MEDICAL CENTER, San Diego, CA; Mary Jane Hess, James C Grotta, Univ of Texas, Houston, TX; Patrick D Lyden, Cedars Sinai Medical Ctr, Los Angeles, CA

Abstract Body:

Introduction: The purpose of this study is to determine whether the combination of thrombolysis and hypothermia is superior to thrombolysis alone for the treatment of acute ischemic stroke. The study will be conducted in two stages: a Phase 2 study to assess the safety of various protocol changes, to demonstrate sufficient recruitment, and to allow an interim analysis for futility; a Phase 3 efficacy study will follow if pre-specified milestones are achieved.

Methods: This is a prospective, randomized, single-blind, multi-center Phase 2/3 study. We aim to include 1600 ischemic stroke patients (400 in phase 2, 1200 in phase 3) treated within 3 hours of symptom onset with IV tPA (according to FDA or EMEA protocol), NIHSS ≥ 7 and ≤ 20 , age 22-80. Patients are randomly assigned to either hypothermia permissively targeted to 33°C or normothermia. Favorable outcome is defined as a 90-day Modified Rankin score (mRS) of 0 or 1. Secondary outcome measures are: 90-day NIHSS, Barthel Index (BI), mortality, shift analysis of the mRS, global odds ratio of mRS, BI, NIHSS, incidence of symptomatic intracranial hemorrhage and 90-day Montreal Cognitive Assessment. An interim analysis for futility is planned after phase 2 and includes frequency of target temperature reached within 6 hours from symptom, pneumonia rate, safety profile of iced saline infusion and study-wide average enrollment of at least 0.4 patients/site/month.

Status: The study team initiated 11 study sites in the US and 2 in Europe. Enrolment began December 2010. Currently, 21 subjects are enrolled. A safety review after the first 50 patients is expected in early 2012.

Author Disclosure Block: **T.M. Hemmen:** None. **K.S. Rapp:** None. **R. Raman:** None. **M. Concha:** None. **G. Brössner:** None. **G. Tafreshi:** None. **V. Misra:** None. **S. Cruz-Flores:** None. **R. Kollmar:** None. **D. Brown:** None. **I. Altafullah:** None. **P. Michel:** Research Grant; Modest; Swiss Cardiology Foundation, Lundbeck, Paion. Consultant/Advisory Board; Modest; Servier, Piaon. **S. Poli:** None. **F. Chang:** None. **A.V. Alexandrov:** Consultant/Advisory Board; Modest; Genentech, Inc.. **C. Smith:** None. **J. Jurf:** None. **M. Hess:** None. **J.C. Grotta:** None. **P.D. Lyden:** None.

Presentation Number: CT P29

Trial Abbreviation: AMORE

Trial Contact Information: Satoshi Kuroda, skuroda@med.hokudai.ac.jp, +81-708-7737, +81-706-5987

Trial Email: skuroda@med.hokudai.ac.jp

Trial Name: Asymptomatic Moyamoya Disease

Trial Registry Number ID: UMIN000006640

Trial Sponsor: Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan

Trial Web Site: <http://www.neurosurgery-hokudai.jp/>

Publishing Title: Asymptomatic Moyamoya Registry (AMORE) Study - A Nation-wide, Multicenter Prospective Survey on Prognosis of Asymptomatic Moyamoya Disease in Japan

Author Block: Satoshi Kuroda, Hokkaido Univ Hosp, Sapporo, Japan; AMORE Study Group

Abstract Body:

Background and Purpose - Recent development of a non-invasive MR examination has increased the opportunity to identify asymptomatic patients with moyamoya disease who have experienced no stroke episodes. Previously, we carried the first multi-center study on asymptomatic moyamoya disease in Japan. As the results, totally 40 patients were enrolled and their annual risk for any stroke was 3.2% (Stroke 38:1430-1435, 2007). However, their clinical features, prognosis, and treatment strategy are still unclear because of small number of subjects and short follow-up periods. Therefore, we have designed Asymptomatic Moyamoya Registry (AMORE) Study in Japan. The objectives of this nation-wide, multi-center prospective study are to clarify long-term prognosis of asymptomatic patients with moyamoya disease and to determine the risk factors to cause ischemic and hemorrhagic stroke in them.

Study Design - AMORE Study is conducted in Japan, using a multicenter prospective observational design. The AMORE Study Group is composed of 16 Japanese neurosurgery/neurology centers. In this study, all consecutive patients diagnosed as asymptomatic moyamoya disease between January 2012 and December 2014 are registered. Inclusion criteria is as follow: Thus, all patients must (a) be between 20 and 70 years at initial diagnosis; (b) fulfill the guidelines for the diagnosis criteria of the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan; (c) experience no ischemic or hemorrhagic cerebrovascular events since they were born; and (d) be independent in daily life (modified Rankin scale 0~1). In addition to MRI/MRA, cerebral blood flow and its reactivity to acetazolamide must be quantitatively measured. After informed consent is obtained, their clinical and radiological data are registered. Subsequently, they are followed up at outpatient clinic for five years after enrollment. MR imaging and angiography are repeated every year during follow-up period. The following items constitute the primary endpoint: TIA with cerebral infarct, ischemic stroke or hemorrhagic stroke. The following items constitute the secondary endpoint: TIA, radiological occurrence of silent cerebral infarction, silent intracranial bleeding, or silent disease progression or all death.

Conclusion - In this conference, we emphasize the importance to determine the prognosis of asymptomatic moyamoya disease, and also present the precise protocol of AMORE Study.

Author Disclosure Block: S. Kuroda: None.

Presentation Number: CT P30

Trial Abbreviation: ENCHANTED

Trial Contact Information: Professor Craig Anderson, canderson@georgeinstitute.org.au

Trial Email: in preparation

Trial Name: The Enhanced Control of Hypertension AND Thrombolysis stroke Study (ENCHANTED): evaluation of low-dose rtPA and early intensive blood pressure lowering in acute ischaemic stroke

Trial Registry Number ID: ENCHANTED

Trial Sponsor: Investigator initiated

Trial Web Site: in preparation

Publishing Title: The Enhanced Control of Hypertension AND Thrombolysis stroke Study (ENCHANTED): Evaluation Of Low-dose intravenous tissue plasminogen activator (tPA) And Early Intensive Blood Pressure Lowering In Acute Ischaemic Stroke

Author Block: Vijay K Sharma, Natl Univ Hosp, Singapore, Singapore; Yining Huang, Peking Univ First Hosp, Beijing, China; Sully Fuentes, The George Inst for Global Health, Royal Prince Alfred Hosp and Univ of Sydney, Sydney, Australia; Nguyen H Thang, 115 Hosp, Ho Chi Minh city, Viet Nam; Jeyaraj Pandian, Christian Medical Coll, Ludhiana, India; Richard Lindley, The George Inst for Global Health, Royal Prince Alfred Hosp and Univ of Sydney, Sydney, Australia; Christian Stapf, Lariboisière Hosp, Paris, France; Hisatomi Arima, The George Inst for Global Health, Royal Prince Alfred Hosp and Univ of Sydney, Sydney, Australia; Mark Parsons, Chris Levi, John Hunter Hosp, Univ of Newcastle, Newcastle, Australia; John Chalmers, Craig Anderson, The George Inst for Global Health, Royal Prince Alfred Hosp and Univ of Sydney, Sydney, Australia; for the ENCHANTED Investigators

Abstract Body:

Background: Controversy exists over the optimal dose (0.6 vs 0.9 mg/kg) of intravenous tissue plasminogen activator (IV-tPA) and control of elevated blood pressure (BP) in acute ischaemic stroke. Asian studies suggest low dose IV-tPA is efficacious, while elevated BP (>140-150 mmHg systolic) 'before' and 'after' tPA predicts poor outcomes.

Aims: ENCHANTED will assess in IV-tPA-eligible patients whether: (i) 0.6 mg/kg tPA provides equivalent benefits and lower risk of major intracerebral hemorrhage (ICH) to 0.9 mg/kg tPA; and (ii) early intensive BP lowering (target systolic 140-150 mmHg) provides superior benefits and lower ICH risk to the current BP guideline recommendations (systolic <180-185 mmHg).

Methods: An independent, quasi-factorial, active-comparative, prospective, randomised, open blinded endpoint (PROBE), clinical trial evaluating [a] 'IV-tPA dose' and/or [b] 'BP control', using central internet randomisation of patients fulfilling local criteria for tPA and uncertainty over the study treatments. Following a launch in late 2011, the study will expand across a global network (100+ sites) to achieve the required sample size of 5000 (3300 per treatment arm) to provide >90% power to detect non-inferiority of low-dose IV-tPA and superiority of intensive BP lowering. The study is funded by the Australian government (NHMRC project grant 1020462).

Conclusions: Low-dose IV-tPA and early intensive BP lowering could provide more affordable and safer treatments in the management of ischaemic stroke worldwide.

Author Disclosure Block: V.K. Sharma: None. Y. Huang: None. S. Fuentes: None. N.H. Thang: None. J. Pandian: None. R. Lindley: None. C. Stapf: None. H. Arima: None. M. Parsons: None. C. Levi: None. J. Chalmers: None. C. Anderson: Research Grant; Significant; Received financial grant for the trial from Australian Govt. (NHMRC project grant 1020462).

Presentation Number: CT P31

Trial Abbreviation: WASSABI

Trial Contact Information: Tareq Kass-Hout, MD. email address: kasshouttareq@gmail.com, Phone number: (716) 887-5548, Fax number: (716) 887-5409

Trial Email: kasshouttareq@gmail.com

Trial Name: Wake Up Symptomatic Stroke in Acute Brain Ischemia

Trial Registry Number ID: NCT01455935

Trial Sponsor: Genentech

Trial Web Site: <http://clinicaltrials.gov/ct2/show/NCT01455935>

Publishing Title: Wake Up Symptomatic Stroke in Acute Brain Ischemia (WASSABI)

Author Block: Tareq Kass-Hout, Omar Kass-Hout, Maxim Mokin, Emad Nourollahzadeh, Robert Sawyer, Adnan Siddiqui, Kenneth Snyder, Elad Levy, SUNY at Buffalo, Buffalo, NY

Abstract Body:

TRIAL TITLE: Wake Up Symptomatic Stroke in Acute Brain Ischemia

TRIAL ABBREVIATION: WASSABI

TRIAL REGISTRY NUMBER: NCT01455935

BACKGROUND: Acute stroke is the fourth leading cause of mortality and a major cause of long-term disability in the developed world. Approximately 25% of ischemic stroke patients awaken with stroke symptoms, this subset of patients are ineligible to thrombolysis therapy simply because the time of onset is not known. Perfusion studies may help to identify patients with preserved salvageable tissue that might benefit from acute intervention therapy.

OBJECTIVE: To study the safety and effectiveness of using CT Perfusion studies as an indicator to treat stroke patients with unknown time of onset.

METHODS: Single center, randomized, single blinded and prospective study to compare between medical therapy and interventions in patients with wake up stroke. Ninety patients 18-80 years of age presenting with wake up ischemic stroke and considerable salvageable tissue on perfusion studies (defined as Time To Peak (TTP) > 8 Sec and volume loss < 20% of the size of the penumbra) and a National Institutes of Health Stroke Scale (NIHSS) of 8-22 will be considered for enrollment. Patients will be randomized into one of three prospective groups; Best medical therapy (standard of care with anti-platelets vs. anticoagulation and statins), intravenous thrombolysis (IV t-PA with a total dose of 0.9 mg/kg) or intra-arterial intervention (IA t-PA and/or MERCI device and/or PENUMBRA device). The primary end point (mRs-90 days) will be compared among the different subgroups, initially using Analysis of Variance (ANOVA) using SAS v 9.1. If the ANOVA analysis provides us with statistically significant difference among our subgroups then binary comparisons of means between each of the subgroups using the t-Student test will be performed. Secondary outcomes including NIHSS at 24 hours post therapy and at discharge, MRS-30 days, Thrombolysis In Myocardial Infarction (TIMI) post procedure and Thrombolysis In Cerebral Ischemia (TICI) post procedure will be compared between the three groups. Safety measurement defined by ECASS III criteria as a symptomatic intracranial hemorrhage will also be compared between the three groups.

TRIAL STATUS: Recruiting patients.

PI/Coordinator Names: Tareq Kass-Hout, MD/AnneMarie Crumlish.

PI/Coordinator Affiliations: University at Buffalo Neurosurgery (UBNS) and Jacobs Neurological Institute (JNI).

TRIAL SPONSOR: Genentech Medical Education Department.

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TRIAL WEB SITE: <http://clinicaltrials.gov/ct2/show/NCT01455935>

Author Disclosure Block: **T. Kass-Hout:** Research Grant; Significant; Genentech Medical Education Department. **O. Kass-Hout:** None. **M. Mokin:** None. **E. Nourollahzadeh:** None. **R. Sawyer:** None. **A. Siddiqui:** Research Grant; Significant; National Institutes of Health 1R01NS064592-01A1,. Speakers' Bureau; Modest; Codman & Shurtleff, Genentech.. Honoraria; Modest; American Association of Neurological Surgeons, Emergency Medicine Conference, Genentech, Neocure Group LLC, Abbott Vascular, Codman & Shurtleff, Inc.. Ownership Interest; Modest; StimSox. Ownership Interest; Significant; Hotspur, Intratech Medical, Valor Medical. Consultant/Advisory Board; Modest; Codman & Shurtleff, Inc, Concentric Medical, ev3/Covidien Vascular Therapies, GuidePoint Global Consulting, Penumbra. **K. Snyder:** Other Research Support; Modest; Toshiba Research Center in Buffalo. **E. Levy:** Research Grant; Significant; Boston Scientific. Other Research Support; Modest; ev3/Covidien Vascular Therapies. Other Research Support; Significant; Codman & Shurtleff, Inc, Boston Scientific.. Honoraria; Modest; Boston Scientific.. Expert Witness; Significant; Renders medical/legal opinions as an expert witness.. Ownership Interest; Modest; Intratech Medical Ltd.. Ownership Interest; Significant; Mynx/Access Closure.. Consultant/Advisory Board; Modest; ev3/Covidien Vascular Therapies, TheraSyn Sensors, Inc.. Consultant/Advisory Board; Significant; Codman & Shurtleff, Inc.. Other; Significant; Abbott Vascular, ev3/Covidien Vascular Therapies..

Presentation Number: CT P32

Trial Abbreviation: PLASTIC CHAMPS

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Trial Email: adam.kirton@albertahealthservices.ca

Trial Name: Measurement and modulation of brain plasticity in children with perinatal stroke

Trial Registry Number ID: NCT01189058

Trial Sponsor: Heart and Stroke Foundation of Alberta

Trial Web Site: www.perinatalstroke.com

Publishing Title: Enhancing Motor Plasticity After Perinatal Stroke With Brain Stimulation And Constraint: Safety And Feasibility Of The Plastic Champs Trial.

Author Block: Adam Kirton, Alberta Children's Hosp, Calgary, AB, Canada; John Andersen, Glenrose Rehabilitation Hosp, Edmonton, AB, Canada; Archana Vijay, Aleksandra Mineyko, Gillian Hoyt-Hallett, Clare O'Byrne, Lisa Carsolio, Colleen Lane, Tamara Thicke, Jamie Roe, Jacquie Hodge, Alberta Children's Hosp, Calgary, AB, Canada; Michael Hill, Hotchkiss Brain Inst, Calgary, AB, Canada; PLASTIC CHAMPS Investigators

Abstract Body:

Trial details: Abbreviation: PLASTIC CHAMPS; Status: enrolling; Registration: www.clinicaltrials.gov/NCT01189058; PI: Kirton A; Affiliation: University of Calgary; Contact: adam.kirton@albertahealthservices.ca; Sponsor: Heart and Stroke Foundation of Alberta; Web: www.perinatalstroke.com/research

Objective. Perinatal stroke causes most hemiplegic cerebral palsy. Emerging developmental plasticity models have identified central therapeutic targets. Constraint-induced movement therapy (CIMT) evidence is substantial but not specific to perinatal stroke. Non-invasive brain stimulation can target adult stroke models but is unexplored after perinatal injury. We aim to determine the ability of repetitive transcranial magnetic stimulation (rTMS) and CIMT to enhance upper extremity function in children with perinatal stroke hemiparesis.

Design. Randomized, blinded, factorial clinical trial. Inclusion criteria include unilateral perinatal stroke, current age 6-18 years, and hemiparesis with functional motor deficit and some voluntary movement. Baseline function and neurophysiology are quantified. Children then attend a two week, intensive motor learning camp, randomized 1:1 to CIMT and/or daily rTMS/sham. The primary outcome measure is the Canadian Occupational Performance Measure (COPM) at 1 week, 2 and 6 months. Objective motor function and quality of life measures are completed at the same timepoints. Pediatric TMS Safety/Tolerability Measures are recorded at 4 timepoints.

Results. A pre-defined safety analysis was performed (n=14, median 14.4 years, 57% male). All children completed the 2 month outcomes with no drop-outs. Interventions were well tolerated with no serious adverse events. TMS tolerability scores were excellent and comparable between rTMS and sham. The primary safety outcome was achieved as mean COPM scores did not decrease: Performance scores 3.78±1.4 (baseline) to 6.84±1.2 (1 week) to 7.21±1.2 (2 months); Satisfaction scores 3.90±1.5 (baseline) to 6.90±1.4 to 7.57±1.5. Objective measures of bilateral function (e.g. Assisting Hand Assessment) also did not decrease. Child and parent measures suggested additional psychosocial benefits.

Conclusions. TMS clinical trials are safe and feasible in children with CP. Intensive rehab camps are appealing for both physical and psychosocial benefits.

Author Disclosure Block: A. Kirton: None. J. Andersen: None. A. Vijay: None. A. Mineyko: None. G. Hoyt-Hallett: None. C. O'Byrne: None. L. Carsolio: None. C. Lane: None. T. Thicke: None. J. Roe: None. J. Hodge: None. M. Hill: None.

Presentation Number: CT P33

Trial Abbreviation: COOL

Trial Contact Information: john.wang@carle.com

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Trial Name: COOL BRAIN Trial IIC

Trial Registry Number ID: HDTRA 1-07-RDINO-BAA

Trial Sponsor: Department of Defense

Trial Web Site: carle.com

Publishing Title: Selective Cerebral Hypothermia Using a Cooling Head Cover, the COOL BRAIN Trial IIC: An Assessment of Cognitive Functioning in Patients Undergoing Coronary Artery Bypass Graft Surgery

Author Block: Mary K Brethour, Huan Wang, William C Olivero, Kevin Jackson, Tracey Wszalek, Neal Cohen, Arthur Kramer, Mary K Davis, Carle Fndn Hosp, Urbana, IL

Abstract Body:

Background: Coronary artery bypass graft (CABG) surgery remains one of the most commonly performed procedures even with significant advances in coronary artery stenting and angioplasty. Surgical techniques and anesthesia management have improved since the 1980's; however, mortality has steadily declined in spite of an increasingly complex and older patient profile. Studies have identified postoperative cognitive decline (POCD), or a decrease from pre-operative levels on neuropsychological tests, in 5-30% of patients who have undergone CABG both on and off-pump, and POCD may be one of the most commonly reported complications after cardiac surgery. Proposed mechanisms include the lack of blood flow pulsatility during on-pump procedures, and an unfavorable intracranial temperature gradient resulting in insufficient hypothermic protection to the surface gray matter, the neocortex.

Hypothermia is by far the most potent neuro-protectant identified in animal studies. The results of whole-body hypothermia in cardiac arrest, trauma, and stroke patients have been mixed, perhaps due to significant systemic complications. Therefore, selective cerebral hypothermia as a neuro-protectant mechanism may have great potential to maximize brain cooling while minimizing systemic complications.

A new head-and-neck cooling head cover, developed using a NASA spin-off spacesuit technology, may have the potential for use intra-operatively, as an adjunctive cooling technique to the whole body hypothermia. Our published pilot study demonstrated rapid and selective brain cooling with this device.

Intra-operatively, combining the head-neck surface cooling to the whole body circulatory cooling may minimize an unfavorable intracranial temperature gradient, potentially optimizing the hypothermic neuroprotection to the surface neocortex.

Selective brain cooling intra-operatively during CABG in addition to standard intra-operative cooling may optimize neurological protection, resulting in better functional recovery post surgery and less POCD.

Objectives: To determine if application of a cooling head cover during CABG surgery will result in less POCD at 3 months post-surgery.

Methods: A prospective, randomized study utilizing a cooling head cover during non-emergent CABG surgery for 200 patients will be undertaken to evaluate whether selective cerebral hypothermia, in addition to standard intra-operative whole body hypothermia, will provide neurological protection and decrease the burden of POCD (Department of Defense Contract Award (HDTRA 1-07-RDINO-BAA)). All eligible perspective CABG patients will be approached pre-operatively for potential enrollment in the study and randomized in a one-to-one manner to either head-and-neck cooling head cover during CABG or no device. All enrolled patients will undergo neuropsychological testing pre and post operatively at 3 months. The head-and-neck cooling head cover will be applied in the pre operative holding area, and removed before transfer to the cardiovascular ICU.

Results: SPSS Version19 will be used for all statistical analyses.

Discussion: If POCD can be minimized by head cooling in CABG patients, this intervention could have significant potential for utilization in both acute ischemic and hemorrhagic stroke patients.

Author Disclosure Block: **M.K. brethour:** None. **H. Wang:** Research Grant; Modest; DOD Award HDTRA 1-07-RDINO-BAA. **W.C. Olivero:** None. **K. Jackson:** None. **T. Wszalek:** None. **N. Cohen:** None. **A. Kramer:** None. **M.K. Davis:** None.

Presentation Number: CT P34

Trial Abbreviation: COOL

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Trial Name: COOL BRAIN Trail II

Trial Registry Number ID: HDTRA 1-07-RDINO-BAA

Trial Sponsor: Department of Defense

Trial Web Site: carle.com

Publishing Title: Ultra-early Field Delivery of Selective Hypothermia in Brain Injury Patients Using A Cooling Helmet Cover, the COOL BRAIN Trial II: A Feasibility and Safety Study

Author Block: Mary K Davis, Huan Wang, William Olivero, Kevin Jackson, Tracey Wszalek, Neal Cohen, Arthur Kramer, Mary Brethour, Carle Fndn, Urbana, IL

Abstract Body:

Ultra-early Field Delivery of Selective Hypothermia in Brain Injury Patients Using A Cooling Helmet Cover, the COOL BRAIN Trial II: A Feasibility and Safety Study

Mary Kathleen Davis, DNP(c), APN; Huan Wang, MD; William C. Olivero, MD; Kevin Jackson, PhD; Tracey Wszalek, PhD; Neal Cohen, PhD; Arthur Kramer, PhD; Mary Brethour, PhD, APN

Background: Brain injury is one of the foremost causes of morbidity and mortality. The relative lack of effective treatments greatly compromises the well being of patients inflicted with brain injuries each year. To date, hypothermia is by far the most potent neuro-protectant in animal studies. However, although the neuro-protective effects of hypothermia instituted in both the pre-injury and peri-injury periods are well established, most potential clinical applications of hypothermia would limit its use in the post-injury (resuscitative) period. Numerous animal studies have demonstrated that 1-2°C temperature change in the brain can result in significantly different neurological and histological outcomes. From these data, it is now established that hyperthermia intensifies the brain injury while hypothermia protects the brain. It has been shown that hyperthermia is an independent predictor of adverse neurologic sequelae and increased resource utilization after brain injury. Hypothermia therapy may therefore accomplish its clinical efficacy via two routes: 1) prophylaxis against hyperthermia; 2) therapeutic hypothermia.

The clinical application of resuscitative brain hypothermia remains a challenge due to the narrow post-injury therapeutic window and the attendant systemic risks of whole body hypothermia. Therefore, ultra-early delivery of selective cooling of the brain in the field may be a more successful way of treating brain injury patients and needs to be studied.

A new head-and-neck cooling head cover, developed using a NASA spin-off spacesuit technology, may have the potential for use in the pre-hospital setting. Our published pilot study demonstrated rapid and selective brain cooling with this device.

Primary Hypothesis: Initiation of selective cerebral hypothermia prior to the arrival to the hospital using a new head-and-neck cooling head cover is feasible and safe in brain injury patients.

Secondary hypothesis: Pre-hospital induction of selective cerebral hypothermia using a new head-and-neck cooling head cover improves functional outcome in brain injury patients at 90 days as measured by Modified Rankin Scale, Barthel Index, and NIH Stroke Scale.

Methods: This pilot study is a prospective, non-randomized trial involving 100 brain injury patients. Inclusion criteria for this study will encompass patients eighteen to eighty years of age, head traumas (all severities), strokes, and pre-hospital cardiac arrests. Once the patient qualifies, cooling head cover will be placed on by the EMS personnel or the life-flight team to initiate selective cerebral hypothermia in the field. The newly designed head-and-neck cooling head cover has a built-in ASPEN Collar for cervical spine protection

(Department of Defense Contract Award (HDTRA 1-07-RDINO-BAA). Upon arrival to the emergency department, patients will be stratified based on their brain injury severities and assigned to different brain cooling protocols accordingly. Enrolled patients will all receive standard monitoring and treatments for their brain injuries. Data will be collected and evaluated regarding the feasibility and safety of the cooling device, and the potential neuroprotective benefits, including neurocognitive parameters.

Results: SPSS Version 19 will be utilized for statistical analysis.

Discussion: Initiation of selective cerebral hypothermia in the field is expected to lengthen the therapeutic window preventing further neurological deterioration and improving functional outcome. Once feasibility and safety data are collected, efforts will be directed in planning for an outcome study.

Author Disclosure Block: **M.K. Davis:** None. **H. Wang:** Research Grant; Modest; Department of Defense. **W. Olivero:** None. **K. Jackson:** None. **T. Wszalek:** None. **N. Cohen:** None. **A. Kramer:** None. **M. Brethour:** None.

Presentation Number: CT P35

Trial Abbreviation: GAMES Pilot

Trial Contact Information: Kevin Sheth, ksheth@som.umaryland.edu, 443-615-4729

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Trial Name: GAMES (Glyburide Advantage in Malignant Edema and Stroke) Pilot

Trial Registry Number ID: NCT01268683

Trial Sponsor: Remedy Pharmaceuticals

Trial Web Site: ksheth@som.umaryland.edu

Publishing Title: GAMES (Glyburide Advantage in Malignant Edema and Stroke) Pilot: Initial Design and Enrollment

Author Block: Kevin N Sheth, Univ of Maryland Sch of Med, Baltimore, MD; Jordan Elm, Medical Univ of South Carolina, Charleston, SC; Barney Stern, Karen Yarbrough, Univ of Maryland Sch of Med, Baltimore, MD; Sydney O'Connor, Massachusetts General Hosp, Boston, MA; Maxim Hammer, April Kane, Univ of Pittsburgh, Pittsburgh, PA; Katharina Busl, Terry Cole, Rush Univ, Chicago, IL; Sven Jacobson, Remedy Pharmaceuticals, New York City, NY; Albert J Yoo, R. Gilbert Gonzalez, Massachusetts General Hosp., Boston, MA; W. Taylor Kimberly, Massachusetts General Hosp, Boston, MA

Abstract Body:

Background: Malignant infarction occurs in 10-12% of stroke victims and is characterized by rapidly accumulating cerebral edema. Secondary neurological decline leads to mortality rates as high as 60-80%. Decompressive craniectomy is the only effective therapy for this syndrome. The NC (Ca-ATP) channel and its regulatory SUR1 co-receptor are implicated in the development of brain edema after stroke. Expressed in all components of neurovascular unit, the activity of the SUR1 receptor is blocked by the sulfonylurea glyburide. In multiple preclinical models of large stroke, glyburide treatment results in the attenuation of brain water content and increased preservation of white matter and cortex up to 10 hours after stroke onset. We have developed an IV form of glyburide (RP-1127) for testing in patients with malignant infarction.

Objective: The primary objective is to assess the safety and feasibility of enrolling, evaluating, and treating with RP-1127 severe anterior circulation ischemic stroke patients, whether or not treated with IV rtPA. The secondary objective is to compare clinical and MRI outcome data with historical reference.

Design: This is a four-center prospective, open label, phase IIa trial of RP-1127.

Population studied: The study will enroll 10 patients with a baseline MRI DWI lesion between 82 cm³ and 210 cm³, age 18-80 years, and time from symptom onset to drug infusion of ≤ 10 hours. Patients who receive intra-arterial reperfusion therapy, prophylactic decompressive craniectomy, or are on sulfonylurea treatment at presentation will be excluded.

Intervention: Enrolled patients receive a RP-1127 bolus and continuous infusion for 72 hours. Following the baseline MRI, patients undergo follow up MRI at 24, 48, and 72 hours. Neurological assessments including NIHSS, GCS, and Full Outline of Unresponsiveness (FOUR) Score are performed. Safety parameters, including hypoglycemia, are assessed through days, 7, 30, and 90. mRS assessment occurs at days 30 and 90.

Outcome measure: Outcomes relating to safety and tolerability include symptomatic hypoglycemia or refractory hypoglycemia. Feasibility will be assessed by rate of enrollment, percent yield of screened patients enrolled into the study, ability to perform serial MRI scanning and adhere to the glucose management protocol. Imaging endpoints will include changes in absolute and percent DWI lesion, ipsilateral hemisphere volume, and frequency of brain hemorrhage.

Analysis Plan: Summary statistics will be compared to benchmarks from published literature.

Trial Status: To date, 4 patients have been enrolled into GAMES-Pilot to date. There have been no episodes of

symptomatic or refractory hypoglycemia or drug related significant adverse events. One patient suffered neurological deterioration and progressed to surgical decompression within 48 hours (baseline DWI volume 155 cc³). The three remaining patients had mean baseline and day 3 DWI volumes of 131 and 159 cc³, respectively. Mean 30 day modified Rankin score was 3.5 without decompressive craniectomy. Conclusions: GAMES Pilot is an ongoing pilot therapeutic study of a novel compound against malignant edema after stroke. To date, enrolled patients have had no adverse events and improved outcomes compared to historical data.

Author Disclosure Block: **K.N. Sheth:** Research Grant; Modest; Remedy Pharmaceuticals. Other Research Support; Modest; American Heart Association. **J. Elm:** Research Grant; Modest; Remedy Pharmaceuticals. Other Research Support; Modest; NIH. **B. Stern:** None. **K. Yarbrough:** None. **S. O'Connor:** None. **M. Hammer:** None. **A. Kane:** None. **K. Busl:** None. **T. Cole:** None. **S. Jacobson:** Employment; Modest; Remedy Pharmaceuticals. **A.J. Yoo:** None. **R. Gonzalez:** None. **W.T. Kimberly:** None.

Presentation Number: CT P36

Trial Abbreviation: ATACH II

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Trial Name: Antihypertensive Treatment of Acute Cerebral Hemorrhage II

Trial Registry Number ID: NCT01176565

Trial Sponsor: University of Minnesota - Clinical and Translational Science Institute

Trial Web Site: <http://www.atach-2.com/>

Publishing Title: Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: Design, Methods, and Rationale

Author Block: Adnan I Qureshi, Univ of Minnesota, Minneapolis, MN; Yuko Y Palesch, Medical Univ of South Carolina, Charleston, SC; ATACH II Investigators, Univ of Minnesota, Minneapolis, MN

Abstract Body:

The December 2003 report from a National Institute of Neurological Disorders and Stroke (NINDS) Workshop on priorities for clinical research in intracerebral hemorrhage (ICH) recommended clinical trials for evaluation of blood pressure management in acute ICH as a leading priority. The Special Writing Group of the Stroke Council of the American Heart Association in 1999 and 2007 emphasized the need for clinical trials to ensure evidence-based treatment of acute hypertension in ICH. To address important gaps in current knowledge, we conducted a pilot study funded by the NINDS, Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH I) Trial, in 2004-2008 to determine the appropriate level of systolic blood pressure (SBP) reduction. We now have initiated a multi-center, randomized Phase III trial, the ATACH II Trial, to definitively determine the efficacy of early, intensive antihypertensive treatment using intravenous (IV) nicardipine initiated within 3 hours of onset of ICH and continued for the next 24 hours in subjects with spontaneous supratentorial ICH. The primary hypothesis of this large (N=1,280), streamlined, focused trial is that SBP reduction to ≤ 140 mm Hg reduces the likelihood of death or disability at 3 months after ICH, defined by modified Rankin scale (mRS) score of 4-6, by at least absolute 10% compared to standard SBP reduction to ≤ 180 mm Hg .

The ATACH II Trial is a natural extension of numerous case series, the subsequent ATACH I pilot trial, and a preliminary randomized controlled trial in this patient population funded by the Australian National Health and Medical Research Council. Both trials recently confirmed the safety and tolerability of both the regimen and goals of antihypertensive treatment in acutely hypertensive patients with ICH, as proposed in the present trial. The underlying mechanism for this expected beneficial effect of intensive treatment is presumably mediated through reduction of the rate and magnitude of hematoma expansion observed in approximately 73% of patients with acute ICH. The Australian trial provided preliminary evidence of attenuation of hematoma expansion with intensive SBP reduction. The ATACH II trial will have important public health implications by providing evidence of, or lack thereof, regarding the efficacy and safety of acute antihypertensive treatment in subjects with ICH. This treatment represents a strategy that can be made widely available without the need for specialized equipment and personnel, and therefore, can make a major impact upon clinical practice for treating patients with ICH.

Author Disclosure Block: A.I. Qureshi: Employment; Modest; University of Minnesota. Research Grant; Significant; NIH (ATACH)-II. 1R01NS062091-01A2. Y.Y. Palesch: None. A. Investigators: None.

Presentation Number: CT P37

Trial Abbreviation: ATAS

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Trial Email: qureshai@gmail.com

Trial Name: Antihypertensive Treatment of Acute Stroke

Trial Registry Number ID: TBD

Trial Sponsor: University of Minnesota

Trial Web Site: Adnan I Qureshi, MD; qureshai@gmail.com: 612-626-8221

Publishing Title: Antihypertensive Treatment of Acute Stroke (ATAS) Registry

Author Block: Adnan I Qureshi, ATAS Investigators, Univ of Minnesota, Minneapolis, MN

Abstract Body:

We propose to conduct a two-year multicenter open-labeled non-randomized Phase I pilot trial. The primary objective is to determine the tolerability and safety administering pre-mixed, ready to use IV nicardipine for acute hypertensive response in subjects with suspected stroke in the pre-hospital settings. The trial will recruit a maximum of 150 subjects with suspected stroke who meet the inclusion criteria. The primary safety outcome is the rate of major and minor adverse events during the duration of pre-hospital treatment. A secondary outcome is treatment as measured by successfully achieving and maintaining the specified systolic blood pressure goals. The pilot trial is the natural development of numerous case series evaluating the effect of antihypertensive treatment of acute hypertension in subjects with ICH. The proposed trial will have important public health implications by providing necessary information for initiating antihypertensive treatment in pre-hospital settings in subjects with suspected stroke.

The specific aims of the present pilot grant proposal are to:

1. Define the safety, assessed by the rate of major and minor adverse events during treatment using intravenous nicardipine infusion.
2. Determine the rate of treatment as assessed by the achieving and maintaining the systolic blood pressure goals with intravenous nicardipine infusion in subjects with stroke who present within 3.5 hours of symptom onset.

Author Disclosure Block: **A.I. Qureshi:** Employment; Modest; University of Minnesota. Research Grant; Significant; NINDS (ATACH)-II. 1R01NS062091-01A2. **A. Investigators:** None.

Presentation Number: CT P38

Trial Abbreviation: HDS-SAH

Trial Contact Information: Prima Chan, primachan@surgery.cuhk.edu.hk, fax: +857 26377974, phone: +852 26322624

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Trial Name: High-dose Simvastatin for Aneurysmal Subarachnoid Haemorrhage: Is it better?

Trial Registry Number ID: NCT01077206

Trial Sponsor: Health and Health Service Research Fund, Research Fund Secretariat, Food and Health Bureau, Hong Kong Special Administrative Region, China.

Trial Web Site:

<http://clinicaltrials.gov/ct2/show/NCT01077206?term=aneurysmal+subarachnoid+hemorrhage+and+hong+kong&rank=2>

Publishing Title: High-dose Simvastatin for Aneurysmal Subarachnoid Haemorrhage: Is it better?

Author Block: George KC Wong, The Chinese Univ of Hong Kong, Hong Kong SAR, Hong Kong

Abstract Body:

Trial Abbreviation: HDS-SAH **ClinicalTrials.gov Identifier:** NCT01077206

Background: Although aneurysmal subarachnoid haemorrhage (SAH) accounts for only 3-5% of strokes, its profound consequences and unique window of intervention have justified it being classified as a separate entity. Early aneurysm occlusion, expert endovascular neurosurgery and microsurgery, use of oral nimodipine and neuro-intensive care are now the standards of care [Wong GK 2008]. Despite these standards, aneurysmal subarachnoid haemorrhage is still associated with mortality at one month for half of all patients, whereas the half that survives is left with disability.

Following the acute bleed, many patients with SAH show deterioration as a consequence of secondary ischaemic processes affecting the cerebral circulation [Knuckey NW 1985]. The clinical consequences manifest as delayed ischaemic deficits (DIDs), and usually develop after a lag of several days. There is therefore a potential to intervene before clinical deterioration. The diffuse nature of SAH by means of red cell breakdown products has widespread effects on the large vessels of the circle of Willis and smaller vessels within the sub-pial space [van Gijn 2001]. Processes are complex, and combine to impair the cerebral blood flow (CBF) to widespread areas of the brain. Low CBF correlates with clinical outcome following SAH, hence candidate neuroprotective agents may be targeted according to CBF enhancing characteristics which offset low flow states and the related metabolic consequences. Given the diffuse nature of the pathological process, local vascular therapies (such as angioplasty) have been disappointing [Andaluz N 2002, Murai Y 2005, Liu JK 2004]. A more global approach is more appropriate. As a reflection of the complex array of pathological process underlying DID, a preferred strategy would be to target a multitude of potentially important mechanisms underlying DID by using a drug which has the potential for multiple efficacious actions. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and block the formation of mevalonate, an important precursor for both cholesterol and other nonsterol products [Delanty N 1997, Goldstein JL 1990]. This mechanism may account for some of the known neuroprotective properties of statins by improving endothelial vasomotor function, increasing endothelial cell fibrinolytic activities, reducing thrombogenic potential, blocking platelet activation, and suppressing cytokine responses during cerebral ischemia [Goldstein JL 1990, Vaughan CJ 1993]. Statins also improve CBF by up-regulation of endothelial nitric oxide synthase (eNOS), properties which are of particular relevance to SAH in light of low CBF and impaired autoregulation.

Experimental evidences supported the benefit of Simvastatin in subarchnoid haemorrhage [McGirt MJ 2002, Chen J 2003, Sugawara T 2008]. Moreover, Simvastatin is a potent agent in achieving LDL reduction with a

proven safety profile. There are three randomized placebo-controlled pilot trials in the literature supporting the use of statins (two with simvastatin 80mg and one with pravastatin 40mg) in aneurysmal subarachnoid haemorrhage [Lynch JR 2005, Tseng MY 2005, Tseng MY 2007, Chou SH 2008]. A subsequent meta-analysis supports the routine use of statins in the care of patients with aneurysmal SAH [Sillberg VA 2008]. There is also an ongoing multi-centre placebo controlled phase III trial assessing the clinical benefit of daily simvastatin 40mg treatment [<http://www.stashtrial.com/home.html>].

However, there is no clinical data to compare the efficacy of different dosage regimens (namely whether high-dose regimen is better) and related cost-effectiveness analysis, although biochemical actions and related neuroprotective mechanisms were thought to be dosage-related. This gap in knowledge is important, on how to implement the use of statin and interpret different trial results.

Objective: To assess whether daily Simvastatin 80mg (high dose) treatment given within 96 hours of the ictus will reduce incidence and duration of delayed ischemic deficits following subarachnoid haemorrhage when compared to daily Simvastatin 40mg (normal dose) treatment, leading to improvement in clinical outcome, which then translates into advantage in terms of cost-effectiveness.

Design: Prospective randomized double-blinded clinical trial.

Population studied:

Inclusion criteria

1. Patients (age 18-75 years) in which the admitting neurosurgeon has a high index of suspicion of a spontaneous aneurysmal subarachnoid haemorrhage with a convincing CT scan findings.
2. Any clinical grade accepted provided a reasonable prospect of survival.
3. Delay to randomization and initiation of trial medication from the time of the presenting ictus does not exceed 96 hours.

Exclusion criteria

1. Unsalvageable patients: Fixed and dilated pupils after resuscitation, and/or a devastating scan, which precludes definitive therapy.
2. Already taking statin therapy.
3. Those taking Warfarin-type drugs.
4. Pregnancy.
5. Known renal or hepatic impairment.
6. Suspected or known additional disease process, which threatens life expectancy (e.g. malignancy).
7. Known or strong suspicion of drug abuse, alcoholism, or those who are likely to be amendable to 3 month follow up.
8. Those already taking amiodarone, verapamil or potent CYP3A4 inhibitors.

Sample size

Assume that high dose group has a 35% delayed cerebral ischemia risk with a 20% absolute reduction in delayed cerebral ischemia as compared to the standard dose group with a 55% delayed cerebral ischemia, a total of 212 patients is required (80% power and 2-sided $\alpha=0.05$). Assume a 10% loss to follow up, 240 patients recruitment is planned.

Interventions: Simvastatin 80mg daily versus 40mg daily for 21 days.

Method: Ethical approvals will be obtained from respective institutional review boards. After informed consent from patient or next of kin, subject is randomized to receive Simvastatin 80mg (two tablets of Simvastatin 40mg) per day or Simvastatin 40mg (one tablet of Simvastatin 40mg and one placebo tablet) per day, for 21 days. Drug-related morbidities including rhabdomyolysis and hepatitis were rare. In the two reported pilot studies, only one patient withdrew due to elevated liver parenchymal enzymes which reversed upon cessation of medication. Plasma creatinine phosphokinase (CPK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are monitored every 7 days or with clinical suspicion, for early signs of hepatitis or myositis. Study drug will be stopped if ALT/AST is more than 3-fold normal ($>180\text{U/L}$) or $\text{CPK}>1,000\text{U/L}$. Cholesterol levels will also be monitored weekly.

Randomization: A permuted-block randomization will be carried out once the eligibility criteria have been fulfilled using a computer system with an allocation list of random order generated by a statistician un-related to the project team in order to protect the blinding and integrity of the study.

Primary Outcome Measures:

- Presence of delayed ischemic neurological deficit [Time Frame: One month]

Secondary Outcome Measures:

- Liver function derangement or rhabdomyolysis [Time Frame: Three months]
- Modified Rankin Scale [Time Frame: Three months]
- Incremental cost-effectiveness analysis (ICER) [Time Frame: Three months]

Analyses: We perform intention-to-treat analysis using two-sided probability. $P < 0.05$ is considered statistically significant. Proportions with (a) favorable outcome and (b) delayed cerebral ischemia are compared with Chi Square statistic. Sensitivity analysis for ICER is carried out to find the limits of proportions with (a) favorable outcome and (b) delayed cerebral ischemia that show threshold values.

Trial Status: The study started recruitment in March 2010. There are currently 6 Southern China neurosurgical centers recruiting patients. One hundred and seven patients were randomized as of 30th September 2011. Another 190 control patients were also recruited for matched analyses. We aim to complete patient recruitment in March 2013.

Principal Investigator: George Kwok Chu WONG, MD, the Chinese University of Hong Kong.

Trial Sponsor: Health and Health Service Research Fund, Research Fund Secretariat, Food and Health Bureau, Hong Kong Special Administrative Region, China.

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Author Disclosure Block: G.K. Wong: None.

Presentation Number: CT P39

Trial Abbreviation: CHIMES

Trial Contact Information: Christopher Chen; email phccclh@nus.edu.sg

Trial Email: phccclh@nus.edu.sg

Trial Name: The CHInese Medicine Efficacy on Stroke recovery Trial

Trial Registry Number ID: ClinicalTrials.gov Identifier : NCT00554723

Trial Sponsor: CHIMES Society

Trial Web Site: <http://chimes-society.org/>

Publishing Title: The CHInese Medicine Efficacy on Stroke recovery (CHIMES) Trial

Author Block: Christopher Chen, Natl Univ of Singapore, Singapore, Singapore; **Claire Yim**, Moleac Pte Ltd, Singapore, Singapore; The CHIMES Investigators

Abstract Body:

Background and Objective : Stroke is a leading cause of death and disability worldwide. Despite improvements in acute stroke treatment, many patients only make a partial or poor recovery. During the early days to weeks following stroke, repair spontaneously occurs and the neurobiology of these events suggests a number of therapeutic targets to further promote recovery. Traditional Chinese Medicine (TCM) is commonly used to enhance the recovery process after stroke in China but lacks a reliable evidence base. Because TCM may be potentially beneficial with an encouraging safety profile, large well designed clinical trials using TCM focused on stroke rehabilitation and repair, such as CHIMES are important.

Design : CHIMES is a double blind, placebo controlled, randomized, multicenter study to test the hypothesis that MLC601 is superior to placebo in reducing neurological deficit and improving functional outcome.

Population Studied : A planned total of 1100 patients with cerebral infarction of an intermediate range of severity recruited within 72 hours of stroke onset.

Interventions : MLC 601, a TCM widely used in China to improve recovery after stroke, has recently been shown to restore neurological and cellular function in animal models of stroke by processes involved in repair. Previous clinical trials have shown that MLC601 shows good tolerability and superiority over another TCM in terms of neurological disability and functional outcome.

Outcome Measures : Primary : Distribution modified Rankin Scale grades for all randomized subjects.

Secondary : NIHSS, Barthel Index, MMSE

Analysis : Intention to Treat and Per Protocol

Trial Status : 991 patients have been randomised as of October 2011 from 17 sites in 5 Asian countries.

Author Disclosure Block: **C. Chen:** Research Grant; Significant; National Medical Research Council of Singapore. **C. Yim:** None.

Presentation Number: CT P40

Trial Abbreviation: CLOTBUSTER

Trial Contact Information: Gordon Brandt, MD

Trial Email: cerevast@cerevast.com

Trial Name: A Phase 3, Randomized, Active Controlled, Double-Blinded Trial of the Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator for Emergent Revascularization in Acute Ischemic Stroke

Trial Registry Number ID: NCT01098981

Trial Sponsor: Cerevast Therapeutics

Trial Web Site: www.cerevast.com

Publishing Title: A Phase 3, Randomized, Active Controlled, Double-Blinded Trial of the Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator (tPA) for Emergent Revascularization (CLOTBUSTER) in Acute Ischemic Stroke

Author Block: Gordon Brandt, Cerevast Therapeutics Inc., Seattle, WA; Andrei V Alexandrov, University of Alabama at Birmingham, Birmingham, AL; for the CLOTBUSTER Investigators

Abstract Body:

The primary objective of this trial is to provide information regarding the efficacy of a combined treatment with transcranial ultrasound delivered with a proprietary operator-independent device and systemic tPA (Target group) compared to systemic tPA alone (Control group) in subjects with acute ischemic stroke. The primary efficacy endpoint is functional outcome at 3 months from stroke onset (modified Rankin Score 0-1). The primary safety endpoint is the proportion of subjects in the Target vs Control group experiencing symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment.

Major patient inclusion criteria:

1. Patients receiving systemic tPA therapy by local/national guidelines
2. Pre-tPA NIHSS \geq 10 points

Sample size: 800 patients.

Projected number of centers: 50+ world-wide.

Center recruitment: ongoing.

Author Disclosure Block: **G. Brandt:** Consultant/Advisory Board; Modest; Cerevast Therapeutics, Inc. **A.V. Alexandrov:** Consultant/Advisory Board; Significant; Cerevast Therapeutics, Inc.

Presentation Number: CT P41

Trial Abbreviation: ABYSS

Trial Contact Information: ykh1030@hallym.ac.kr

Trial Email: ssbrain@hallym.ac.kr

Trial Name: Prospective, Matched Case Control, Multicenter, Observational Study for the association of serum Apolipoprotein B-48 level and large artery atherosclerotic iSchemic Stroke (ABYSS)

Trial Registry Number ID: NCT01233986

Trial Sponsor: MSD Korea

Trial Web Site: www.stroke-crc.or.kr/ecrf/

Publishing Title: Prospective, Matched Case Control, Multicenter, Observational Study For The Association Of Serum Apolipoprotein B-48 Level And Large Artery Atherosclerotic Ischemic Stroke (ABYSS)

Author Block: **Mi Sun Oh**, Kyung-Ho Yu, Hallym Univ Sacred Heart Hosptial, Anyang, Korea, Republic of; Keun-Sik Hong, Yong-Jin Choe, Inje Univ Ilsan Paik Hosp, Ilsan, Korea, Republic of; Hee-Joon Bae, Seoul Natl Univ Bundang Hosp, Seongnam, Korea, Republic of; Joung-Ho Rha, Inha Univ Coll of Med, Incheon, Korea, Republic of; Ja-Seong Koo, Catholic Univ of Korea, Seoul St. Mary's Hosp, Seoul, Korea, Republic of; Jong-Moo Park, Eulji Univ, Nowon Eulji Hosp, Seoul, Korea, Republic of; Ju-Hun Lee, Kangdong Sacred Heart Hosptial, Seoul, Korea, Republic of; Oh Young Bang, Samsung Medical Ctr, Sch of Med, Sunkyunkwan Univ, Seoul, Korea, Republic of; Byung-Woo Yun, Seoul Natl Univ Hosp, Seoul, Korea, Republic of; Ki Hyun Cho, Chonnam Natl Univ Medical Sch, Gwangju, Korea, Republic of; Jae-Kwan Cha, Dong-A Univ Hosp, Busan, Korea, Republic of; Hyo Suk Nam, Yonsei Univ Coll of Med, Seoul, Korea, Republic of; Byung-Chul Lee, Hallym Univ Sacred Heart Hosptial, Anyang, Korea, Republic of

Abstract Body:

BACKGROUND and OBJECTIVE: Increased postprandial triglyceridemia has been recognized as one of risk factors for cardiovascular disease or ischemic stroke, and postprandial triglyceride-rich lipoproteins (TRLs) also have been thought to contribute to the development of atherosclerosis. Recently, it was reported that the serum apolipoprotein B48 (apoB48) level, good marker for TRLs derived from intestine, was associated with the presence of carotid plaque. However, it remains uncertain whether the serum apoB48 level is incorporated into the large artery atherosclerotic ischemic stroke. ABYSS has aims to determine whether the apoB48 is a potential risk factor of atherosclerosis in patients with ischemic stroke. **DESIGN:** ABYSS is a prospective, matched case control, multicenter, observational study that will evaluate the association of serum apoB48 with large artery atherosclerotic ischemic stroke. We plan to recruit 56 patients with large artery atherosclerotic ischemic stroke (LAA) presenting within 48 hour after symptom onset. Fifty six patients with small vessel occlusive ischemic stroke (SVO) with similar age and sex are recruited as matched controls. Patients are enrolled from the twelve tertiary-hospitals in South Korea. The fasting serum apoB48 levels and nonfasting serum apoB48 levels at 3 hours after standardized meals are compared between patients with LAA and those with SVO. This study is registered at the ClinicalTrials.gov with the number NCT01233986. **ASSESSMENT:** There are two primary assessments: the nonfasting and fasting serum apoB48 levels measured by enzyme-linked immunosorbent assay. Secondary assessments are to access the postprandial lipaemia: the nonfasting serum level of triglyceride, low density lipoprotein cholesterol, and high density lipoprotein cholesterol. **CURRENT STATUS:** This study started in South Korea in 2010, and 54 patients (64.2±11.2 age, 62 % male gender) were included during the first year. **FUNDING:** This study was partially supported by grant of MSD Korea and the Korea Healthcare technology R & D project, Ministry of Health and Welfare, Republic of Korea (A102065).

Author Disclosure Block: **M. Oh:** None. **K. Yu:** None. **K. Hong:** None. **Y. Choe:** None. **H. Bae:** None. **J. Rha:** None. **J. Koo:** None. **J. Park:** None. **J. Lee:** None. **O. Bang:** None. **B. Yun:** None. **K. Cho:** None. **J. Cha:** None. **H. Nam:** None. **B. Lee:** None.

Presentation Number: CT P42

Trial Abbreviation: POINT

Trial Contact Information: mary.farrant@ucsfmedctr.org

Trial Email: clay.johnston@ucsfmedctr.org

Trial Name: Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial

Trial Registry Number ID: NCT00991029

Trial Sponsor: UCSF and NIH/NINDS

Trial Web Site: pointtrial.org

Publishing Title: Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial

Author Block: S Claiborne Johnston, UCSF Medical Ctr, San Francisco, CA

Abstract Body:

The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial is a prospective, randomized, double-blind, multicenter trial with the primary null hypothesis that, in patients with TIA or minor ischemic stroke treated with aspirin 50-325 mg/day, there is no difference in survival free of ischemic stroke, myocardial infarction, and ischemic vascular death at 90 days in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared to placebo when therapy is initiated within 12 hours of the time last known free of new ischemic symptoms.

Subjects are 18 years of age or older with high-risk TIA (defined as an ABCD² score \geq 4) or minor ischemic stroke (an NIHSS \leq 3); each subject is followed for 90 days from randomization. A total of 4,150 patients will be recruited and the trial will be completed in 7 years. The first subject was enrolled on May 28, 2010.

Principal Investigator: S. Claiborne Johnston, MD, PhD, University of California, San Francisco

Co-Principal Investigator: J. Donald Easton, MD, University of California, San Francisco

Contact: Mary Farrant, MBA, BSN, RN, University of California, San Francisco, Stroke Sciences Group (SSG), San Francisco, California, United States, 94143; Phone 1-415-502-2096; Email: mary.farrant@ucsfmedctr.org.

Planned Number of Centers: 150; Present Number: 127 (30 SEP 2011)

Planned Number of Subjects: 4,150; Present Number: 466 (30 SEP 2011)

Sponsor: University of California, San Francisco (UCSF); National Institute of Neurological Disorders and Stroke (NINDS)

Collaborators: Neurological Emergencies Treatment Trials Clinical Coordinating Center (NETT CCC) at the University of Michigan; Statistics and Data Management Center (SDMC) at the Medical University of South Carolina (MUSC); POINT Clinical Research Collaboration (POINT-CRC) at EMMES Corporation

Dates of Study: October 2009 - September 2016

ClinicalTrials.gov Identifier: NCT00991029;

<http://clinicaltrials.gov/ct2/show/NCT00991029?term=POINT&rank=1>

Author Disclosure Block: S. Johnston: None.