

Clinical Trials Methodology Course

Andrew M. Southerland, MD, MSc
Assistant Professor of Neurology and Public Health Sciences
University of Virginia Health System
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Disclosures

U.S. Provisional Patent Application Serial No. 61/867,477

Research Support

- HRSA GO1RH27869-01-00
- American Heart Association – American Stroke Association
- Virginia Alliance of Emergency Medicine Research
- UVA Neuroscience Center of Excellence
- American Academy of Neurology, American Board of Psychiatry and Neurology

Additional

- Deputy Section Editor, Neurology Podcast®
- Legal expert review



Circa 1983





Academic Timeline

Circa 2011 – 2012

- ▶ Completed Vascular Neurology Fellowship
- ▶ Completed Masters in Science (Clinical Research)
- ▶ Received early career award from the AHA/ASA National Center Clinical Research Program
 - Gene expression analysis in cervical artery dissection
- ▶ Had a child...
- ▶ Took over the Neurology Residency Program



Reducing in-hospital delay to 20 minutes in stroke thrombolysis



Atte Meretoja, MD, PhD,
MSc (StrokeMed)

Daniel Strbian, MD, PhD

Satu Mustanoja, MD,

PhD, MSc
(StrokeMed)

Turgut Tatlisumak, MD,

PhD

Perttu J. Lindsberg, MD,

PhD

Markku Kaste, MD, PhD

Correspondence & reprint
requests to Dr. Meretoja:
atte.meretoja@finnet.fi

ABSTRACT

Objectives: Efficacy of thrombolytic therapy for ischemic stroke decreases with time elapsed from symptom onset. We analyzed the effect of interventions aimed to reduce treatment delays in our single-center observational series.

Methods: All consecutive ischemic stroke patients treated with IV alteplase (tissue plasminogen activator [tPA]) were prospectively registered in the Helsinki Stroke Thrombolysis Registry. A series of interventions to reduce treatment delays were implemented over the years 1998 to 2011. In-hospital delays were analyzed as annual median door-to-needle time (DNT) in minutes, with interquartile range.

Results: A total of 1,860 patients were treated between June 1995 and June 2011, which included 174 patients with basilar artery occlusion (BAO) treated mostly beyond 4.5 hours from symptom onset. In the non-BAO patients, the DNT was reduced annually, from median 105 minutes (65–120) in 1998, to 60 minutes (48–80) in 2003, further on to 20 minutes (14–32) in 2011. In 2011, we treated with tPA 31% of ischemic stroke patients admitted to our hospital. Of these, 94% were treated within 60 minutes from arrival. Performing angiography or perfusion imaging doubled the in-hospital delays. Patients with in-hospital stroke or arriving very soon from symptom onset had longer delays because there was no time to prepare for their arrival.

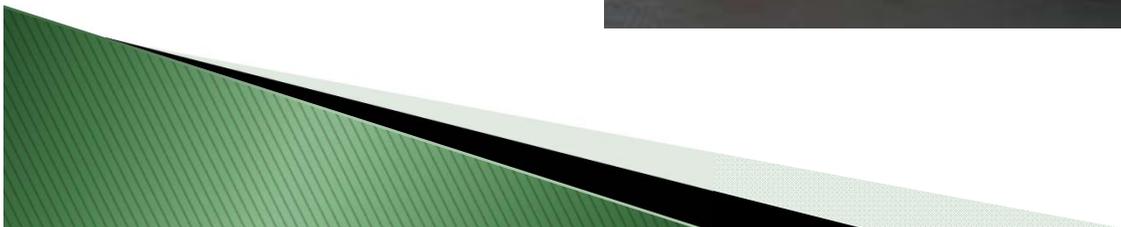
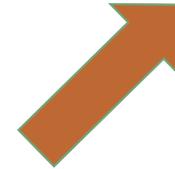
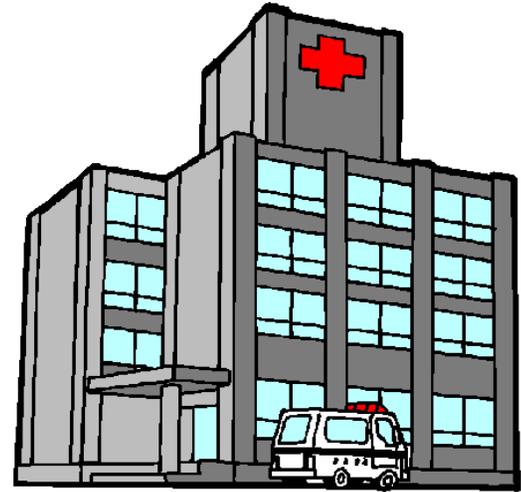
Conclusions: With multiple concurrent strategies it is possible to cut the median in-hospital delay to 20 minutes. The key is to do as little as possible after the patient has arrived at the emergency room and as much as possible before that, while the patient is being transported. *Neurology*® 2012;79:308–313

“The key is to do as little as possible after the patient has arrived at the emergency room and as much as possible before that, while the patient is being transported.”

– Meretoja et al. *Neurology* 2012



TELESTROKE



PUBLIC RELEASE 2-FEB-1998

Telemedicine On Ambulances May Save Stroke Patients

UNIVERSITY OF MARYLAND MEDICAL CENTER

Doctors at the University of Maryland Medical Center are the first in the nation to use sophisticated video and computer technology to assess a stroke patient's condition during an ambulance ride, before arrival at the hospital. Two Maryland Express Care ambulances have been outfitted with digital cellular equipment that allows neurologists in their hospital office to see a stroke patient in real time video and speak to the emergency medical personnel on the ambulance as they rush the patient to the hospital.

"Every moment counts, now that we have a drug to dissolve clots causing the stroke. If we can save time and get a head start in evaluating patients even before they arrive at the hospital, we may be able to prevent more death and disability," says Marian LaMonte, M.D., director of the Brain Attack Team at the University of Maryland Medical Center.

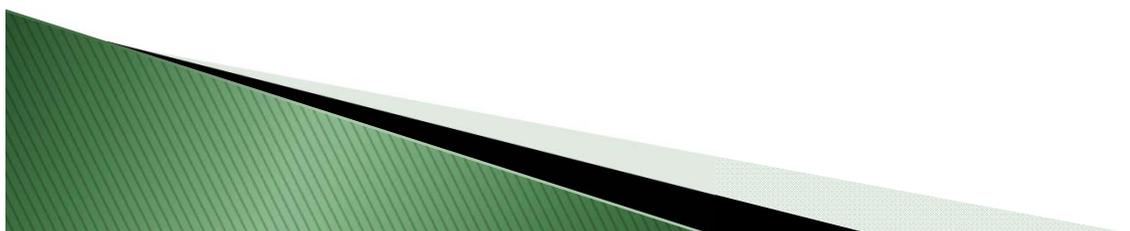
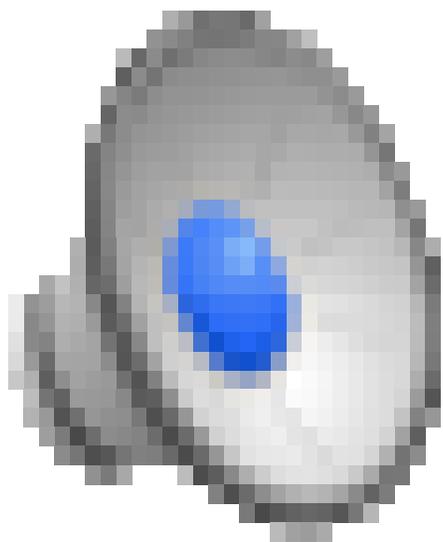


The iTREAT Study

Improving Treatment with Rapid Evaluation of Acute stroke via mobile Telemedicine

- ▶ Apply mHealth technology to facilitate telestroke systems in the prehospital setting – i.e. mobile videoconferencing between neurologist and EMS provider during ambulance transport
- ▶ System: low-cost, portable, and reliable in a rural stroke network
- ▶ Impact:
 - Improve accuracy of prehospital stroke diagnosis
 - Facilitate appropriate patient triage
 - Reduce stroke onset-to-treatment time
 - Enhance prehospital stroke research





System Components

- ▶ Tablet-based telemedicine endpoint
- ▶ Cisco Jabber (Movi)[™] video conferencing application (HIPAA compliant)
- ▶ 4G LTE CradlePoint[®] modem
- ▶ Multiple-Input-Multiple-Output Antenna (x2)
- ▶ Blue tooth portable speaker
- ▶ Suction cradle mount
- ▶ Verizon[®] 4G Mini SIM card
- ▶ Durable Pelican case

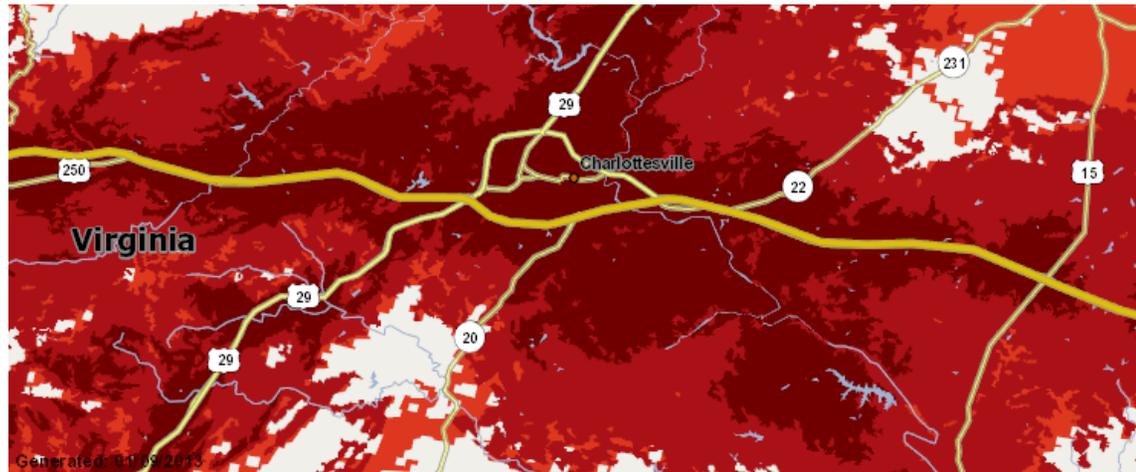


Components cost/ambulance (USD): ~\$1850

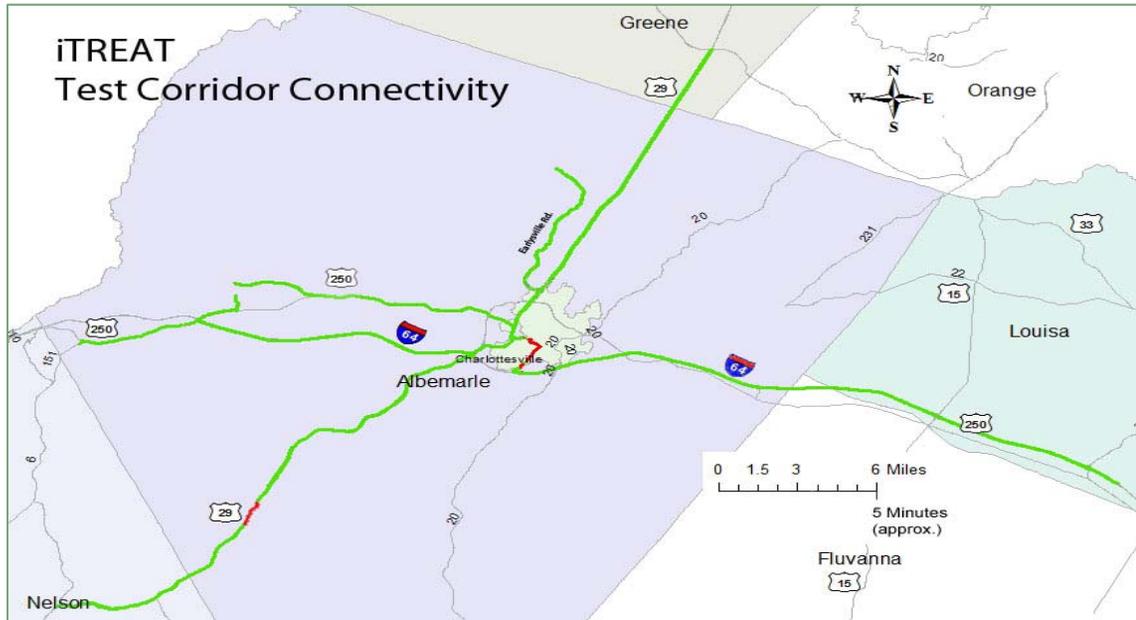
Connectivity Mapping

Verizon© Map

93% of all runs achieved
at least 9 minutes of
continuous connectivity
between all raters
Mean: 18 minutes



Connectivity Map

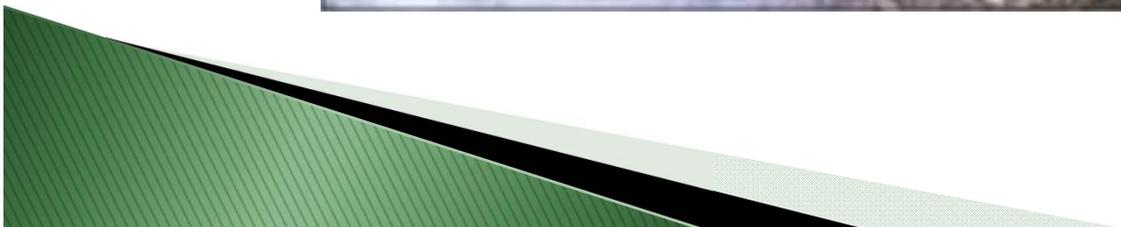


Submitted some grants...

- ▶ Institutional grant
 - FUNDED
- ▶ State grant
 - FUNDED
- ▶ Foundation grant
 - FUNDED
- ▶ NIH grant (R41 / 42 STTR)
 - **NOT FUNDED**



Circa 2012–2013



THE MENTOR

**Enabler of mastery
Embodiment of the goal**



new clinical trials training course

Worrall, Bradford *HS

Wed 4/23/2014 4:16 PM

Junior faculty and Fellows,

The new NINDS "Vale course" has been funded. It is now the Iowa City course. The University of Michigan and University of Iowa are co-running it.

Although there is very little info on the web site – <http://neurotrials.training>, the application process is open only until May 16th.

Please consider applying. You will need an idea for an intervention that you are excited about and in a position to develop.

KCJ would need to write a letter of endorsement. We are a NeuroNEXT site and KCJ works very closely with the NETT.

I am happy to speak more or refer you to people who can speak to more specifically as to the value.

Brad

Bradford B. Worrall, MD, MSc
Harrison Distinguished Teaching Professor and
Vice-Chair for Clinical Research of Neurology;
Professor of Public Health Sciences
434-924-2783 (Odessa)
bwu0r@virginia.edu



Protocol Development

- ▶ **Primary Objective (Feasibility):**
 - Determine if mobile telestroke using the tablet-based iTREAT system is clinically reliable to evaluate acute stroke patients during ambulance transport in a rural setting, compared to bedside assessment.
- ▶ *Hypothesis:*
 - The iTREAT mobile telestroke system is clinically reliable for prehospital stroke assessment during ambulance transport measured by interrater agreement of the NIHSS between mobile telestroke and blinded face-to-face assessments following hospital arrival (intraclass correlation > 0.70).



Design and Outcome

- ▶ Single-center, single-blinded, non-randomized, comparative Phase II feasibility study of iTREAT mobile telestroke system versus face-to-face assessment for acute stroke diagnosis
- ▶ **Primary Outcome**: Interrater agreement of the NIHSS between mobile telestroke (prehospital) and face-to-face assessments (following hospital arrival)



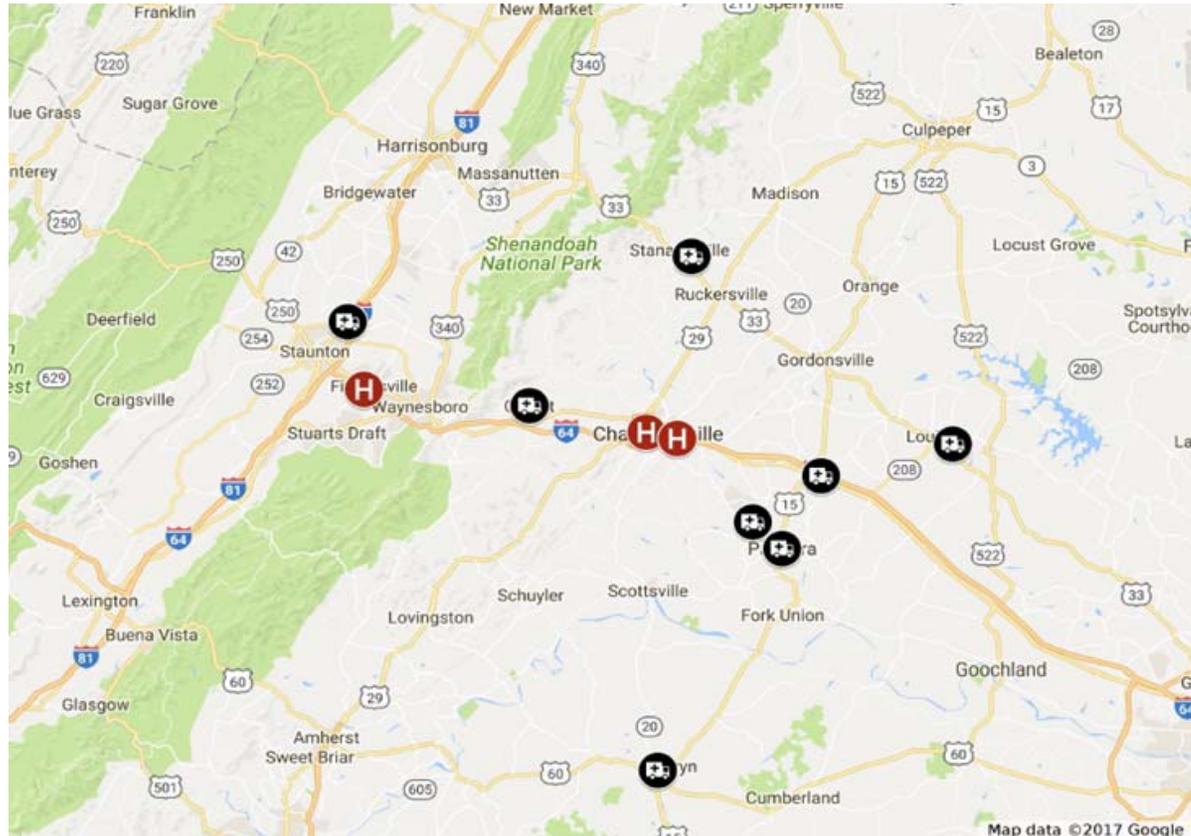
Eligibility Criteria

- ▶ Inclusion Criteria
- ▶ Suspected stroke identified by positive CPSS (EMS) or acute neurological emergency
- ▶ Ambulances with at least 10 min transport time
- ▶ Age ≥ 18

- ▶ Exclusion Criteria
- ▶ Major trauma
- ▶ Severe respiratory distress
- ▶ Cardiac instability
- ▶ Non-English speaking
- ▶ Prisoners



Study Network



Agency	Distance to UVA	Distance to MJH	Distance to AH	Personnel
Buckingham County	40 miles	N/A	N/A	Volunteer/Career
Western Albemarle	12 miles	16 miles	N/A	Volunteer Only
Louisa County	33 miles	29 miles	N/A	Volunteer/Career
Zions Crossroads	20 miles	16 miles	N/A	Volunteer Only
Greene County	22 miles	24 miles	N/A	Volunteer/Career
Lake Monticello	20 miles	16 miles	N/A	Volunteer/Career
Fluvanna County	26 miles	22 miles	N/A	Volunteer/Career
Augusta County	N/A	N/A	10 miles	Volunteer/ Career

Simple Protocol

EMS notifies MedCom of iTREAT
Activation



MedCom sends alert page to study
investigator



Study investigator calls iPad
designated to transporting ambulance



Study investigator and EMS provider
work through NIHSS

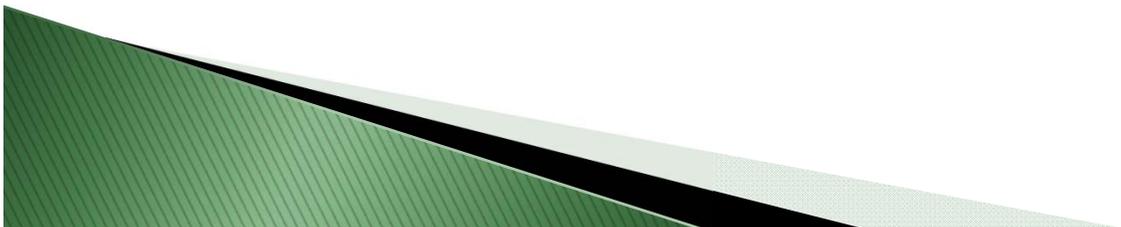


Sample Size

- ▶ Defining interrater agreement (primary outcome measure) to be a yes/no binary response , and the null as the proportion of agreements 0.5 and the alternative > 0.5 in order to show agreement greater than 50%, we would need 37 participants for a null of 0.5 and alternative of 0.7 to achieve 80% power with a type I error 0.05.
- ▶ In order to account for any technical failures or drop out, we will plan to prospectively enroll 50 participants in this Phase II feasibility study.



Kathyrn Chaloner 1954 – 2014



Informed Consent

- ▶ Learned more about consent procedures for emergency trials (e.g. EFIC)
- ▶ Ultimately received an exemption from informed consent for the feasibility phase



Results

n = 39 successful evaluations

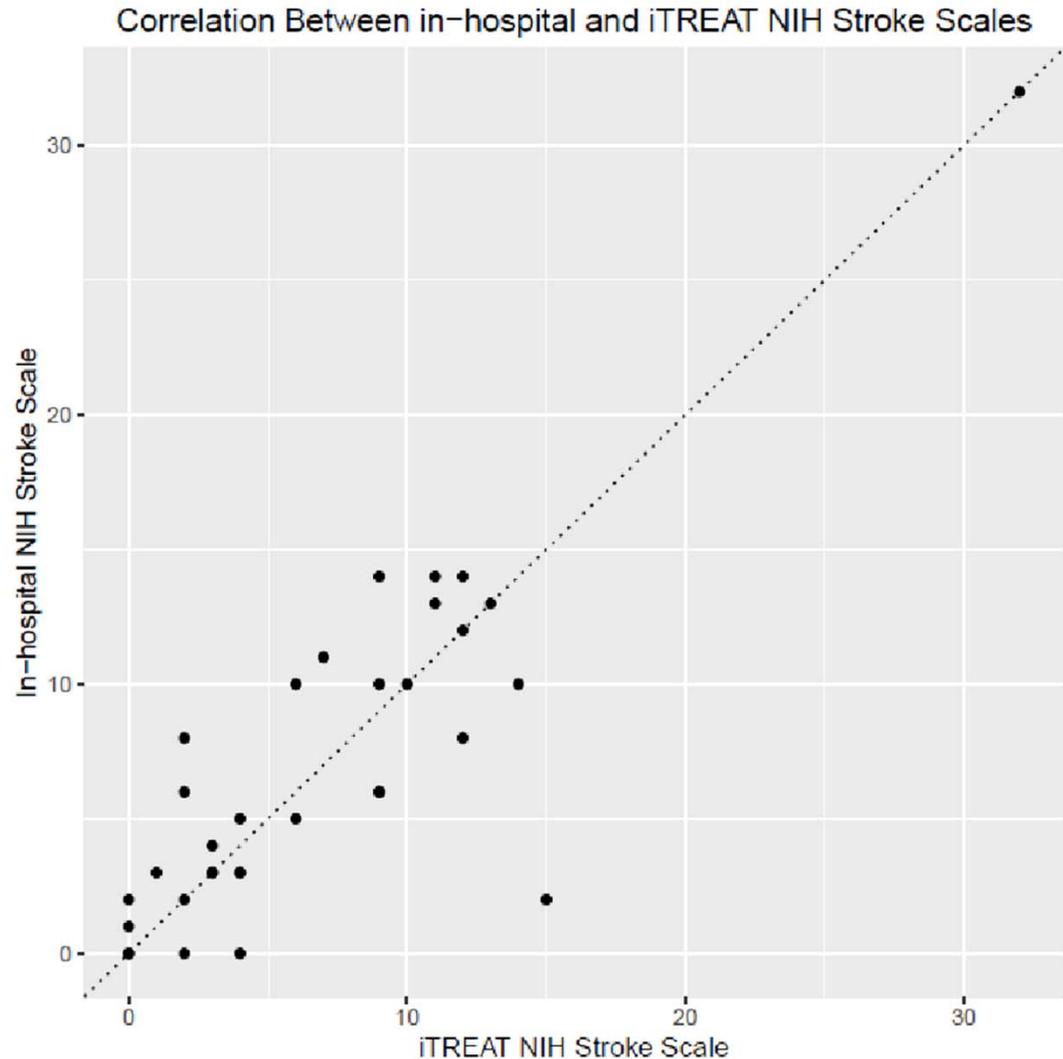
Median ambulance transport duration: 25 min

Median mobile connectivity time: 10 min

Spearman's rank correlation between mobile and in-person NIHSS assessments:

$\rho = 0.76$

$p = 2.06 \times 10^{-7}$



Original Research

Mobile Telestroke During Ambulance Transport Is Feasible in a Rural EMS Setting: The iTREAT Study

Jason M. Lippman, BA,¹ Sherita N. Chapman Smith, MD,²
Timothy L. McMurry, PhD,³ Zachary G. Sutton, BS,⁴
Brian S. Gunnell, BS,⁵ Jack Cote, BS, MPA,¹ Debra G. Perina, MD,⁶
David C. Cattell-Gordon, MDiv, MSW,⁵ Karen S. Rheuban, MD,⁵
Nina J. Solenski, MD,¹ Bradford B. Worrall, MD, MSc,^{1,3}
and Andrew M. Southerland, MD, MSc^{1,3}

Departments of ¹Neurology, ³Public Health Sciences, and ⁶Emergency Medicine and ⁵Center for Health Systems Research and Analysis, University of Virginia Health System, Charlottesville, Virginia; ²Department of Neurology, Virginia Commonwealth University Health System, Richmond, Virginia; ⁴The Brody School of Medicine, East Carolina University, Greenville, North Carolina.

assessment of emergency conditions in which direct observational exam may improve prehospital diagnosis and treatment. Thus mobile telestroke assessment is feasible using low-cost components and commercial wireless connectivity. More research is needed to demonstrate clinical reliability and efficacy in a live-patient setting.

ARTICLES

A low-cost, tablet-based option for prehospital neurologic assessment The iTREAT Study



Sherita N. Chapman
Smith, MD*
Prasanthi Govindarajan,
MD, MAS*
Matthew M. Padrick, MD
Jason M. Lippman, BA
Timothy L. McMurry,
PhD
Brian L. Resler, MD
Kevin Keenan, MD
Brian S. Gunnell, BA
Prachi Mehndiratta, MD

ABSTRACT

Objectives: In this 2-center study, we assessed the technical feasibility and reliability of a low cost, tablet-based mobile telestroke option for ambulance transport and hypothesized that the NIH Stroke Scale (NIHSS) could be performed with similar reliability between remote and bedside examinations.

Methods: We piloted our mobile telemedicine system in 2 geographic regions, central Virginia and the San Francisco Bay Area, utilizing commercial cellular networks for videoconferencing transmission. Standardized patients portrayed scripted stroke scenarios during ambulance transport and were evaluated by independent raters comparing bedside to remote mobile telestroke assessments. We used a mixed-effects regression model to determine intraclass correlation of the NIHSS between bedside and remote examinations (95% confidence interval).

Output following CTMC

- ▶ 5 related manuscripts, 2 in press
- ▶ Supported research for multiple students and trainees (2 awardees of AHA/ASA scholarships)
- ▶ Platform presentations at ISC and AAN meetings
- ▶ Participated in several state meetings on stroke systems of care (VA, NC, SC, NY)
- ▶ Presented before Brain Attack Coalition
- ▶ Received HRSA grant to support ongoing work (PI Solenski, HRSA GO1RH27869-01-00)



Controversies in Stroke

Section Editors: Carlos A. Molina, MD, PhD, and Magdy H. Selim, MD, PhD

Suspected Large Vessel Occlusion

Should Emergency Medical Services Transport to the Nearest Primary Stroke Center or Bypass to a Comprehensive Stroke Center With Endovascular Capabilities?

Andrew M. Southerland, MD, MSc; Karen C. Johnston, MD, MSc;
Carlos A. Molina, MD, PhD; Magdy H. Selim, MD, PhD; Noreen Kamal, MD; Mayank Goyal, MD

(Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.011149.)



NIH StrokeNet Proposal

▶ Aim 1:

- Determine whether prehospital neurological assessment using a mobile telestroke system can improve outcomes for acute stroke patients as measured by a reduction in stroke onset-to-treatment decision times compared to standard methods of prehospital assessment.

▶ Aim 2:

- Determine whether prehospital neurological assessment using a mobile telestroke system is more accurate for the diagnosis and triage of large vessel occlusion (LVO) acute ischemic stroke as measured by sensitivity/specificity (ROC analysis) compared to *standard* methods of prehospital assessment

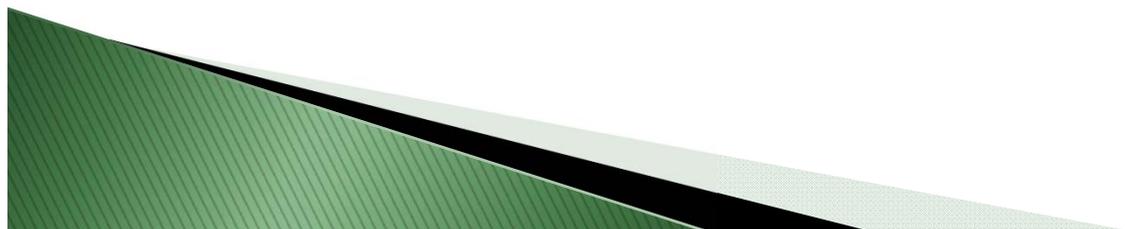


NIH StrokeNet Proposal

- ▶ Goal: Feb 2017 grant submission
- ▶ Timeline:
 - June 2016 – called Laurie and Will
 - July 2016 – submitted synopsis to program officer
 - Sept 2016
 - Presented to StrokeNet Acute Stroke Working Group
 - Nov 2016 – completed plans for protocol and budget
 - Feb 2016 – decided not to submit...



DO, OR DO NOT. THERE IS NO TRY.



Back to the drawing board

- ▶ Considering iTREAT as a tool rather than an intervention
- ▶ External validation of new EMS “LVO-sensitive” screening scales
- ▶ Implementation of neuroprotection drug treatment trials
- ▶ Computation video analysis of neurological signs using machine learning (NIH proposal pending)



Life After the CTMC

- ▶ Continue to develop protocol
- ▶ Extended mentorship
- ▶ Come back to gatherings (AAN)
- ▶ Do your surveys!
- ▶ Publish
- ▶ Keep the momentum going



Pitfalls to Success

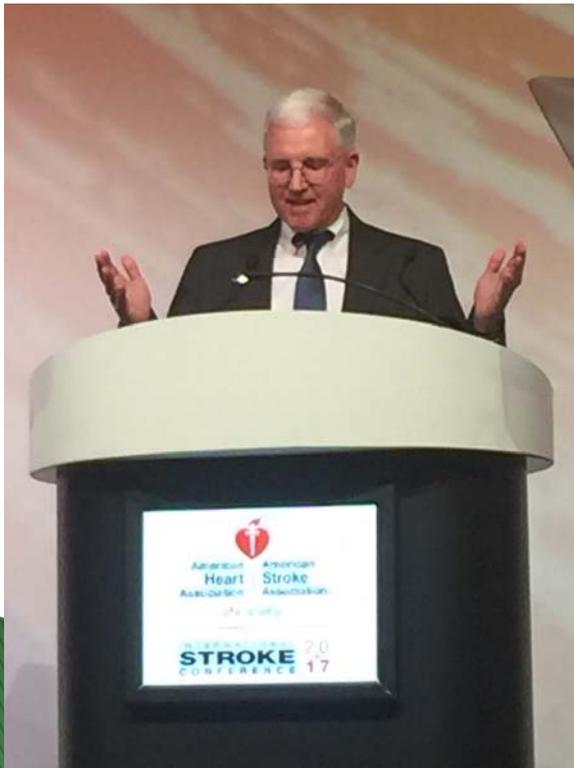
- ▶ Time management
- ▶ Death by a thousand emails
- ▶ A:P ratio
- ▶ Lack of mentorship
- ▶ Imposter syndrome
- ▶ Untapped enthusiasm
- ▶ Over commit...under deliver
- ▶ Plain old inertia



Special Report

With a Little Help From My Friends Seeking Consistent and Persuasive Evidence

E. Clarke Haley, Jr, MD



Although there is certainly a role for patient experience data, novel statistics, and observational research in a variety of circumstances, when it is really crunch time, we must insist on consistent and persuasive evidence that in most cases can only be provided by properly designed and executed randomized, concurrently controlled, and as much as possible, blinded clinical trials.

– Haley EC *Stroke* 2017

“It is important to reinvent yourself
before your patent expires.”



May the force be with you...



ACKNOWLEDGMENTS

Sponsors:

NINDS CTMC

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AHA-ASA

VAEMR

UVA Neuroscience CoE



UVA Center for Telehealth

Karen Rheuban

David Cattell-Gordon

Brian Gunnell

Virginia Burke

Kathy Wibberly

Lara Otkay

UVA Stroke Team

Sherita Chapman Smith

Nina Solenski

Brad Worrall

Heather Turner

Timothy McMurry

Jack Cote

Max Padrick

Jason Lippman

UVA Emergency Medicine

Debra Perina

Donna Burns

TJEMS Council

Business Partners

Verizon Wireless©

Cisco systems ©

UCSF

Prasanthi Govindajaran

Contact:

Andy Southerland

as5ef@virginia.edu

@asouth01

