The **INSTINCT** Trial

INcreasing **S**troke **T**reatment through **IN**terventional Behavior **C**hange **T**actics

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Abstract

Only 1 to 3 percent of stroke patients in community settings are receiving tPA therapy seven years after FDA approval. Data from academic stroke teams, stroke patient arrival times and thrombolytic use in myocardial infarction suggest substantially higher treatment rates are possible. The development and implementation of educational interventions to motivate physicians and other healthcare providers, along with health care organizations, to learn the principles of acute stroke care has been declared a high-priority objective of the NINDS.

Limited prior work found a combination of community and professional education increased thrombolytic use in stroke from a pre-intervention rate of 2.2% to a post-intervention rate of 11.3%, with the data suggesting the professional education component was the critical element in increasing use.

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

The Primary Specific Aims of this Study are:
1. To test whether a barrier assessment – interactive educational intervention, realistic in scope and effort, is effective in increasing appropriate thrombolytic use in stroke.
2. To assess whether a BA-IEI enhances emergency physician knowledge, beliefs and attitudes regarding the use of tPA in acute stroke

A Specific Aims — INSTINCT Behavior Intervention Trial to Increase TPA Use in Stroke

Only 1 to 3 percent of stroke patients in community settings are receiving tPA therapy eight years after FDA approval.[2, 5-9] Data suggest substantial improvement in treatment rates is possible. Assuming 500,000 ischemic strokes per year in the United States[10], a modest 4% increase in appropriate tPA delivery translates to an additional 20,000 treated patients per year. This potentially returns 2,200 stroke victims (11%) to the community normal - with improvement across the entire spectrum of neurologic outcomes for treated patients.[11] This underscores the need for developing and testing methods to efficiently increase appropriate thrombolytic use in stroke and achieving the overarching goal of this project - to improve stroke outcomes by maximizing the likelihood eligible candidates receive thrombolytic therapy.

Previous studies have demonstrated community and academic hospitals can deliver tPA effectively.[7, 12-19] However, numerous barriers exist to expanding the delivery of tPA in stroke.[20, 21] *We hypothesize that identifying and addressing these barriers using a barrier assessment-interactive educational intervention will increase appropriate tPA use.* Only limited data exist on proven methods to overcome these barriers and increase physician and hospital utilization of tPA. We previously found a combination of community and professional education increased thrombolytic use in stroke from a pre-intervention rate of 2.2% to a post-intervention rate of 11.3% (p=0.007), with the data suggesting the professional education component was the critical element in increasing use.[2, 22] Our previous study was limited by its quasi-experimental design and single community setting.[2] A standardized, educational intervention to increase tPA use in stroke has yet to be tested in a prospective, randomized, controlled trial.

This multi-center, randomized, controlled trial is designed to evaluate an innovative, standardized, multi-level, barrier assessment and interactive educational intervention (BA-IEI) in increasing appropriate tPA use in stroke. The proposed study is based on adult education and behavior change theory and will consist of three phases. A *pre-intervention pha*se establishing 1) the baseline proportion of patients with ischemic cerebrovascular disease treated with thrombolytic therapy and 2) emergency physician knowledge and attitudes regarding thrombolytic use in stroke. An *intervention phase* consisting of developing "local stroke champions"; conducting on-site assessments of barriers to tPA use in stroke and conducting two separate interactive educational interventions (at 3 month intervals) which will be standardized in their design but with selection of elements tailored for specific barriers identified at each study site. Additionally, the following mechanisms will be provided to enhance behavior change in the intervention group: providing physicians access to thrombolytic stroke expertise as needed (24/7); providing electronic messaging feedback on hospital thrombolytic use; and providing critical incident debriefing for tPA complications (ICH). The final phase, *the post-intervention phase*, will consist of 1) monthly assessment of tPA use, 2) quarterly review of ICD-9 reports, 3) review of all tPA treated cases and 4) re-assessment of physician attitudes and knowledge regarding thrombolytic use in stroke 12 months following the second IEI. *Outcome measures* include: 1) Changes in tPA use, with assessment of appropriateness of use and complications and 2) Changes in emergency physician knowledge and attitudes regarding thrombolytic use.

The Primary Specific Aims for this Study are:

1. **To test whether a barrier assessment – interactive educational intervention, realistic in scope and effort, is effective in increasing appropriate thrombolytic use in stroke.**

   Hypothesis: Hospitals receiving the BA-IEI will have a 4% or greater increase in the proportion of patients admitted with ischemic cerebrovascular disease appropriately receiving intravenous tPA compared to matched control hospitals.

2. **To assess whether a BA-IEI enhances emergency physician knowledge, beliefs and attitudes regarding the use of tPA in acute stroke**

   Hypothesis: Emergency physicians in the intervention group are more likely to have evidence of increased knowledge on the appropriate use of tPA in stroke and are more likely to consider its use, compared to their pre-intervention baseline and control physicians.

B Background and Significance

B.1 Current rates of thrombolytic use in stroke are low

IV tPA therapy remains unused in the vast majority of patients with ischemic stroke. Data reported in February 2003 from the multi-state Paul Coverdell Stroke Registry indicate only 3% of patients received some form of fibrinolytic therapy (either intravenous or intra-arterial).[9] These data support previous reports of usage rates of 1 to 3 percent in stroke patients treated in the community setting.[2, 5-8]

B.2 Potential exists for substantially increasing thrombolytic use in stroke

While the above treatment rates are disappointing, recent data suggests substantial improvements are possible. A veteran stroke service in Houston, TX reports 8.7% of all admitted patients with symptoms of cerebral ischemia were treated with intravenous tPA from 1996 to 2000. Impressively, during the study's final six-months, 12.9% of all patients were treated with IV tPA.[23] Data from Cleveland indicates 17% of ischemic stroke patients were admitted within 3 hours of symptom onset, yet only 1.8% received intravenous tPA.[6]

Contrasting these figures to the cardiac data is revealing. In the NRMI registry of 240,989 patients with myocardial infarction (between 1990 and 1993) 35% received thrombolytic therapy.[24] Thus, based on the experience of well-developed thrombolytic stroke teams and the utilization of thrombolytics in the setting of myocardial infarction, it appears possible to increase stroke treatment beyond current levels.

B.3 The need for improved systems in emergency stroke care

An examination of the barriers to improving the treatment of stroke patients is found within the NINDS Proceedings on the Rapid Identification and Treatment of Acute Stroke. The authors note "Delivery systems for acute stroke hospital care are relatively primitive compared to systems for…cardiac care…and the recent approval of intravenous tPA has exposed these deficiencies and mandates changes in the hospital care system."[21] The lack of a systems-based approach is of major concern to emergency physicians. The American College of Emergency Physicians current policy on the use of tPA in stroke states: "There is insufficient evidence at this time to endorse the use of intravenous tPA in clinical practice *when systems are not in place to ensure that the inclusion/exclusion criteria established by the NINDS guidelines for tPA use in acute stroke are followed." (emphasis added)*[25]

B.4 Need for improved physician stroke education

Published data reveals, in part, the magnitude of the educational task to increase acute stroke treatment. Substantial numbers of medical students and internal medicine house officers have no stroke training.[26] In 1998, only 76% of emergency medicine training hospitals had stroke protocols in place and two-thirds of the residency coordinators were "somewhat" or "very uncomfortable" administering tPA without specialty consultation.[27] A 1999 survey of over 700 emergency medicine residents found that while 25% considered tPA a "major advance" in stroke treatment, only 35% had cared for a tPA-treated stroke patient and 35% would only give tPA with a neurologist present.[28]

B.5 Altering health professional behavior and practice: Theory and Methods

B.5.1 Theory of behavioral change

Physicians and other health care providers have traditionally relied on persuading individuals to change through "informational power" (sharing facts about disease processes) and "expert power" (using professional credentials to impress others with the potential effectiveness of the prescribed behavioral change).[29] Such approaches, however, do not fully mesh with current theories of health promotion and behavior change theories.

Knowledge appears to be necessary, but not sufficient, for behavioral changes to be enacted and multi-level interventions are often required to successfully change behavior. While differences exist among the predominant behavioral change theories (Health Belief Model, Theory of Reasoned Action, Subjective Expected Utility Theory and Social Cognitive (Learning) Theory) several core concepts are common among

them: perceived *probability* of disease occurring, perceived *severity* of disease, perceived *effectiveness* of the behavioral change in decreasing the probability and severity of disease, and perceived *cost* of (or barriers to) enacting the change.[30-32] Some component of *self-efficacy*, the perception of one's own ability to successfully take action, has also been incorporated into most current theories of health promotion behavior. Our project incorporates these principles of behavior change theory into the designed intervention.

B.5.2 Methods to change physicians' behavior

In general, six methods of changing physicians' behavior have been outlined: education, feedback, physician participation in the effort to change, administrative oversight, financial incentives and financial disincentives. [33] Those elements that represent the focus of our proposed interventions are underlined below.

Continuing Medical Education: Post-training education of physicians typically consists of "traditional" continuing medical education (CME) offered as a didactic lecture to enhance physician knowledge. While successful in increasing knowledge the impact of traditional CME alone in changing physician behavior is extremely limited. In randomized, controlled studies of traditional CME addressing cholesterol screening [34], family practice topics, breast and cervical cancer screening[35] all failed to alter physician performance. Randomized controlled trials of the impact of "interactive" CME (small group, workshops, training sessions, etc.) and "mixed" CME (elements of both didactic and interactive) have found greater success with five of seven randomized, controlled trials finding positive effects on physician performance.[36-42]

Repetition appears important in increasing the likelihood of success. In a review of randomized controlled trials of CME, Davis et al. found seven of 10 repetitive CME interventions (the majority using 2 sessions in a series) had a positive effect compared to two of seven singular interventions – supporting our use of multiple interventions in series.

Clinical practice guidelines: Clinical practice guidelines, another form of physician education, have only limited effects on changing physician behavior[43-45] often due to multiple barriers, both internal and external to the behavior change process.[46] The advantages of these, however, are low cost and ease of distribution.

Local champions / opinion leaders: While guidelines by themselves may not change practice, evidence exists that providing them to local "opinion leaders" appears to hold substantial promise in altering physician behavior and maintaining the change. In one study, cesarean delivery rates fell dramatically after opinion leaders were recruited and trained to promote compliance with a guideline for the management of women with a previous cesarean section.[47] In another study, significant changes in antibiotic use were found when authoritative senior staff members were targeted for person-to-person messaging on appropriate use in conjunction with ordering reminders.[48] Thus active physician participation in the process has a sound theoretical and experimental basis.

Academic detailing: While targeting only opinion leaders is an efficient strategy to alter physician behavior, the process known as "academic detailing" – targeting populations of individual physicians – has proven remarkably effective in almost every study in which it has been used.[49-52] Limitations of targeting individual physicians have included the time and expense of contacting each physician.

Feedback: Feedback involves providing information to physicians regarding their practices or individual patient outcomes. Previous studies of feedback mechanisms in altering behavior have been variable in their outcomes. Conditions proposed for successful feedback strategies include 1) physician recognition of need for improvement, 2) physician ability to act upon information, 3) prospective reminders appear more successful than retrospective feedback and 4) achievable target expectations.[53-57]

Administrative intervention / barrier evaluation: Administrative interventions can effect behavior change by creating barriers to alter practice or removing barriers to desired practice (e.g. enhancing CT access for stroke, providing stroke treatment protocols, providing thrombolytic stroke expert access, etc.). Administrative interventions have been successful in reducing drug costs by altering available selections or requiring drug selection review.[58] However, as Greco et al. wrote, there is a risk of achieving desired changes in practice

which may ultimately cause harm to patients.[33] As an example, they cite a Medicaid program limiting reimbursement for prescription drugs which successfully reduced the number of drugs prescribed, but inadvertently increased the rates of admission to nursing homes.[59] Greco also cautions such adverse events may go unrecognized if there is no evaluation of patient outcomes. Our project incorporates outcome assessment into its design by actively searching for adverse outcome events associated with thrombolytic use in stroke - off-protocol use and hemorrhagic complications – and provides timely feedback to stroke care providers in such events.

B.6 Significance

The development and implementation of educational interventions to motivate physicians and other healthcare providers, along with health care organizations, to learn the principles of acute stroke care has been declared a high-priority objective of the NINDS.[60] Current data indicate national thrombolytic treatment rates for acute stroke remain considerably below those reported in optimized stroke care systems and in myocardial infarction. Given the societal burden of stroke, the proven efficacy of thrombolytic therapy, and the advent of even more aggressive stroke treatment strategies (GP 2B3A inhibitors $\pm$ thrombolytics, intra-arterial clot disruption, etc.) effective and efficient methods to enhance physician delivery of acute stroke care must be developed and tested. Failure to do so marginalizes the impact of proven and future stroke therapies at current treatment rates.

Our project *specifically* targets increasing tPA use by utilizing a system-based approach focusing on the emergency department that incorporates fundamental principles of behavior change theory and methods. The development of these delivery systems represents an integral step in the second stage of translational research – moving therapies from a clinical trial setting to accepted clinical practice. The proposed barrier assessment – interactive educational intervention has been *designed to use an economy of resources to allow replication outside a clinical trial setting where external funding support may be limited or non-existent*. If successful, this project may serve as a model for enhancing delivery of stroke and other acute therapies.

C Preliminary Studies

In the Preliminary Studies section we will present data supporting the following key elements of our proposed project:

1. Previous success in promoting effective emergency physician delivery of tPA in stroke.
2. Evidence of success in increasing tPA use using a multi-level educational intervention.
3. Work supporting ICD-9 code use to identify admitted patients with cerebrovascular disease.
4. Preliminary work supporting a novel mechanism for efficient tPA case identification using computerized pharmacy dispensing systems.

C.1 Evidence for promoting effective emergency physician tPA delivery

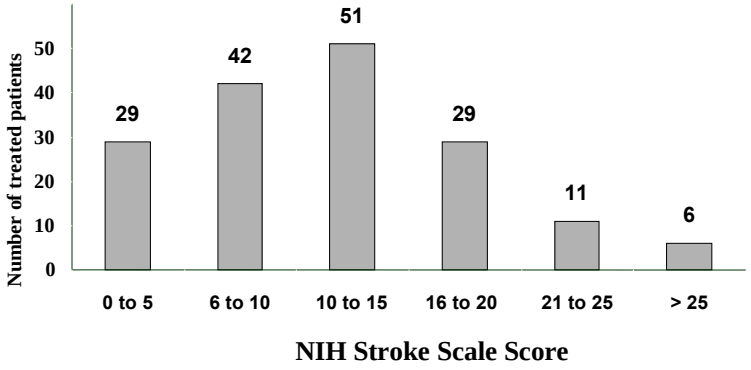
Dr. Phillip Scott is the Principal Investigator of a series of studies evaluating the effectiveness of community emergency physicians (EPs) in delivering tPA in acute ischemic stroke (AIS).[18, 19, 61-64] These studies report data describing stroke treatment at four Michigan hospitals using an alternative delivery model emphasizing EP delivery of tPA using standard neurology consultation methods – in contrast to classic stroke team approaches. This system, developed by Dr. Scott and colleagues at Michigan, has treated over 200 patients using 80 separate emergency physicians since its implementation. Treatment and outcome data have been maintained in the UM Stroke Registry.

Advantages of the UM alternative model include the use of personnel immediately available to the patient on ED arrival and the potential for widespread implementation in locations without thrombolytic stroke specialists physically present, but available via telephone for consultation. Potential difficulties include rapidly and accurately identifying patients with AIS, minimal individual physician experience because of the small number of patients qualifying for tPA therapy, obtaining emergent cranial CT interpretation, and EP discomfort in being called upon to initiate therapy with a known risk of intracerebral hemorrhage (ICH). These issues have been addressed through specific mechanisms in the proposed project which build upon our experiences of developing this alternative delivery system – including local stroke champion development, barrier assessments and targeted education with feedback mechanisms. Data regarding the effectiveness of this approach is presented below.

C.1.1 EPs are willing to treat a broad range of stroke severity

Previous reviews of Michigan data indicate emergency physicians using this model are willing to treat a wide variety of stroke severity as measured by the NIH stroke scale (Figure C1).

Figure C1: Pre-treatment NIH Stroke Scale for Emergency Physician treated strokes (1996-2001)[19]



C.1.2 EPs can achieve onset to treatment times equal to stroke teams

Emergency physicians in this system appear capable of achieving onset-to-treatment and door-to-treatment times matching systems using dedicated thrombolytic stroke teams (Table C1).

Table C1: Treatment times for emergency physician delivery of tPA (1996-1999 data)[62]

Time Intervals (h:min)	n	Mean	SD	95% CI	NINDS	Cinci	STARS
Stroke Onset to Door	87	1:00	0:29	0:54, 1:06			
Door to MD	88	0:15	0:21	0:11, 0:19	0:10	0:04	
Door to CT	84	0:47	0:24	0:42, 0:52	0:25	0:26	
Door to Drug	87	**1:36**	0:32	1:30, 1:42	1:00	1:23	
Onset to Drug	89	**2:37**	0:29	2:31, 2:43		2:30	2:45

NINDS = NINDS recommendations on time to treatment[21]; Cinci = Cincinnati mean time to treatment; STARS = median treatment time in STARS study[17]

C.1.3 Diagnostic accuracy of emergency physicians delivering tPA

The large cohort (n = 80) of treating physicians within the Michigan dataset delivered tPA in stroke with a diagnostic error rate of 4% (95% CI: 1% - 7%) in treated patients – a figure at, or below, the lower end of the reported spectrum for diagnostic error in stroke identification by other systems using acute stroke teams.[63, 65, 66]

C.1.4 EP tPA-treated patients have ICH complications and long-term mortality similar to NINDS study

Our data demonstrates emergency physicians are capable of achieving complication rates for intracranial hemorrhage[19] and long-term (one-year) mortality rates which match the NINDS investigators.[64] Hemorrhage rates are presented in Table C2 below. With regards to mortality, at one-year, 27% [95% CI: 0.19-0.34] of emergency physician treated patients were dead compared to 24% [95% CI: 0.20-0.29] in the NINDS study tPA treatment group (p = 0.71) with an attributable risk of death at one-year in community treated patients of 2.2% [95% CI: -0.07 to 0.11].[64] While the numbers are too small to definitively prove equivalence, this data is reassuring in excluding large, clinically significant, differences in the two populations. Combined, the results of these studies demonstrate the investigative group is capable of conducting successful hospital and emergency department based interventions to safely and effectively deliver thrombolytic therapy.

Table C2: ICH rates for Emergency Physician delivered tPA in acute stroke (1996-2001)[19]

	EP Delivery[19]	NINDS I[11]	NINDS II[11]	Grond[13]	Cleveland[6]
n	168	144	168	100	70
Symptomatic ICH	8%	6%	7%	5%	14%
Asymptomatic ICH	2%	3%	5%	6%	not reported
Total ICH	**11%**	**9%**	**12%**	**11%**	**14+%**

C.2 Success in increasing tPA use using an educational intervention

C.2.1 TLL Temple Foundation Stroke Project

Dr. Lewis Morgenstern is the Principal Investigator of the TLL Temple Foundation Stroke Project.[2] This community-based, health promotion project successfully increased IV-tPA use in stroke in rural Texas.

C.2.2 Intervention planning and conduct for the Temple Project

The intervention that proved successful in the TLL Temple Foundation Stroke Project was created through a systematic development process[67] which included focus groups, community leaders, health care professionals, and literature sources. The resulting intervention used a multi-level educational process that included: individual contact and explanation of guidelines to EPs; system changes within the targeted hospitals; changing staff perceived norms; reinforcement of behavior change through peer interaction; encouraging multidisciplinary team development; providing treatment protocol development assistance; continuing medical education and conducting mock stroke codes for the hospital.

C.2.3 TLL Temple evidence for educational efforts to increase tPA use

Five rural Texas hospitals were recruited for the study. The goal was to increase the proportion of ischemic stroke patients treated with intravenous tPA in the intervention community. There was an 8-month baseline phase and 15-month intervention phase (consisting of intensive community and professional education). 1736 patients were prospectively evaluated with 1191 validated as having cerebrovascular events. A 6-month follow-up phase identified an additional 238 cerebrovascular events and has been recently reported.[22] Table C3 provides the primary outcome measure demonstrating a significant increase in thrombolytic use compared to baseline in the intervention hospitals. Of note, 11.25% of patients with ischemic stroke were treated with tPA in the follow-up phase.

Table C3: TLL Temple Study: Proportion of ischemic stroke patients treated with intravenous tPA

	Baseline Phase (N=424)		Intervention Phase (N=767)			Follow-up Phase (N=238)		
Community	N	%	N	%	p	N	%	p*
Intervention	3/136	**2.21**	23/267	**8.61**	**0.02**	9/80	**11.25**	**0.007**
Comparison	1/141	0.71	2/234	0.85	1.00	1/70	1.43	1.00

* Fischer's Exact Test for comparison of Baseline and Follow-up phases

C.2.4 TLL Temple evidence for the importance of professional education in increasing tPA use

Of eligible IV tPA candidates, treatment increased in the intervention community from 14% to 52%, p=0.003, and was virtually unchanged in the comparison community, 7% to 6%, p=1.00. Additionally, patients eligible for IV tPA experienced less hospital delay and less unexplained non-treatments in the intervention phase at the treatment hospitals compared to baseline and control groups. This supports our contention that the professional component was likely the critical element of the combined community and professional education process in the Temple project.

C.2.5 TLL Temple evidence for durability following termination of the educational intervention

The final phase of the TLL project has been published and consists of the six-month period following removal of the intensive community and professional educational campaign. The proportion of ischemic stroke patients treated with IV tPA continued to increase in the intervention community hospital (Table C3); increasing five-fold compared to their baseline data. There was no appreciable change in the comparison community hospitals. Thus, it appears the intervention is durable in the short-term following termination of the educational effort.[22]

C.2.6 TLL Temple project summary

The results of the TLL Temple project demonstrate focused educational efforts can increase the rate of thrombolytic use in stroke and that the professional educational component likely had the largest impact on tPA delivery. Limitations of the TLL project include its non-randomized design, exclusion of urban populations and lack of standardization of the intervention – elements that have been included in our proposed project.

C.3 Use of ICD-9 codes to determine admission CVD case frequency - data from the BASIC study

Dr. Morgenstern is also the Principle Investigator on The Brain Attack Surveillance in Corpus Christi (BASIC) study (RO1 NS 38916). The goal of this project was to provide a scientific rationale for choosing an optimal stroke surveillance method by comparing active and passive stroke surveillance. Project data has been published for calendar year 2000 analyzing the use of ICD-9 codes in passive surveillance for ischemic cerebrovascular disease. Of the 2,099 screened hospital admissions, 815 had been assigned an ICD-9 discharge diagnosis of 430-438. Of these 815, 666 were validated as acute cases of cerebrovascular disease by study neurologists. 593 of these were correctly identified by ICD-9 codes as acute cerebrovascular events. Therefore, the sensitivity and positive predictive value of discharge ICD-9 codes for admitted hospital events were 89 percent (593/666) and 73 percent (593/815), respectively.[68]

The advantages of using ICD-9 codes (passive surveillance) include its efficiency and the possibility of review of completed charts at a future time following code assignment. While a combined active and passive surveillance approach would improve the sensitivity of identification of admitted cerebrovascular disease cases in the BASIC study an additional 11% it would come at a prohibitive cost for our proposed project.

C.4 Development of process to identify cases of tPA use in stroke

As part of the UM Stroke Registry we have used the capability of computerized pharmacy dispensers to track emergency department use of tPA. These systems provide monthly reports on all thrombolytics used in the emergency department. The reports specify drug, date/time used and patient and nurse identification and can be run on daily, weekly, monthly or annual periods.

The February, 2003 release of Michigan state data from the Paul Coverdell National Stroke Registry (MASCOTS; Dr. Susan Hickenbottom, UM Principle Investigator) has provided a unique opportunity to evaluate the accuracy and efficiency of our tPA case identification method by comparing pharmacy reports with the validated MASCOTS data set. Preliminary data (12 of 16 MASCOTS sites reporting) indicate computerized dispensers are ubiquitous in their distribution. Comparison of dispenser data from a 2 hospital subset (UM and SJMH) indicate 100% accuracy in case identification and required less than 30 minutes of investigator time at each hospital to complete case ascertainment for all records over a six month period. (Unpublished data: Phillip Scott). This novel approach to identifying tPA use in stroke offers unique advantages in the frequency of data capture and ease of data gathering (by eliminating previous emergency department and ICU log reviews) with the potential of enhanced accuracy over previous processes.

C.5 Evidence for quantitative and qualitative analysis of treatment barriers

The following studies demonstrate our team's experience in assessing barriers to guideline adherence and endorsed "best practices," such as the use of tPA for stroke.

Our team previously reviewed barriers to physician adherence to clinical practice guidelines using a systematic review.[46] After reviewing 5658 articles, we found 76 articles that included 120 different surveys investigating 293 potential barriers to physician guideline adherence. This review allowed our team to develop a framework for why physicians do not follow practice guidelines or best practices of care, such as the appropriate use of tPA. This barrier framework includes lack of awareness (n=46), familiarity (n=31),

agreement (n=33), self-efficacy (n=19), outcome expectancy (n=8), ability to overcome the inertia of previous practice (n=14), and absence of external barriers to perform recommendations (n=34).

Most studies of guideline adherence (70 of 120, 58%) examined only 1 type of barrier. We found that studies on improving physician guideline adherence may not be easily generalized, since barriers in one setting may not be present in another. From this work in developing a theoretical foundation we were able to develop tools to assess barriers to guideline adherence.

In 2000, members of our team developed qualitative methods to assess barriers to adherence.[69] We conducted a series of focus groups with physicians to understand barriers to the use of national guidelines, in this case, for asthma. We found that physician characteristics are related to which barriers are prominent for the prescription of medications. We identified 171 comments about barriers to adherence and found that senior physicians mentioned lack of agreement with medication recommendations, whereas younger physicians described lack of confidence in dosing or recognizing contraindications. Only senior physicians described the inertia of previous practice as a barrier. All groups mentioned time limitations. As a result, interventions to improve guideline adherence should be tailored to these factors. This study allowed our team to develop qualitative methods to assess barriers to adherence that we will apply to the proposed study.

Finally, our team has previously demonstrated expertise in surveying practicing physicians to identify barriers to physician adherence to national guidelines for asthma, based on our focus group analysis.[70] After controlling for demographics and other barriers, we found non-adherence was associated with specific barriers for each guideline component. For daily inhaled corticosteroid prescription, lack of agreement (OR, 6.8; 95% CI, 3.2-14.4) was a significant barrier to adherence. Although pediatricians in this sample were aware of the national guidelines, a variety of barriers precluded their successful use. We also learned that controlling for the presence of other barriers in the analysis was important in finding the most significant barriers. This study allowed our team to develop quantitative methods to assess barriers to adherence that we will apply to the proposed study.

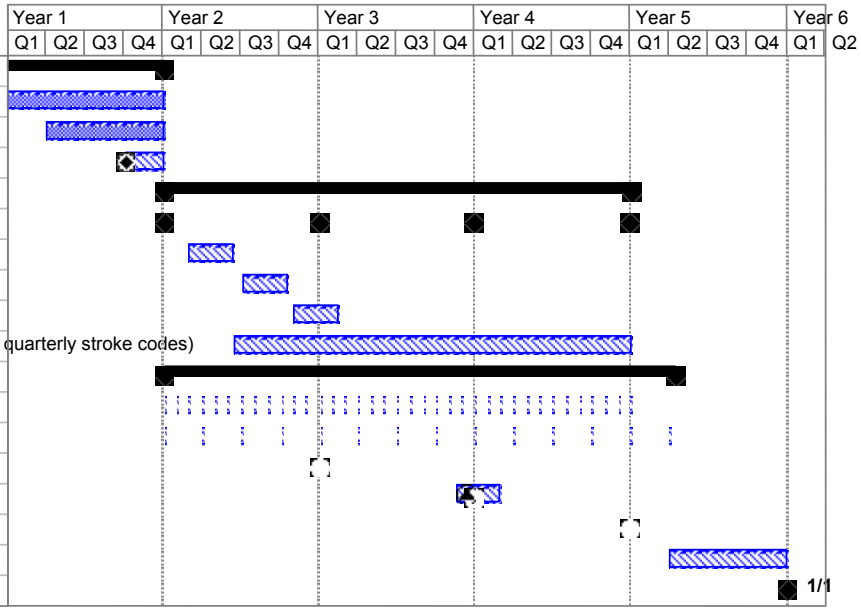
C.6 Investigational team expertise in developing educational interventions

We are currently applying tailored message techniques to an educational intervention (R01 HL70771, Enhancing Pediatric Asthma Management; M. Cabana, PI; see C.5) to improve outpatient, primary-care physician prescription of inhaled-corticosteroids for asthma. Inhaled daily corticosteroids for asthma have similarities to tPA use in stroke, as they are both proven cost-effective medications underutilized by physicians. We plan to apply these techniques in designing appropriate educational messages and interventions for physicians to improve their use of tPA for stroke in the emergency department. We recognize many EDs lack resources to develop an infrastructure to deliver tPA for stroke patients and external funding/support is limited. Therefore, our educational system represents a “turnkey” intervention. The process incorporates what we believe is the maximum educational intervention which could be duplicated by a comprehensive stroke center in a small set of regional hospitals without substantial external funding.

D Research Design and Methods

D.1 Project timeline

ID	Task Name
1	**Pre-Intervention Phase**
2	Hospital recruitment, contracts, baseline data
3	Instrument/Curriculum development and testing
4	EP pre-test
5	**Intervention Phase**
6	**Champions Meeting (n=4)**
11	Barrier Assessments (sites 1 - 12)
12	Interactive Educational Intervention 1 (sites 1-12)
13	Interactive Educational Intervention 2 (sites 1-12)
14	Other interventions (email, CID, stroke team access, quarterly stroke codes)
15	**Post Intervention Assessment**
16	**Monthly tPA use data**
86	**Quarterly ICD-9 discharge data**
114	
115	EP 12-month post-test
116	
117	Data Analysis/Publication
118	Final investigators briefing



D.2 Overview

The INSTINCT Trial (**IN**creasing **S**troke **T**reatment through **IN**terventional behavior **C**hange **T**actics) will be a multi-center, randomized, controlled trial testing the effectiveness of a standardized educational intervention in increasing the use of IV tPA in acute ischemic stroke. Our intervention specifically targets emergency departments and emergency physicians for improvement in adherence to NINDS recommendations regarding thrombolytic use in stroke using a multi-level, systems-based, educational approach. Due to its economy and straightforward approach, the intervention is designed for inclusion in community public health initiatives.

The primary endpoint will be an absolute increase of ≥ 4% in the proportion of stroke patients appropriately treated with IV tPA in intervention hospital emergency departments compared to matched hospital controls. We will also measure pre- and post-intervention changes in emergency physician knowledge, attitudes and beliefs regarding tPA use in stroke in both control and treatment groups.

The educational intervention combines barrier-assessment methodology - identifying why physicians are reluctant to adhere to published guidelines regarding stroke treatment[46, 70] - with targeted interactive educational interventions adapted from our previously successful TLL Temple project to increase tPA use in stroke.[2] This Barrier Assessment – Interactive Educational Intervention (BA-IEI) method incorporates additional educational elements from the Michigan stroke team's experience in developing emergency physician delivery systems for tPA administration.[18, 19]

The pre-intervention phase of the project will begin in Year 1. We have already accomplished many of the originally stated goals of the pre-intervention period since our initial submission of Feb 2004. We have randomly selected and recruited 12 pairs of hospitals (24 sites), matched for number of patients admitted with ischemic cerebrovascular disease and hospital demographics from the population of all eligible Michigan hospitals, and have successfully enlisted their participation in the study. We have also recruited two experienced clinical nurse coordinators to assist in study and data management.

Important objectives remaining for Year 1 include: establishing and testing data collection links with each hospital, and local site IRB approvals. We will then collect a total of 12 months of retrospective baseline data on tPA use from the study sites to establish the pre-intervention proportion of patients with ischemic cerebrovascular disease receiving tPA at each hospital. Hospitals will then be randomized to intervention or control groups, within pairs, using adaptive randomization techniques as described in Section D.7.2. Over the first year, we will complete development of the emergency physician survey instruments to assess knowledge,

attitudes and beliefs regarding TPA use. The survey instruments and planned standardized educational interventions will be pilot-tested at sites not participating in the study. The baseline knowledge/beliefs survey will be given to ≈ 400 emergency physicians in the 4th quarter of Year 1, with the intervention to begin afterwards.

At the beginning of the intervention phase, the site-investigator/physician "stroke champion" and other personnel from each of the 12 intervention hospitals will meet for a one-day, "Champions meeting." This session will primarily provide acute stroke treatment training and a preliminary exploration of the barriers to thrombolytic use at their respective facilities. The barrier assessment portion will be conducted using appropriate focus group methodology and recorded. Transcripts from the recordings will be analyzed by two researchers and comments regarding barriers will undergo a structured assessment designed to assign comments to a specific barrier taxonomy using our framework detailed in section C.5. Follow-up meetings with the investigator/champion teams will occur annually to reinforce institutional change.

Following the Champions meeting, each intervention hospital will undergo a one-day, site visit by an Intervention Team consisting of physician investigators and nurse coordinators / health educators from the coordinating center to complete the evaluation of barriers to tPA use in stroke. This will provide both qualitative and quantitative detail to the above preliminary assessment. To achieve this, a series of focus group meetings will be conducted with 1) the emergency physician staff and 2) emergency department nursing/ancillary staff along with a series of structured interviews with representatives of 1) neurology, 2) radiology and 3) hospital administration focusing on barriers to stroke treatment. The recorded transcripts of these meetings will be analyzed in the same fashion as those obtained from the Champions meeting. An assessment of physical resources and available stroke treatment tools will also be completed at this visit.

Each intervention hospital will then have two interactive educational interventions conducted by the coordinating center Intervention Team, each lasting approximately one day in length and occurring at three-month intervals. These interventions will begin with the conduct of a standardized mock "stroke code" scenario for the emergency department and be followed by a mixed CME session which will address specific barriers identified earlier. Ongoing stroke "champion" development will continue during these sessions along with tPA protocol development/refinement as needed.

After the first interactive educational intervention, the emergency department will be provided with 1) 24/7 telephone access to the Michigan stroke team for questions regarding thrombolytic use; 2) information on web-based resources for stroke treatment; 3) targeted e-mail / telephone feedback on site performance with respect to tPA use; and 4) physician/staff critical incident defusing/debriefing for serious protocol violations or any post-treatment ICH. Following the second interactive educational intervention the local champion/investigator will conduct quarterly mock stroke code drills for the emergency department using a standardized scenario. Emphasized within this intervention are the use of readily available, low-cost, interventions and automated data collection methods to enhance acute treatment of ischemic stroke and evaluate intervention effectiveness.

Post-intervention assessments of emergency physician knowledge, attitudes and beliefs regarding tPA use will be completed in both intervention and control groups 12 months following the second interactive educational intervention. Data on tPA use will be collected from all sites monthly along with admission data for patients with ischemic cerebrovascular disease (CVD) which will be collected quarterly. Appropriate use of tPA, and complications, will be determined by blinded retrospective chart review of the EMS, emergency department and inpatient records to provide feedback reinforcement to individual sites/physicians. These outcome measures include evaluation of the impact of the intervention on emergency physician knowledge and beliefs as well as actual behavior in using tPA in stroke.

D.3 Study population

D.3.1 Development of the hospital sample (study unit)

The study hospitals will be drawn from the pool of all Michigan acute care hospitals located in the Lower Peninsula.

Exclusion criteria:

- Primary children's, psychiatric, or long-term (convalescent) care hospital

- Established academic comprehensive stroke center (Detroit Receiving Hospital, Henry Ford Hospital, University of Michigan)
- Annual emergency department volume greater than 100,000 patients per year (only one hospital)

The exclusions for non-acute care and academic medical centers allow the intervention to focus on the unit of interest for future interventions, community hospitals which treat patients with acute stroke. The exclusion of hospitals in the Upper Peninsula of Michigan was made for travel and budget considerations, allowing access to recruited sites by automobile travel alone. The exclusion of hospitals with emergency department volume greater than 100,000 patients per year was made to exclude one hospital outlier with a stroke volume of 1,741 discharges per year for which no match was possible. Small hospitals with less than 100 stroke discharges per year were excluded to ensure an adequate number of treatable strokes in the sample.

Selected hospitals must subsequently meet the following *inclusion criteria* for participation:

- Physician staffed emergency department at all times
- 24/7 CT scanning availability
- Computerized pharmacy dispensing system for the emergency department or thrombolytic use log
- Agreement to participate and identified site investigator.

These criteria ensure only physicians would be responsible for patient identification and drug delivery, that the study was not confounded by sites without CT access (and therefore could not treat), that tPA use could be monitored, and the hospital desired to participate.

Hospital (study unit) recruitment

Based on our original sample size estimates (+ 20% oversampling), we drew a sample of 12 pairs of hospitals matched on the basis of stroke volume, location (urban/rural) and for-profit/not-for-profit status which were geographically isolated from each other. See Section D.7.1 for Selection and Matching procedure. The investigators, with the assistance of the Michigan Hospital Association and Michigan State Medical Society, contacted the identified hospitals regarding participation and inclusion / exclusion criteria. A total of twenty-eight hospitals were contacted. The four hospitals not participating were all excluded on the basis of failure to agree to participate. At this time, we have recruited the originally proposed 12 pairs (see Fig D1, below and Appendix A). This suggests broad community physician interest in the project.

The hospital sample is representative

Because this study is being conducted for the purpose of recommending an intervention for broad scale adoption, considerations regarding the external validity of the results are important.

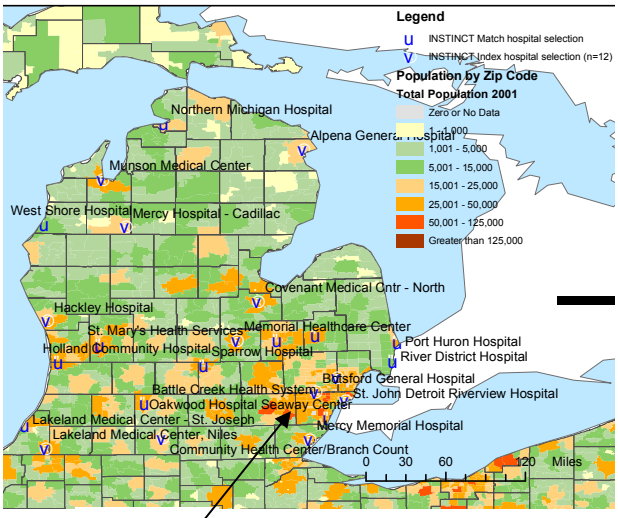
The available hospital population for sampling includes hospitals from a variety of practice settings: Although our sample is not drawn from the entire U.S. population of hospitals we believe the results can be generalized to a variety of hospital settings. The available hospitals represent for-profit and not-for-profit facilities along with teaching and non-teaching centers and span a substantial range in size, volume, and locations. Because we will assess hospital and emergency department practice characteristics we will be able to make comparisons to the broader group of hospitals and emergency departments across the country.

The available hospital population includes diverse geographic regions. Figure D1 provides the location of the recruited hospitals along with data on surrounding population density. The selected hospitals represent a wide spectrum of demographic regions - encompassing urban, suburban and rural populations – and therefore will allow comparisons to a broad group of hospitals nationally. As a result of this variety, the patients with acute stroke seen by these facilities can be expected to come from diverse socioeconomic populations.

Requirement and importance of geographic separation between study hospitals

The development of a stroke treatment system in an intervention hospital could be perceived as a competitive disadvantage by a nearby control hospital. As assignment to intervention or control groups does not occur until the end of Year 1, all hospitals will be geographically isolated from all other study hospitals at the time of selection from the eligible hospital pool to avoid future potential contamination or loss from the study. See D.7.1 for detail. A separation of ≥15 miles between facilities is required, with this distance selected on the basis of previous EMS system modeling for acute stroke care delivery in southeastern Michigan.[71]

Figure D1: Recruited Hospitals and Population



D.3.2 Assessment of secular trends in stroke treatment

We will assess secular changes in stroke treatment by monitoring volume and demographic characteristics of patients discharged with an ICD-9 diagnosis of ischemic cerebrovascular disease.

D.3.3 Validity and maintenance of the physician sample

The study targets community physicians. Given the diverse nature of the hospitals involved, the hospital-based emergency physician, neurology and radiology staffs are likely to reflect diverse training and practice backgrounds. Evidence to support this contention in our hospital sample with respect to gender and minority distributions are presented in Section E.7 and E.8. We will assess the educational and training background of participating emergency physicians, in order to make comparisons to the broader group of emergency physicians across the country. We anticipate a 2 percent or less turnover per year in the emergency physician staffs at the participating hospitals based on available data[72, 73] and have oversampled the needed number by approximately 10%.

D.4 Outcome measures

Outcome measures of the effect of the intervention include both behavioral and knowledge assessments, specifically: 1) Change in the proportion of admitted patients with ischemic CVD treated with tPA between intervention and control groups. 2) Change in the proportion of patients with ischemic CVD appropriately treated with tPA. 3) Pre- and post-intervention changes in tPA use. 4) Pre- and post-intervention change in physician knowledge, beliefs and attitudes toward tPA use in stroke comparing treatment and control groups and 5) Pre- and post-intervention change in physician knowledge, beliefs and attitudes within groups. Other outcome measures include: interval treatment times, post-treatment ICH and frequency and type of inappropriate use of tPA. We also plan on performing exploratory cost-effectiveness analysis of the intervention in the proposal. Dr. Mark Fendrick, Professor of Internal Medicine at UM, is a recognized expert in this area and has been included in the project to assist in the design of data collection and analysis in the proposal.

D.4.1 Proportion of patients with ischemic CVD treated with tPA

The multi-level intervention may influence the distribution of the time from symptom onset to presentation at the hospital, as well as the emergency department's response once the patient has arrived. We therefore do not think that the appropriate denominator for analysis is the proportion of patients that are eligible for tPA since this is a variable we are trying to influence, Additionally, accurate determination of total patient eligibility would require an active patient screening at both intervention and control hospitals which could influence behavior at the control hospitals. Preliminary and published data suggest that combining computerized pharmacy surveillance for tPA case identification with ICD-9 coding surveillance for admitted patients with

ischemic CVD will provide an optimum combination of accuracy and practicality in determining the proportion of patients with ischemic CVD treated with tPA. By using the proportion of patients treated, we control for the possibility of sudden large changes in local referral patterns for stroke care (e.g. hospital closures, EMS system changes, or population demographic changes) – a consideration in a multi-year study. The change in proportion will be measured in each matched pair from the date of the first interactive educational intervention in the treatment hospital going forward for 24 months. This time-frame was selected to provide a measure of the durability of the educational intervention.

D.4.2 Use of computerized pharmacy dispenser surveillance to identify thrombolytic use

Our use of monthly pharmacy dispenser surveillance to identify tPA use in acute stroke (see C.4 for detail) provides data for outcome assessment and inexpensive and proximate monthly feedback to intervention hospitals and staff on the number of tPA treated stroke patients - an important factor in enhancing changes in adult behavior.[74] 92% (22/24) of recruited hospitals use computerized dispensers. The two hospitals without electronic dispensers use thrombolytic logs currently and are planning to upgrade. We anticipate 100% computerized dispenser availability by study initiation. Pharmacy Department charge reports will be used if the computerized dispensing system is not able to provide the necessary data.

D.4.3 Use of ICD-9 coding to identify admitted patients with ischemic cerebrovascular disease

We will establish the total number of admitted patients with ischemic cerebrovascular disease using computerized hospital discharge ICD-9 billing codes of 430 through 438 (see C.3 for detail). ICD-9 discharge codes 434, 435, 436, 437.1 and 437.6 will provide the denominator for determination of the proportion of patients with ischemic cerebrovascular disease appropriately treated with tPA. This data will be obtained quarterly from all study sites. Corresponding updated ICD-10 codes will be included when released.

D.4.4 Determination of "appropriate" tPA use and patient characteristics

Previous studies have found an association between increased risk of ICH and tPA use outside recommended guidelines.[75] Thus, one outcome measure incorporates a determination of "appropriateness" for the use of tPA in all cases based on a medical chart audit instrument we have previously developed and used with the UM stroke registry. Each tPA treated stroke case will undergo evaluation by 2 separate, independent reviewers blinded to intervention or control status for determination of appropriateness of use. We consider a patient to have appropriately received tPA if there are no absolute contraindications to tPA use on retrospective evaluation of the patient's admission record. Due to slight variations between the recommendations over time, three sources will be used for comparison: inclusion/exclusion criteria for the NINDS trial, the 2005 AHA/ASA Guidelines for Thrombolytic Therapy for Acute Stroke [10], and the FDA approved labeling for Activase. Cases will be reviewed monthly from all study sites using an explicit chart review instrument and rules (see C [Definitions and Rules] and Appendix M [Medical Reviewer's Chart Review]). In addition, the following data elements will be obtained quarterly (see Appendix B [Nursing Chart Review]):

- Interval treatment times
- Sociodemographic data
- Medical history
- Medications
- Co-morbid conditions
- Concurrent interventions and diagnostic studies, including neuroimaging
- Clinical course
- Disposition

In the case of disagreement between the reviewers, a third, blinded reviewer will adjudicate. This outcome measurement will be assessed within each hospital pair from the time of completion of the first interactive educational intervention in the treatment group and continuing for a period of 24 months.

D.4.5 Emergency physician knowledge, attitudes and beliefs regarding tPA use in stroke

Changes in physician knowledge or attitudes regarding tPA use represent intermediate outcomes. We will use a professionally developed, self-administered, self-reported, physician survey to assess knowledge and attitudes regarding the use of thrombolytics in stroke (Appendix D). The instrument will be based on similar

assessments of physician adherence to guidelines[76-78] and adapted from our previous work[70] for use in stroke. This assessment will evaluate changes in physician knowledge concerning label and NINDS recommendations for the use of tPA in acute ischemic stroke (awareness and familiarity); attitudes regarding use of tPA in acute stroke (agreement, self-efficacy, outcome expectancy, and inertia, or readiness to change); willingness to use tPA and the implementation of system changes to improve physician use of tPA in acute stroke. This instrument will also provide demographic data on the study physicians to allow comparison to the emergency medicine community as a whole. We will also measure the presence of "external" barriers using the assessment tool. These include: lack of educational materials, lack of efficient screening tools, perceived lack of specialty support and lack of time or volume considerations. Changes in external barriers may reflect the effects of the BA-IEI intervention in promoting systems changes.

Design of the physician knowledge survey

All emergency physicians at each participating hospital are eligible and will be surveyed in the same month with the same methodology. The survey will be pre-tested and pilot tested during the development phase on samples of similar physicians in hospitals not included in the study. Pre-testing will focus on length, validity and question design. Pilot testing will focus on these issues and also on feasibility and implementation of the on-line survey system described below. Since we already use this approach successfully, we do not anticipate any significant problems. The survey assessments will be completed at baseline (pre-intervention) and 12 months following the second IEI as detailed in the timeline (see D.1). This will allow pre- and post-interactive educational intervention evaluation among physicians at intervention hospitals and between treatment and control hospital physicians.

Sampling. The total number of eligible physicians is ≈ 400. We will include all ED physicians in both intervention and control hospitals in the survey and repeat the survey to all regardless of response to previous surveys. This provides two points of comparison for examining changes over the study period. Therefore, a maximum total of about 800 surveys will be administered. The average number of ED physicians per hospital is 14, ranging from 5 to 35 with some differences in the number of physicians between matched intervention and control hospitals. We have decided on a universal sample to limit the possibility of small cell sizes at analysis. Our online survey methodology will allow this to be done efficiently.

Sampling frame. Each hospital site principal investigator will provide us with email and phone contact numbers for the emergency physicians at their facility which will be updated just prior to each survey wave.

Methods of survey administration.

The survey will be administered via a highly secure, web-based system (Survey Monkey) that is in use by Dr. Haan's research projects. Draft online forms have been designed and pre-tested and include automatic quality controls. We expect all hospitals will have computer/web access for ED physicians. For physicians that indicate a preference for paper surveys, we will send them the survey with a stamped return envelope. We have programmed quality and logic checks built into the system that can generate error reviews. This will be done for every returned/completed survey. The staff will re-contact the physician to clarify responses that are missing or are not logical.

Participation rate. Each individual will be contacted, via email or letter, up to 3 times to complete the consent and survey (either online or paper). Non-responders after 3 contacts will be contacted by staff from the Clinical Coordinating Center by phone or email, and offered the survey by phone interview, internet or paper. For persistent non-responders, the local site investigator will be asked to personally contact them and hand them a copy of the survey and Self Addressed Stamped Envelope and encourage completion. Each hospital emergency physician group will be allocated one $50 incentive for each set of surveys (total = 2) to be awarded by random selection following completion of surveys from the site. Given the small group structure of the emergency physicians supporting each hospital, we anticipate this will bring additional encouragement for timely survey completion.

Retention. Emergency departments are likely to experience some turnover in ED physicians during the study period. We estimate that 2% per year of the physician cohort will move to other employment or retire during the study period, for a total of 22/390 over the study period. There may be more interest among those in the intervention hospitals to remain in the study. The local site PI is essential in ensuring retention. They will be asked to (a) provide updated lists of providers before each survey date; (b) encourage

participation, and (c) provide follow up information so we can locate physicians who have moved, retired or died.

Since we expect some turnover in the sample, we will replace ED physicians who leave the hospitals with whoever takes their place. If they move to another hospital in the study, we will still include them even if they move from an intervention to control or vice versa. One could argue that physicians who move from intervention to control would affect the knowledge level. These will be categorized in a manner analogous to those who switch drug therapy in a clinical trial. Since we will use an intention-to-treat analysis for the physician knowledge study, it is appropriate to include these. We will also attempt to obtain surveys for those moving to other hospitals outside of the study or retiring in keeping with this standard approach.

D.5 Treatment protocol

PRE-INTERVENTION PHASE

D.5.1 Establishing baseline tPA use in ischemic stroke

In the pre-intervention phase, 12 months of retrospective data on tPA use in ischemic stroke, and the total number of patients discharged with a diagnosis of ischemic cerebrovascular disease will be collected from study hospitals to establish the baseline proportion of stroke patients receiving tPA.

D.5.2 Establishing baseline emergency physician knowledge, attitudes and beliefs regarding tPA use

During the pre-intervention phase we will establish the baseline knowledge and attitudes of emergency physicians regarding tPA use in stroke using the questionnaire described in D.4.5. This will provide qualitative and quantitative data on the barriers to tPA delivery along with EP demographic data.

INTERVENTION PHASE

D.5.3 INSTINCT site Champions meeting

Representatives from the 12 hospitals randomized to the treatment group will meet in Ann Arbor, MI at the initiation of the intervention phase for a one-day meeting. Attendees will include the identified local INSTINCT site investigator, local champion (this may be the same individual) and additional 2-5 key hospital personnel from nursing and administration as selected by the site investigator. In addition to the goals below, this allows an opportunity for networking and collaboration among intervention hospitals and provides a basis for the development of competition between sites in achieving the project goals of increasing appropriate tPA use.

The purpose of this meeting is to:

- Review the objectives of the INSTINCT project
- Develop local champions' knowledge base to assist them as institutional acute stroke leaders
- Assess local barriers to acute stroke treatment with tPA
- Determine local resources needed to enhance tPA use
- Evaluate planned site interventions

The INSTINCT objectives and background on tPA use will be a two-hour interactive session conducted by the investigators. Following the presentations, the investigators will conduct focus group sessions with the attendees to assess site barriers to the use of tPA in acute stroke, local resource needs, and assess the proposed interventions. Attendees will be organized into groups by hospital. Two teams of moderators will lead the sessions in a standard format. These sessions will be approximately 3 hours in length and recorded in their entirety using non-concealed microphones.

We will ask open-ended questions to elicit barriers to the use of tPA and specifically, emergency physician acceptance. We will specifically ask about needed physician skills and local resources to adhere to tPA use recommendations. We will also assess our planned interventions by asking participants about the appropriateness, acceptability, and predicted success of the proposed interventions. If the group indicates low

likelihood of success for a given intervention, we will ask why the intervention is incorrect, and what modifications can be made to improve its usefulness. The interventions are described in detail in D.5.5 - 5.12.

Analysis: Recordings of the focus group sessions will be transcribed verbatim, except for identifying information. Two investigators will independently analyze each transcript, using accepted methods from grounded theory[79] and content analysis[80], and mark comments about barriers to adherence. They will classify comments into the taxonomy of barriers described in C.5, above. To standardize analysis, each investigator will be provided with a brief description of each category of barriers and asked to classify the barriers as an internal barrier, external barrier, or ambiguous.

The remaining portion of the initial INSTINCT Champions meeting will be dedicated to reviewing data collection methodology, quality assurance feedback and establish individual site priorities for the upcoming site visits.

D.5.4 INSTINCT on-site barrier assessment

Following completion of the initial INSTINCT local champions' meeting and completion of the focus group data analysis, a coordinating center team (comprised of the physician investigators, nurse coordinator / health educator) will visit each of the 12 intervention hospitals to conduct an on-site barrier assessment. This one-day site assessment will consist of both qualitative and quantitative barrier assessments with input from emergency physicians, emergency department nursing, triage and ancillary personnel; and representatives of radiology, neurology and primary care (internal medicine and family practice).

The purpose of the on-site assessment is to extend and confirm the information obtained from the individual site representatives obtained at the Champions meeting. More important, however, it initiates a broader process of adult learning based on principals of adult education[60] for the emergency department and hospital as a whole and the emergency physicians and staff in particular. While health care providers possess strong internal motivation to assimilate new information in order to improve the quality of care they provide, this desire must compete against numerous environmental barriers. Since behavioral change to increase tPA use in stroke needs to occur within a complex organization (hospital) the organization's barriers to treatment must be identified, understood and removed for education to succeed.

The on-site presence of external investigators working in collaboration with a local champion and local administrative support (as evidence by participation in the INSTINCT trial) to visibly identify treatment barriers utilizes optimum methods of behavior change with regards to stroke care.[81, 82] Further, it represents the initiation of a multi-sequence educational intervention – the qualities attributed to the most successful methods of professional education.[83] The specific time of the assessment will be arranged with the INSTINCT site investigator and local champion and their participation will be required. The following qualitative assessments will be completed:

Site emergency physician focus group:

The coordinating and site investigators will begin by introducing the specific aims of the INSTINCT trial and reviewing background data on the utilization of tPA in stroke both statewide and nationally. A barrier assessment using the format above (D.5.3) will be conducted. This session will be approximately 1 hour in length and tape recorded in its entirety using non-concealed microphones. Particular care will be made to include the Emergency Department director and other educational influentials identified by the site investigator. Open-ended questions to elicit barriers to successful use of tPA, insufficient local resources and intervention appropriateness - similar to the Champions meeting - will be used. We will use the same mechanism as described in the previous section for transcript analysis throughout the barrier assessment interviews.

Site emergency nursing and ancillary staff focus group:

This will be similar in conduct, duration and execution as the Emergency Physician focus group. The session will be arranged in advance and will include 4 – 8 individuals from the emergency department nursing and ancillary staffs. Particular care will be made to include the Emergency Department nursing administrative director and any other nursing and ancillary staff educational influentials identified by the site investigator. Open-ended questions to elicit barriers to successful use of tPA in acute ischemic stroke will

be used. We will also ask about specific nursing skills needed to: identify stroke patients, use a triage stroke tool (e.g. Cincinnati Pre-hospital Stroke Scale), tPA dosing, recognizing differences between various available thrombolytics, mechanisms to obtain and use thrombolytics from pharmacy, stroke protocol awareness. Additional specific questions will assess external barriers: patient transport issues, nursing staff shortages and emergency department overcrowding and diversion. We will ask open-ended questions to identify gaps in physical resources. We will specifically ask about stroke protocol availability and ICU bed availability. We will also ask about the acceptability of the interventions proposed in the project.

Structured site interviews (3)

Structured interviews will be conducted at each site with representatives of Neurology, Radiology and Hospital Administrations. These will be arranged in advance and will be individual or small group interviews (1-3 individuals) to assess the local environment with respect to size, specialist availability, practice constraints and internal and external barriers to thrombolytic use in stroke. They will be conducted in a private location using a standard discussion guide for structured interviews. Each session will last approximately 1 hour and be recorded. Both open-ended and specific questions will be used with probing techniques utilized to clarify incomplete or unclear responses. Specific elements for inclusion within each interview are listed below. We will also ask about the appropriateness, acceptability, and predicted success of the interventions proposed in the project. Particular attention will be given to any opinions regarding enhanced physician telephone access to an outside stroke thrombolytic expert. If the interviewee indicates unfavorable responses for a given intervention, we will ask why the intervention is incorrect, and what modifications can be made to improve its usefulness. Specific elements of each interview are:

Site Neurology Interview

We will specifically inquire about the number of neurologists at the participating hospital, after-hours and on-call neurologist availability, prior use of thrombolytics (both intravenous and intra-arterial) in stroke and agreement with American Academy of Neurology guidelines for tPA use in stroke. We will specifically ask about stroke protocol availability, CT availability and presence of dedicated neurological ICU space.

Site Radiology Interview

Open-ended questions to elicit barriers to emergent CT imaging in acute ischemic stroke will be used. We will also specifically ask about the number of radiologists at the participant hospital, after-hours and on-call availability, the use of telemedicine resources for CT image interpretation (along with information on image transfer time and quality), prior experience with thrombolytic delivery (both intravenous and intra-arterial) in stroke and knowledge of professional recommendations for tPA use in stroke.

Site Hospital Administrator Interview

Open-ended questions to assess knowledge of professional and governmental (NINDS) recommendations for use of tPA in stroke will be used. We will also specifically ask about hospital certification as either a Primary Stroke Center as qualified by the Brain Attack Coalition and HMO requests for demonstration of stroke treatment capability. Additional questions will address plans to meet *Joint Commission on Accreditation of Healthcare Organizations (JCAHO) "Core Measures"* recommendations regarding thrombolytic use[84] and meeting proposed JCAHO recommendations for stroke center certification - a powerful motivator for improving acute stroke care.

Quantitative site resource assessment

We will quantitatively assess the physical presence of resources considered important in the delivery of tPA in stroke at both treatment and control hospitals. The absence of such would represent external barriers to tPA delivery. This assessment is a separate element from the emergency physician survey described in D.4.5. This assessment will be conducted by a representative of the coordinating center and site investigator using a checklist tool during a physical walk-through of the triage, emergency, radiology and inpatient areas. Accompanying the coordinating center team will be the site investigator and nursing director.

Descriptive statistics will be generated evaluating each element of the resource evaluation. Exploratory data analysis will be conducted and comparison made to emergency physician survey data. We hypothesize hospitals with EPs reporting greater barriers to tPA use will have a lower frequency of physical elements enabling acute stroke care.

D.5.5 Targeting interactive educational interventions

As outlined above, analysis of these evaluations will use our previously developed barrier classification framework (see C.5). Subsequent, interactive educational interventions will target specific barriers as identified. Interventions for each site will include the following standard elements:

- Local "stroke treatment" champion(s) development
- Thrombolytic stroke treatment protocol development / refinement
- First interactive educational intervention sessions (two parts, 1 and 2)
- Mock "code stroke" scenarios for system testing
- Telephone access to the Michigan Stroke Team for thrombolytic use expertise
- Academic detailing / tPA use feedback messaging
- Critical incident debriefing for serious protocol violations or any post-treatment ICH
- Second interactive educational sessions (two parts, 3 and 4)

D.5.6 Local stroke champion development / use

The use of educational influentials in the intervention hospitals has been imbedded throughout the design of the trial to further address issues on lack of agreement. Educational influentials are opinion leaders within a community who influence the acceptance of an innovation or practice by that community.[85] Interventions that target these persons may be effective in altering local consensus or agreement regarding a guideline.[86, 87]

To increase the likelihood emergency physicians will adhere to recommendations for the use of tPA in stroke we will assist the site investigator and other identified opinion leaders from the intervention hospitals in emerging as the local champion(s) for the management of acute stroke. In addition to the site investigator, we will also identify other local opinion leaders from the emergency physician baseline survey, particularly primary care physicians. The questions to identify this leader will be based on a previously validated questionnaires to identify opinion leaders.[87, 88] The individual receiving the highest number of endorsements (other than the site investigator) will be asked to participate in the study interventions (mock codes and interactive sessions).

D.5.7 INSTINCT first Interactive Educational Intervention

Approximately 3 months following the site barrier assessment the coordinating center Intervention Team (physician investigator, nurse coordinator, health educator) will again return to the intervention hospital in each matched pair and conduct an Interactive Education Intervention (IEI) to address hospital specific barriers to emergency physician delivery of tPA in stroke. This will begin with the conduct of a mock "code stroke" – designed to simulate the arrival of a tPA-eligible patient with acute ischemic stroke and followed by an interactive didactic session addressing hospital specific barriers as identified above. The combination of these elements allows active participation by the emergency department staff in addition to the use of traditional CME communication. This design promotes multi-level learning of concepts of acute stroke care – a method demonstrating greater success in changing physician behavior than isolated educational interventions.[33]

First Interactive Mock Stroke Code session

Theoretical Basis for Intervention: "Code" situations are medical or surgical emergencies requiring an immediate response for successful patient resuscitation. Patients presenting with acute stroke eligible for tPA represent a neurologic "code" situation. However, even in large hospitals, a stroke "code" represents a low-frequency event – more akin to pediatric/neonatal resuscitation codes than the more familiar cardiac or trauma.

Previous work indicates residents in medical training fail to maintain knowledge and skills learned in advanced life support courses and may return to their pre-training level within 12 months.[89, 90] Methods to reinforce learned cardiac arrest code behaviors by providing follow-up materials appear successful in improving long-term physician knowledge retention but do not maintain performance.[91] The use of cardiac code testing is also an effective measure of code leader performance and can be used to customize follow-up educational interventions.[92, 93] In a study of resident physician performance in pediatric codes, Cappelle et al. found a series codes simulations resulted in significant improvements in residents' perceived need for additional knowledge, confidence in their performance and motor skills in arrest situations.[94]

Implementation: Based on this data we propose to develop and conduct a series of standardized acute stroke "codes" for training purposes within intervention hospitals. Planning of the session will proceed with both

nursing and physician input from the participating site using the framework advocated by Funkhouser et al in the development of multidisciplinary mock codes.[95] This utilizes an assessment-planning-implementation-evaluation process and designates various on-site responsibilities prior to the session. This enhances "buy-in" of the process from key personnel. The mock stroke codes will be given quarterly to ensure different personnel are exposed, will be interdisciplinary, conducted with advance notification to staff to enhance participation and reduce anxiety, utilize pre- and post-code sessions to review objectives and evaluate performance, use actual supplies (protocols, triage tools, communication assets), and will include usual nursing and physician charting.

Each mock stroke code scenario will incorporate a vignette, role-played by a staff-member, which includes baseline information on the mock patient's condition. The codes available for selection as a platform will include standard acute stroke presentations both eligible and ineligible for tPA. The actions of the participants determine the outcome of the vignette and the observer/reviewer will have detailed instructions for critical decision points. The mock code will last approximately 20-40 minutes and be followed by a 10-minute debriefing and post-test to allow participants to evaluate their success and areas for improvement. The observer/reviewer will use a standardized evaluation form to assess critical performance elements pre-determined for each scenario. Continuing education credit will be offered and used as a tracking measure for attendance.

Mixed CME sessions 1 & 2

There will be two, one-hour, CME sessions given by physicians from the coordinating center team and the site investigator/local champion and delivered in conjunction with the mock stroke code session. The content of the sessions will address identified needs from the barrier assessment evaluation. By utilizing interactive techniques in multiple formats we have maximized the probability of outcome success (increasing tPA use) by adhering to principles of adult education – delivering content in a learner-centered, active format; relative to the learner's needs; which is simultaneously engaging and reinforcing.[36] The multiple sequencing of events, both within a single day, and over multiple months offers the learn-work-learn opportunity in which education may be translated into practice and discussed at follow-up sessions.

The two major categories of barriers identified by the reviewers (lack of awareness, familiarity, agreement, self-efficacy, outcome expectancy, inertia or external barriers) will be targeted in the first interactive sessions. Below we address each barrier and how it may reduce emergency physician use of tPA in stroke and our planned intervention within the mixed CME sessions. We plan to offer CME credit to encourage physician attendance. To promote the widest exposure by physicians and staff we will develop a multimedia set for use by those unable to attend the sessions. For each session addressing the specific barrier elements below there will be a training manual, presentation slides and video, discussion points and self-evaluation tests as appropriate. These will be accessible from both CD-ROM and online formats for individual use. In addition, there will be tests evaluating change in knowledge as a part of each interactive educational intervention among attendees evaluating the impact of specific educational modules.

Improving awareness: Physicians may be unaware of recommendations for the use of tPA by the NINDS and other national groups (American Heart Association, American Academy of Neurology). Conversely, they may adhere to more limited recommendations by the American Academy of Emergency Medicine or American College of Emergency Physicians. A didactic lecture describing the recommendations, the process of their development, and the data used to develop them will be presented to address this barrier.

Increasing agreement: Within the emergency medicine, considerable debate has emerged regarding agreement on the appropriateness of the use of tPA in stroke. In a recently published BMJ article a member of the board of the American College of Emergency Physicians was quoted, "Leaders in emergency medicine are raising significant scientific, ethical and implementation issues [regarding the use of tPA in stroke]." This stance has been heatedly debated within the emergency medicine community.[96-98]

The essential issues voiced in these debates regard concern over lack of efficacy, concern over lack of effectiveness - that results obtained by highly motivated researchers are not replicable in the general community – and limited system support for TPA delivery. To address these issues we will conduct an

interactive, small-group, discussion on examining the results of the original NINDS trial and the subsequent independent re-examination of the data recently published.[99] To address issues regarding effectiveness we will review our multi-hospital data on the use of tPA by emergency physicians. This represents the largest series of emergency physician tPA-treated patients reported and includes outcomes on complication rates, time to treatment, long-term mortality and diagnostic accuracy. [18, 19, 61-64] Local stroke champions will be prominently featured within this interactive session to enhance practice agreement.

Enhancing self-efficacy: Self-efficacy is the belief that one can actually perform a behavior, such as a guideline recommendation. Increased self-efficacy is associated with increased likelihood that a person will perform a behavior.[100] The delivery of tPA in stroke requires confidence in: patient evaluation skills; knowledge on indications and contra-indications of tPA use; expected risks and benefits for discussion with patients/families; and the ability to coordinate care between the emergency department, radiology and neurology. Physician investigators on the coordinating center team will address this barrier within the mixed CME sessions using an interactive, small-group discussion. Session examples include: reviewing neurologic assessment skills using case-presentation formats and the use of the NIH stroke scale as an evaluation tool; reviewing EP accuracy in stroke diagnosis; implementation of tPA treatment protocols; use of physician reminders within the treatment protocols for critical knowledge areas and promotion of access to telephone consultation with a thrombolytic stroke team member from the coordinating center (UM Stroke Team).

Increasing outcome expectancy: Outcome expectancy is the belief that performing a behavior will lead to the desired outcome. High outcome expectancy is associated with an increased likelihood of performing a behavior.[100] Emergency physicians are naturally insulated from the ultimate outcome of treated patients. These factors could contribute to low outcome expectancy within the emergency department. This barrier element will be addressed with multiple source data during an interactive CME session. This session will begin with outcome data from the NINDS trial and other published community successes and utilize case presentations from the local site as available or from records of the Michigan Stroke Team. Mechanisms for local feedback systems using computerized data as part of the study will be emphasized.

Removing inertia of previous practice: The inertia of previous practice due to habit, custom or previous training is also a barrier to the use of tPA in stroke. To address this element, physicians will have to be motivated to move from a pre-contemplative stage to an action stage in terms of readiness to change practice. Techniques that may help overcome the inertia of previous practice include performance feedback and opinion leader beliefs.[77] The design of the CME sessions incorporate the use of local opinion leaders and discusses provisions for performance feedback as described below in D.5.8. Furthermore, the design of the trial creates a competitive environment between the intervention hospital site investigators by providing individual site performance feedback in comparison to the other treatment group hospitals.

Given the complexity of tPA delivery, one potential contributor to the inertia of prior practice concerns lack of reimbursement both for the hospital or physician staff. Currently, proper billing coding for tPA use reimbursement is unclear. A didactic element of this CME session will provide required elements of essential documentation, coding and reimbursement for the emergency department and hospital (using appropriate Evaluation and Management (E/M), critical care, stroke and other thrombolysis use codes).

Reducing external barriers: These barriers represent impediments to tPA delivery in stroke beyond the physician's immediate control. We will address barriers of this nature using an interactive CME session focusing on the site investigators and/or local champions planned or completed modifications to enhance stroke care delivery. The coordinating center, with the site investigator/local champion(s) will provide and explain templates for EMS use, ED triage, ED treatment protocols, and ICU management protocols as needed. It will emphasize the removal of hospital specific barriers as identified above. To remove barriers to stroke thrombolytic expert access the availability of telephone consultation with study physicians from the Michigan Stroke Team will be reviewed.

D.5.8 Initiate targeted telephone/email messaging from coordinating center

Theory and evidence for use: Two-way communication maintained over time allows for the convergence of ideas between CME teachers and physician learners – a central component of communication theory.[101] The addition of enabling strategies such as 1) audit and feedback mechanisms and 2) reminders, can help facilitate change in practice behavior.[36, 83, 102, 103] Audit and feedback techniques encompass any summary of clinical performance over a specified period and can include reminders or recommendations for clinical action.

With the advent of electronic mail systems such feedback can be easily accomplished within constraints of time and funding, and can reach a greater number of individuals than previously possible. Previous work has demonstrated the use of electronic mail-based case discussions in a small group learning experience[104] and as part of a successful multi-level intervention to improve hand-washing behavior[105] among physicians. From the perspective of addressing hospital specific barriers, an effective audit-feedback/reminder system addresses elements of outcome expectancy, lack of awareness and familiarity, lack of agreement and external barriers.

Implementation: The primary target of the messaging intervention will be the site investigator, other local champions, and the emergency department director. The site investigator will be responsible for secondary distribution within the institution and maintaining distribution lists and may be assisted by the Clinical Coordinating Center. Planned secondary distribution targets include emergency physician, nursing and ancillary personnel, radiology and neurology leaders, and administration personnel as available via e-mail systems. To efficiently communicate with the primary and secondary distribution targets we will utilize a web based e-mail collection and newsletter distribution program.

A distribution frequency of one message per month has been selected to coincide with the frequency of data collection from a given site. This will allow the delivery of site-specific outcome treatment data (number of tPA treated patients, total number of stroke patients discharged from hospital) and monthly comparison to other (anonymous) intervention hospitals – thereby promoting competition. This raw data will be combined with: 1) a brief reminder on stroke treatment and 2) reminders on accessing the Michigan Stroke Team for treatment questions. An additional advantage this method allows is incorporation of pertinent new stroke literature, highlighting of local stroke treatment successes, distribution of printable reminders regarding tPA use in stroke and promotion of access to other electronically available stroke treatment tools (triage and personal device assistant (PDA) stroke protocols). For hospitals where the site investigator does not have email access we plan on communicating the above data to the primary distribution list via telephone on the same basis with a follow-up fax.

D.5.9 Initiate Critical Incident Defusing (CID)

Theory and evidence: Healthcare professionals are regularly featured in the literature exploring critical incident stress and the results of such critical incidents may include sudden change in the daily standard operating procedures for those experiencing them. Critical incident stress management, through the use of debriefing protocols and support, has been shown to reduce the recovery period and improve job performance.[106, 107] It is reasonable, therefore, to believe a formal response to tPA-associated critical incidents (ICH and protocol violations) is potentially beneficial in assisting professional behavioral change given the high mortality of the event.[11]

Implementation: A search for TPA-associated critical incidents will be performed on monthly review of tPA-treated strokes. To ensure CID occurs in proximity to the incident and that all incidents are identified, local site investigators at intervention sites will conduct a brief review of tPA treated patients' medical records (Appendix L) prior to forwarding them to the EBDM group. Critical incident defusing is an abbreviated form of critical incident stress debriefing, typically lasts less than 1 hour, and is designed to resolve the emotional content of an incident.[108] The target of the CID will be the treating emergency physician, staff and associated physician consultants. These will be conducted by the respective coordinating center staff (physician/nurse) in concert with the local site investigator and will be based on the three components of the critical incident defusing process: introduction, exploration, and information. The intent is to provide professional support in a review of the process leading to the treatment decision. This will be conducted in a descriptive manner and avoids performance critique. At this time, data on hemorrhage, mortality and patient outcomes from the NINDS tPA trial and other community studies will be reviewed to enhance future use of tPA.

D.5.10 Initiate Michigan thrombolytic stroke team telephone access

Following the first interactive educational intervention physicians and staff of the treatment hospitals will be provided with access to physicians on the Michigan stroke team for telephone consultation of specific treatment questions. The availability will be promoted using multiple media sources directed primarily toward emergency department staff. Contact is made by activating a statewide pager system for stroke team members. The Michigan stroke team provides coverage on a 24/7 basis with a rotating schedule of 8 physicians (4 emergency medicine, 4 neurology). Calls from hospitals other than UM will be logged and a standard information evaluation completed. Specific treatment recommendations will be recorded and compared to local treatment decision upon monthly data collection. Calls from non-treatment facilities cannot ethically be refused but will not be promoted. There are currently less than 5 outside calls to the stroke team per year. A letter from the University of Michigan Health System's legal council indicating malpractice protection and coverage of the team's physicians in this activity has been obtained.

D.5.11 Second Interactive Educational Intervention

We plan a follow-up, on-site, interactive education intervention by the coordinating center Intervention Team approximately 3 months after the first session to provide additional educational content and reinforce behavior change. This "sequencing" of multiple interactions over time improves the impact of professional education in creating behavior change.[36] This one-day session will address hospital specific barriers as previously identified and will again utilize both mock stroke "codes" and mixed CME sessions (3 and 4) to address identified needs. See D.5.7 and D.1 for details.

D.5.12 Initiate quarterly Mock Code Strokes

Following completion of the second Interactive Educational Intervention session the local site investigator will initiate the conduct of quarterly (± 2 weeks) mock stroke codes. These will use a standardized scenario provided by the coordinating center to reinforce earlier behavior change strategies.

D.6 Data collection and blinding procedures

For assessment of tPA use, each site will generate monthly reports on all tPA use from the computerized pharmacy dispensers and forward to their site investigator. The site investigator will maintain the dispensing log and review the associated medical record for each case to determine rationale for use. In a large emergency department (> 65,000 visits per year) this report will typically identify ≈ 6 cases of tPA use per month. The site investigator will copy the record for cases identified with tPA use for stroke, convert each to a HIPAA compliant "limited data set" (Section E.10.6), assign a case identification code and forward to the Clinical Coordinating Center to ensure completeness and removal of patient identifiers. The cleaned chart is then forwarded to Epidemiology, Biostatistics and Data Management group at UM (EBDM, Drs. Haan and Kalbfleisch, Directors).

The EBDM group will also review the record to ensure patient and site confidentiality and forward to blinded reviewers. These blinded reviewers will determine appropriateness of tPA use, adverse events and important clinical events as previously described (D.4.4). The reviewer's determination will be returned to the EBDM which will forward the information (for intervention sites only), along with identification of the specific site, to the INSTINCT coordinating center for incorporation into the targeted messaging and critical incident defusing feedback systems as outlined above. Figures D.2 and D.3 describe the data flow processes for the outcome measures of tPA use and physician knowledge surveys, respectively.

Figure D.2: TPA Use Data Flow

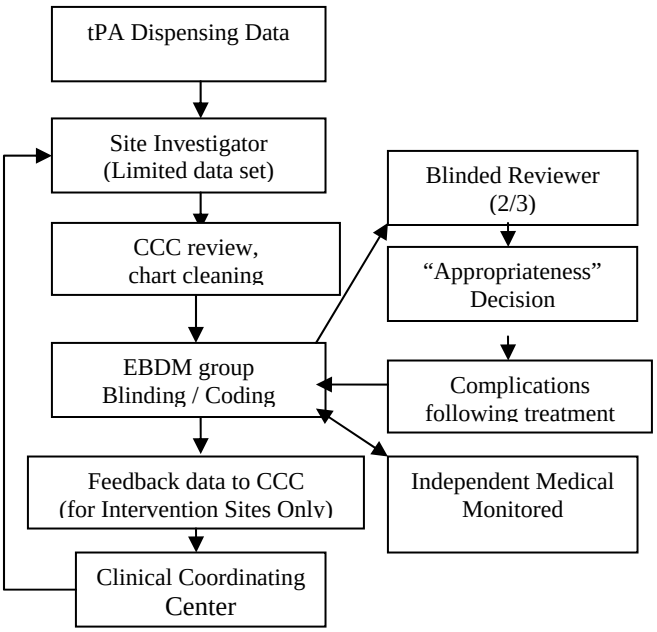
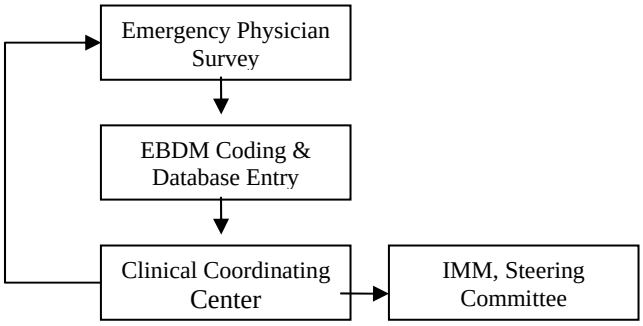


Figure D.3: EP Survey Data Flow



D.7 Design and analyses

The INSTINCT trial is a cluster randomized trial where hospitals form clusters and sample size calculations and statistical analyses need to take this aspect of the design into account. The hospitals are also matched pairs where one member within each pair will be randomized to treatment or control. The primary analyses will be based on change in appropriate tPA usage in the study hospitals and the study is powered to detect meaningful changes in this variable. Analyses will also examine the effect of the intervention on physician knowledge through response to questionnaires administered before and following the intervention phase.

D.7.1 Hospital (study unit) selection and matching

We reviewed the stroke literature to identify potential confounders. Available data indicate time to emergency department presentation is the primary cause for patient exclusion from the use of tPA, accounting for approximately 70-85% of patients to be ineligible for treatment.[109-111] After time to arrival, the most important exclusion appears to be mild stroke severity.[109, 112] Published data do not identify patient gender as a factor influencing early hospital arrival[113, 114] or treatment with tPA.[112, 115, 116] Data evaluating the impact of distance on access to stroke care also failed to identify a significant association.[117] This may represent faster door-to-needle times for rural patients, however, as treated patients from those areas have demonstrated longer stroke onset to arrival times.[118]. One primary reason for matching is that pairs will enter the study at the same chronological time and so the matching will help to control for any temporal changes that might occur through, for example, seasonal variation in numbers of strokes or educational programs that might affect tPA usage.

The data evaluating ethnicity on tPA treatment is mixed, with 3 reports failing to find difference in tPA use or access to stroke care between ethnic groups[112, 116, 117] and 2 reports finding a difference in the likelihood of black patients receiving tPA.[8, 115] No differences have been identified in any report for other ethnic groups studied (Hispanic Americans, Mexican Americans, Latino, Native American and Asian).[115, 117, 119] No data was identified to identify the impact of hospital type (for-profit/not-for-profit). An association between increasing stroke volume and increasing numbers of treated patients was identified.[6]

Given the above data, each pair will be matched within ±20% of the number of ischemic stroke discharges at each hospital (volume), on location (urban/suburban/rural), and for-profit/not-for-profit status. Other inclusion and exclusion criteria for the sample have been described above (Section D.3.1). 64 hospitals were initially eligible for inclusion in the study and comprised the sampling frame for hospitals with > 100 stroke discharges. There are an additional 36 eligible hospitals with < 100 stroke discharges. Variables such as

racial composition, population density, hospital size and socioeconomic status will be collected and accounted for at the analysis stage

Our sampling strategy will be as follows:

1. From the sampling frame, a hospital will be randomly selected to participate in the study.
2. A list of matching hospitals will be found for the selected hospital based on the number of ischemic stroke discharges in the previous 12 months.
3. Those potential matches that are located within 15 miles of any selected study hospital will be dropped from the selection pool for that match.
4. If there is more than one potential matching hospital, the match will be randomly selected from the pool of potential matches. Otherwise, the match will be completed, and the pair established.
5. This procedure will repeat until all required pairs (n = 12) are filled.

D.7.2 Adaptive randomization for treatment assignment within pairs

Assignment to treatment group will be done utilizing an adaptive randomization procedure that will balance hospital characteristics identified in the Year 1 data collected to reduce confounding. One such variable will be the baseline rate of tPA usage. The randomization will be constrained so as to achieve balance with respect to this variable so that for those pairs with substantial differences in tPA usage, the randomization will assure nearly equal numbers of hospitals with the larger rate will be assigned to control and intervention groups. Other variables considered will include hospital measures of racial mix, gender and age.

D.7.3 Analysis plan

The primary comparison will be between the proportional change in usage of tPA between the 12 month prior to randomizations and the 24 months immediately following the first IEI session. More generally, the analysis will investigate the general pattern of tPA usage in the two groups. Other endpoints investigated will include knowledge data as obtained from questionnaires of emergency physicians.

Statistical analysis of tPA usage

The frequency of tPA usage will be analyzed using a Poisson mixed model. Data will be aggregated by time intervals, perhaps year or six month intervals, beginning with entry of hospitals to study, and followed sequentially in time. The number of appropriate tPA usages in the kth member of the ith pair at time period j will be modeled as a Poisson distribution with mean $p_{ijk}N_{ijk}$, where N_{ijk} is the corresponding number of ischemic stroke discharges, i=1,…,n; j=1.,,,m and k=1,2 where n is the number of hospital pairs and m is the number of time points. A log linear model for p_{ijk} will be used to investigate possible time dependent treatment effects and to adjust baseline rates for such variables measured on hospitals as size, population density, or racial mix. More specifically, we consider models of the form $X_{ijk} \sim$ Poisson $(p_{ijk} N_{ijk})$ where log $(p_{ijk}) = \mu + \lambda_{ij} + \gamma_j(k-1)+Z_{ijk}\beta + b_i+e_{jk}$. In this the errors e_i, e_{i2} for the ith pair are independent with mean 0 and variance σ^2 and b_i, the block random effect for the ith pair, is normal σ_b^2. Also, Z_{ijk} is the vector of covariate measurements, λ_{ij} specifies the effect of time j for the ith pair, and γ_j measures the treatment effect at the jth time point. For identifiability, it is assumed that $\lambda_{i1}=\gamma_1=0$, i=1,…n. Various models can be investigated to examine possible trends in the baseline log rates λ_{ij} or to model possible time dependent trends in the treatment effects. This model allows for a separate random effect of each hospital and a correlation between members of the matched pairs. More general models can also be considered with errors or random effects that are correlated across time. Generalized Linear Mixed Model (GLMM) software can be used to fit such models.

The primary analysis will be based on the mixed effects model in which there are only two time intervals (m=2), the first being the year preceding randomization and the second being the two years following randomization without incorporation of covariates. This analysis will have somewhat better power properties than the simple comparison of proportions described in the sample size section below.

Statistical analyses of emergency physician knowledge change

One mechanism by which this intervention may work is by increasing the knowledge of individual ER physicians about tPA treatment in the intervention hospitals compared to controls. Appropriate analysis of

such data must use an intention to treat approach and also take account of the cluster randomization. As is well known for clustered studies, a larger number of individuals must be studied for the same power than in a trial where individual physicians can be randomized and treated separately. In fact, if r is the number of individuals in the cluster and ρ is the intra-class correlation, D = [1+(r-1)ρ] is the factor by which the sample size of individual physicians needs to be increased above that needed for an individually randomized trial to compensate for the cluster randomization.

The number of physicians within each ED will vary from approximately 5 in the smallest hospitals to as many as 40 in large hospitals with more than 500 stroke discharges per year. The intervention will target all physicians in an ED; the questionnaire will be administered to them at both the intervention and control hospitals. These physicians at each hospital will respond over time to each questionnaire (Baseline and 12 months after the second interactive educational intervention). We have decided on canvassing all physicians since the overall N is relatively small and there is clustering. The census will help to improve statistical power

A part of this study will be the administration of a survey instrument to measure knowledge. Comparison of the intervention to the control groups over time for changes in scores on the survey will form the basis of the analysis. For purposes of exposition, we suppose that an overall knowledge score on a scale from 1 to 100 will be available from each completed questionnaire and we suppose that the change in knowledge from baseline to post intervention for the *jth* physician in hospital *ik,* where *i* designates the pair and k designates the treatment group, is Y*ijk*. We suppose that the within hospital standard deviation of knowledge change is σ and that the intraclass correlation is ρ. We consider r=14 physicians per cluster, which would be approximately the average number of physicians per cluster, ρ=0.25 and a correlation of 0.25 between members of pairs. If the true difference in knowledge change between intervention and control were equal to one standard deviation, this study would yield a power of about 90% on a two-tailed test of size 1% with 10 pairs of hospitals included. Thus, there would be ample power here to detect clinically meaningful differences between intervention and control and the sample size would be adequate to address multiple comparisons on various aspects of knowledge. The planned study has 12 pairs of hospitals and will yield good power even with somewhat higher intraclass correlation or with the loss of some pairs.

More general analyses of the knowledge data can be carried out again using general linear mixed model techniques. Specifically, repeated measures obtained from repeated administrations of the questionnaires will be analyzed by specifying hierarchical random effects models with terms that incorporate random effects for the hospital and the pair. These models could also allow for correlations in the errors over time in a manner similar to the tPA analyses discussed above.

Stopping rules

We will monitor and evaluate the data on an interim basis for possible inappropriate tPA usage after 80, 160, 240 and 320 patients have received tPA in the treatment group of hospitals. A signal that will call for a more detailed review by the IMM will be given if the total number of inappropriate uses at the interim time points exceeds 29, 53, 76 and 99, respectively. Previous studies suggest that the rate of inappropriate use may be as high as 25% in tPA treated patients. If there is no difference between the treatment group and this historical value, this rule will lead to a signal requiring a more thorough review by the IMM with a probability of 0.022. The rule will produce a signal with probability 0.41 and 0.94 if the true proportion of inappropriate use in the treatment group is 0.30 or 0.35, respectively. It is expected that the educational program will reduce the rate of inappropriate use; if the true rate of inappropriate use in intervention hospitals is 0.20 or less, this rule would lead to a signal with probability less than 0.01. The IMM will have final approval of the above process prior to study initialization.

We will also monitor tPA usage in the control hospitals as well as inappropriate use. These will also be reported at the same chronological times as the review for the intervention hospitals described above. There will be no formal stopping rules for efficacy in this intervention trial though the comparative data will be reviewed by the IMM. Guidelines for IMM monitoring are presented in E.10.

D.7.4 Power and sample size calculations for tPA outcomes

To assess power, we concentrate on the primary outcome of change in appropriate use of tPA in treatment of ischemic stroke. As discussed above, we rely on ICD-9 or 10 discharge diagnoses with an indication of ischemic cerebrovascular disease. The validity of this approach is based on the assumption that this measure would be approximately proportional to the total number of ischemic strokes entered at the hospital. Proportionality here is in the sense that the true numbers of ischemic strokes admitted would be highly correlated with the number of ischemic strokes recorded on the ICD-9 codes.

As discussed above, the primary endpoint will be the proportions of ischemic stroke patients appropriately treated with tPA during a 12 month period before randomization and the 24 months following the first IEI. Let N and M represent the number of ischemic stroke discharges per ICD-9 codes over the period preceding and following randomization respectively. Let X and Y represent the numbers of cases respectively treated with tPA before and after randomization. Let p_1 represent the baseline rate prior to randomization and p_2 the baseline rate following randomization. For periods with no intervention, we suppose that p_1 has mean 0.025 and standard deviation 0.0075. We also assume a modest correlation of 0.25 between p_1 and p_2. The null hypothesis asserts that there is no difference between control and intervention groups. The study is powered to detect an alternative hypothesis in which the post randomization rate p_2 in the intervention group has a mean of 0.06 and standard deviation 0.015. We make a conservative assumption that responses between matched hospitals are uncorrelated.

We suppose that, given p_1 and p_2, X and Y are independent Poisson variables with means Np_1 and Mp_2. This Poisson mixture model is a natural way to incorporate the intra-class correlations expected within institutions, and also accounts for natural variation among hospitals in the baseline usage of tPA. Effectively, we suppose that about 70% of the hospitals would have an underlying baseline rate of between 1.75% and 3.25% prior to intervention. The alternative hypothesis under intervention allows a corresponding range of 4.5% to 7.5%.

For a given hospital, let D=(Y/M)-(X/N) be the difference in the proportions of ischemic strokes treated with tPA pre and post randomization. For the i^{th} pair, let D_{i1} represent this difference for the control hospital and D_{i2} represent the difference for the Intervention hospital. For purposes of determining approximate power and appropriate sample size, a primary test of the null hypothesis can be based on the paired t statistic $T=\bar{U}/SE(\bar{U})$, where $\bar{U}=\Sigma U_i/n$, $U_i=D_{i2}-D_{i1}$, and n is the number of hospital pairs. $\bar{U}$ has mean p_2-p_1 and variance $2\Sigma\ (p_1M_i^{-1}+p_2N_i^{-1})/n^2 + (\sigma_1^2+\sigma_2^2 -2\rho\sigma_1\sigma_2)/n$.

For the null hypothesis, we assume that $p_1=p_2=0.025$, $\sigma1=\sigma_2=0.007$ and $\rho=0.25$. For the alternative hypothesis, p1=.025, $p_2=0.060$, $\sigma_1=0.007$, $\sigma_2=0.015$ and $\rho=0.25$. Consider a sample of 10 pairs of hospitals and suppose that the specific numbers of yearly strokes in each hospital for the ten pairs are 100, 150, 200, 200, 250, 250, 300, 300, 350, and 400. We consider a comparison of 12 months' baseline measurement prior to randomization with a 24 month period following the first interactive educational intervention. Based on the t statistic and the variance estimates above, a test with significance level 5%, would yield a power of 96%; with significance level 2%, the resulting test would yield a power of 84% against the stated alternative. The test would also have power to detect a smaller shift of say 3% in the proportion of ischemic stroke cases treated. A test of size 5% would have power 83% against this alternative. These powers are based on simulation of the paired t statistic as outlined above.

The log linear Poisson mixed model outlined above is more closely related to a difference in differences analysis of log proportions. The very simple approach used here for comparing proportions would be a reasonable approximation, however, and would provide a conservative estimate of the power. We have also used only 10 hospital pairs in the above analysis although our current sampling frame has 12 hospital pairs and would give even better power properties.

D.8 Contingency plans for loss of hospitals in sample

Although 10 pairs are required for sufficient power, we now plan to oversample by 2 pairs for any loss.

D.9 Data management, collection and quality assurance

All data management and analysis will be handled at the Epidemiology, Biostatistics and Data Management (EBDM) group at the University of Michigan under the direction of Dr. Mary Haan. The physician survey and

the medical reviewer forms will both transmitted directly from the respondent through Survey Monkey directly into SAS 9.1, the secure study database. The remainder of the forms will be transmitted on paper by FAX or mail and these will be entered using study specific ACCESS forms. The resulting data will be stored in the SAS 9.1 secure study database. Computer reports of ICD-9 codes will be double entered at the EBDM group. Intervention meetings will be taped and transcribed by study secretaries. The study investigators will review and grade the results of each session for potential barriers with the resulting data on barriers entered into the SAS 9.1 secure study database .

The nurse coordinator will visit each site on a quarterly basis to review pharmacy dispenser logs and verify each site is conducting the trial and data collection as outlined in the Manual of Operations. The principal investigator will meet with the site investigators annually to review trial conduct. The EBDM group will randomly select a sample of survey responses and verify the information according to a specified schedule. Also, the EBDM group will do computer runs to check the data for patterns of errors not detected by simple range checks. Areas for review include receipt of monthly pharmacy data, limited data set records, ICD-9 data receipt, survey return, missing data, location of individual documents and rate of aberrant data. Regular reports will be generated on the trial status, including survey response rates, schedule of interventions, data collection, adverse events and missing data.

E Protection of Human Subjects

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements. The following information relates to all sites participating in the trial.

E.1 Risks to the subjects

E.1.1 Human subject involvement

The study population consists of physicians primarily from the specialty of emergency medicine. Detail on demographics of both physician and patient populations can be found in Sections E.7 and E.8. Other specialties, particularly neurology, radiology and primary care physicians will be involved - as well as hospital nursing, administrative, EMS and ancillary staffs, as part of the barrier assessment process and as participants in educational sessions. The patients treated at participating hospitals, while not objects of the intervention, represent a primary outcome measure of the study and are considered to be secondary subjects of the study since their medical records will be retrospectively reviewed.

E.1.2 Sources of data and materials

Sources of research material include physician responses to the surveys listed in the research plan and data regarding tPA use from hospital and patient specific records. Prospective physician survey data from participating physician subjects will be obtained specifically for research purposes. Data on tPA use will come from retrospective analysis of existing patient records and hospital data and reports generated specifically for the research study.

E.1.3 Potential risks

Participating physicians and staff

There are no foreseeable risks to the physician and/or staff participants from the educational intervention or survey beyond that associated with any standard medical education effort or survey, and potential inadvertent disclosure of personal information or opinions.

Patients at participating hospitals

Patients treated by physicians following intervention are secondary subjects of the study in that their treatment represents an outcome measure. TPA is an FDA-approved, standard, treatment for patients with acute ischemic stroke. Patients treated with tPA at hospitals participating in the study face two separate risks:

Privacy risks: The use of patient data is required to measure the success of the educational effort. The risk associated with measurement of tPA use and patient outcome using the blinded retrospective chart review is the release of patient specific information.

Treatment risks: The aim of the study is to increase the use of tPA in eligible patients with acute stroke. The treatment risks to eligible patients at hospitals participating in the study are the same as for any other stroke patient treated with thrombolytic therapy. The known risks include: symptomatic intracranial hemorrhage (6.4%) or major systemic bleeding. Allergic reactions consisting of oral-lingual edema are also possible with tPA use (<1%).

The possibility exists that our behavioral change intervention will inadvertently increase tPA treatment in stroke patients ineligible for thrombolytics. Though this is believed unlikely, we will closely monitor for increases in the proportion of patients receiving tPA inappropriately as the use of tPA outside of label eligibility requirements has been associated with increased risks of intracranial and systemic hemorrhage beyond those noted above.[75]

E.2 Adequacy of protection against risks

E.2.1 Recruitment and informed consent

Participating physicians
All emergency physicians participating in the study and surveys will agree to participate under an approved Waiver of Documentation of Informed Consent. The following process will be employed. At the beginning of the on-line survey, information (purpose, requirements, risks, benefits, etc) about the study will be provided (Appendix E) and participants will indicate their agreement (consent) by "clicking" ACCEPT, and proceeding with the survey questions. If a paper version of the survey is required, those participants will receive the same information in writing. Their completion and return of the paper survey will be considered to be their consent.

Participating hospital staff
While not considered to be subjects of the study, information will be obtained from ED nursing and ancillary staff, administrators, neurologists, and radiology staff as part of focus groups or interviews conducted during the barrier assessment process. To assure their voluntary participation, staff will be required to sign a written informed consent prior to participation. (Appendix G)

Patients at participating hospitals
Consent for the patient involves two issues: 1) Consent for treatment with standard tPA therapy and 2) consent for study participation by permitting review of Protected Health Information (PHI) in medical records.

Regarding consent for standard tPA treatment of stroke. Since treatment of eligible acute ischemic stroke patients with tPA is an FDA-approved, accepted practice, the treating physician will obtain informed consent from patients undergoing this treatment according to their own hospital's current procedure. We will provide informed consent templates (Appendix F) to all sites for their use if needed. The provided consent document will include specific tPA treatment data regarding mortality, intracranial hemorrhage and expected benefit.

Regarding consent for review of PHI. Given the need to ensure complete case ascertainment for the determination of ongoing patient safety parameters (appropriate use of tPA), we will also seek IRB permission to retrospectively review all tPA-treated patient records under the rules for Waiver or Alteration of Consent.

E.2.2 Protection against risk

The intervention itself is designed to increase tPA use by improving physician knowledge regarding the indications for its use and physician performance by allowing actual decision making in practice "stroke codes." This type of focused and repetitive training, targeted messaging, in conjunction with performance feedback and access to thrombolytic stroke expertise provides a greater set of resources to enact appropriate treatment compared to the control group.

In the event of a intracranial hemorrhage or other known tPA complications, the (intervention) site investigators will be able to contact the Michigan thrombolytic team for additional expertise in patient stabilization and management. This provides a wealth of specialized knowledge on the management of tPA-associated ICH complications.

Beyond this, the Independent Medical Monitor will provide safety monitoring oversight (See Section E.10) to rapidly review any adverse events and provide feedback to the study investigators, and hospitals, by extension. The data review elements of the study have been carefully designed to ensure protection of patient privacy as above.

E.3 Potential benefit of the proposed research to the subject and others

E.3.1 Participating physicians

The potential benefits of the proposed research for participating physicians includes increased knowledge, experience and safety in the delivery of thrombolytic therapy in the setting of acute stroke. This may translate to individual patient benefit, increased diagnostic comfort, and reduced medical liability.

E.3.2 Participating hospitals

This includes increasing the level of stroke care given to their patient population and the potential reduction of medical liability from treating patients with acute stroke. It may offer competitive advantages in the cardio- and neurovascular market segments.

E.3.3 Participating communities

The INSTINCT trial offers to substantially increase the proportion of patients with acute ischemic stoke receiving appropriate thrombolytic therapy. It may also reduce the incidence of inappropriate use of tPA in stroke patients.

E.3.4 Participating patients

The potential benefits for stroke patients associated with the educational intervention include increased knowledge, experience and safety in the physician and staff administering tPA in stroke. This may translate into a reduced risk of intracerebral hemorrhage or other complications of therapy. It may also increase the possibility of improved outcome by allowing better patient selection for treatment and more rapid administration of tPA.

E.4 Importance of the knowledge to be gained

The INSTINCT trial offers an efficient, reproducible, method of increasing thrombolytic use in acute stroke. More broadly, the elements utilized in the trial can conceivably be used in enhancing the second stage of translational research – from clinical trial to public acceptance - in other disease processes.

E.5 Disclosure of data

Physician, hospital and patient information obtained by this study is confidential, and disclosure to third parties other that those noted above is prohibited without express consent. Data generated by this study must be available for inspection upon request by representatives of the NINDS, national and local health authorities, the Clinical Coordinating Center, and the IRB/EC for each study site as appropriate.

E.6 Collaborating sites

Following completion of hospital recruitment a list of collaborating sites and accompanying OHRP assurance numbers will be provided. A list of recruited sites, and associated FWA numbers, can be found in the Appendix.

E.7 Inclusion of women

Physicians: The participation of women as study physicians is specifically encouraged at all levels of the study. As hospitals are the randomly selected unit of study we expect the participation of female physicians to reflect that of women in emergency medicine. This has been the case in recruited hospitals to date. Physician enrollment will occur from the start of Year1 to the end of Year 2. Within the group of site investigators identified (Oct 2004) 17% are women. Within the group of all emergency physicians from the 24 recruited sites (n = 348) 21% are women. This approximates the overall population of emergency physicians in Michigan. Data from the Michigan chapter of the American College of Emergency Physicians (ACEP) indicate 33% of their members are women (personal communication, Karen Price, ACEP, April 2004).

Patients: The participation of women as patients is specifically encouraged at all levels of the study. We anticipate the gender composition of the population of patients treated by centers participating in the study to reflect the overall population of the service area of the hospitals. An analysis of the counties where the 24 recruited hospitals are located identifies 51% of the population as female. Additionally, data obtained from the Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) – a statewide, hospital-based (n = 16), stroke registry which was part of the Paul Coverdell National Acute Stroke Registry - found 51% of all acute ischemic stroke admissions seen in the emergency department within three hours of stroke onset and no physician documented exclusion for tPA treatment were women.[123]

We will monitor gender in both physician participants and the population of patients treated with tPA to assess trends within the study.

E.8 Inclusion of minorities

Physicians: The participation of minorities is specifically encouraged at all levels of the study. As hospitals are the randomly selected unit of study we expect the participation of minority physicians to reflect that of minorities in emergency medicine. This has been the case in recruited hospitals to date. Physician enrollment will occur from the start of Year1 to the end of Year 2. Within the group of site investigators identified (Oct 2004) 4% are African-American. Within the group of all emergency physicians from the 24 recruited sites (n = 348), 11.2% are minorities with 4% being African-American. This approximates the overall emergency physician ethnicity of Michigan. Michigan data from the American College of Emergency Physicians provides some insight into that composition with 3% Asian, 1% African American, 1% Hispanic and 2% other (personal communication, Karen Price, ACEP, April 2004).

Patients: The participation of minorities is specifically encouraged at all levels of the study. We anticipate the minority composition of the population of patients treated by centers participating in the study to reflect the overall population of the service area of the hospitals. The overall ethnic composition of the population of the counties serviced by the recruited hospitals approximates that of Michigan, with 80% White, 14% African-American, 3% Hispanic or Latino origin and 2% Asian. Additionally, data obtained from the Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) indicates 14% of all acute ischemic stroke admissions seen in the emergency department within three hours of stroke onset (and no physician documented exclusion for tPA treatment) occur in African-Americans, with 9% listed as Other minorities.[123]

We will monitor ethnicity in both physician participants and the population of patients treated with tPA to assess trends within the study.

E.9 Inclusion of children

Children are not expected in the population of physicians/hospital staff and are excluded from appropriately receiving tPA in the study by label eligibility requirements for thrombolytic use in stroke unless specifically offered as compassionate use.

E.10 Data and safety monitoring plan

E.10.1 Overview

The safety of the participants, and their patients, is of paramount concern to the investigators. The INSTINCT trial uses a multi-level approach to ensure physician and staff subject safety, patient data safety and thorough data monitoring. This includes: on-site assessments by study personnel; Independent, blinded, medical chart review; local/central IRB review; and an Independent Medical Monitor (IMM). The study will follow NIH/NINDS policies and procedures regarding Safety and Data Monitoring and appropriate Institutional Review Board policies.

The INSTINCT trial evaluates the effectiveness of an educational intervention directed towards Emergency Department physicians and hospital systems in influencing their adoption and implementation of approved professional guidelines regarding the use of an FDA-approved medication (tPA) in the treatment of patients with acute ischemic stroke. **The risks associated with the educational intervention and outcome assessments are "no more than minimal risk".**

Specifically, risks to the physician and staff subjects in the trial are primarily the potential for inadvertent disclosure of personal opinions and information. Such disclosure could, in rare instances, conceivably lead to social or psychological trauma, such as embarrassment, stigmatization, or loss of job, etc. **The interventions pose essentially no physical risks other than those associated with completing a Continuing Medical Education (CME) activity and survey questionnaire.**

Patients treated with tPA at the participating sites are receiving standard treatment with an FDA-approved drug. **The study does not require any direct contact with patients, nor does it require altering their care in any way. There is no planned direct patient interaction on the part of the study, however, a retrospective chart review of tPA-treated stroke patients will be completed to monitor the effectiveness of the educational intervention and provide the primary and secondary outcome measures.** For these patients, the risk is inadvertent disclosure of protected health information which could conceivably lead to social or psychological trauma, such as embarrassment, stigmatization, or loss of job, etc.

E.10.2 Definition and Reporting of Adverse Events and ORIOs

E.10.2.1 Adverse Events Defined

Physician and Staff subjects at participating hospitals

Adverse events for the participating physicians and staff will be limited to those associated with social/psychological trauma resulting from their participation in the study or inadvertent disclosure of their confidential information.

Patients at participating hospitals

Adverse events for those patients whose charts undergo retrospective review will be limited to those associated with social/psychological trauma resulting from inadvertent disclosure of confidential information.

E.10.2.2 Other Reportable Information or Occurrences (ORIOs) Defined

In addition to standard IRB ORIOs (defined as inadvertent disclosure of confidential information **not** resulting in social/psychological trauma) we will consider errors in the educational message to physicians and staff as an Other Reportable Information or Occurrences (ORIOs) and will report these according to standard IRB procedures on an annual basis as part of the scheduled review.

E.10.2.3 Adverse Event and ORIO Reporting

Any adverse events and/or ORIO identified will be recorded on the appropriate page(s) of the CRF. All Adverse Event (Serious and Non-serious) and ORIO Reports sent to the EBDM group will be entered into the project database for generation of reports for review in the Project Meetings. This data will be reported to the Independent Medical Monitor (IMM) on a review schedule the IMM will determine.

The principal investigator and nurse coordinators will be responsible for notifying the participating IRBs in accordance with IRB and NIH regulations. For any serious adverse event, the Independent Medical Monitor will be the final arbiter of its classification and establishing the causal relationship to the study intervention as probable, possible, unlikely, or unrelated.

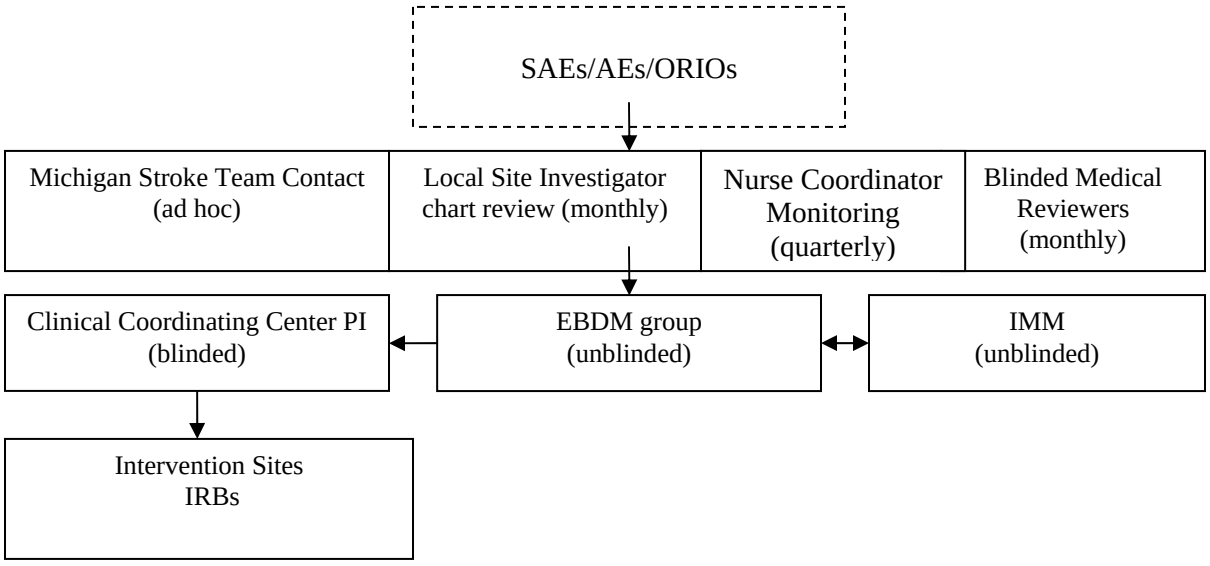
E.10.3 Data and Safety Monitoring Responsibilities

The project will follow the NINDS policies and procedures regarding Safety and Data Monitoring. See Figure E.1 for a diagrammatic overview of data and safety monitoring processes. We briefly describe each element and their responsibilities here.

E.10.3.1 Study Investigators and Staff

Each site principal investigator will screen for the presence of any adverse events and/or ORIOs as part of their monthly assessment to identify tPA treated patients. The blinded medical reviewers will also evaluate for the presence of adverse events and/or ORIOs as part of their monthly blinded chart review. Additionally, adverse events and/or ORIOs may be identified at anytime through contact from participating physicians and staff to the Michigan Thrombolytic Stroke Team or Clinical Coordinating Center responding to their call – the team member will then initiate an adverse event/ORIO report. Finally, adverse events and/or ORIOs may be identified in the course of site monitoring at the planned quarterly visits by the nurse coordinators reviewing data collection and procedures.

Figure E.1: INSTINCT SAE/AE/ORIO Monitoring Process



The study investigators/coordinators will perform ongoing (monthly and quarterly) monitoring of study implementation parameters (e.g., recruitment, follow-up, compliance) in order to manage day-to-day study aspects and ensure quality control. If in the course of such monitoring, the investigator uncovers issues that

may threaten the integrity of the study or subject safety (e.g., excessive dropout rate, adverse events or other important clinical events) they will alert the Epidemiology, Biostatistics and Data Management group who will be responsible for notifying the IMM, as described below.

E.10.3.2 Independent Medical Monitor (IMM)

An Independent Medical Monitor (IMM) will be appointed by the principal investigator to oversee the project as it involves no more than minimal risk to the participants. The IMM will be independent of the project, have no real or perceived conflict of interest, and be approved by the NINDS program director.

The IMM is responsible for undertaking the monitoring responsibilities that are often the responsibility of a DSMB or SMC. The NINDS Program Director must approve the IMM and specific monitoring procedures she/he will follow. In general, the IMM will operate in a manner similar to that of a SMC/DSMB and will be unblinded to the group assignment (educational intervention or control) for each hospital and its associated physicians and staff.

E.10.4 Data to Monitored by IMM

Both performance and safety data will be monitored by the Independent Medical Monitor.
In general, the IMM will evaluate sufficient data to:

1. Assess the performance of the trial with respect to data integrity and study quality.
    a. Evaluate reasons for losses of hospital from study sample.
    b. Evaluate baseline comparability of treatment groups.
    c. Evaluate recruitment and maintenance of physician subjects.
2. Assess performance of the the trial with respect to protocol adherence.
    a. tPA treatment accrual and timeliness of study completion.
    b. Data completeness.
3. Review serious adverse events and assess other study participant safety issues.
4. Review patient safety issues
    a. Evaluate inappropriate treatments with tPA in the event of a data analysis signal (see E.10.5).
5. Review protection of confidentiality of the trial data and results of monitoring.
6. Make recommendations to the NINDS and Principal Investigator concerning continuation or conclusion of the trial or suggest modifications due to a finding in the monitoring process.
7. Make recommendation on future type and frequency of data for review.
8. Prepare report summarizing his/her conclusions for the Principal Investigator and NINDS representative.

Additionally, the IMM will review and consider protocol modifications proposed by study investigators. The suggested initial IMM review is following completion of the six-month emergency physician survey with a subsequent review every six months and schedule interim data analysis as described in E.10.5 below (and in section D.7.3). The final determination of data elements, frequency and reporting will be at the discretion of the IMM

E.10.5 IMM Monitor guidelines

As described in the analysis plan (D.7.3), we will monitor and evaluate the data on an interim basis for possible inappropriate use of tPA after 80, 160, 240 and 320 patients have received tPA in the treatment group of hospitals. A signal that will call for a more detailed review by the IMM will be given if the total number of inappropriate uses at the interim time points exceeds 29, 53, 76 and 99, respectively. Previous studies suggest that the rate of inappropriate use may be as high as 25% in tPA treated patients. If there is no difference between the treatment group and this historical value, this rule will lead to a signal requiring a more thorough review by the IMM with a probability of 0.022. The rule will produce a signal with probability 0.41 and 0.94 if the true proportion of inappropriate use in the treatment group is 0.30 or 0.35, respectively. It is expected that the educational program will reduce the rate of inappropriate use; if the true rate of inappropriate use in

intervention hospitals is 0.20 or less, this rule would lead to a signal with probability less than 0.01. The IMM will have final approval of the above process prior to study initialization.

We will also monitor the tPA usage in the control hospitals as well as inappropriate use. These will also be reported at the same chronological times as the review for the intervention hospitals described above. There will be no formal stopping rules for efficacy in this intervention trial though the comparative data will be reviewed by the IMM.

In the event of a signal suggesting an excessive frequency of inappropriate use, the IMM may recommend stopping, modifying or continuing the study, following detailed review. For example, potential modifications, if needed, could include increasing the frequency of the on-site educational CME/mock stroke codes by a single additional visit to each of the intervention sites and/or increasing the frequency of the electronic messaging feedback provided. Final determination of any modifications will be at the discretion of the IMM.

E.10.6 IMM reporting

At each monitoring interval, the IMM will issue a report to the appropriate NIH/NINDS program official that she/he has reviewed the research protocol and ongoing study activities with emphasis on data integrity, protocol adherence and study participant safety issues.

This report will especially include the review of adverse events and reasons for losses to follow-up, raising any concerns or issues with both the NINDS and the Principal Investigator (PI), and recommending to the NINDS and PI the continuation, modification or conclusion of the trial, while protecting the confidentiality of the trial data and the results of monitoring.

The IMM will also issue a report to the appropriate NIH/NINDS program official regarding his/her review of each interim data analysis or when the IMM is contacted due to concerns related to the study (i.e. excess protocol violations, activation of “stopping rules”, etc.) or she/he has other concerns.

Routine feedback on the study from the IMM, not due to concerns of the study, will be included as part of the annual progress report submitted to the NIH/NINDS.

E.10.7 NIH/NINDS reporting

In addition to the above reporting requirements a copy of each interim analysis will be forwarded to the appropriate NIH/NINDS program official for review.

E.10.8 Site Monitoring Plan

Experienced nurse coordinators from the University of Michigan Clinical Coordinating Center will have extensive contact with each participating site. An assessment of each site’s compliance with Good Clinical Practices, HIPAA privacy requirements, federal, state and all IRBMED (and local IRB, if necessary) will be conducted on a quarterly basis.

We propose conducting and documenting the following specific assessments at the listed time points.

1. **Site Initiation / Start-Up**
    a. Verification of site investigator’s affiliation with institution
    b. Assessment of the site investigator’s qualifications
    c. Verification of site investigator’s licensure status
    d. Verification of site investigator’s completion of human subject’s protection training
    e. Verification of HIPAA compliance for study
    f. Provide copies of the Belmont Report and Common Rule to site investigator
    g. Review study protocol and procedures with each site principal investigator
    h. Review site principal investigator’s responsibilities
    i. Document valid FWA and verify identification of IRB of record
    j. Assist sites without FWA number in obtaining one
    k. Verify copies of all documents are located on site with duplicate copy at UM Clinical Coordinating Center.

2. Quarterly Site Monitoring

a. Review study administrative records
b. Review all regulatory documents to ensure they are current and maintained
c. Review site data on tPA use assessing:
    i. completeness of documentation
    ii. completeness of case identification
    iii. appropriateness of use
    iv. identification of treatment complications
d. Review site compliance with study protocol

3. Site Close-Out Visit

a. Final review of all administrative/regulatory records and files
b. Clarify/ resolve any data discrepancies
c. Discuss plan for site record maintenance
d. Assure final IRB reporting

Copies of the documentation assessing the above criteria will be located at each site with a duplicate copy at the UM Clinical Coordinating Center. Deficiencies, if found, will be documented and reported to the study Principal Investigator (Phillip A. Scott, MD) and local site investigator for resolution. Copies of the monitoring documentation will be made available to IRBMED on an annual basis to assist in the oversight function of IRBMED for those sites utilizing the IRBMED as the IRB of record.

E.10.9 Institutional Review Board or Ethics Committee approval

This protocol and relevant supporting information must be submitted to the local IRB/EC for review and approval prior to study initiation. Sites may elect to cede oversight responsibility to the IRBMED at the University of Michigan in place of local IRB review. The study will be conducted in accordance with U.S. FDA applicable national and local health authority, and IRB/EC requirements. The Principal Investigator at each clinical site is responsible for keeping the IRB/EC informed of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once per year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events. Some IRBs or ECs may have other specific adverse event requirements that the investigators are expected to meet. Investigators must immediately forward to their IRB/EC any written safety report or update provided by the Independent Medical Monitor, or Clinical Coordinating Center (e.g. Safety Reports, Study Amendments and updates, etc.)

E.10.10 Provisions for privacy protection (HIPAA compliance)

Emergency physician survey: Unique identification numbers will replace the physician names and identifiers once the data has been entered into the database. Physician names will only be used to address envelopes/emails with the surveys. Individual names will not appear anywhere in the spreadsheets for the analysis of the data. There will be two copies of a master file that can link the identifiers with physicians. The master file will be kept in an envelope in a locked file cabinet. Only the EBDM group and project manager will have access to the cabinet. This master file will be destroyed at the earliest opportunity following study completion.

Patients: We will use a HIPPA compliant “limited data set” to ensure privacy protection when forwarding charts for blinded review. The site investigator, prior to forwarding medical records of tPA treated stroke patients, will strike all patient specific identifiers (name, unique hospital identification number, addresses including zip codes, telephone and fax numbers, email addresses, social security numbers, health plan numbers, license numbers, vehicle identification numbers account numbers, full face photos, biometric identifiers, or device identifiers). The record will meet the HIPAA definition of a “limited data set” (45 C.F.R. § 164.514(e)) and can be shared outside the originating institution without patient authorization under a data use agreement between

the coordinating center and local sites. The remaining data is allowed to contain date treated, gender, race and patient date of birth.

Each site investigator will maintain a sequential numerical log of patients who have a limited data set sent to the Biostatistics Core. This log will be used by the site investigator in the event that communication regarding a specific dataset is received from the INSTINCT Coordinating Center. The log is kept in a locked cabinet and will be available only to the researcher at the site. After completion of the research, the Coordinating Center will notify site investigators when they should destroy the logs (as determined by applicable regulatory guidelines).

E.11 Data and Safety Monitoring administrative structure

Independent Medical Monitor (IMM): Dr. Steven R. Levine, Professor of Neurology and Director of Cerebrovascular Education Program at The Mount Sinai School of Medicine & Medical Center in New York City will be the Independent Medical Monitor for the INSTINCT study. Dr. Levine was a principal investigator for the NIH funded NINDS rt-PA Stroke Trial. He will act independently and be advisory to the PI, EBDM and NIH.

UMHS Epidemiology, Biostatistical and Data Management (EBDM) Group : Directed by Drs. Mary Haan and Jack Kalbfleisch, Professors in Epidemiology and Biostatistics, respectively, at The University of Michigan.

Clinical Coordinating Center: Directed by Dr. Phillip Scott.

Participating Centers: Each site will identify a site Principal Investigator and other necessary staff as outlined. Site investigators unable to participate or perform their duties may be replaced at the discretion of Dr. Scott.

Steering Committee: The NIH project officer, Drs. Scott, Morgenstern, Haan, and Kalbfleisch.

Publication Committee: Drs. Scott, Morgenstern, Haan and Kalbfleisch and site PIs (TBD).

NIH: A medical officer from the NIH responsible for oversight of this trial will serve as liaison to the Independent Medical Monitor.

F Vertebrate Animals

There are no vertebrate animals in this proposal.

G Literature Cited

1. Luepker RV, Raczynski JM, Osganian S, et al. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: The Rapid Early Action for Coronary Treatment (REACT) Trial. *Jama.* Jul 5 2000;284(1):60-67.

2. Morgenstern LB, Staub L, Chan W, et al. Improving Delivery of Acute Stroke Therapy: The TLL Temple Foundation Stroke Project. *Stroke.* January 1, 2002 2002;33(1):160-166.

3. Ellekjær H, Holmen J, Kruger O, Terent A. Identification of Incident Stroke in Norway : Hospital Discharge Data Compared With a Population-Based Stroke Register. *Stroke.* January 1, 1999 1999;30(1):56-60.

4. Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke.* Aug 1998;29(8):1602-1604.

5. Chiu D KD, Villar-Cordova C, Kasner SE,, Morgenstern LB BP, Yatsu FM, Grotta JC. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. *Stroke.* 1998;29(1):18-22.

6. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *Jama.* Mar 1 2000;283(9):1151-1158.

7. Chapman KM, Woolfenden AR, Graeb D, et al. Intravenous tissue plasminogen activator for acute ischemic stroke: A Canadian hospital's experience. *Stroke.* 2000;31(12):2920-2924.

8. Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG, Wang DZ. Treatment With Tissue Plasminogen Activator and Inpatient Mortality Rates for Patients With Ischemic Stroke Treated in Community Hospitals. *Stroke.* August 1, 2001 2001;32(8):1832-1840.

9. Hickenbottom S. Preliminary Results from Four State Pilot Prototypes of the Paul Coverdell National Acute Stroke Registry. Ann Arbor, MI; 2003.

10. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke.* Feb 1998;29(2):415-421.

11. Anonymous. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *New England Journal of Medicine.* 1995;333(24):1581-1587.

12. Davenport J, Hanson SK, Altafullah IM, et al. tPA: a rural network experience. *Stroke.* 2000;31(6):1457-1458.

13. Grond M, Stenzel C, Schmulling S, et al. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke.* 1998;29(8):1544-1549.

14. Katzan IL, Sila CA, Furlan AJ. Community use of intravenous tissue plasminogen activator for acute stroke: results of the brain matters stroke management survey. *Stroke.* 2001;32(4):861-865.

15. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC. Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. *Stroke.* 2000;31(1):77-81.

16. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. The t-PA Stroke Survey Group. *Neurology.* 1999;53(2):424-427.

17. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study [see comments]. *Jama.* 2000;283(9):1145-1150.

18. Smith RW, Scott PA, Grant RJ, Chudnofsky CR, Frederiksen SM. Emergency physician treatment of acute stroke with recombinant tissue plasminogen activator: a retrospective analysis. *Academic Emergency Medicine.* 1999;6(6):618-625.

19. Scott P, Davis L, Frederiksen S, Smith R. Emergency Physician Administration of rt-PA in Acute Stroke: Five-year Analysis of Treatment and Outcome (abstract). *Acad Emerg Med.* May 2002;9(5):447.

20. Alberts MJ. tPA in acute ischemic stroke: United States experience and issues for the future. *Neurology.* 1998;51(3 Suppl 3):S53-55.

21. Anonymous. Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke. Paper presented at: Rapid Identification and Treatment of Acute Stroke, 1997; Bethesda, MD.

22. Morgenstern LB, Bartholomew LK, Grotta JC, Staub L, King M, Chan W. Sustained Benefit of a Community and Professional Intervention to Increase Acute Stroke Therapy. *Arch Intern Med.* October 13, 2003 2003;163(18):2198-2202.
23. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous Tissue-Type Plasminogen Activator Therapy for Ischemic Stroke: Houston Experience 1996 to 2000. *Arch Neurol.* December 1, 2001 2001;58(12):2009-2013.
24. Rogers W, Bowlby L, Chandra N, et al. Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. *Circulation.* Oct 1994;90(4):2103-2114.
25. Anonymous. ACEP Policy Statement: Use of Intravenous tPA for the Management of Acute Stroke in the Emergency Department. *American College of Emergency Physicians* [Internet]. Available at: http://www.acep.org/1,5006,0.html. Accessed November, 2002.
26. Alberts MJ. Undergraduate and postgraduate medical education for cerebrovascular disease. *Stroke.* 1995;26(10):1849-1851.
27. Scott P, Davis L, Beck P. Residency Training on the Use of Thrombolytic Therapy for Acute Stroke (abstract). *Journal of Stroke and Cerebrovascular Disease.* July-Aug 1999;8(4):276.
28. Kunnel B, Heller M. Thrombolytics and Stroke: What do Emergency Medicine Residents Perceive? *Academic Emergency Medicine.* 1999;6(11):1174-1176.
29. Joos S, Hickam D. How health professionals influence health behavior: Patient provider interaction and health care outcomes. In: Glanz K, Lewis F, Rimer B, eds. *Health Behavior and Health Education: Theory, Research and Practice*. San Francisco, CA: Jossey Bass; 1990:216-241.
30. Hickenbottom S, Morgenstern L. Educating North America: Lessons Learned. *Seminars in Cerebrovascular Disease and Stroke.* 2001;1(2):167-175.
31. Sutton S. Social-psychological approaches to understanding addictive behaviours: attitude-behaviour and decision-making models. *Br J Addict.* Apr 1987;82(4):355-370.
32. Weinstein N. Testing four competing theories of health-protective behavior. *Health Psychol.* Jul 1993;12(4):324-333.
33. Greco PJ, Eisenberg JM. Changing physicians' practices. *N Engl J Med.* 1993;329(17):1271-1273.
34. Browner W, Baron R, Solkowitz S, Adler L, Gullion D. Physician management of hypercholesterolemia. A randomized trial of continuing medical education. *West J Med.* Dec 1994;161(6):572-578.
35. Boissel J, Collet J, Alborini A, et al. Education program for general practitioners on breast and cervical cancer screening: a randmomized trial. PRE.SA.GF Collaborative Group. *Rev Epidemiol Sante Publique.* Dec 1995;43(6):541-547.
36. Davis D, O'Brien MAT, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of Formal Continuing Medical Education: Do Conferences, Workshops, Rounds, and Other Traditional Continuing Education Activities Change Physician Behavior or Health Care Outcomes? *JAMA.* September 1, 1999 1999;282(9):867-874.
37. Kottke TE, Brekke ML, Solberg LI, Hughes JR. A randomized trial to increase smoking intervention by physicians. Doctors Helping Smokers, Round I. *Jama.* Apr 14 1989;261(14):2101-2106.
38. Levinson W, Roter D. The effects of two continuing medical education programs on communication skills of practicing primary care physicians. *J Gen Intern Med.* Jun 1993;8(6):318-324.
39. Maiman LA, Becker MH, Liptak GS, Nazarian LF, Rounds KA. Improving pediatricians' compliance-enhancing practices. A randomized trial. *Am J Dis Child.* Jul 1988;142(7):773-779.
40. Ockene IS, Hebert JR, Ockene JK, Merriam PA, Hurley TG, Saperia GM. Effect of training and a structured office practice on physician-delivered nutrition counseling: the Worcester-Area Trial for Counseling in Hyperlipidemia (WATCH). *Am J Prev Med.* Jul-Aug 1996;12(4):252-258.
41. Roter DL, Hall JA, Kern DE, Barker LR, Cole KA, Roca RP. Improving physicians' interviewing skills and reducing patients' emotional distress. A randomized clinical trial. *Arch Intern Med.* Sep 25 1995;155(17):1877-1884.
42. White CW, Albanese MA, Brown DD, Caplan RM. The effectiveness of continuing medical education in changing the behavior of physicians caring for patients with acute myocardial infarction. A controlled randomized trial. *Ann Intern Med.* May 1985;102(5):686-692.
43. Hayward RS. Clinical practice guidelines on trial. *Cmaj.* Jun 15 1997;156(12):1725-1727.

44. Lomas J, Anderson GM, Domnick-Pierre K, Vayda E, Enkin MW, Hannah WJ. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. *N Engl J Med.* Nov 9 1989;321(19):1306-1311.

45. Woolf SH. Practice guidelines: a new reality in medicine. III. Impact on patient care. *Arch Intern Med.* Dec 13 1993;153(23):2646-2655.

46. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *Jama.* Oct 20 1999;282(15):1458-1465.

47. Lomas J, Enkin M, Anderson GM, Hannah WJ, Vayda E, Singer J. Opinion leaders vs audit and feedback to implement practice guidelines. Delivery after previous cesarean section. *Jama.* May 1 1991;265(17):2202-2207.

48. Everitt DE, Soumerai SB, Avorn J, Klapholz H, Wessels M. Changing surgical antimicrobial prophylaxis practices through education targeted at senior department leaders. *Infect Control Hosp Epidemiol.* Nov 1990;11(11):578-583.

49. Soumerai SB, Salem-Schatz S, Avorn J, Casteris CS, Ross-Degnan D, Popovsky MA. A controlled trial of educational outreach to improve blood transfusion practice. *Jama.* Aug 25 1993;270(8):961-966.

50. Avorn J, Soumerai SB. A new approach to reducing suboptimal drug use. *Jama.* Oct 7 1983;250(13):1752-1753.

51. Ray WA, Schaffner W, Federspiel CF. Persistence of improvement in antibiotic prescribing in office practice. *Jama.* Mar 22-29 1985;253(12):1774-1776.

52. Ray WA, Blazer DG, 2nd, Schaffner W, Federspiel CF, Fink R. Reducing long-term diazepam prescribing in office practice. A controlled trial of educational visits. *Jama.* Nov 14 1986;256(18):2536-2539.

53. Pimlott NJ, Hux JE, Wilson LM, Kahan M, Li C, Rosser WW. Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial. *Cmaj.* Apr 1 2003;168(7):835-839.

54. Parrino TA. The nonvalue of retrospective peer comparison feedback in containing hospital antibiotic costs. *Am J Med.* Apr 1989;86(4):442-448.

55. Hershey CO, Goldberg HI, Cohen DI. The effect of computerized feedback coupled with a newsletter upon outpatient prescribing charges. A randomized controlled trial. *Med Care.* Jan 1988;26(1):88-94.

56. McPhee SJ, Bird JA, Jenkins CN, Fordham D. Promoting cancer screening. A randomized, controlled trial of three interventions. *Arch Intern Med.* Aug 1989;149(8):1866-1872.

57. Tierney WM, Hui SL, McDonald CJ. Delayed feedback of physician performance versus immediate reminders to perform preventive care. Effects on physician compliance. *Med Care.* Aug 1986;24(8):659-666.

58. Coleman RW, Rodondi LC, Kaubisch S, Granzella NB, O'Hanley PD. Cost-effectiveness of prospective and continuous parenteral antibiotic control: experience at the Palo Alto Veterans Affairs Medical Center from 1987 to 1989. *Am J Med.* Apr 1991;90(4):439-444.

59. Soumerai SB, Ross-Degnan D, Avorn J, McLaughlin T, Choodnovskiy I. Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes. *N Engl J Med.* Oct 10 1991;325(15):1072-1077.

60. Lyden P, Hickenbottom S. Professional Education: Draft Task Force Reports. Paper presented at: Improving the Chain of Recovery for Acute Stroke in Your Community; December 12-13, 2002; Arlington, VA.

61. Scott PA, Smith RW, Chudnofsky CR, et al. Emergency Physician Administration of rt-PA in Acute Stroke: Analysis of Treatment and Outcome (abstract). *Stroke.* 1999;30(1):244.

62. Scott P, Smith R, Davis L, Frederiksen S, Chudnofsky C, Maino J. Time Analysis of Emergency Physician Delivery of rt-PA in Acute Ischemic Stroke (Abstract A327). *Acad Emerg Med.* May 2000 2000;7(5):535.

63. Scott P, Silbergleit R. Misdiagnosis of stroke in tissue plasminogen activator-treated patients: Characteristics and outcomes. *Annals of Emergency Medicine.* 2003/11// 2003;42(5):611-618.

64. Scott P, Silbergleit R, Frederiksen S, Smith R. Long Term Mortality in Stroke Patients Treated with TPA: Emergency Physicians vs NINDS (abstract). *Acad Emerg Med.* May 2003 2003;10(5):433.

65. Ferro JM, Pinto AN, Falcao I, et al. Diagnosis of stroke by the nonneurologist. A validation study. *Stroke.* Jun 1998;29(6):1106-1109.
66. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. *Arch Neurol.* Nov 1995;52(11):1119-1122.
67. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence-based health education programs. *Health Educ Behav.* Oct 1998;25(5):545-563.
68. Piriyawat P, Smajsova M, Smith MA, et al. Comparison of active and passive surveillance for cerebrovascular disease: The Brain Attack Surveillance in Corpus Christi (BASIC) Project. *Am J Epidemiol.* Dec 1 2002;156(11):1062-1069.
69. Cabana MD, Ebel BE, Cooper-Patrick L, Powe NR, Rubin HR, Rand CS. Barriers pediatricians face when using asthma practice guidelines. *Arch Pediatr Adolesc Med.* Jul 2000;154(7):685-693.
70. Cabana MD, Rand CS, Becher OJ, Rubin HR. Reasons for pediatrician nonadherence to asthma guidelines. *Arch Pediatr Adolesc Med.* Sep 2001;155(9):1057-1062.
71. Scott PA, Temovsky CJ, Lawrence K, Gudaitis E, Lowell MJ. Analysis of Canadian Population with Potential Geographic Access to Intravenous Thrombolysis for Acute Ischemic Stroke. *Stroke.* 1998;29(November):2304-2310.
72. Goldberg R, Boss RW, Chan L, et al. Burnout and its correlates in emergency physicians: four years' experience with a wellness booth. *Acad Emerg Med.* Dec 1996;3(12):1156-1164.
73. Hall KN, Wakeman MA. Residency-trained emergency physicians: their demographics, practice evolution, and attrition from emergency medicine. *J Emerg Med.* Jan-Feb 1999;17(1):7-15.
74. Eisenberg J. *Doctors' decisions and the cost of medical care*. Ann Arbor, MI: Health Administration Press; 1986.
75. Lopez-Yunez AM, Bruno A, Williams LS, Yilmaz E, Zurru C, Biller J. Protocol violations in community-based rTPA stroke treatment are associated with symptomatic intracerebral hemorrhage. *Stroke.* 2001;32(1):12-16.
76. Hyman DJ, Maibach EW, Flora JA, Fortmann SP. Cholesterol treatment practices of primary care physicians. *Public Health Rep.* Jul-Aug 1992;107(4):441-448.
77. Main DS, Cohen SJ, DiClemente CC. Measuring physician readiness to change cancer screening: preliminary results. *Am J Prev Med.* Jan-Feb 1995;11(1):54-58.
78. Pathman DE, Konrad TR, Freed GL, Freeman VA, Koch GG. The awareness-to-adherence model of the steps to clinical guideline compliance. The case of pediatric vaccine recommendations. *Med Care.* Sep 1996;34(9):873-889.
79. Strauss A, Corbin J. *Grounded theory methodology: an overview*. Thousand Oaks, CA: Sage Publications; 1998.
80. Manning P, Cullum-Swan B. *Narrative, content, and semiotic analysis*. Thousand Oaks, CA: Sage Publications; 1998.
81. Cameron C, Naylor CD. No impact from active dissemination of the Ottawa Ankle Rules: further evidence of the need for local implementation of practice guidelines. *Cmaj.* Apr 20 1999;160(8):1165-1168.
82. Holloway RG, Gifford DR, Frankel MR, Vickrey BG. A randomized trial to implement practice recommendations: design and methods of the Dementia Care Study. *Control Clin Trials.* Aug 1999;20(4):369-385.
83. Mazmanian PE, Davis DA. Continuing medical education and the physician as a learner: guide to the evidence. *Jama.* Sep 4 2002;288(9):1057-1060.
84. Zibrat F. Oryx Core Measure Set Selection Update. *Joint Commission on Accreditation of Healthcare Organizations*. March 20, 2003. Available at: http://www.jcaho.org/about+us/news+letters/this+month/state+medical+society+edition/print/october+2002.html. Accessed April, 2003.
85. Greer AL. The state of the art versus the state of the science. The diffusion of new medical technologies into practice. *Int J Technol Assess Health Care.* 1988;4(1):5-26.
86. Mittman BS, Tonesk X, Jacobson PD. Implementing clinical practice guidelines: social influence strategies and practitioner behavior change. *QRB Qual Rev Bull.* Dec 1992;18(12):413-422.

87. Soumerai SB, McLaughlin TJ, Gurwitz JH, et al. Effect of local medical opinion leaders on quality of care for acute myocardial infarction: a randomized controlled trial. *Jama.* May 6 1998;279(17):1358-1363.
88. Hiss R, MacDonald R, David W. Identification of physician educational influentials in small community hospitals. *Res Med Educ.* 1978;17:283-288.
89. Gass DA, Curry L. Physicians' and nurses' retention of knowledge and skill after training in cardiopulmonary resuscitation. *Can Med Assoc J.* Mar 1 1983;128(5):550-551.
90. Lum ME, Galletly DC. Resuscitation skills of first year postgraduate doctors. *N Z Med J.* Aug 9 1989;102(873):406-408.
91. Stross JK. Maintaining competency in advanced cardiac life support skills. *Jama.* Jun 24 1983;249(24):3339-3341.
92. Kaye W, Mancini ME. Use of the Mega Code to evaluate team leader performance during advanced cardiac life support. *Crit Care Med.* Feb 1986;14(2):99-104.
93. Kaye W, Mancini ME, Rallis SF. Advanced cardiac life support refresher course using standardized objective-based Mega Code testing. *Crit Care Med.* Jan 1987;15(1):55-60.
94. Cappelle C, Paul RI. Educating residents: the effects of a mock code program. *Resuscitation.* Apr 1996;31(2):107-111.
95. Funkhouser MJ, Hayward MF. Multidisciplinary mock codes: dream it, plan it, do it, rate it. *J Nurs Staff Dev.* Sep-Oct 1989;5(5):231-237.
96. Anonymous. IV t-PA Inteventional Therapy for Acute Stroke Patients: A Debate. Paper presented at: Canadian Association of Emergency Physicians annual Scientific Meeting, 2002; Calgary, Alberta, Canada.
97. Hoffman JR. Predicted impact of intravenous thrombolysis. Another trial is needed. *Bmj.* Apr 8 2000;320(7240):1007.
98. Hoffman JR. Alteplase for stroke. Why were these authors of the commentaries chosen? *Bmj.* Jun 29 2002;324(7353):1581; author reply 1581.
99. Ingall TJ, O'Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke.* Oct 2004;35(10):2418-2424.
100. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Engelwood Cliffs, NJ: Prentice-Hall, Inc.; 1986.
101. Berlo D. *The Process of Communication: An Introduction to Theory and Practice*. New York, NY: Holt, Rinehart & Winston; 1960.
102. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *Jama.* Sep 6 1995;274(9):700-705.
103. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Cmaj.* Aug 15 1997;157(4):408-416.
104. Marshall JN, Stewart M, Ostbye T. Small-group CME using e-mail discussions. Can it work? *Can Fam Physician.* Mar 2001;47:557-563.
105. Salemi C, Canola MT, Eck EK. Hand washing and physicians: how to get them together. *Infect Control Hosp Epidemiol.* Jan 2002;23(1):32-35.
106. Anonymous. Emergency Nurses Position Statement. Chicago, IL: Emergency Nurses Association; 1998.
107. Dyregrov A. The process in psychological debriefings. *J Trauma Stress.* Oct 1997;10(4):589-605.
108. Oster NS, Doyle CJ. Critical incident stress and challenges for the emergency workplace. *Emerg Med Clin North Am.* May 2000;18(2):339-353, x-xi.
109. Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke: A Population-Based Study. *Stroke.* February 1, 2004 2004;35(2):27e-29.
110. Kleindorfer D. Temporal Trends in Emergency Department (ED) Arrival Times for Acute Ischemic Stroke (IS): A Population-Based Study (abstract submitted 2005 ASA Meeting, New Orleans); 2005.
111. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology.* 2001;56(8):1015-1020.

112. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM. Utilization of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke. *Arch Neurol.* March 1, 2004 2004;61(3):346-350.
113. Barsan WG, Brott TG, Broderick JP, Haley EC, Levy DE, Marler JR. Time of hospital presentation in patients with acute stroke. *Archives of Internal Medicine.* 1993;153(22):2558-2561.
114. Barsan WG, Brott TG, Broderick JP, Haley EC, Jr., Levy DE, Marler JR. Urgent therapy for acute stroke. Effects of a stroke trial on untreated patients. *Stroke.* 1994;25(11):2132-2137.
115. Johnston SC, Fung LH, Gillum LA, et al. Utilization of Intravenous Tissue-Type Plasminogen Activator for Ischemic Stroke at Academic Medical Centers : The Influence of Ethnicity Editorial Comment : It Is Time to Implement Stroke Practice Improvement Programs and Prevent the Racial Disparity in Stroke Care. *Stroke.* May 1, 2001 2001;32(5):1061-1068.
116. Kleindorfer D. rt-PA Use in a Population Based Study: the Post-FDA approval era. Cincinnati, OH; 2004.
117. Menon SC, Pandey DK, Morgenstern LB. Critical factors determining access to acute stroke care. *Neurology.* 1998;51(2):427-432.
118. Merino JG, Silver B, Wong E, et al. Extending Tissue Plasminogen Activator Use to Community and Rural Stroke Patients. *Stroke.* January 1, 2002 2002;33(1):141-146.
119. Brown DL, Lisabeth LD, Garcia NM, Smith MA, Morgenstern L. Emergency deparmtent evaluation of ischemic stroke and TIA: The Basic Project. *Neurology (in press).* 2004.
120. Asimos AW, Norton HJ, Price MF, Cheek WM. Therapeutic Yield and Outcomes of a Community Teaching Hospital Code Stroke Protocol. *Acad Emerg Med.* April 1, 2004 2004;11(4):361-370.
121. Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. *Arch Intern Med.* 2002;162(17):1994-2001.
122. Szoeke CE, Parsons MW, Butcher KS, et al. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust.* Apr 7 2003;178(7):324-328.
123. Deng Y, Reeves M, Group ftMW. Intravenous Recombinant Tissue Plaminogen Activator Use in Acute Stroke: Experience from a Statewide Hospital-based Stroke Registry. *(Draft manuscript)*; 2004.

Appendix

A. List of participating hospitals
B. Nurse Coordinator Chart Review Instrument
C. Nurse Coordinator Chart review definitions and rules
D. Physician survey
E. Physician Informed consent
F. tPA use patient consent template
G. Focus group consent
H. Oral recruitment script
I. ED focus group outline
J. Recruitment process for focus groups
K. Focus group recruitment letter
L. Site Investigator Chart review instrument
M. Medical Reviewer Chart review instrument