PROTOCOL TITLE:

Randomized Placebo Controlled Trial of Intravenous N-Acetylcysteine for the Treatment of Acute Ischemic Stroke

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FDA IND:

#145,538

VERSION NUMBER:

1.6

DATE:

10/24/2023

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1) Protocol Title

Randomized Placebo Controlled Trial of Intravenous N-Acetylcysteine for the Treatment of Acute Ischemic Stroke

2) HSC Review History

Version 1.5 dated 6/16/2021: NAC dosing regimen changed to complete the 2-bag regimen in 20 hours. Modified regimen will infuse a total 50 mg/kg/hr N-AC over 4 hours for a total of 200 mg/kg following by 100 mg/kg over 16 hours.

Version 1.6 dated 10/24/2023: Inclusion criteria changed to allow screening and enrollment of subjects with at least an NIH Stroke Scale (NIHSS) of 5. Use predetermined enrollment caps of 39 subjects 0in each group: moderate (NIHSS = 5-15), moderate to severe (NIHSS = 16-20) and severe stroke (NIHSS = 21-42).Population target revised to 117.

3) Investigator

David A. Tanen, MD

4) Objectives

To determine the efficacy of a 20-hour intravenous N-Acetylcysteine regimen in patients suffering from acute ischemic stroke.

5) Lay Summary

Stroke is a major cause of death and long-term disability in the developed world. While t-PA (an FDA approved medication that is currently used within the first 4.5 hours after a stroke) and mechanical thrombectomy (a procedure that is done to try and remove the clot using wires placed into the blood vessels in the brain by interventional radiologist) have been shown to decrease disability in properly selected patients, many patients are left with lifelong symptoms. There are currently limited options available for patients who are not candidates for treatment with t-PA and/or mechanical thrombectomy. Finding additional or supplemental strategies are urgently needed.

N-Acetylcysteine (NAC) is an FDA approved antioxidant and anti-inflammatory agent that has been used safely for many years in the treatment of acetaminophen (Tylenol) overdose. In studies, the oral form has been shown to improve outcomes in acute ischemic stroke and has been shown to decrease the effects of ischemic brain injury (stroke) in animal models. In a small human trial, it improved outcomes in patients suffering from mild traumatic brain injury (TBI). The intravenous formulation has a long safety record for intravenous (IV). It is not FDA approved for treating stroke but was reviewed by the FDA and was given an FDA IND for the study.

We propose a prospective randomized, double-blind, placebo-controlled study to evaluate the efficacy of administering intravenous N-acetylcysteine to patients with acute ischemic stroke. Eligible subjects will receive a commercially available form of intravenous NAC (Acetadote®) through an IV for the first 20 hours following their enrollment. Patients enrolled who receive t-PA for thrombolysis will have their intravenous NAC infusion delayed for 24 hours after the completion of their t-PA infusion. Patients undergoing thrombectomy will be excluded from enrollment. Subjects will be evaluated by emergency department and/or division of neurology physicians at the time of enrollment, during their hospitalization, as well as 30 days and 90 days after enrollment. At each visit, subjects will be assessed for functional status and quality of life by using well known and tested evaluations: National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (MRS), Glasgow Outcome Scale (GOS), and Barthel Index (BI).

This study is designed to compare the efficacy of intravenous N-acetylcysteine compared to normal treatment in patients with acute ischemic stroke. Secondarily, we will also look at whether there was any benefit or harm to the subjects over the time course of the study.

6) Background

Stroke is a leading cause of death and long-term disability in the United States, affecting more than 795,000 individuals annually (1). Of these, about 87% are ischemic strokes. In properly selected patients, intravenous recombinant tissue plasminogen activator (t-PA) has been shown to improve functional outcomes if given within 4.5 hours of the onset of stroke symptoms (2, 3). Endovascular treatment both via clot retrieval devices and catheter directed t-PA has demonstrated benefit in well-selected patients with a large vessel occlusion and significant salvable tissue, also known as the penumbra (4-6). For patients who are not candidates for treatment with t-PA or mechanical thrombectomy, current treatment is centered on supportive care.

N-Acetylcysteine (NAC) is an FDA approved medication that has been used successfully for many years in the treatment of acute acetaminophen overdose (79). It is generally well tolerated with the exception of rare anaphylactoid type reactions to the intravenous formulation (10, 11).

In mouse studies, N-acetylcysteine (NAC) has led to an increase in glutathione levels in the neurons along with a reduced number of microbleeds in ischemic models (12). NAC treated rats have been demonstrated to have increased level of glutathione in the astrocytes which provides a neuroprotective effect. This reduced the number of microbleeds and prevented further thrombosis or infarct (12). The efficacy of NAC by scavenging of ROS and increasing mitochondrial activities has been shown to reduce noise-induced hearing loss in chinchilla models (13). Another study on transient cerebral ischemia rat models defined a new pharmacokinetic in which the neuroprotective effects of NAC are mediated

by the increased protein levels of hypoxia-induced factor 1 (HIF-1), its target erythropoietin (EPO) and glucose transporter (GLUT-3) (14).
Studies have shown consistent, similar results for ischemic brain injury in rat (12, 15-17). Consistent human studies showing neuroprotective effects which lead to reduced symptoms after traumatic brain injury, reduced noise-induced hearing loss and as a treatment for Parkinson's disease (18-20).

NAC has been shown to stimulate mitochondrial Complex 1 and 4 activities in vivo and in vitro in pre-synaptic terminals (17). The antioxidant effect of NAC by scavenging of ROS may prevent intracellular damage by inhibiting NF-κB (21, 22), TNFα (23, 24) and Na^+, K^+ -ATPase inhibition (25) of the neurons.

In a human study of NAC for Parkinson's disease, NAC was found to mitigate the effects of ischemic brain injury in animal models (12). The antioxidant effect from repletion of intracellular glutathione is thought to preserve mitochondrial function and decrease cellular apoptosis (26, 27). A placebo-controlled human trial demonstrated that NAC is able to decrease the effects of mild traumatic brain injury 7 days after blast injury (18).

A recent study has shown that sufficient plasma and CSF levels can be achieved at well tolerated doses: 7 mg/kg, 35 mg/kg and 50 mg/kg (28).

A recent randomized placebo-controlled trial demonstrated improvement in patients given oral N-acetylcysteine every four hours for a total of 72 hours after enrollment in their NIH stroke scale and modified Rankin Score at 90 days. Intravenous N-Acetylcysteine given over 20 hours has proven to be equally efficacious in the treatment of acetaminophen toxicity and is currently the standard of care for that indication. We aim to determine if similarly dosed intravenous NAC regimen completed over a 20-hour course will improve NIH Stroke Scale at 90 days. of NAC following an acute ischemic stroke. (37)

7) Setting of the Human Research

This is a prospective randomized placebo-controlled study evaluating the efficacy of N-acetylcysteine for the treatment of acute ischemic stroke. It will be conducted at Harbor UCLA Medical Center.

8) Resources Available to Conduct the Human Research

Faculty and residents of the Departments of Emergency Medicine and Neurology at Harbor-UCLA will participate in the recruitment, execution, and analysis of the trial. The required number of suitable subjects is 117. We will ensure that all persons assisting with the trial are adequately informed about the protocol, research method, and their trial-related duties and functions.

Intravenous N-Acetylcysteine will be donated by the manufacturer, Cumberland Pharmaceuticals (Acetadote®). Cumberland Pharmaceuticals will not have a role in the design, conduct, or analysis of the study.

9) Prior Approvals

The FDA has reviewed the study and gave an FDA IND (#145,538). Approved was also given by the research divisions of Cumberland Pharmaceuticals (Cumberland Pharmaceuticals have agreed to donate N-acetylcysteine for the study).

10) Study Design

1) The treating ED physicians (other than the investigator or coinvestigators) will identify potential subjects in the Emergency Department at Harbor UCLA via initial evaluation (standard of care) including blood draw for a standard CVA panel (CBC, Chemistries, PT, PTT, neuronal specific enolase, s100b) and brain imaging. Subjects who present with neurological deficits consistent with stroke without hemorrhage less than 24 hours since symptom onset will be asked to whether they would be interested in participation in a research in our study and if so, the treating ED physician will contact investigators or study team member. Investigators or study team member may access medical record to confirm eligibility before approach subject.

If treating physician is member a co-investigator/ study team member, s/he will approach subject about participation once deemed to meet eligibility criteria. (See inclusion and exclusion criteria below). Informed consent will be obtained for all subjects either from the subjects themselves or if they do not have capacity, from their legally authorized representative (See Section 16 below).

2) Each subject will undergo, as part of standard of care, evaluation and assessment using the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (MRS) which have been similarly used in the European Cooperative Acute Stroke Study III, ECASS III (3). The NIHSS is a 15-item scale that measures the level of neurologic impairment. The MRS is a measure of disability with scores ranging from 0 (no symptoms at all) to 6 (death). Individuals must have an NIHSS of at least 5 to be eligible for this study. This data will be recorded for study purposes using a standard data collection sheet.

3) Subjects will receive standard of care with the study intervention being considered an “add-on” therapy. Thirty minutes after enrollment, eligible subjects will be randomized into one of two arms: placebo or NAC.

Any patient receiving t-PA who enrolls in the study will have their study drug infusion delayed by 24 hours after the completion of the t-PA infusion.

The dosing of NAC will be similar to the standard intravenous acetaminophen toxicity dosing: 200mg/kg in 1 liter of 5% Dextrose (D5W) infused over 4 hour, then 100mg/kg in 1000 milliliters D5W infused over 16 hours (29,38).

Prior to receiving NAC, subjects will also receive 12.5 mg diphenhydramine (an antihistamine) to further reduce the chance of an allergic reaction.

All subjects will be monitored closely by hospital staff either in the Emergency Department or the hospital's monitored units (Intensive Care Unit or Step Down Unit) with vital signs obtained every 15 minutes for the first four hours of the infusion, and neurologic symptom checks completed every hour for the 20 hours of the study drug infusion in addition to the standard of care for stroke patients. The staff will be trained to observe for common side effects of the NAC infusion which may include nausea, vomiting, flushing, and pruritus along with the more uncommonly seen wheezing and bronchospasm or rarely angioedema and hypotension. Investigators will also prospectively ask the subjects every four hours up to 48 hours after administering the NAC to report if they are or have experienced any nausea, vomiting, flushing, itchiness or experienced wheezing or had any trouble breathing. Investigators will also prospectively record vital signs and look for evidence of anaphylactoid reactions or other allergic reactions. If any of the uncommon or rare drug effects are detected by nursing or by the investigators, there will be standing orders to stop the NAC infusion and immediately contact the physician caring for the patient. If a mild symptom occurs, the staff will be informed to contact the treating physician to assess the patient. At the same intervals, subjects will also be queried as to whether they have had any new symptoms or problems since the last study assessment to obtain data on a broader range of possible adverse and serious adverse events that may be unexpected or not typically associated with NAC infusions.

Blood glucose levels will be monitored as part of the standard of care for stroke patients admitted to the hospital by the treating physicians. In addition, a finger stick glucose will be obtained prior to meals (three times daily) and recorded by the investigators. If an abnormal glucose measurement is noted, the treating neurology team will be notified.

4) Subjects will be contacted by telephone 24 hours post discharge, 3 days post discharge, and at 7 days to be monitored for adverse events and asked whether they have had any new symptoms or problems since the last study assessment. This will be an open question that will be recorded prospectively for each subject. If the subject reports an adverse event this is still present at the time of the phone call and wants to be further evaluated, they will be told to return to the emergency department and seen by a physician not associated with the investigation. Further the investigator from

the team will also meet them in the Emergency Department to detail the information. All adverse events, whether they are deemed mild or serious, will be forwarded immediately to the Medical Monitor who will have discretion on whether to halt the study or continue. The Medical Monitor's reports will be forwarded to the Institutional Review Board (IRB). In addition, all unanticipated problems pose a risk to subjects or others will be reported to the Institutional Review Board (IRB) as required by FDA regulations. (There is no sponsor for this study, so no report needs to go to a sponsor).

4) Subjects will be instructed to return to the neurology clinic on day 30 and day 90 for re-evaluation. The same assessment will be performed as on day zero: the NIHSS and the MRS as well as the Glasgow Outcome Scale (GOS) and Barthel Index (BI). The GOS is a 5-point scale on which 5 indicates independence and 1 death. The BI assesses the ability to perform activities of daily living, on a scale that ranges from 0 (complete dependence on help with activities of daily living) to 100 (independence). These scores will be recorded on a standard data collection sheet. A representative from the neurology department will perform the examination, blinded from the previous scoring and treatment. In addition to the neurologic evaluation, patients will be queried at this time as to whether they experienced any nausea, vomiting, flushing, and itchiness, wheezing or difficulty breathing between the time of their discharge and the reevaluation.

For convenience, the 30 day follow up will have a tolerance range +/- 3 days and the 90 day follow up will permit +/- 10 day window.

These follow-up visits are standard of care. The tests are standard physical assessments done by the neurologists, and no specific interventions will be made for the study. Our study team will review EMR to obtain results/notes.

5) Subjects will be instructed to return to the emergency department if their condition is worsens or if they develop new neurological symptoms.

6) In addition to the clinic data, as standard of care, patients will have an MRI of the brain performed during the first 48 hours of their hospital admission and a follow-up MRI of the brain at 3 months as part of the standard of care for stroke patients. As per standard neurology evaluation, a blood test for s100b, neuronal specific enolase level will be obtained by the neurology team while the subject is admitted. MRI data will be analyzed initially for the type of stroke (either embolic, or thrombotic), stroke associated edema, for volumetric changes at three months poststroke, and gliosis at three months.

7) Telephone contact will be attempted if a subject is transferred to an outside hospital following admission, or if a subject does not show up to clinic for re-evaluation as scheduled, and efforts will be made to evaluate the patient in the time allotted. We will make a maximum of 3 phone calls within a 1 week period.

a) Inclusion and Exclusion Criteria

Inclusion Criteria:

Consecutive subjects between ages 18 years or older evaluated in the emergency department at Harbor-UCLA Medical Center with signs and symptoms of acute ischemic stroke presenting within 24 hours of symptom onset. Individuals must have a NIHSS of at least 5 to be included. All individuals regardless of gender or race will be included. For adults who cannot consent for themselves because of the severity of their stroke, one of the investigators will offer participation in the study to the family member who possesses the authority for medical decision making for the patient. There is no financial incentive for either the patient or the investigator. It will also be explained that the potential benefit of giving N-acetylcysteine is unknown and that the patient will receive excellent care (standard for their presentation) whether they participate or not and outside of not receiving the study drug.

Our patients tend to be economically disadvantaged but since there are no financial incentives either for the patient or for the investigators, this bias has been minimized. Patients will receive the same care whether they participate in the study or decline.

Exclusion Criteria:

-Evidence of hemorrhagic stroke on initial CT scan
-Need for thrombectomy as determined by the treating neurologist -Known allergy to NAC
-Protected populations, including age < 18, known pregnancy, and prisoners
-Patients who are DNR/DNI at the time of presentation with a short life expectancy

b) Local Number of Subjects

The total number of local subjects will be 117 (39 subjects with moderate stroke = NIHSS 5-15; 39 subjects with moderate to severe stroke = NIHSS 16-20; 39 subjects with severe stroke = NIHSS = 21-42)

This number was derived using a group size analysis based on previous work on oral NAC for ischemic stroke (37) and a hypothesis of finding no

difference (defined as a change in NIHSS < 4) between NIHSS scores at 90 days. With a power of 0.80 and an alpha 0.05 we would need 47 subjects in each group. Assuming a dropout rate of 25% or lost to follow-up, we would enroll 59 in each group for a total of 117.

(Group sample sizes of 47 and 47 achieve 81% power to detect a difference of 4.0 using a one-sided Mann-Whitney U or Wilcoxon Rank-Sum test assuming that the actual data distribution is normal when the significance level (alpha) of the test is 0.05 and the standard deviation is 7.4 in both groups.)

c) Study-Wide Number of Subjects

This is a single center study at the Harbor-UCLA Medical Center.

d) Study Timelines

Estimated time to complete enrollment is December 2025. Review of the neurology services revealed that Harbor-UCLA typically sees 20 patients per month that would be eligible for the study.

e) Study Endpoints

The primary study endpoint will be comparison between groups (NAC treated group versus treatment) of the NIHSS at 90 days.

Secondary endpoints include changes in the MRS, GOS, BI, and blood tests at 30 days and 90 days, as well as MRI data including changes in brain volume and gliosis at 90 days.

f) Procedures Involved in the Human Research

First, subjects will be screened for neurological deficits consistent with cerebral vascular accident via history, physical examination and emergent evaluation in the Emergency Department which will include a noncontrast CT of the brain and an emergent Stroke Code, where our Neurology team will immediately consult on the patient at the bedside.

As part of the initial evaluation, the patient will be assessed with the National Institutes of Health Stroke Scale (NIHSS) which uses a 15-item scoring system to assess the level of neurological impairment. The items assessed include: Level of consciousness (LOC) responsiveness, LOC questions, LOC commands, best gaze, visual field, facial palsy, best motor arm, best motor leg, limb ataxia, sensory function, neglect, dysarthria, best language, extinction and inattention, formerly called neglect (31, 32).

A Modified Rankin Scale (MRS) will also be obtained; The MRS is a simple scoring system that runs from 0-6, from perfect health without symptoms to death. 1- no significant disability, able to carry out all usual activities, despite some symptoms. 2 - slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities. 3 - moderate disability, requires some help, but able to walk unassisted. 4 - moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted. 5 - severe disability, requires constant nursing care and attention, bedridden, incontinent.

The neurology consult team in conjunction with the Emergency Department will then make an assessment as to whether the patient is eligible to receive treatment with t-PA (based on national criteria of the American Heart Association and American Stroke Association - https://www.stroke.org/-/media/Stroke-Files/Ischemic-StrokeProfessional-Materials/AIS-Toolkit/AIS-Professional-EducationPresentation-ucm_485538)

NAC or placebo infusion will be started 30 minutes after the enrollment of the study. For subjects who receive t-PA, NAC or placebo infusion will be started 24 hours after the conclusion of the t-PA infusion.

Prior to the starting of the study medication, all subjects will receive 12.5 mg intravenous diphenhydramine to reduce the incidence of allergic reactions.

All subjects would then be admitted to the Neurology Service to either an Intensive Care Unit bed or a Step-down intensive care unit bed.

Subjects will return to neurology clinic on days 30 and 90 and undergo reevaluation by a neurology resident using the same assessments performed on day 0. Data will be collected on a standard data collection sheet at each visit. In addition, the subjects will undergo the following two assessments:

Glasgow Outcome Scale (GOS, follow-up visits only):
GOS is a 5-point scale on which 1- death, 2- persistent vegetative state, 3- severe disability, 4- moderate disability, and 5- low disability.

Barthel Index (BI, follow-up visits only):
BI evaluates the ability to perform activities of daily living, on a scale that ranges from 0 to 100. Activities assessed include: presence or absence of fecal incontinence, presence or absence of urinary incontinence, help needed with grooming, with toilet use, with feeding, with transfers, with walking, with dressing, with climbing stairs, and with bathing.

These follow-up visits are standard of care. These tests are standard physical assessments done by the neurologists, and no specific interventions will be made for the study. Our study team will review EMR to obtain results/notes.

5. Each patient will complete two separate MRI's of the brain, which are both standard of care. The MRI's are considered standard of care and will not be different in acquisition then MRI's currently obtained for stroke patients. We will use software packages available to post-process these images for research purposes as outlined in the protocol.

6. Patients will have a "stroke panel" of lab tests as mentioned above, which are the standard of care at our facility. The total amount of blood obtained for the entire duration of the study will be less then 100ml.

7. We will also pre-define a per-protocol (excluding Stroke Mimics as defined as a negative brain MRI obtained within 2 weeks of the onset of symptoms) versus an intent to treat protocol. This would allow for the loss of study subjects who might stop the NAC after a negative MRI who are no longer thought to have had a Stroke.

g) Data and Specimen Banking

No specimens will be stored.

Data Collection sheets will be utilized for initial assessment and follow up. See attached documents.

h) Data Management

Data from the patient examinations will be stored in REDCAP database after being de-identified. It will be stored until this study completes. The data will be shared among the principal investigator and co-investigators. Principal investigator will be responsible for receipt or transmission of the data.

i) Confidentiality

Confidentiality will be maintained by use of coded data sheets and an enrollment logbook. Data will be stored in a password locked REDCAP database. It will be stored till the completion of this study. Only research investigators and research associates will have access to this data.

j) Provisions to Monitor the Data to Ensure the Safety of subjects

Dr Timothy Horezcko is an Emergency Physician and Researcher located at the Lundquist Institute at Harbor-UCLA Medical Center who is not associated with the study and who will act as a Safety Monitor. Although NAC has FDA approval for acetaminophen poisoning, it does not have an FDA indication for Acute Ischemic Stroke and Dr Horezcko will review the prospectively collected safety data specifically looking for adverse events (both non-serious and serious adverse events), and will also analyze each subjects' medical record which includes nursing notes, physician notes, ancillary care notes, vital signs, laboratories, clinical studies.

Since this a single hospital trial, Dr Horezcko will the sole Safety Monitor and will act as an independent overseer who will access the care of each subject and the ongoing compilation of safety data throughout the trial and have the authority to modify or stop the trial at his discretion.

Tracking adverse events

All subjects will be monitored closely by hospital staff either in the Emergency Department or the hospital's monitored units (Intensive Care Unit or Step Down Unit) with vital signs obtained every 15 minutes, and neurologic symptom checks completed every hour. The staff will be trained to observe for common side effects of the NAC infusion which may include nausea, vomiting, flushing, and pruritus along with the more uncommonly seen wheezing and bronchospasm or rarely angioedema and hypotension. Investigators will also prospectively ask the subjects every four hours to report if they are or have experienced any nausea, vomiting, flushing, itchiness or experienced wheezing or had any trouble breathing. Investigators will also prospectively monitor/record vital signs every 15 minutes for the first 4 hours after the NAC administration and look for evidence of anaphylactoid reactions or other allergic reactions. If any of the uncommon or rare drug effects are detected by nursing or by the investigators, there will be standing orders to stop the NAC infusion and immediately contact the physician caring for the patient. If a mild symptom occurs, the staff will be informed to contact the treating physician to assess the patient. For serious adverse events (defined by the discretion of the treating physician), the NAC will be unblinded and the information given to the treating physician and the medical monitor. At the same intervals, subjects will also be queried as to whether they have had any new symptoms or problems since the last study assessment to obtain data on a broader range of possible adverse and serious adverse events that may be unexpected or not typically associated with NAC infusions. All adverse events will be immediately reported to the Medical Monitor who will have the authority to immediately halt the study pending further review by the Lundquist Institute's IRB and the FDA.

In addition, subjects will be contacted by telephone 24 hours post discharge, 3 days poste discharge, and at 7 days to be monitored for adverse events and asked whether they have had any new symptoms or problems since the last study

assessment. This will be an open-ended question that will be recorded prospectively for each subject. If the subject reports an adverse event this is still present at the time of the phone call and wants to be further evaluated, they will be asked to return to the emergency department and seen by a physician not associated with the investigation. Further the investigator from the team will also meet them in the Emergency Department to detail the information. All adverse events, whether they are deemed mild or serious, will be forwarded immediately to the Medical Monitor who can immediately halt or terminate the study. In addition, all adverse events will be reported to the IRB of the Lundquist Institute by the investigators (and independently by the Medical Monitor). In a written IND safety report, any adverse experience associated with the use of the drug that was both serious and unexpected will be immediately reported to the FDA.

Definition of adverse events for this protocol:

Adverse Events

Symptoms that are new or unexpected reported by the subject

Nausea, diaphoresis, chest pain, abdominal pain, paresthesias, headache, visual complaints

Cough, pruritis, rash

Laboratory abnormality

Minor bleeding from gums, nares

Mild Sedation

Serious Adverse Events

Significant adverse events that led to an intervention, including withdrawal or dose reduction in the investigation drug or the need for concomitant therapy

Wheezing, bronchospasm, angioedema requiring rescue medications

Bleeding requiring an intervention

Hemorrhagic conversion of the ischemic CVA

Worsening neurologic condition as measured by the NIHSS at 4 hour intervals after enrollment in the study (or sooner as dictated by the care of the neurology team)

Laboratory abnormality requiring intervention (e.g. severe hyponatremia or hyperkalemia)

Death

k) Withdrawal of Subjects

Subjects will be withdrawn if they leave AMA/elope during their initial hospitalization or do not complete their 30 day or 90 day follow up prior to completion of the study

11) Risks to Subjects

Risk of N-Acetylcysteine:
Most adverse drug reactions that have been reported are minor and easily managed. Serious anaphylactoid reactions are extremely rare (11, 33-36)
Common: Nausea, vomiting, flushing, and pruritus,
Uncommon: Wheeze and bronchospasm (7.1%) Rare: Angioedema, and hypotension (25-28)

Risks of Diphenhydramine

Most common side effects included drowsiness, dizziness, headache, irritability, stomach upset, vision changes (blurred vision), decreased coordination or dry mouth/nose/throat

12) Potential Benefits to Subjects

Improved functional outcomes after a cerebral vascular event.

13) Provisions to Protect the Privacy Interests of Subjects

Data confidentiality is maintained as above. Only research investigators will have access to this data.
The enrollment will be performed in the emergency department. We will not discuss private medical information in a setting with other than a health care provider or in other than a private clinical setting.
We will make sure situations such as answering sensitive questions by telephone while at home or work will not happen in this study.
We will limit the information being collected to only the minimum amount of data necessary to accomplish the research purposes.

14) Compensation for Research-Related Injury

There is no commitment to provide any compensation for research-related injury. In the event that subjects are injured as a result of participating in this research, emergency care will be available on site. Subjects will, however, be responsible for the charges for the emergency and/or inpatient care.

15) Economic Burden to Subjects

None – subjects will already be present at the hospital for care.

16) Consent Process

Consent process will take place in the emergency department, ensuring subject privacy away from other on-going activities and personnel. The standard operating procedure for informed consent will be followed (SOP: Informed Consent Process for Research, HRP-090). Investigators or HIPPA trained research associates will seek consent for participation in this study from patients, their next of kin, or their legally authorized representative. The study will be explained during an approximately 15 minute discussion with the patient or their representative. They will be given as much time as they want to decide whether to participate in the study. The informed consent process requires that patients, their next of kin, or their legally authorized representative must able to understand, retain, and repeat the purpose, risks and benefits of the study to the consenting physician. Participants will be reminded that participation in the study is voluntary and their questions, if any, will be answered. All participants will be immediately withdrawn from the study if they appear to be unduly distressed. If subject requires some time for the information to be absorbed and appreciated, the researcher allow a period of time to elapse between imparting the information and requesting a signature on the consent form.

Non-English Speaking Subjects

Other than English, we expect Spanish speaking population to be participated in the study. In such case, consent form written in Spanish will be provided, and we will provide oral information using language line or by Spanish speaking investigators.

Subjects who are not yet adults (infants, children, teenagers) Only subjects over the age of 18 will be included in this study.

Cognitively Impaired Adults & Adults Unable to Consent

Stroke victims may have cognitive impairment and lack capacity to provided informed consent. The study team will assess each patient's capacity for decision-making using a post consent survey (Appendix 1: Decision-Making Evaluation Form) and decision tree/flow diagram (Appendix 2).

Some stroke victims may be able to understand and communicate their willingness to participant but unable to physically sign a consent document. In these instances, we will seek permission/consent from their legally authorized representative for participation and seek the subjects "assent" (verbal) for participation as they are deemed able.

If subject is deemed incapable of decision-making or unable to physically sign a consent document, consent will be sought from the subject's the Legally Authorized Representative (as per HRP-013 SOP LARs, Children, Guardians). This individual will complete the Self-Certification of Surrogate Decision Makers form (Appendix 3) for documentation.

Study participation will be discussed with both the patient and the physician of record/primary medical providers. Patient capacity to make decisions will be determined by the primary medical providers per routine. The study team will also determine each patient's (potential subject's) decision making capacity for participation in the study. Patients without capacity to make decisions and who lack a surrogate decision maker will be excluded from the study. Surrogate decision makers will be informed about the study in the same way as described above and offered to provide consent for the patient to enroll in the study.

If and when a subject regains their capacity for decision-making, consent for continued participation in the study will be sought. The standard operating procedure for informed consent will be followed (SOP: Informed Consent Process for Research, HRP-090).

17) Process to Document Consent in Writing

We are following "SOP: Written Documentation of Consent (HRP-091)."

Individuals who are not yet adults, pregnant women, and prisoners will be excluded in this study. Other vulnerable subjects, such as students, subjects with limited or no treatment options, and socially and economically disadvantaged, may be included in this study. This study does not involve more than minimal risk to the subject.

18) Drugs or Devices

N-Acetylcysteine and placebo. Study drugs will be stored, handled and dispensed by an ED pharmacist who is working at the time of study enrollment.

Sylvia Youn, Pharm.D., the ED Pharmacist will maintain drug accountability logs in compliance with FDA regulations. She will instruct other ED pharmacists about the study and the randomization log which will

be kept in the pharmacy room in the ED. She will also create study drug labels to keep the nurses, physicians and patients blinded to the study medication.

19) Multi-Site Human Research

N/A

20) Community-Based Participatory Research

This is not a community-based participatory research project.

21) Sharing of Results with Subjects

There are no results to be shared with the subjects until completion of the study. At that time, publication and study results will be available to participants at their request.

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Appendix 1: Lundquist Institute for Biomedical Innovation At Harbor-UCLA Medical Center

John F. Wolf, M.D. Human Subjects Committee

DECISION-MAKING EVALUATION FOR CAPACITY TO PROVIDE INFORMED CONSENT FOR RESEARCH

Patient Data:

Name:_____

Date of Birth:_____

Directions:
Make a subjective judgment regarding item 1 below. Ask the patient or proxy/surrogate questions 2 through 5. The investigator may select the appropriate language to use in formulating the questions in order to assist the subject's understanding.

Items:

1) Is the individual alert and able to communicate with the examiner? ☐ Yes ☐ No

2) Ask the individual to name at least two (2) potential risks that may occur as a result of participating in the research.

_____

_____

3) Ask the individual to name at least two things that will be expected of him/her in terms of patient cooperation during the study.

_____

_____

4) Ask the individual to explain what he/she would do if he/she decides that they no longer wish to participate in the study.

_____

_____

5) Ask the individual to explain what he/she would do if he/she is experiencing distress or discomfort.

_____

_____

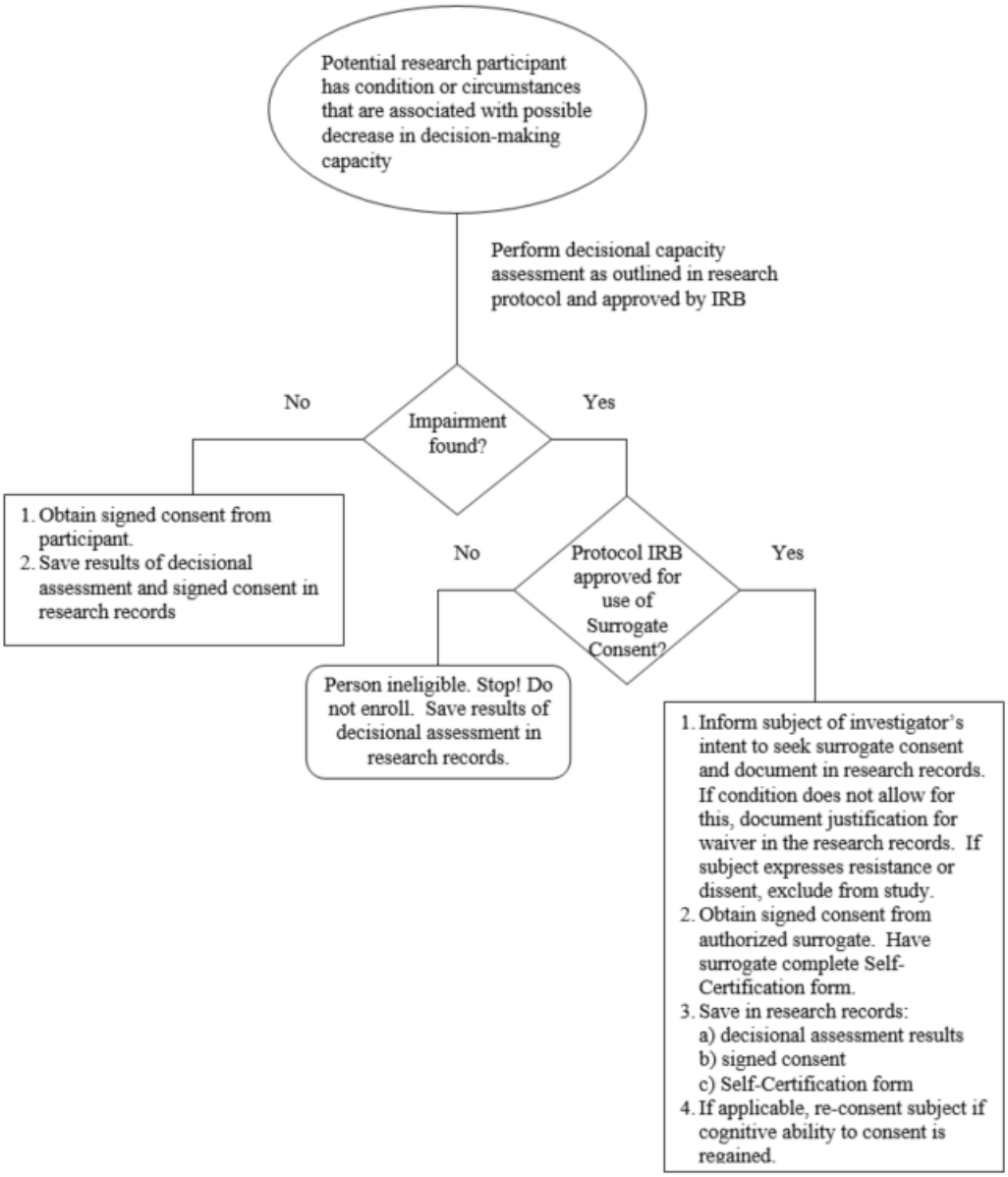
☐ I hereby certify that the above person is alert, able to communicate and able to give acceptable answers to items 2, 3, 4 and 5 above.

☐ In my judgment, the above person does not appear to be able to give ***informed*** consent, based on answers to items 2, 3, 4 and 5 above.

_____

Investigator's Signature Date/Time

Appendix 2: Flowchart



Appendix 3:

Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research

Section 1:
I am willing to serve as a surrogate decision maker for _____
(Potential Subject)
to participate in _____
(Title of research project and IRB #)
research conducted by _____
(Principal Investigator)

Section 2:
Category of Potential Surrogate

	Check the category that best describes your relationship to the potential subject:	For the categories listed above yours, provide the name(s) of other relatives. *(For example, if you are the adult son or daughter of the potential subject, provide the names of adults, if any who are best described in categories 1-4 only.)*
1. Agent named in the potential subject's advanced health care directive.	☐ 1.	_____
2. Conservator or guardian of the potential subject, with authority to make health care decisions for the potential subject.	☐ 2.	_____
3. Spouse of the potential subject.	☐ 3.	_____
4. Domestic partner of the potential subject.	☐ 4.	_____
5. Adult son or daughter of potential subject.	☐ 5.	_____
6. Custodial parent of the potential subject.	☐ 6.	_____
7. Adult brother of sister of the potential subject.	☐ 7.	_____
8. Adult grandchild of the potential subject.	☐ 8.	_____
9. Adult whose relationship to the does not fall within one of the above listed categories and is best described as: _____ (Example: cousin, aunt, etc.)	☐ 9.	_____

Section 3:
The following section information must be completed only for surrogate consent to participate in research non-emergency settings: (Check the statement which ***best*** describes the basis of your knowledge of the potential subject)

_____ I live with the potential subject and have done so for _____ years.

_____ I have discussed participation in research with the potential subject and believe that I can carry out his/her preferences.

_____ Other (please describe): _____

Section 4:
Potential Surrogate's Contact Information:

Name: _____
Address: _____

Home Phone: ( ) _____
Work Phone: ( ) _____
Cell Phone: ( ) _____
Email: _____

_____ __/__/__ _____ __/__/__
Signature of Potential Surrogate Date Signature of Witness Date

UNIVERSITY OF CALIFORNIA Research Policy Analysis & Coordination