The Effect of N-Acetylcysteine on Mortality and Neurological Disability in Patients with Aneurysmal Subarachnoid Hemorrhage

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Introduction

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The proposed investigation is a double blinded, randomized pilot study. The study will test the ability of N-acetylcysteine (NAC) to reduce mortality and neurological disability in patients with subarachnoid hemorrhage.

The target population is patients with aneurysmal SAH who are at high risk for development of delayed vasospasm and/or hydrocephalus. Each subject will be randomized into one of three treatment groups in a double-blind fashion. The treatment groups include placebo, N-acetylcysteine, or N-acetylcysteine plus acetaminophen.

This study has enrolled 89 patients to date. An additional 30 patients will be randomized to either N-acetylcysteine or placebo in a ratio of 2 (NAC) to 1(placebo).

Patient Eligibility Requirements

Patients with aneurysmal subarachnoid hemorrhage are eligible for the study if the following criteria are met:

Inclusion criteria

- Ages ≥ 20
- Fisher Grade III or III + IV SAH based upon admitting CT scan
- Aneurysm secured by either clipping or coiling within 72 hours of SAH
- Intracranial aneurysm confirmed by angiography or CTA
- Presence of ventriculostomy for external ventricular drainage (EVD) prior to randomization

Exclusion criteria

- Consent unobtainable
- Enrollment in another interventional study
- Patient is pregnant or lactating
- Known co-morbidities that could affect outcome of this study
- Contraindication to CTA
- Serum creatinine > 1.4
- Documented allergy to iodinated contrast that cannot be adequately treated with premedication
- Baseline liver disease
- History of recent alcohol abuse with documented ALT or AST above normal laboratory values
- Documented history of both malnutrition and decreased serum albumin below normal lab values
- Documented abnormal platelet count below normal lab values
- Documented abnormal PT or PTT above normal lab values
- Active asthma or chronic treatment to prevent asthma in the past year-this does not include exercise-induced asthma
- Documented allergy and/or intolerance to N-acetylcysteine
- Currently taking phenytoin, carbamazepine, or phenobarbital
- Currently taking isoniazid (INH, Lanzid, Nydrazid)
- Severe life-threatening complications resulting from standard aneurysm treatments that will likely prevent completion of the study
- Patient unsuitable for the study, in the opinion of the investigator(s)

Recruitment Procedures

Eligibility is assessed immediately following evaluation of the initial CT scan and cerebral angiogram or CT angiogram. The initial CT scan must show a Fisher Grade III or III + IV, as determined by the principal investigator or neurosurgical co-investigators. The criteria of Fisher grading for CT scan evaluation, as described in Fisher's original publication (Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by CT scanning. Neurosurgery 6:1-9, 1980), are as follows. Measurements of the greatest longitudinal and transverse diameter of the subarachnoid

clots in fissures and cisterns are made. The thickness of vertical layers (i.e., blood in cisterns of fissures lying in a plane perpendicular to the plane of CT sections: interhemispheric fissure, ambient cistern, insular cistern) is measured in millimeters. Classification is in four grades:

I. No blood detected
II. A diffuse deposition or thin layer with all vertical layers less than 1 mm thick
III. Localized clots and/or vertical layers of blood greater than 1 mm in thickness
IV. Diffuse or not subarachnoid blood, but with intracerebral or intraventricular clots

Eligibility for the study is established by the principal investigator, other neurosurgical co-investigators, or the study coordinator in consultation with the neurosurgical investigators. A pregnancy test will be administered to rule-out pregnancy for all women of child-bearing potential (no history of hysterectomy or tubal ligation) below the age of 55. Informed consent is obtained from either the patient or from an appropriate surrogate.

Randomization Procedures

After eligibility is established, exclusion criteria evaluated, and informed consent obtained, all patients are randomized to receive either placebo or N-acetylcysteine (NAC). Randomization takes place after the aneurysm has been secured by either surgical clipping or endovascular coiling and within 72 hours after the onset of SAH. When severe complications occur during standard treatments in the judgment of the principal investigator or neurosurgical co-investigators, patients do not proceed to randomization.

Randomization will be performed by the Investigational Drug Serviceof the Vanderbilt University Medical Center, employing a computer program that generates a modified permuted block randomization scheme (see statistical considerations). Patients will be randomized to receive one of the following regimens in a double blinded investigation:

Placebo for N-acetylcysteine (N=20)

N-acetylcysteine IV infusion at 0.5 gm hourly (N=10)

Acetaminophen 1.5gm every 6 hours, plus N-acetylcysteine IV infusion at 0.5 gm hourly (N=20)

Placebo infusions will simulate the N-acetylcysteine infusions. Treatment will continue for 12 days or until hospital discharge, whichever comes first.

An intent to treat paradigm will be preserved once the patients are randomized. Once randomized, whatever the treatment, the patient will enter that arm for purposes of data analysis.

Assessments for Vasospasm

This will occur on a daily basis until SAH Day 21 or discharge from hospital, whichever comes first. Vasospasm assessment includes standard of care procedures such as neurological exams, TCDs, CTAs, MRAs and angiography. On SAH Day 8 (+/- one day if day 8 is on a weekend), a CTA or MRA will be performed to assess for presence of vasospasm. Also as part of this study, collection of CSF for

isoprostanes measurement will occur daily.

Assessments for Potential Toxicity
This will occur every other day in which treatment is administered for 12 days plus any additional hospital days up to day 21 and includes ALT and INR.

CSF Collection

The CSF will be collected from standard of care ventricular drain Buritrol (CSF would normally be discarded) by a nurse, rotating resident, fellow, or study coordinator (if appropriate) once a day until discharge or day 21, whichever occurs sooner, and stored in a -80 freezer.

Blood Draws

Blood will be drawn from IV line, when at all possible or venipuncture if necessary or incorporated into daily standard of care blood draws.

DNA Extraction: Blood will be drawn once for DNA extraction and storage in the VUMC DNA Resources Core.
Prothrombin Time: The prothrombin time (INR) will be measured every other day until discharge or day 21, whichever occurs sooner. In the unlikely event that a patient's INR were to exceed 1.4, the routinely administered low-dose heparin would be discontinued. An INR of 1.7 or greater would lead to discontinuation of the drug(s).

Liver Function Test: Liver function tests (LFTs) of the study participants will be monitored every other day until discharge or day 21, whichever occurs sooner. If ALT levels rise to more than 3-fold above the upper limit (120 IU/L) of normal, the study drug will be withheld, and the test will be repeated immediately. If the elevation is confirmed, the study drug will be discontinued.

Testing for Hepatitis B and Hepatitis C Surface Antigen: Upon subject enrollment, testing for Hepatitis B surface antigen and Hepatitis C antibody will be performed. Subjects with presence of Hepatitis B and/or C surface antigen will not be excluded from this study, however, presence of antigen will be documented.

Computed Tomographic Angiography and Perfusion (CTA and CTP)

A CTA and CTP will be performed on every patient, as part of their standard of care treatment, on SAH Day 8 + or – 1 day, and these images will be used to determine the presence and severity of cerebral vasospasm and/or brain ischemia. The CTA/CTP will not be performed if the patient's serum creatinine is > 1.4. In addition, if a patient develops a delayed neurological deficit (DND) at any time between SAH Day 3-21, then additional CTAs/CTPs will be performed as part of the patient's standard of care management to determine the presence and severity of cerebral vasospasm and/or brain ischemia at the time of DND. Standard of care treatments for cerebral vasospasm will proceed in the best interest of the patient, which could include intracranial angioplasty, intraarterial infusion of vasodilators, etc. If this occurs, then the worst CTA/CTP results will be used for statistical analysis for the purposes of this study. If no DND occurs, then the SAH Day 8 (+ or – 1 day) CTA/CTP will be used for statistical analysis for the purposes of this study.

If a patient is too sick to be transferred to the CT scanner on SAH Day 8 (+ or – 1 day) in the opinion of the patient's treating physicians, he or she will not have the scans performed. All available imaging, TCD

ultrasound, and neurological examinations used to assess vasospasm as part of standard of care will be collected and data recorded on the case report forms and in the database.

The CTA techniques currently available allow measurement of arterial diameters under normal conditions, and those of vasospasm of varying severity. For this study, we will measure the diameter of each target arterial segment in 1 mm increments for the entire length of each segment. We will also measure the diameter of a reference arterial segment in 1 mm increments for the entire length of each reference arterial segment. The target arterial diameters will be divided by the reference arterial segments to provide the target arterial ratio. The average arterial diameter, average arterial ratio, the smallest arterial diameter (most severe vasospasm), and smallest arterial ratio will be reported for each target arterial segment. There are 11 target arterial segments which relate to 5 reference arterial segments as follows:

I. Right extradural internal carotid artery (eRICA) Reference (measured at the right petrous/cavernous junction posterior ascending straight segment, centered around the midpoint of this ascending straight segment). This reference arterial segment is used for the following 3 target arterial segments:
   1. Right intradural internal carotid artery (iRICA) (measured at the supraclinoid segment from the origin of the right ophthalmic artery to the iRICA bifurcation)
   2. Right Middle Cerebral Artery M1 Segment (RMCA-M1) (Measured from the origin of the right MCA-M1 segment off the RICA bifurcation to the largest arterial branch of the M1 segment as it ascends superiorly (on the AP view) at the limen insula.
   3. Right Anterior Cerebral Artery A1 Segment (RACA-A1) (measured from the origin of the right ACA-A1 segment off the RICA bifurcation to the origin of the right A2 segment at the Anterior Communicating (ACOM) complex.

II. Left extradural internal carotid artery (eLICA) (measured at the left petrous/cavernous junction posterior ascending straight segment, centered around the midpoint of this ascending straight segment).
   1. Left intradural internal carotid artery (iLICA) (measured at the supraclinoid segment from the origin of the left ophthalmic artery to the iLICA bifurcation)
   2. Left Middle Cerebral Artery M1 Segment (LMCA-M1) measured from the origin of the left M1 segment off the LICA bifurcation to the largest arterial branch of the M1 segment as it asends superiorly (on the AP view) at the limen insula.
   3. Left Anterior Cerebral Artery A1 Segment (LACA-A1) measured from the origin of the left ACA-A1 segment off the LICA bifurcation to the origin of the left A2 segment at the ACOM complex.

III. Right extradural vertebral artery (eRVERT) (measured from the inferior border of the C1 vertebral body (atlas) to the superior border of the C1 vertebral body
   1. Right intradural vertebral artery (iRVert) (measured from the origin of the right posterior inferior cerebellar artery (R PICA) to the vertebrobasilar junction).

IV. Left extradural vertebral artery (eL Vert) (measured from the inferior border of the C1 vertebral body (atlas) to the superior border of the C1 vertebral body
   1. Left intradural vertebral artery (iL Vert) (measured from the origin of the right posterior inferior cerebellar artery (R PICA) to the vertebrobasilar junction).

V. The Dominant (largest) extradural vertebral artery (eDVert) (measured from the inferior border of the C1 vertebral body (atlas) to the superior border of the C1 vertebral body on whichever vertebral artery is the largest (right or left)
   1. Basilar artery (measured from the vertebrobasilar junction to the basilar apex)
   2. Right Posterior Cerebral Artery P1 segment (RPCA-P1) (measured from the origin of the right

PCA off the basilar apex to the branch of the right posterior communicating (PCOM) artery as the right PCA turns around the cerebral peduncle of the midbrain)
3. Left Posterior Cerebral Artery P1 segment (LPCA-P1) (measured from the origin of the left PCA off the basilar apex to the branch of the left PCOM artery as the left PCA turns around the cerebral peduncle of the midbrain)

Therefore, a total of 15 arterial segments (11 target arteries and 4 reference arteries) will be measured in 1 mm increments. The percentage stenosis for vasospasm is defined as the target arterial measurements on the SAH Day 8 (+ or – 1 day) CTA divided by the reference measurements on the baseline CTAs (if performed) or other baseline reference measurements.

Ischemic Volume Determination: CT Perfusion will be used to assess the presence and severity of brain ischemia. The volume of brain ischemia and the severity of brain ischemia will be calculated and reported. The CTP data includes cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), and mean transit time (MTT) of each cerebral hemisphere.

Clinical Outcome Evaluation and Follow-Up

The study coordinator should maintain frequent contact with the family to maximize the probability of follow-up. The outcome examiner will receive a list of patients enrolled in the study from the study coordinator. Only the essential information to identify and locate the patient should be given to the outcome examiner so as to maintain their blinded status.

Contact with families up to the follow-up exam is maintained by the study coordinator, with payment for transportation, if necessary. If the patient is unable to come for the followup visit, the study will be considered completed.

The clinical outcome measures: The Modified Rankin Scale (MRS), the Glasgow Outcome Scale (GOS), the Barthel Index (BI), and the NIHSS at 3 months post-SAH (+ or – 10 days).

The MRS is a simple measure of functional outcome after stroke. The scale is from 0–6. 0 = no deficits or functional limitations, 1 = a subtle deficit but no gross disability, etc. The MRS has good inter-observer reliability. A structured interview will be used to improve reliability of the measure.

The GOS emphasizes how major functioning has been affected, rather than emphasizing specific neurological deficits. The GOS uses broad divisions to categorize overall outcome: Deceased, Vegetative state, Severe Disability, Moderate Disability, Good Recovery. A structured interview will be used to improve the reproducibility of the GOS.

The BI measures ability to perform normal activities of daily living (ADL) including feeding, moving, using the toilet independently, bathing, walking, and dressing. The BI has been shown to have excellent inter-rater reliability.

The NIHSS is a widely used and validated tool for assessment of clinical stroke severity. The NIHSS is essentially a quantitative neurological examination, evaluating alertness, orientation, speech and language, eye movements, visual fields, facial sensation and movement, extremity strength and coordination, and sensation. The NIHSS score in the acute phase of stroke is a powerful predictor of final clinical outcome.

Study Endpoints

Primary Endpoint:
There will be two primary endpoints that will be assessed in this study:

1. The extent of vasospasm will be assessed by the results of the patients' worst angiographic images that are obtained following 48 hours post-randomization. The worst angiographic images includes the CTA performed on SAH Day 8 + or – 1 day as well as any other CTA, catheter angiogram, or MRA performed as standard care for clinical reasons, such as for DND.
2. Neurological outcome, including death, at 3 months follow-up, assessed by NIHSS, MRS, GOS, and Barthel Index.

Exploratory Endpoints: This study also includes the analysis of 5 exploratory endpoints as follows:

1. The extent of brain ischemia will be assessed by the results of the patient's worst CT Perfusion (CTP) scan, performed at the same time as the above CTA.
2. Presence of any DND assessed by neurological exam. DND is defined as any change in neurological assessment that occurs between SAH Day 3 (>72 hours after SAH) and SAH Day 21 which is not clearly attributable to a known intervention (e.g., surgery, ventriculostomy, medical procedures, etc.)
3. Presence of any evidence of SAH induced vasospasm as assessed daily by all clinical means available (TCDs, CTA, MRA, or catheter angiography), classified as mild, moderate, or severe.
4. Incidence of interventional treatment including intracranial balloon angioplasty for vasospasm or intra-arterial infusion of vasodilators.
5. Presence of SAH induced hydrocephalus as assessed by the following hydrocephalus grading scale:

Grade 0=EVD weaned off on first attempt without Mental Status Decline (MSD), neuro deficit, or sustained intracranial pressure (ICP) elevation >20 mm Hg
Grade 1A=EVD weaned off (after more than one trial) eventually without MSD, neuro deficit, or sustained ICP elevation > 20 mm Hg
Grade 1B=Requires permanent CSF diversion

Mechanisms for Blinding

The only person aware of the treatment assignment during the study is the research pharmacists at Vanderbilt Investigational Drug Service. No one else will be present for the randomization. After the study has been completed the Investigational Drug Service will give the randomization assignment to the study coordinator for entry into the study database. If in the investigator's judgement, medical care would be affected by knowledge of the treatment assignment, the treatment may be unblinded. Recording of complication and physiologic data is by unblinded personnel, of necessity. These personnel are, however, blinded to outcome data. Blinding is also done for all personnel performing clinical outcome assessment.

The study database will be web-based designed by the GCRC bioinformatics division. The persons capable of accessing the database will be classified accordingly. The study coordinator is responsible for maintaining the aggregate study database, generating trial progress and safety reports. The statistician reviews SAE data by treatment assignment for safety monitoring purposes.

Data Collection and Management

Data Collection: The investigators (neurosurgical department, neurology department, and clinical pharmacology division) are experienced researchers with skills in interviewing families, reviewing

medical records, and performing clinical assessment of patients.

The study database is established to be accessible to all the investigators from each department, with variable accessible levels. The database is a custom-designed, web-based software application and will be used to record, store, and transmit data. The software application will be able to log on from each investigator's PC with user name and password. It may contain all the data elements required to answer the questions raised in our hypotheses except for treatment assignment.

Data entry in the database is designed to ensure data validation. The parameters are checked against data validation rules before they are accepted into the database. This real-time feedback greatly enhances the accuracy of entered data. Examples of these validation rules include:

Range values: numeric, non-date fields have range values specified to minimize data entry errors. (I.e. typos)
Selection lists: categorical data fields have drop-down lists of possible selections that have been predetermined as appropriate entries.
Date checking: all dates entered are checked to ensure that events recorded in the database occurred during the time of the study.

Data Management: Data entered from each department will be stored and may be viewed by all the investigators depending on their classification levels. The study coordinator will be responsible for maintaining the aggregate database. Data encryption, user access codes, and no patient identifiers assure patient confidentiality.

A web-based database will be able to monitor study performance, protocol compliance, safety data and to provide administrative reports. The statistician from the bioinformatics department may move data to an analytic package (R, SAS, or SPSS) for interim analysis and final analysis of the data. Protocol compliance and consistency of management will be monitored by the principal investigator and study coordinator.

Safety and Monitoring

Although hepatotoxicity is not anticipated with these regimens, levels of ALT will be determined every other day, with a stopping rule for increases in ALT of more than three-fold the upper limit of normal.

The prothrombin time (INR) will be measuredevery other day. In the unlikely event that a patient's INR were to exceed 1.4, the routinely administered low-dose heparin would be discontinued. An INR of 1.7 or greater would lead to discontinuation of the drug(s).

With the slow infusion of these doses of N-acetylcysteine, the possibility of the reactions previously seen with high dose, rapid administration of the drug should be minimized. The study would be discontinued for precipitation of asthma, systemic manifestations of mast cell activation, or urticaria not controlled with antihistamines. Should serious adverse reactions occur, they will be assessed by the Data Safety and Monitoring Board and reported to the IRB.

Potential Risks

Risks of N-acetylcysteine: Adverse reactions reported with rapid intravenous NAC at dose of 150 mg/kg in 15 minutes include bronchospasm, nausea, vomiting, stomatitis, rhinorrhea, headache, tinnitus, urticaria, angioedema, gastrointestinal disturbances, pruritis, tachycardia, hypotension, hypertension, rashes, chills, and fever. There are rare reports of anaphylactic reactions. The most common symptoms of

those experiencing anaphylactoid reactions are rash, pruritis, flushing, nausea, vomiting, angioedema, tachycardia, bronchospasm, hypotension, hypertension and ECG change. The intended very slow infusion of NAC at lower doses is expected to minimize the probability of the side effects seen with rapid intravenous administration.

Risks of phlebotomy: Risks include mild discomfort of needle stick for blood drawing, low risk of bruising and infection from needle stick, and small risk of fainting.

Risks of CTA/CTP scanning: Although CTAs and CTPs are standard of care diagnostic imaging studies for patients with aneurysmal SAH, patients who have a contraindication to CTA scanning, including kidney failure, or allergy to iodinated contrast that cannot be treated with premedication, will be excluded from this study because of the importance of obtaining CTA/CTP data for this study. If the patient meets all criteria for inclusion in this study and after randomization serum creatinine exceeds 1.4, then the SAH Day 8 (+ or – 1 day) CTA will not be performed. Either no angiographic image will be performed or an MRA/MRI may be substituted if no contraindication exists.

Risks of MRA/MRI scanning: There are no known major risks with an MRA/MRI scan. Patients who have a contraindication to MR scanning, including a pacemaker and/or implantation of MR incompatible devices, will not receive an MRA/MRI scan on SAH Day 8 (+ or -1 day).

Protection Against Risks

We have excluded enrollment of patients with risk factors for development of serious adverse effects – documented allergy and/or intolerance to N-acetylcysteine, baseline liver disease, ethanol abuse, malnutrition, history or evidence of active asthma. Liver function tests (LFTs) of the study participants will be monitored every other day throughout the duration of the study. If ALT levels rise to more than 3-fold above the upper limit of normal, the study drug will be held and the test will be repeated immediately. If the elevation is confirmed, the study drug will be discontinued. The prothrombin time (INR) will be measured every other day in the first 16 patients receiving N-acetylcysteine. A monitoring plan for the subsequent patients would be devised based on the data from these initial 16 patients. In the unlikely event that a patient's INR were to exceed 1.4, the routinely administered low dose heparin would be discontinued. An INR of 1.7 or greater would lead to discontinuation of the drug(s).

Data and Safety Monitoring Plan

A Data Safety and Monitoring Board (DSMB) will be established. The members of the DSMB are Joseph Awad, M.D. (Chairman), Associate Professor of Pharmacology and Medicine; Daniel Byrne, M.S., Director of Biostatistics and Study Design, GCRC; Anne E. O'Duffy, M.D., Assistant Professor of Neurology; and Harvey Murff, M.D., M.P.H., Assistant Professor of Medicine.

The responsibilities of the Board will include:

1. Review of study design prior to initiation of the investigation
2. Review of clinical data and the primary endpoint at planned intervals during the study.
3. Review of the clinical and or related data at unplanned intervals when appropriate or when safety issues occur.
4. Provide recommendations to the PI about whether or not to continue patient enrollment in the study.
5. Ensure that any analysis performed by or provided to the DSMB is recorded, handled, and stored in a way that allows the PI to accurately interpret, verify, and report the data.

The DSMB will provide summary reports to the investigators.

During the conduct of the trial, any serious adverse event will be reported to the DSMB and the IRB within10 business days after the Investigator learns of the event or problem. Board members will be provided with all of the available clinical data surrounding the occurrence. A serious adverse event (SAE) is any untoward medical occurrence that a) results in death, b) is life-threatening, c) requires prolongation of existing hospitalization, d) results in persistent or significant disability/incapacity. AEs will be graded as Mild (no limitation of usual activities), Moderate (some limitation), or Severe (inability to carry out usual activities) and attributed to the relationship to the study drug and/or procedures as Not related, Unlikely, Possible, Probable, or Definite.

The investigators and study coordinators will monitor the patients, and liver function tests will be performed daily for the purpose of tracking adverse events (AE). The research team will be informed of the participants' progress. If any change in a participant's status is deemed to be unsafe for further participation in the study, for example, the liver enzymes are greater than 3 times normal, the study drugs/placebo will be stopped, the test results confirmed, and if confirmed, the patient will be withdawn from the study. Necessary treatments will be carried out based on individual condition. Any AE related or unrelated to the research will be discussed by the research team.

Summary reports will be submitted to the DSMB and IRB and will contain a) The number of adverse events and an explanation of how each event was handled, b) The number of complaints and how each complaint was handled, c) The number of subject withdrawals and an explanation of why the subject withdrew or was withdrawn, and d) The number of protocol violations and how each was handled.

Statistical Considerations

Objectives and Study Design

The primary objective of this placebo-controlled, double-blind, randomized trial is to assess the effects of N-acetylcysteine (NAC on clinical outcomes, including mortality and the power analysis and sample size estimation are based on the mortality data. Vasospasm and ischemia, DND, neurological outcomes, presence, absence, or resolution of hydrocephalus are secondary endpoints for this pilot study, but are not the basis for the power analysis.

Power Analysis, Sample Size Estimation, and Randomization

All of the arms that include acetaminophen will be dropped.

The remaining 2 arms of placebo and N-acetylcysteine will be continued. Using the data, the failure rate for placebo subjects is 0.2 and setting the failure rate among N-acetylcysteine subjects to 0.0001, we will need to study a total of 34 placebo subjects and 34 N-acetylcysteine subjects to be able to reject the null hypothesis that the failure rates for placebo and N-acetylcysteine subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. To date, there has been 25 placebo patients and 16 N-acetylcysteine patients enrolled. The study groups will be increased by 9 and 18 respectively resulting in a randomization of 1:2 (Placebo to N-acetylcysteine) yielding a 1:1 randomization at the end of the study. Estimating a 10% dropout rate, a total of 30 will be enrolled.

Statistical Analysis Plan

The Analysis of Variance (ANOVA) method and General Linear Model (GLM) with the Bonferroni adjustment will be applied to test mortality and mortality plus neurological deficitsamong study groups. Normality assumption will be checked graphically and visually (e.g. normal probability plot, stem-leaf plot) as well as statistically (e.g. Kolomogorov D statistic, Shapiro-Wilk statistic W). If data suggest a deviation from normality, then the transformations, e.g., log, will be performed to achieve normality. If needed, the data will be analyzed using a non-parametric test such as Kruskal-Wallis test that does not assume any distributional form. For secondary endpoints, such as neurological outcomes, The General Liner Model, Generalized Liner Model, e.g., Logistic Regression, Poisson regression will be applied to the single time point data. The mixed effect model and the Generalize Estimating Equation (GEE) method will be used to study the association among the neurological parameters among different study time points, the adjusted p-values as well as the adjusted 95% confidence intervals will be reported. The model selection will be based on Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC) with different covariance structures, e.g., First-Order Autoregressive, Compound Symmetry etc. The detailed model fitting strategies are described in the Biostatistics Component of the Administration Core.

Appendix

A. Fisher Grading Scale

Fisher Grade	CT SAH Findings
I	No blood detected
II	A diffuse deposition or thin layer with all vertical layers less than 1 mm thick
III	Localized clots and/or vertical layers of blood greater than 1 mm in thickness
IV	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots.

B. Hunt and Hess Grading Scale

Grade	Clinical Condition
I	Asymptomatic or mild headache and slight nuchal rigidity
II	Cranial nerve palsy, nuchal rigidity, and moderate-to-severe headache
III	Drowsy, confused, or mild focal deficit (eg., hemiparesis, hemianesthesia)
IV	Stupor, moderate-to-severe hemiparesis, early decerebrate rigidity
V	Comatose, decerebrate rigidity, moribund appearance

C. Glasgow Outcome Scale

Summary Definitions	Code
Good Recovery	**G**
❖ Capacity to resume normal occupational and social activities. (may be minor physical or mental deficits or complaints) ❖ Full recovery without sign or symptoms. But for reasons (other than physical or mental deficit), subject might not have resumed all previous activities, in particular might not be working. ❖ The principal discriminatory factors for this category are employability and personality. ❖ A patient would fall into this category if all of the following apply: - if they are able to work at or close to the same capacity (e.g. responsibility, hours, etc.) - if they have resumed interest in their normal social and leisure activities - if they have had no personality change that is disruptive to family relationships and/or friendships	
Moderate Disability	**M**
❖ Independent but disabled ❖ Independent in activities of daily living (i.e., can travel by public transport and look after self at home). ❖ Some previous activities, either at work or social life, are now no longer possible due to either physical or mental deficit. ❖ Despite evident post-SAH signs, subject can either resume activities at a lower level or can resume most former activities whether full or part-time. ❖ Some subjects can return to certain kinds of work, even to a former job if it happens not to involve a high level of performance. ❖ The principal discriminatory factors for this category are employability and personality. ❖ A patient would fall into this category it any of the following apply: - if they are unable to work at the same capacity (e.g. responsibility, hours, etc.) - if they have not resumed or lost interest in their normal social and leisure activities because of a mental or physical impairment - if they have a personality change that is disruptive to family relationships and/or friendships	
Severe Disability	**S**
❖ Conscious but dependent ❖ Resumption of former life and work not possible due to many post-SAH complaints and/or deficits. ❖ Communication possible, minimally by emotional response. ❖ Patient is conscious but needs assistance of another person for some activities of daily life. ❖ Patient is conscious but almost totally dependent on another for activities of daily life. ❖ Range can be from continuous total dependency to need for assist with only one activity, such as dressing. ❖ The principal discriminatory factor for this category is dependence. ❖ A patient would fall into this category if **any** of the following apply: - if they cannot be left alone at home for a day if necessary - if they require a significant amount of assistance in an activity of normal living (e.g., toileting, dressing, feeding, bathing, etc.) - if they can not shop or keep track of money for themselves - if they can not leave their home unaccompanied and/or require someone to provide them with or arrange their local travel	
Vegetative State	**V**
❖ Non-sentient, not obeying commands, no verbal contact, no meaningful response; may have sleep-wake rhythm. ❖ No evidence of meaningful responsiveness ❖ Breathes spontaneously; might have periods of spontaneous eye opening or follow moving objects with their eyes. ❖ Might show reflex response in limbs (to postural or painful stimuli) ❖ Might swallow food placed in their mouths ❖ This non-sentient state must be distinguished from other conditions of wakeful, reduce responsiveness, such as locked-in syndrome, akinetic mutism and total global asphasia.	
Death	**D**

Helpful Hints on the Glasgow Outcome Scale (GOS)

- Focus on how the injury/illness to the brain has affected functioning in major areas of life rather than on particular deficits and symptoms caused by illness/injury.

- Background knowledge (any pre-SAH disabilities as well as nature and extent of brain illness/injury) is necessary to obtain an accurate GOS.

- Consider only how current (past week) level of capability compares to pre-SAH status.

- Remember to always ask why or to what extent when a patient admits to a change or an impairment in activity or function.

- Whenever possible, seek independent verification on functional status from a family member or close friend of the patient.

- Limitations to function and restrictions on activity due to a post-SAH seizure(s) should be considered a disability when determining the GOS.

- Do not distinguish between changes that result from the brain injury/illness from those caused by disease in other parts of the body, i.e. base your rating on the current level of disability regardless of the cause.

Rate GOS based on the worst impairment in activity or function. Indicate in your notes, the worst impairment(s) on which you based the GOS.

Structured Interview for the Glasgow Outcome Scale (GOS) and Glasgow Outcome Scale - Extended (GOSE)

Patient's name:	Date of interview:
Date of Birth:	Date of SAH:
Gender: M / F	
Age at SAH:	Interval post-SAH:
Respondent: Patient alone Relative/friend/caregiver alone Patient + relative/friend/caregiver	
Interviewer:	Title:
Confirmed by:	Title: Date:

INSTRUCTIONS: Cover the points listed in this worksheet during the interview, and make sure to complete the worksheet and comment section following the interview. Interview the patient, family members, friends and/or rehabilitation caregivers to obtain information. Remember to always ask WHY the patient is or is not involved in certain activities. Items should only be rated as 'No' if patients cannot perform the activity due to physical or mental deficits AS A RESULT OF THE BRAIN INJURY. For example, if a patient is safe to be at home alone, but is not left alone because parents/spouse are overprotective, they should still be rated as independent (yes) in that area. A second example, if a patient is disabled because of another illness/injury and that is the only reason they can not return to performing activities at work, they should still be rated as 'Yes', since the disability is not a "Brain Related Injury". Please note to answer questions 5b, 6b, 7b, and 8b only if applicable (e.g., If 5a is answered 'Yes', then a response is not required in 5b).

CONSCIOUSNESS	
1 Is the patient person able to obey simple commands, or say any words? Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in Jennett et al. (1981). The Royal College of Physicians has published guidelines for deciding whether a patient is in a persistent vegetative state, and the simple approach suggested here is not intended to replace these guidelines in the management of the individual patient. If the patient is unable to obey commands or say words for some other reason, for example, because they are severely demented, then they are not in the vegetative state. Any words includes repetition of a simple word such as No. A person able to communicate using a code would no longer be in the vegetative state.	1 = No (VS) 2 = Yes

INDEPENDENCE IN THE HOME	
2a Is the assistance of another person at home essential every day for some activities of daily living? For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight. Dependency may be caused by physical impairment, but it is also often due to mental changes. People may require actual assistance with activities of daily living, they may need prompted or reminded to do things, or they may need someone with them to supervise them because they would be unsafe otherwise. In all these cases, they are dependent. However, many people receive assistance, but do not absolutely depend on it. This care or protection that is given by others should be distinguished from dependency: the person may well benefit from this help and may well have a real need for it, but such care does not mean that they are dependent in the sense required here. A difficulty may arise if - an activity was not normally carried out before the injury. For example, many men have little practical involvement in domestic matters and quite often will not usually prepare meals for themselves. In this case, it is sufficient that the person could, if the necessity arose, prepare food, even if this would be in a simple fashion. Examples of minor domestic crises: what you do if … a glass gets dropped and broken, a tap is left running, a light goes out, it begins to get cold, a stranger comes to the door … The person should be able to use the telephone to report problems or summon help.	1 = No 2 = Yes (SD)
2b Do they need frequent help or someone to be around at home most of the time? For a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves. The patient is considered to be in the lower category of severe disability if they cannot be left alone for 8 hours. This limit implies that a relative who is caring for them cannot work. If it is necessary to establish a time limit, it can be helpful to ask "what is the maximum amount of time they can be left alone?"	1 = No (Upper SD) 2 = Yes (Lower SD)
2c Was assistance at home essential before the SAH?	1 = No 2 = Yes

INDEPENDENCE OUTSIDE THE HOME	
3a Are they able to shop without assistance? This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so. **3b Were they able to shop without assistance before the SAH?** Independence outside the home requires ability to plan, to take care of money, and behave appropriately in public. It must be established if the person is actually capable of carrying out these activities, rather than whether they do or not.	1 = No (Upper SD) 2 =Yes 1 = No 2 = Yes
4a Are they able to travel locally without assistance? They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver. **4b Were they able to travel without assistance before the SAH?**	1 = No (Upper SD) 2 = Yes 1 = No 2 = Yes

WORK	
5a Are they currently able to work to their previous capacity? If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the brain injury/illness should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before SAH then their capacity for study should not have been adversely affected. Work refers to jobs that are paid at a reasonable rate and which, in principle at least, are open to others. Reduced capacity for work Any of the following indicate reduced capacity for work: (a) change in level of skill or responsibility required; (b) change from full-time to part-time working; (c) special allowances made by employer (e.g., increased supervision at work); and (d) change from steady to casual employment (i.e., no longer able to hold steady job). Note that sometimes change in employment status may be unrelated to brain injury/illness, e.g., due to end of contract, retirement, or redundancy. Such changes do not indicate a reduced capacity for work. *Students:* If the person was a student before SAH, then study can be substituted for work. Students should be able to return to their previous course and not have noted adverse effects on their ability to study. If someone has been absent from college because of brain injury/illness, then there may be some disruption caused by the absence itself, and this needs to be discounted when considering if the person has problems due to the brain injury/illness. Examples of problems which indicate reduced capacity for study: (a) increased difficulties in studying (e.g., needing to spend much more time than before); (b) unaccustomed problems with progress (e.g., failing examinations); and (c) revised program of study because of problems (e.g., studying for a lesser degree).	1 = No 2 = Yes

5b How restricted are they? a) Reduced work capacity. b) Able to work only in a sheltered workshop or non-competitive job, or currently unable to work. Noncompetitive work includes work done voluntarily, jobs that are specifically designated for disabled people, and work in sheltered workshops. Normally, ability to work is indicative of independence; however, occasionally, someone in the upper severe disability range may be working in a sheltered workshop. *Students:* (a) If the student has a reduced capacity for study but is still studying, then they are Upper Moderate disability; and (b) if the student is currently unable to study, then they are Lower Moderate disability.	1 = a (Upper MD) 2 = b (Lower MD)
5c Were they either working or seeking employment before the SAH (answer 'yes') or were they doing neither (answer 'no') Work is only used as an indicator of outcome if the person was working or actively seeking work before the SAH, or if they were studying.	1 = No 2 = Yes

SOCIAL & LEISURE ACTIVITIES	
6a Are they able to resume regular social and leisure activities outside home? They need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability. Social and leisure activities will vary depending upon the age and background of the patient. Representative social and leisure activities include the following: (a) participating in sport, e.g., football, swimming etc., (b) attending sporting events as a spectator, (c) going walking, (d) going to a club or pub, and (e) visiting friends. Some leisure activities are seasonal – be careful to exclude changes in activity that are simply due to this factor. Typical problems that may interfere with social and leisure activities: lack of motivation or initiative, avoidance of social involvement, physical problems such as loss of mobility, cognitive problems such as poor concentration, and problems such as poor temper control or impatience.	1 = No 2 = Yes
6b What is the extent of restriction on their social and leisure activities? a) Participate a bit less: at least half as often as before SAH. b) Participate much less: less than half as often. a) Participate much less or unable to participate If it is necessary to question in detail, then ask the person how often they participated in social and leisure activities outside the home before the SAH (i.e., how many occasions per week) and how often they participate now. Measuring extent of participation is in terms of occasions per week emphasizes a quantifiable aspect of social and leisure activities. Sometimes, quality of participation is affected by the brain injury/illness; for example, the person may become a spectator in a sport rather than an active participant. However, changes such as this are very difficult to quantify and can reflect the specially demanding nature of some sports. Thus, for the sake of simplicity, it is the fact of participation that is rated in the interview. Experience suggests that the main effect of brain injury/illness on social and leisure activities tends to be withdrawal from activities that involve social interaction: the simple approach adopted here is sensitive to such changes.	1 = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD)

6c	**Did they engage in regular social and leisure activities outside home before the SAH?** Participating regularly in social and leisure activities means participating in at least one activity outside the home each week.	1 = No 2 = Yes

FAMILY & FRIENDSHIPS		
7a	**Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?** The question is specifically aimed at alterations in relationships as a result of brain injury/illness. The presence of a reported change in personality is not of itself sufficient to warrant classifying the person as moderately disabled. The change must be having an adverse impact on family and friendships. Typical post-brain injury/illness personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable or childish behavior.	1 = No 2 = Yes

7b What has been the extent of disruption or strain? a) Occasional - less than weekly b) Frequent – once a week or more, but tolerable. b) Frequent or constant - once a week or more The following definitions apply: (a) Occasional - Some problems since SAH, but less than once a week and not causing continuous strain. For example, occasional bad temper, but things blow over. (b) Frequent Problems at least weekly, strain on relationships, but regarded as tolerable. For example, temper outbursts at least once a week resulting in modification of closeness of relationships. (c) Constant daily problems: Breakdown or threatened breakdown of relationship within family or friendship; problems regarded as intolerable. If a family have become very withdrawn and socially isolated as a result of brain injury/illness, then this also represents constant disruption.	l = a (Lower GR) 2 = b (Upper MD) 3 = c (Lower MD)
7c Were there problems with family or friends before the SAH? If there were problems before SAH, but these have been markedly worse since SAH then answer 'No' to 7c.	1 = No 2 = Yes

RETURN TO NORMAL LIFE	
8a Are there any other current problems relating to the brain injury/illness which affect daily life? Other typical problems reported after brain injury/illness: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems. These problems are impairments; in order to cause disability, they must impinge on functioning in everyday life. Similar problems are reported in the general population: it is thus important to establish that the problems have developed since SAH.	1 = No (Upper GR) 2 = Yes (Lower GR)
8b Were similar problems present before the SAH? If there were some problems before the SAH, but these have become markedly worse since SAH then answer 'No' to 8b.	1 = No 2 = Yes

GOS Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to helpful hints and definitions for further information concerning administration and scoring.

1 Dead
2 Vegetative State (VS)
3 Severe Disability (SD)
4 Moderate Disability (MD)
5 Good Recovery (GR)

GOSE Scoring: The patient's overall rating is based on the lowest outcome category indicated on the scale. Refer to helpful hints and definitions for further information concerning administration and scoring.

1 Dead
2 Vegetative State (VS)
3 Lower Severe Disability (Lower SD)
4 Upper Severe Disability (Upper SD)
5 Lower Moderate Disability (Lower MD)
6 Upper Moderate Disability (Upper MD)
7 Lower Good Recovery (Lower GR)
8 Upper Good Recovery (Upper GR)

VERIFICATION

Has the information obtained for the GOSE been verified by a family member? Yes No

Explain any discrepancies between the subject's and family member's responses:

COMMENTS
In this box, please include any pertinent details regarding the rating of the GOS or GOSE. Make sure to record the worst impairment(s) in activity or function on which you based your rating.

THE BARTHEL INDEX

Patient: _____

Examiner: _____

Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____

TOTAL (0–100): _____

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Used with permission.

Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
***Stroke.* 1990;21:78-81.**

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
***Arch Phys Med Rehabil.* 1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study.*1988;10:61-63.**

Copyright Information

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Examiner Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; requiring some help, but able to walk without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

References

Rankin J. "Cerebral vascular accidents in patients over the age of 60."
Scott Med J 1957;2:200-15

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke."
***Stroke* 1988 Dec;19(12):1497-1500**

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients."
***Stroke* 1988;19(5):604-7**

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www.strokecenter.org

NIHSS Stroke Scale

Patient ID: _____

Visit Type: ___Baseline ___Pre-Discharge ___30 Day ___1 Year ___Other

Patient #: _____

Date: _____Time: ___ ___:___ ___ [ ]am [ ]pm Site #: _____
Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____

4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.

0 = **Normal** symmetrical movements.
1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling).
2 = **Partial paralysis** (total or near-total paralysis of lower face).
3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face). _____

5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds.
1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
3 = **No effort against gravity;** limb falls.
4 = **No movement.**
UN = **Amputation** or joint fusion, explain: _____

5a. Left Arm _____

5b. Right Arm _____

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.

0 = **No drift;** leg holds 30-degree position for full 5 seconds.
1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed.
2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity.
3 = **No effort against gravity;** leg falls to bed immediately.
4 = **No movement.**
UN = **Amputation** or joint fusion, explain: _____

6a. Left Leg _____

6b. Right Leg _____

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.

0 = **Absent.**

1 = **Present in one limb.** _____

2 = **Present in two limbs.**

UN = **Amputation** or joint fusion, explain: _____

8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.

0 = **Normal;** no sensory loss.

1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.

2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg. _____

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.

0 = **No aphasia;** normal.

1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.

2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. _____

3 = **Mute, global aphasia;** no usable speech or auditory comprehension.

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.

0 = **Normal.**

1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty.

2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. _____

UN = **Intubated** or other physical barrier,
explain:_____

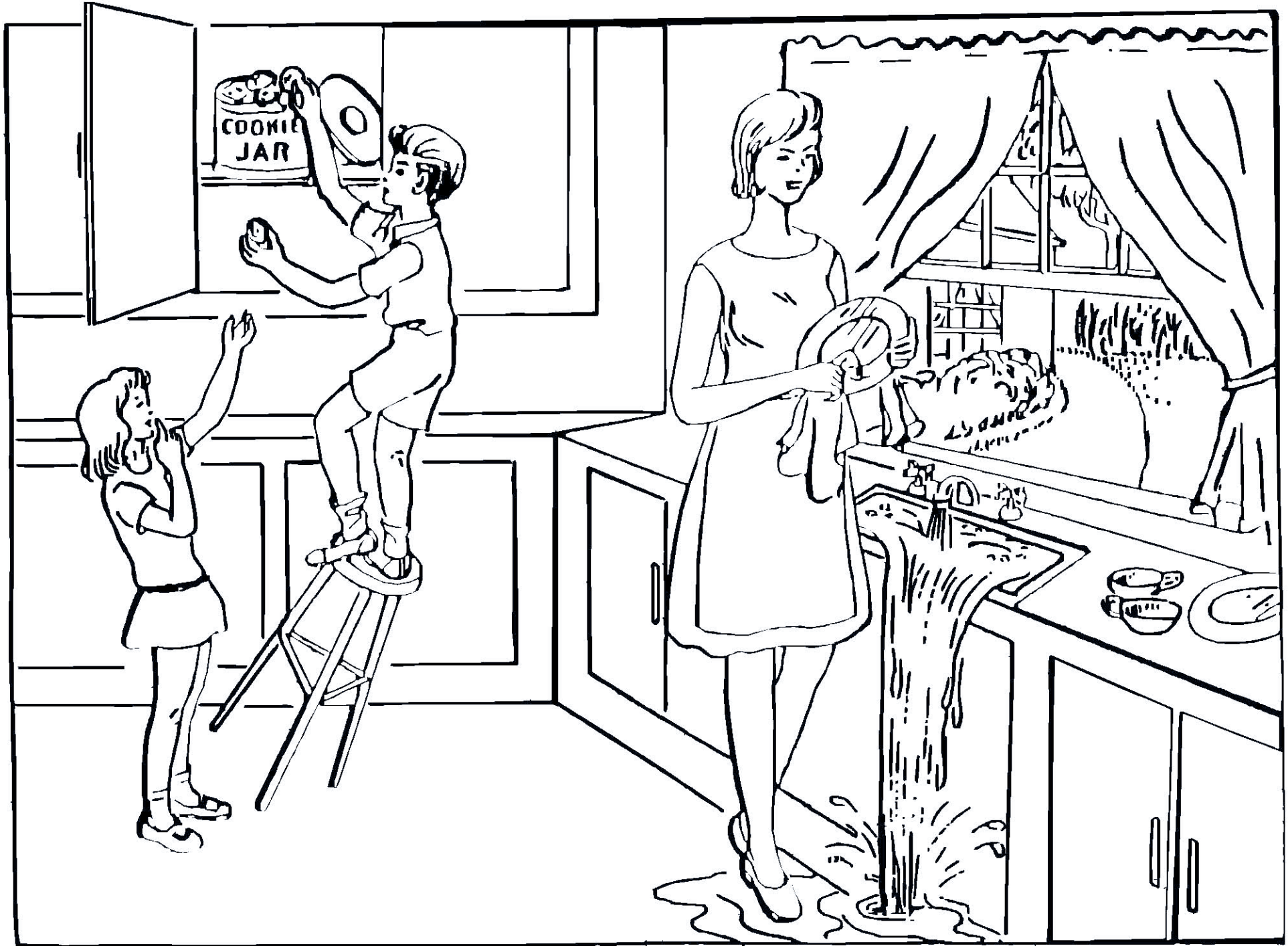
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

0 = **No abnormality.**

1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. _____

2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.

	Total Score	_____


COOKIE
JAR

You know how.

Down to earth.

I got home from work.

<u>Near the table in the dining room.</u>

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER