IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.

21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators' Experience

Professor Edward H Oldfield: the principal investigator is Professor of Neurosurgery and Internal Medicine and Director of the Neuro-endocrine service at UVA. He has published original scientific research in a wide variety of areas within neurosurgery and medicine and has experience as principal investigator of multiple randomized clinical trials.

Associate Professor Max Wintermark: The co-investigator is Associate Professor of Radiology, Neurology, Neurosurgery and Biomedical Engineering and Chief of Neuroradiology at UVA. He has expertise in imaging in cerebrovascular diseases as well as trauma and has participated in many clinical trials.

Daniel M S Raper: the primary sub-investigator is a neurosurgery resident who has published in a number of areas within neurosurgery and will be the resident lead for the project.

Robert M Starke: The co-investigator is a neurosurgery resident who has extensive experience in research in a variety of areas within neurosurgery, and has expertise in statistical analysis and will contribute to this aspect of the project.

The following neurosurgery residents are listed on the protocol as sub-investigators and will be involved in the clinical enrollment and initial assessment of patients in this study: Dale Ding; Robert Dallpiazza; Paul Schmitt; Aaron Bond; Sze Chun Winson Ho; James Nguyen; Alex Ksendzovsky; Peter Christiansen.

Rebecca Hand is a nurse practitioner in the neurosurgery department who has extensive clinical experience in both the inpatient and outpatient management of patients with neurosurgical disorders, and will contribute blinded telephone evaluation of patients' clinical outcomes in this project.

Signatures

Principal Investigator

_____	___Edward H Oldfield_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	___Mark E Shaffrey_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

Brief Summary/Abstract

Title of Study	The DECS Trial: DExamethasone versus burr hole Craniostomy for symptomatic chronic Subdural hematoma
Protocol Number	
Investigational Drug	Dexamethasone
Objectives	The objectives are: • To determine the effect of a 2 week course of dexamethasone on clinical outcomes and extent of chronic subdural hematoma at 6 months • To compare secondary outcomes between dexamethasone and burr hole drainage; namely, rate of treatment failure, GCS, mRS and MGS at hospital discharge, 1-2 weeks and 4-6 weeks, 3 months and 6 months • To compare rates of treatment failure (re-drainage in the burr hole group or drainage in the dexamethasone group)
Study Design	This is a prospective, randomized, controlled trial that is non-blinded to treatment but blinded to assessment of clinical outcome, with a concurrent prospective cohort study. Patients with chronic SDH admitted to the University of Virginia Hospital and who meet entry criteria will be offered enrollment into the study. The patients will be enrolled within 12 hours of diagnosis. Subjects will be treated with either a two week course of dexamethasone or burr hole drainage.
Number of Subjects	The study population will include 300 subjects of both genders, ages $\geq$18, who are diagnosed with chronic SDH and fulfill enrollment criteria.
Treatment and Duration	Subjects will be randomized in a 1:1 ratio to receive a two week course of dexamethasone or burr hole surgical drainage. One hundred and fifty patients will be enrolled per cohort. Randomization will be performed within 12 hours of diagnosis, allowing time to begin the study drug within 24 hours of diagnosis. The drug treatment will be for two weeks unless side effects of the drug dictate stopping the treatment (see toxicity criteria in Section 5.6). The clinical follow-up interval will be for at least 3 months after discharge from the hospital.
Safety Evaluation	Safety assessments will be performed at screening and on a daily basis following initiation of the study drug, until hospital discharge. Safety assessments will include: physical examinations; vital signs (blood pressure, pulse rate, respiration rate, and oral body temperature); standard of care clinical laboratory tests (hematology, serum chemistry, blood glucose levels); and monitoring for clinical signs and symptoms of VTE and infection.
Statistical Methods	This is an equivalence study. The treatment arms will be compared on an intention-to-treat basis. The primary outcome analysis will be a categorical frequency comparison using the Chi-square test. Secondary outcome measures will be analyzed using various tests based on the type of data. Values for continuous variables will be expressed as mean ± SD or median (25th-75th quartile), when appropriate. To compare continuous variables exhibiting a normal distribution, the Student's two-tailed t-test will be used. Nonparametric continuous variables will be compared using Wilcoxon's rank-sum (Mann Whitney U) test. Logistic regression analysis will be used to assess for interaction and confounding as well as to determine predictors of outcome as well as the optimal treatment algorithm.

Background

1. Provide the scientific background, rationale and relevance of this project.

Subacute and chronic subdural hematoma occurs in 1-2 per 100,000 population (1), but is much more common in elderly patients with a reported incidence up to 58 per 100,000 people >70 years (2). This incidence is expected to increase (21). Subacute and chronic subdural hematomas (cSDH) form, often after minor or unrecognized trauma, and slowly accumulate until they cause symptoms from compression, local mass effect, cortical irritation, or herniation. The pathophysiology of cSDH is thought to be secondary to slow and repeated venous bleeding from rupture of cortical draining veins, followed by fibrinolysis and membrane formation (2, 3).

The optimal treatment of cSDH is currently unclear. Surgery, observation, and steroid treatment are the most common options, but there is no clear consensus on the optimal management therapy. The most common treatments for cSDH include burr hole or twist drill craniostomy and drainage, or craniotomy and drainage. Neurological outcomes after surgical drainage have been reported to be improved in 85-90% in large retrospective series (4). In an analysis of 14,000 patients in the Nationwide Inpatient Database, treatment with surgical evacuation was a predictive factor of lower in-hospital mortality (28). However, surgical mortality is 1-5% in the literature but may be as high as 8-10% in patients >80 years (2). Furthermore, there is an 8-22% incidence of re-accumulation of cSDH, with need for additional procedures or further hospitalization (3-5, 16, 18-20).

Conservative management of cSDH has been shown to be associated with poorer options than surgical drainage and is not considered to be a safe option for symptomatic cSDH. Spontaneous resolution of cSDH has been reported, but is not common (1, 17, 27). Non-operative or medical management of cSDH has been reported in certain cases of primarily small cSDH with substantial decrease in SDH volume (26). However, non-interventional management may also result in clinical decline and risk of herniation from enlarging subdural hematoma. Surgical drainage is associated with early and delayed complications including wound infection, epidural hematoma, intracranial hemorrhage, tension pneumocephalus, and death (2, 4).

Corticosteroid treatment for cSDH has been proposed based on the anti-angiogenic properties of steroid treatment and its anti-inflammatory properties. This treatment strategy has been reported in retrospective case series and case reports in the literature (2,10-16). In the largest of these series, favorable results were seen in 71/73 patients (97.2%) exclusively managed with dexamethasone, and surgical drainage was required in 21.8% of patients initially treated with dexamethasone (2). In another series, pre-operative dexamethasone was associated with improved outcome in multivariate analysis, without increased incidence of complications (21).

Despite these various treatment options, there is no clear consensus treatment for cSDH of differing sizes, symptomatology and acuity. Burr hole craniostomy with or without continued subdural drainage has been the mainstay of treatment but is not suitable for all patients. A number of surveys of neurosurgeons in the United Kingdom, Canada and France reveal a wide range of practice regarding the prescription of corticosteroids, with a minority prescribing corticosteroids, and most often as a single treatment (22-24). A review article on the topic concluded that current evidence can neither refute nor deny the use of corticosteroids in this population, but that a randomized trial would be justified based on potential clinical equipoise (25).

Hypothesis to be Tested

The objectives of this study are:

- To determine the effect of a 2 week course of dexamethasone on chronic subdural hematoma
- To compare primary outcome of modified Rankin Score (mRS) 0-2 score at 6 months after diagnosis between dexamethasone and burr hole drainage for chronic subdural hematoma
- To compare rates of radiographic resolution of chronic subdural hematoma between the treatment groups
- To compare secondary outcomes between dexamethasone and burr hole drainage; namely, rate of treatment failure, clinical outcomes (GCS, mRS and MGS) at hospital discharge, 2 weeks, and 4-6 weeks, and 3 months.
- To compare the rates of treatment failure (re-drainage in the burr hole group or drainage in the dexamethasone group, a secondary outcome)
- For patients not consenting to randomization, enrollment in a parallel, prospective cohort study, with the same primary and secondary outcomes
- For patients electing for observation only, a prospective cohort observational study will be offered with collection of the same data for primary and secondary outcomes

The hypothesis to be tested is that:

> *For patients with unilateral, symptomatic chronic subdural hematoma, there is no difference in clinical outcomes, as measured by achievement of modified Rankin Score of 0-2 at 6 months, between those treated with a 2 week course of oral dexamethasone, compared with those treated with burr hole surgical drainage.*

Study Design: Biomedical

1. Will controls be used?

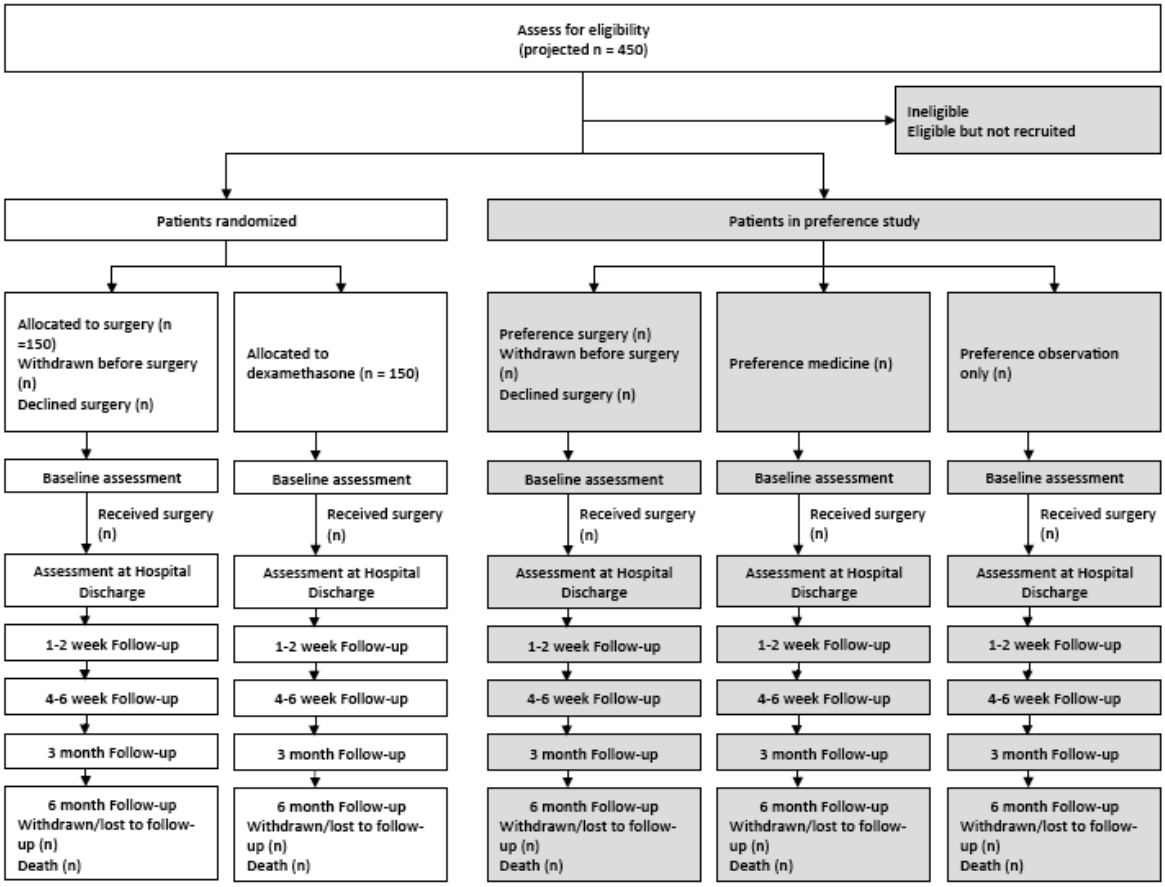
Controls will not be used in this study.

However, the study design incorporates a parallel observational group, comprised of patients who elect not to undergo randomization between treatments but elect for one treatment or the other, or who elect for no active treatment. These patients will be offered enrolment in a prospective cohort study with the same primary and secondary outcomes as the randomized trial. The results of this study will be used as an internal control for the results from the randomized arms.

2. What is the study design?

Our study will be a prospective, randomized controlled trial, non-blinded to treatment but blinded to clinical primary outcome, with a concurrent preference study for patients not electing to undergo randomization, and with concurrent collection of prospective data on patients electing to undergo observation only (Figure 1).

Figure 1. Patient Flow Schema



3. Does the study involve a placebo?

The study does not involve a placebo.

Human Participants

Ages ≥18 years old
Sex Male or female
Race Any

1. Provide target # of subjects (at all sites) needed to complete protocol.

A total of 300 subjects are needed to complete the protocol.

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

The expected rate of screen failure is 10%

The expected rate of dropouts/withdrawals from the randomized study is 25%

Of those declining participation, 80% are expected to participate in the observational study.

3. How many subjects will be enrolled at all sites?

A total of 450 subjects are expected to be enrolled.

4. How many subjects will sign a consent form under this UVa protocol?

450 subjects are expected to sign a consent form under this UVa protocol

5. Provide an estimated time line for the study.

Enrollment:
33% enrolled in 12 months
Interim statistical analysis (at 33% enrolment): 12 months
66% enrolled in 24 months
Interim statistical analysis (at 66% enrolment): 12 months
100% enrolled in 36 months

Completion of follow-up:
Follow-up complete by 40 months

Completion of data analysis:
Data analysis complete by 48 months

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

Subjects meeting all of the following criteria will be considered for admission to the study:

- Male or female subject aged 18 years of age or older;
- Informed consent obtained from a patient or a legal representative before enrollment;
- Enrollment into the study within 12 hours of detection of chronic subdural hematoma on cranial imaging;

- Presence of symptoms referable to chronic subdural hematoma, including one or more of the following:
    - Headache
    - Altered mental status
    - Limb weakness
    - Dysphasia
    - Focal neurological deficit;

- Demonstration of chronic subdural hematoma on cranial imaging, including the following features:
    - On computed tomography imaging, iso- or hypo-intensity extra-axial collection with or without presence of acute component
    - Radiologic interpretation of magnetic resonance imaging consistent with subacute or chronic SDH
    - With or without evidence of acute hemorrhagic component;

- Maximum depth of subdural hematoma of less than 20mm, with less than 10mm of midline shift, as measured on axial CT or MR imaging;
- Absence of skull fracture over the subdural hematoma;
- Able to receive the drug treatment.

2. List the criteria for exclusion

Subjects presenting with any of the following will not be included in the study:

- Presence of skull fracture over the subdural hematoma, or other specific etiology for cSDH not suitable for drainage by burr hole craniostomy, such as presence of a ventriculoperitoneal shunt;

- Extent of subdural hematoma $\geq$ 20mm in maximal depth, or $\geq$ 10mm of midline shift, as measured on axial CT or MR imaging;

- GCS <8 or cSDH of an extent or size for which craniotomy, rather than burr hole drainage alone, is judged necessary by the neurosurgery attending on call

- Prior diagnosis of dementia;

- Presence of symptomatic peptic ulcer, psychosis, active or suspected TB, acute infection, or documented hypersensitivity or allergy to dexamethasone;

- Pregnancy (confirmed by a serum human chorionic gonadotropin pregnancy test) or breast feeding

3. List any restrictions on use of other drugs or treatments.

All patients on anticoagulation will receive consultation with the hematology team to determine safe period of discontinuation of anticoagulant or antiplatelet medications. For patients taking regular anticoagulant or antiplatelet medications, the aim will be to discontinue these for the duration of the study protocol unless cardiologist advice is to resume anticoagulation/antiplatelet medication earlier.

For patients who experience seizure associated with cSDH, treatment is initiated with levetiracetam at a dose of 1000mg BID after a short dose escalation from 500mg BID, unless a contraindication exists. Acute seizures are treated with benzodiazepine and fosphenytoin if needed. Prophylactic AEDs are not routinely prescribed for patients with cSDH. For patients with questionable sub-clinical seizure or non-typical symptoms, EEG is performed and guides antiepileptic treatment. Cessation of AEDs is at the discretion of the treating physician but typically occurs after 3-6 months free of seizure.

Statistical Considerations

1. **Is stratification/randomization involved?**Yes

►IF YES, describe the stratification/ randomization scheme.

Randomization Procedure

Randomization will be performed in a 1:1 ratio between the investigational and control arms. Block randomization will be used, with block size of 8 in an allocation ratio of 1:1. Randomization will be done by a member of the UVA Neurosurgery Clinical Trials Office who is blinded to the clinical treatments and clinical decision making process. The randomization sequence will be determined prior to enrollment of the first patient, using a web-based randomization software – Random Allocation Software version 1.0 (29). This sequence will be determined and accessed only by this non-clinical member of the Clinical Trials Office team. Sealed and opaque Randomization Envelopes will be prepared with cards indicating stops for interim analysis points. The Randomization Envelopes will be stored in a secure location in the neurosurgical ICU. A document matching Randomization Code with treatment group will be stored on the UVA secure server with other study materials and a copy will be kept with the Randomization Envelopes.

Randomization occurs at the Enrollment. If a subject is consented, screened and for any reason is not randomized, the subject will not be considered enrolled. Once screening has been completed, no additional stratification factors will be included in allocating a treatment allocation according to the randomization procedure.

First, the enrolling physician will open the Randomization Envelope with the lowest available sequential number. The enrolling physician will then match the unique Randomization Code inside the Randomization Envelope with the Treatment Group assignment and the randomization code will be recorded in the patient's case report form.

►IF YES, who will generate the randomization scheme?

___X__Other – *non-clinical member of UVA Neurosurgery Clinical Trials Office, to be determined prior to enrollment of the first patient*

2. What are the statistical considerations for the protocol?

Study Design/Endpoints

Primary outcome:

The primary outcome of this equivalence trial is that there is no difference (non-inferior and non-superior) in 6 month favorable functional outcome defined as modified Rankin scale 0-3 between patients treated with a two week course of oral dexamethasone, compared with surgical drainage via burr hole craniostomy with placement of a short-term subdural drain.

The null hypothesis for this **equivalence trial** is that there is a significant difference in 6 month favorable functional outcome defined as modified Rankin scale 0-2 between patients treated with a two week course of oral dexamethasone, compared with surgical drainage via burr hole craniostomy with placement of a short-term subdural drain.

Secondary outcomes:
Secondary outcomes will include treatment failure; the need for repeat surgery (in the burr hole group) or surgery (in the dexamethasone group)

Radiographic resolution of SDH as measured by difference in maximum depth of cSDH between diagnosis and 6 month follow-up scan

Functional outcomes as measured by MGS, GCS and MRS at hospital discharge and 6 month follow up.

Other endpoints to be measured include: resolution of limb weakness, resolution of dysphasia, adverse events (infection, seizure, medication intolerance, DVT and PE).

End of Study Procedures

All subjects are to undergo repeat evaluations after hospital discharge. This will include neurosurgery clinic visits at 1-2 weeks, at 4-6 weeks, at 3 months, and at 6 months after hospital discharge. Cranial imaging with CT Head will be performed at each visit. Clinic records will be reviewed and clinical assessment as well as adverse events, concomitant medications, and clinical laboratory measurements will be recorded in a prospective manner. The final clinical assessment of outcome using the modified Rankin score will be performed by a clinical investigator who is not directly involved in the care of the patients and has been blinded to treatment received. If a subject withdraws before 3 months, the final clinical assessment and evaluations are to be made at the time of withdrawal.

Subjects who die while on the study are to have this noted in their CRFs; death is an expected event. The date of death is to be noted, as well as the cause of death. If an autopsy is undertaken, a copy of the autopsy report is to be attached to the CRF once it becomes available.

Withdrawal of Subjects

Analysis will be carried out as an intention to treat analysis.

Subjects may be withdrawn from study assessment for the following reasons:

- At their own request or at the request of their legally authorized representative

- If the patient's symptoms symptoms worsen to the extent that urgent or emergent surgical intervention is required either for craniotomy and evacuation, or burr hole evacuation of subdural hematoma. These symptoms may include (but are not limited to):
    - Worsening hemiparesis
    - Decreased level of consciousness
    - Worsening CT findings
    - Worsening nausea and/or headache
    - Worsening aphasia
    - Worsening or development of focal neurologic deficit

In all cases, the reason for withdrawal must be recorded in the case report form and in the subject's medical records. The subject must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in Section 9.

As far as possible, all examinations scheduled for the end of study evaluations must be performed on all subjects who participate but do not complete the study according to protocol (see Section 6.2.2). A patient that withdraws from the study for reasons other than due to the occurrence of an adverse event may be replaced at the request of the sponsor.

The investigator must make every effort to contact subjects lost to follow-up.

3. Provide a justification for the sample size used in this protocol.

We plan an interim analysis at 33% and 66% of anticipated study enrollment. This will be performed by the study statistician, and reviewed by the Data Safety Monitoring Board. Predetermined criteria for stopping the trial will be a significant difference in recurrence rates or incidence of adverse effects between groups. In accordance with O'Brien-Flemming analysis we will use a p-value for significance of 0.0052 at the interim analysis and 0.048 at the final analysis. As such, the sample size has been increased by 1.4%.

Based on results of recent randomized clinical trials, it is expected that 85% of patients treated with burr hole drainage with subdural drain placement or steroids will have a favorable outcome at 6 months (mRS 0-2). A delta of 15% difference in outcome was based on the literature and pooled agreement by 7 attending neurosurgeons each with greater than 10 years experience in treating patients with cSDH.

Based on a 80% power calculation to show equivalence between the two treatments and a total, two-sided alpha = 0.05, conservative estimates demonstrate that 125 patients will be necessary in each cohort of the randomized clinical trial.

4. What is your plan for primary variable analysis?

The primary analysis will be a test of proportions between patients receiving treatment with steroids versus surgical drainage via burr hole craniostomy with placement of a short-term subdural drain for the dichotomized modified Rankin scale 0-2 and 3-6 as compared between cohorts. In accordance with O'Brien-Flemming

analysis we will use a p-value for significance of 0.0052 at the interim analysis and 0.048 at the final analysis. This will be carried out using intention to treat analysis as specified above.

5. What is your plan for secondary variable analysis?

Secondary analysis will be carried out both with tests of proportions or mean differences between cohorts as defined in the secondary outcome measures section above. For the assessment of means, analysis will be carried out using parametric analysis with or without equal variance or non-parametric analysis as indicated based on graphical and statistical assessment of normality.

Multivariate logistic regression analysis will be carried out to determine predictors of favorable outcome (mRS 0-2) when controlling for other patient and disease specific variables (age, baseline neurological motor deficit, size of SDH, etc). Stratification and expansion co-efficient will be constructed as necessary to assess for relevant interaction and/or confounding.

Additional, multivariate models will be constructed to assess for multivariate predictors of secondary analysis. This will include multivariate assessment of further surgery (either repeat surgery in the burr hole group or surgery in the cohort assigned to steroid treatment). Multivariate analysis will be carried out to determine predictors of radiographic resolution of SDH.

6. Have you been working with a statistician in designing this protocol?
No outside physician has been consulted on the design of the study

IF YES, what is their name?

Biomedical Research

1. What will be done in this protocol?

Upon enrollment of a patient into the trial, the following clinical data will be collected: detailed neurologic examination, MGS, GCS, mRS, clinical history including details of presenting symptoms, whether the patient had a fall, baseline mobility, amount of assistance needed in activities of daily living, medical history, presence of limb weakness, presence of dysphasia, and seizure. Laboratory findings and imaging performed in the usual course of clinical care will be reviewed.

Subjects will be enrolled, after presenting to the hospital with symptoms which prompted imaging that reveal subacute or chronic subdural hematoma. The enrollment period is 36 months. The study duration is approximately 42 months, with 6 month follow up in all enrolled patients. There will be 1 investigational site.

The goal of the study will be to compare dexamethasone treatment with burr hole drainage in comparable patients. Those judged by the neurosurgery attending on call to require craniotomy for drainage of their subdural hematoma will be excluded, as will patients with acute subdural hematoma. Those in whom the treating surgeon deems non-interventional treatment would be unsafe will be excluded from the trial.

The nature of the interventions being tested will not allow for blinding of treatments. However, data will be anonymized and clinicians will be blinded during evaluation of outcome where possible. Although it is not possible to blind outcome measurement of radiographic resolution due to visible post-surgical changes, functional outcome measures will be blinded to treatment received and will be assessed by telephone interview.

Patients declining to be randomized but who undergo treatment with surgery or dexamethasone will be offered enrollment in a parallel arm of the study which is a prospective, controlled observational cohort arm (Figure 1). In this arm, patients will receive treatment according to their preference (either dexamethasone, surgery or no active treatment) and the same outcome measures will be recorded. These cohorts essentially represent clinical care as it is provided today.

For patients electing observation only, prospective data on outcomes will be collected and used for comparison of the natural history of chronic subdural hematoma.No interventions will be done solely for research purposes, apart from telephone surveys.

Justification of Proposed Drug Treatment Arm

Corticosteroid treatment for cSDH has been proposed based on the anti-angiogenic properties of steroid treatment and its anti-inflammatory properties. This treatment strategy has been reported in retrospective case series and case reports in the literature (2,10-16). In the largest of these series, favorable results were seen in 71/73 patients (97.2%) exclusively managed with dexamethasone, and surgical drainage was required in 21.8% of patients initially treated with dexamethasone (2). In another series, pre-operative dexamethasone was associated with improved outcome in multivariate analysis, without increased incidence of complications (21). A review article on the topic concluded that current evidence can neither refute nor deny the use of corticosteroids in this population, but that a randomized trial would be justified based on potential clinical equipoise (25).

Treatments to be Administered

Dexamethasone will be administered as PO tablet where possible. Each tablet contains 4 mg of dexamethasone as the initial dose. The drug will be obtained from the University of Virginia inpatient pharmacy. For patients completing the course of medication as an outpatient, the dexamethasone taper will be provided upon discharge. All patients receiving dexamethasone will also receive peptic ulcer prophylaxis with pantoprazole or famotidine.

Dosing Schedule

Dosing schedule for dexamethasone treatment is modified from the protocol of Delgado-Lopez and colleagues (2). The initial dosing is 4mg dexamethasone every 8 hours, either oral or intravenous; oral diet if possible (or via nasogastric tube); pantoprazole (40mg per day); and DVT prophylaxis with either subcutaneous heparin (SQH) 5000 units TID s/ and/or lower extremity pneumatic compression device. After 3 days of treatment, the dexamethasone is slowly tapered over 2 weeks according to the following dosing schedule:

Table 2. Proposed Dexamethasone Dosing Schedule

Dose	Duration	Total Doses
4mg q8h	3 days	9
4mg morning / 2mg noon / 2mg night	3 days	9
2mg q8h	3 days	9
2mg q12h	3 days	6
2mg daily	3 days	3

Surgical Protocol

The surgical protocol for burr hole drainage of subdural hematoma is as follows. The procedure is done in the operating room, with general anesthesia. The patient is positioned supine with the head in neutral if bilateral burr holes are planned, or with the head turned to the contralateral side and resting on a Mayfield horseshoe head holder. Burr holes are planned according to the distribution of subdural blood, but are commonly placed over the frontal region and parietal region. Burr holes are placed over the affected hemisphere, using the perforator attachment to the Midas Rex drill. The dura is opened in cruciate manner and the subdural clot is washed out with warm water. Perioperative antibiotics are administered, and continued for 2 doses postoperatively (Cefazolin 1-2g q8h depending on patient weight). The patient is kept supine overnight, and a postoperative CT head is performed to assess resolution of the cSDH. A subdural drain is placed, and is removed within 72 hours.

Length of Hospital Stay

The length of hospital stay is not expected to be significantly different between groups included in this study. Hospital stay for patients presenting with symptomatic subdural hematoma can vary widely based on patient symptoms, co-morbidities and progress. Patients in the surgical group would typically undergo a burr hole craniostomy within the first 24 hours of hospital stay, and be observed for a number of days (typically 3-7 days) post-operatively to monitor for symptom improvement and evaluate the need for any further intervention. Patients treated with dexamethasone would be observed for a number of days (typically 2-3 days) for symptom improvement, monitor potential side effects of medication and to evaluate the need for any intervention.

Treatment of Seizure

For patients who experience seizure associated with cSDH, treatment is initiated with levetiracetam at a dose of 1000mg BID after a short dose escalation from 500mg BID, unless a contraindication exists. Acute seizures are treated with benzodiazepine and fosphenytoin if needed. Prophylactic AEDs are not routinely prescribed for patients with cSDH. For patients with questionable sub-clinical seizure or non-typical symptoms, EEG is performed and guides antiepileptic treatment. Cessation of AEDs is at the discretion of the treating physician but typically occurs after 3-6 months free of seizure.

End of Study Procedures

All subjects are to undergo repeat evaluations after hospital discharge. This will include neurosurgery clinic visits at 1-2 weeks, at 4-6 weeks, at 3 months, and at 6 months after hospital discharge. Cranial imaging

with CT Head will be performed at each visit. Clinic records will be reviewed and clinical assessment as well as adverse events, concomitant medications, and clinical laboratory measurements will be recorded in a prospective manner. The final clinical assessment of outcome using the modified Rankin score will be performed by a clinical investigator who is not directly involved in the care of the patients and has been blinded to treatment received. If a subject withdraws before 6 months, the final clinical assessment and evaluations are to be made at the time of withdrawal.

Subjects who die while on the study are to have this noted in their CRFs; death is an expected event. The date of death is to be noted, as well as the cause of death. If an autopsy is undertaken, a copy of the autopsy report is to be attached to the CRF once it becomes available.

Clinical Data Collection

Screening/Enrollment

Screen Subject

1. Obtain signed ICD and Health Information Release form (if applicable), place in subject file & provide copy to subject
2. Assign MGS score, GCS, MRS, and clinical evaluation including presence of limb weakness or dysphasia
3. Verify patient meets all inclusion/exclusion criteria

Enroll Subject

1. Perform randomization procedure
2. Assign admission scores (MGS, GCS, MRS)
3. Obtain information to complete remaining data points: past medical history, medication history, concomitant medications
4. Ensure subject will receive medication (if randomized to mediation) for the full prescribed course
5. Verify data and complete required documentation; enter into electronic trial registry promptly

If Surgery occurs:

1. Obtain and record:
    a. Operative data
    b. Intraoperative complications and immediate postoperative AE/SAE
    c. Concomitant medications
2. Check documentation for completeness, verify data and enter into electronic registry promptly

If randomized to medication:

1. Obtain and record:
    a. Baseline laboratory values including blood glucose levels
    b. Immediate post-medication AE/SAE
    c. Concomitant medications
2. Check documentation for completeness, verify data and enter into electronic registry promptly

For both groups:

24hr +/- 12hr

1. Perform and record neurological examination, MRS, GCS and MGS scores

2. Order the clinical laboratory tests
3. Obtain and record:
    a. Vital signs
    b. AE/SAE and concomitant medications
4. Obtain CT Head 48-72hr post-injury (at the discretion of the investigator and if standard of care)
5. Check documentation for completeness, verify data and enter into electronic registry promptly

At Discharge from Acute Care

1. Perform and record neurological examination, MRS, GCS and MGS scores
2. Review the clinical laboratory tests
3. Review all AE/SAE and concomitant medications
4. Review any further brain imaging (at the discretion of the investigator and if standard of care)
5. Check documentation for completeness, verify data and enter into electronic registry promptly

1-2 Weeks after Discharge from Acute Care

1. Perform and record neurological examination, MRS, GCS and MGS scores
2. Review the clinical laboratory tests
3. Obtain and record:
    a. Vital signs
    b. AE/SAE and concomitant medications
4. Obtain CT Head 1-2 weeks post-injury
5. Check documentation for completeness, verify data and enter into electronic registry promptly

4-6 Weeks after Discharge from Acute Care

1. Perform and record neurological examination, MRS, GCS and MGS scores
2. Review the clinical laboratory tests
3. Obtain and record:
    a. Vital signs
    b. AE/SAE and concomitant medications
4. Obtain CT Head 4-6 weeks post-injury
5. Check documentation for completeness, verify data and enter into electronic registry promptly

3 Months after Discharge from Acute Care

1. Perform and record neurological examination, MRS, GCS and MGS scores
2. Review the clinical laboratory tests
3. Obtain and record:
    a. Vital signs
    b. AE/SAE and concomitant medications
4. Obtain CT Head 4-6 weeks post-injury
5. Check documentation for completeness, verify data and enter into electronic registry promptly

6 Months after Discharge from Acute Care

1. Perform and record neurological examination, MRS, GCS and MGS scores
2. Review the clinical laboratory tests
3. Obtain and record:
    a. Vital signs

   b. AE/SAE and concomitant medications
4. Obtain CT Head 3 months post-injury
5. Check documentation for completeness, verify data and enter into electronic registry promptly
6. Completion of protocol

2. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?No

3. List the procedures, in bullet form, that will be done for research as stipulated in this protocol.

- Enrollment form and Health Information Release Form
- Randomization to dexamethasone or surgical treatment
- Telephone survey at 1-2 weeks after discharge to determine clinical scores (mRS, MGS, GCS)
- Telephone survey at 4-6 weeks after discharge to determine clinical scores (mRS, MGS, GCS)
- Telephone survey at 3 months after discharge to determine clinical scores (mRS, MGS, GCS)
- Telephone survey at 6 months after discharge to determine clinical scores (mRS, MGS, GCS)

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? No

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures (e.g. ultrasound, CT scans/ x-rays etc.)? **If yes, LIST PROCEDURES:** No

6. Will you be using viable embryos?No

7. **Will you be using embryonic stem cells?**No

8. **Are any aspects of the study kept secret from the participants?** No

9. **Is any deception used in the study?** No

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define <u>adverse events</u> (AE)) for this study?

__X___An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

1.2 How will you define <u>serious adverse events</u>?

__X___A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an unanticipated problem?

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What is the definition of a protocol violation?

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

___X__ Other

Pregnancy is not anticipated to be related to treatments administered in this trial. If pregnancy occurs, the subject will be withdrawn from the study and all information collected prior to the onset of pregnancy will be included in the analysis.

1.6 What is the definition of a Protocol Enrollment Exception?

___X__NA- No outside sponsor

1.7 What is the definition of a data breach?

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Risks associated with Surgical Treatment

Expected Risks related to study participation.	**Frequency**
Temporary drop in blood sodium levels requiring treatment with fluid restriction or salt tablets	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Temporary perioperative confusion	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Need for additional surgical drainage	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Need for a larger surgical procedure with removal of bone and direct washout of subdural hematoma	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Deep infection around the brain requiring surgery	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Wound infection requiring antibiotics or surgery	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Clot development in the legs or lungs, potentially requiring medication or insertion of a venous filter	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Fatal PE	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Perioperative mortality	____Occurs frequently ____Occurs infrequently __X__Occurs rarely

	____Frequency unknown
Reproductive Risks	Minimized due to the requirements of this protocol.
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

Risks associated with Dexamethasone Treatment

Expected Risks related to study participation.	**Frequency**
Temporary increase in blood sugar levels	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Difficulty sleeping	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Mild increase in appetite and/or body weight	__X__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Temporary confusion	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Need for surgical drainage	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Need for a larger surgical procedure with removal of bone and direct washout of subdural hematoma	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Temporary increase in reflux symptoms requiring higher dose of anti-reflux medication	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Hypersensitivity to dexamethasone	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Development of severe systemic infection	____Occurs frequently ____Occurs infrequently

	__X__Occurs rarely ____Frequency unknown
Occurrence of symptomatic venous thromboembolism	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Derangement of liver function tests >2x the upper limit of normal	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Death	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Reproductive Risks	Minimized due to the requirements of this protocol.
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

Risks associated with reflux medication

Expected Risks related to study participation.	**Frequency**
Interaction with other drugs to decrease the effectiveness or increase toxicity of some drugs	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Diarrhea, nausea, vomiting, rash or headaches	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Osteoporosis-related fracture	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Reproductive Risks	**Minimized due to the requirements of this protocol.**
Violation of subject's privacy and confidentiality	**Minimized due to the requirements of the privacy plan in this protocol**

Risks associated with DVT prophylaxis (subcutaneous heparin and/or lower extremity pneumatic compression)

Expected Risks related to study participation.	**Frequency**

Abdominal bruising around injection site	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Allergy to heparin or other components of injectable	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Failure to prevent leg or lung clots from forming	____Occurs frequently __X__Occurs infrequently ____Occurs rarely ____Frequency unknown
Development of heparin-induced thrombocytopenia syndrome	____Occurs frequently ____Occurs infrequently __X__Occurs rarely ____Frequency unknown
Reproductive Risks	**Minimized due to the requirements of this protocol.**
Violation of subject's privacy and confidentiality	**Minimized due to the requirements of the privacy plan in this protocol**

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

To minimize the risks associated with dexamethasone treatment:
All patients receiving dexamethasone will also receive daily proton pump inhibitor for prevention of corticosteroid-induced gastritis, unless there is a contraindication or the patient is already taking a regular H2-receptor antagonist. The patient will also be monitored daily for the presence of signs or symptoms of VTE, including calf pain, shortness of breath, desaturation or tachycardia. Any symptoms will be further investigated with lower extremity venous Doppler ultrasound, arterial blood gas, and/or pulmonary vascular imaging. Elevated blood glucose levels will be controlled during hospitalization using a standardized protocol used for all hospitalized patients of intermittent short-acting insulin. After hospital discharge, blood glucose will be monitored twice weekly during the drug treatment period and treatment with anti-hyperglycemics prescribed as necessary.

The following variables will be collected at various times to assess safety.

Complete physical examinations will be conducted. Medical history (including blood glucose control) and demographics including age, gender, race, height, and weight will be collected at baseline or the time of hospital admission, as available. Concomitant medications will be recorded at baseline.

Vital signs monitored will include blood pressure and pulse rate, respiratory rate, and temperature.

The following laboratory evaluations will be made:

Hematology (at baseline, and daily while hospitalized): hematocrit, hemoglobin, red blood cell count with indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]), reticulocytes, white blood cell count, and platelets (platelet count, PT and APTT);

Serum Chemistry (at baseline, then daily while hospitalized): albumin, blood urea nitrogen (BUN), calcium, creatinine, glucose, cholesterol (including HDL and LDL cholesterol), phosphate, potassium, sodium, chloride

Liver function tests (at baseline, then twice weekly while hospitalized): total bilirubin, AST, ALT, albumin, GGT, total protein

Urinalysis (at baseline): macroscopic (pH, specific gravity, glucose, protein, ketones, blood) and microscopic (RBCs/hpf, WBCs/hpf, bacteria)

To minimize the risk of having >500 ml of blood drawn within 48 hours:
Pregnancy screening will be performed with serum beta-HCG testing in all female patients of childbearing age prior to enrollment in the study. Those with positive beta-HCG will be excluded from enrollment in the trial.

To minimize the risk of having >500 ml of blood drawn within 48 hours:
The blood will not be drawn if the levels do not meet the criteria below:

- African American subjects: hemoglobin $\geq$ 11.g/dL
- Non- African American subjects: hemoglobin $\geq$ 11.5g/dL

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

_____At subject, PI or sponsor's request

___X__Treatment would be stopped if the subject had a serious adverse event deemed related to study

This includes hypersensitivity reaction requiring cessation of drug treatment, development of serious life-threatening pulmonary embolus, development of severe systemic infection requiring hospitalization, or development of hyperglycemia not controllable on insulin therapy.

Subjects withdrawn from receiving additional study drug due to an adverse experience will be followed by the investigator until the outcome is determined. Additional reports will be provided to the regulatory authorities when requested. Every effort will be made to follow the subject for the full study period as per the schedule of study visits.

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

___X__Per IRB, PI, DSMB, or sponsor discretion

2.5 What are the criteria for breaking the blind/mask?

___X__NA – Not blinded/masked

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

___X__IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded?

Yes

►IF NO, what criteria will be used?

_____Only adverse events deemed related/possibly related to study

_____Only adverse events that are deemed serious

_____Only adverse events that are deemed related AND serious

3.2 How will adverse event data be collected/recorded?

___X__Paper AE forms/source documents

___X__Spreadsheet *(electronic*)

3.3. How will AEs be classified/graded?

__X__Serious/Not serious

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__X___The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

___X__After subject signs consent

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

_____End of study drug/device/intervention/participation

_____30 days post study drug/device/intervention

___X__Subject completes intervention and follow up period of protocol

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data-	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html

	UVa Police if breach includes such things as stolen computers.	IMMEDIATELY.	Phone- (434) 924-7166

4. **How will the endpoint data be collected/recorded.** *Check all that apply*
   ___X__Protocol specific case report forms

5. **Data and Safety Oversight Responsibility**

5.1. Who is responsible for overseeing safety data for this study?

_____No additional oversight body other than PI at UVa (*skip question 5.2*)

_____The UVa Cancer Center Data and Safety Monitoring Committee *If your study involves cancer patients, see Question # 6 to help you decide if you should check this option*

_____Medical Monitor *This could include such things as the overall PI of a multisite trial*

___X__DSMB/ DSMC- *If your study is NIH funded, check with the center to determine if they require a DSMB for this study.*

The Data Safety Monitoring Board for this study will consist of the following study personnel: Dr Edward Oldfield, the study PI; Dr Daniel Raper & Dr Robert Starke, the two primary sub-investigators; and Johanna Loomba, the Director of the Department of Neurosurgery Clinical Trials Office.

This Board will convene monthly during the study period to review safety data and reportable events. At 33% and 66% of projected enrolment, the DMSB will review interim statistical analysis to determine the necessity for alteration of the study protocol or early closure of the trial.

_____Research Monitor: *Insert Name* _____

Required for protocols funded by the Department of Defense

_____Other: *specify* _____

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor?

_____Information may be found in the UVa Cancer Center Institutional DSMP

___X__Other- *specify* _____

The Data Safety Monitoring Board for this study will consist of the following study personnel: Dr Edward Oldfield, the study PI; Dr Daniel Raper & Dr Robert Starke, the two primary sub-investigators; and Johanna Loomba, the Director of the Department of Neurosurgery Clinical Trials Office.

This Board will convene monthly during the study period to review safety data and reportable events. At 33% and 66% of projected enrolment, the DMSB will review interim statistical analysis to determine the necessity for alteration of the study protocol or early closure of the trial.

Relationship to study sponsor: N/A, since there is no study sponsor for this trial.

5.3. What items will be included in the aggregate review conducted by the PI?

_____NA- PI is not the overall person overseeing the safety data for this study.
__X___All adverse events

__X___Unanticipated Problems

__X___Protocol violations

___X__Audit results

_____Application of dose finding escalation/de-escalation rules *These should be outlined under 2.4.*

__X__Application of study designed stopping/decision rules

__X__Early withdrawals

__X___Whether the study accrual pattern warrants continuation/action

__X___Endpoint data

_____Other: (*specify*) _____

5.4 **How often will aggregate review occur?**
For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

___X__NA- PI is not the overall person overseeing the safety data for this study.
_____Annually

_____Monthly

_____Other: *specify*

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?

__X___ NA- there is no DSMB/ DSMC overseeing this study

_____Every six months

_____Once a year

_____Other: *specify*

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

___X__Part of IRB-HSR continuation status form

_____Separate report from DSMB/DSMC or UVa PI

_____Other: *specify*

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

Potential benefits for participants in the study assigned to the dexamethasone group include avoidance of surgery with associated risk, including risk of infection, bleeding, as well as anesthetic risks and medical consequences of stress of surgery.

These potential benefits would also be applicable to future patients with this condition. Thus, society may benefit from delineation of evidence in favor of non-surgical treatment as a primary measure for patients with symptomatic chronic subdural hematomas, thus aiding clinical decision making in the future.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

This study provides a potential benefit to individual patients randomized to the dexamethasone group, as outlined above. For the patients randomized to the surgery group, they receive the standard of care treatment. Risks associated with dexamethasone treatment are not anticipated to be less than risks associated with surgery, although they are different and require monitoring. Namely, the most common and clinically relevant risks include: hyperglycemia, VTE, infection and gastritis. These risks will be minimized by the institution of a conservative dexamethasone dosing schedule compared with the literature; by addition of pantoprazole and glucose monitoring for all patients receiving drug treatment; and by close monitoring of drug-associated adverse events. The study poses minimal risk of breach of Protected Health Information that will be minimized by following institutional and federal confidentiality regulations. Overall, the risk-benefit ratio is acceptable.

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APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual as they are not allowed by UVa Policy*
- *All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.*
- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.*
- *The IRB cannot grant clinical privileges.*
- *Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.*
- *Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.*
- *Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.*

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- *No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*
- *No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: Recruitment

1. **How do you plan to identify potential subjects?**

a. ____ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or quality improvement.

b. ____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

c. __X__ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA- *Allowed under Preparatory to Research if PHI will be shared by the health care provider.*

IMPORTANT

Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating.

e. ____ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

I confirm the following to be true:

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

2. How will potential subjects be <u>contacted?</u>

a.____Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

b.____Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

c.__X__Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: *Allowed under Health Care Operations.*

d.____ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

3. **Will any additional information be obtained from a potential subject during "prescreening"?**No

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No

►**IF YES, explain in detail what you will ask them to do**.N/A

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

The consent will not given to the subject prior to the day of the start of study procedures because the study takes place in an emergency type situation which cannot be planned for in advance.

The consent will be performed by a member of the study personnel upon admission of the patient to hospital or upon first evaluation in case of an inpatient consult. This will typically be a neurosurgery "on call" resident who has completed the required training to obtain study consents. Should the "on call" resident not have completed this training, a qualified study personnel will obtain consent. The setting will be Emergency Room or acute care hospital ward.

Once a potential subject is identified, they will be interviewed in a quiet and private place and may have family or friends with them if they choose. If there is concern that the potential subject may not be able to read the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response they will either be offered

the opportunity to read the consent form or have the consent form read to them. Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe will be done to you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form. The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form. Study procedures will then begin. The informed consent process for each individual subject will be documented in the subject's medical record.

As part of the consent process, the potential subject will be first offered enrolment in the randomized portion of the trial. The absence of current clear clinical guidelines, the paucity of high quality evidence, and summary of current understanding of this condition will be presented to the patient. The potential for clinical equipoise between treatments will be explained to the patent. The option of randomization will be presented at the same time as the option for enrolment in the non-randomized, prospective cohort portion of the study. Equal weight will be given to both options. The patient and/or caregiver will be given assurance that no difference in the standard of care or attention to the patient's condition will be given if the patient chooses to be randomized, to participate in the observational cohort, or not to participate in the study at all. Adequate time will be given to the patient to weigh the various options involved in participation in the study.

The time between obtaining written consent and initiation of study procedures (i.e. treatment) will be less than 12 hours.

6. Will subjects sign a consent form for any part of the study? Yes

7. Will the study procedures be started the same day the subject is recruited for the study? Yes

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

The treatment for this condition requires an urgent/emergent procedure or initiation of treatment and may not be delayed for more than 12 hours.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.

In order to ensure that the potential subject has enough time to make an informed decision, either the consent form will be reviewed in full with the patient/surrogate as outlined above, with time

allowed for the patient to think of any questions about participation and with for these questions to be fully answered. The patient/surrogate will be offered extra time to review the documents and discuss with his/her family or care partners prior to discussion of enrollment or requesting signature of the consent form.

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees? Yes

If yes, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

All subjects will be given the opportunity to discuss with, or review the consent documentation and trial materials with family, care partners or surrogate decision maker prior to signing the consent form for participation in the study. Social work and Neurosurgery Clinical Trial Office will be involved to ensure the patient is able to attend scheduled follow up clinic visits and that the cost of medications, ongoing physician visits and follow-up scans, which are part of the standard of care, are not prohibitive.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No

APPENDIX: Safeguards for Cognitively Impaired

1. What additional safeguards that will be employed to protect the cognitively impaired subjects?

- Use of a Surrogate decision-maker when permitted by law, i.e. a legally authorized representative via use of power of attorney/advance directive for research.

2. The following steps will be taken to determine the capacity of a potential subject to give consent for themselves.

A. If there is concern that a potential subject/ subject may be cognitively impaired a determination of incompetence will be made after an evaluation by a person with the appropriate expertise to make such a determination as delegated by the PI. If the subject is a patient in the UVa Medical Center, the Medical Center Policy No. 0024 will also be followed. The determination of competency must be documented in writing.

B. The following methods below will be used to determine capacity for consent:

__X__ Subject is also a patient in the UVa Medical Center and Medical Center Policy No. 0024 will be followed.

__X__ Will rely on individual observation of and interaction with the potential subject as well as the opinion of the medical provider or caregiver, when available. The prospective subject should demonstrate competence in relation to the proposed study in order to be judged capable of providing informed consent for that study. In general, an assessment an individual's capacity to consent will be based on her/his:

- Ability to communicate a choice;
- Ability to understand relevant information;
- Ability to appreciate the nature of the situation and its likely consequences; and,
- Ability to manipulate information rationally (1)

___X__The individual's abilities will be assessed by discussing the proposed study with her/him and then asking specific questions. Such questions may include:

- Can you tell me what will happen if you agree to take part in this study?
- How might this study help you?
- How might this study not help you, or even hurt you?
- Do you have to be in this study?
- What would you do if you wanted to leave the study?
- What will happen if you decide not to be in the study?

C. An individual will be considered unable to provide consent if he or she has:

- An inability to express or communicate a preference or choice (cannot make up his/her mind, is comatose, or has severe psychotic thought disorders, etc.);
- An inability to understand a situation and its potential consequences as well as the impact of study participation on those circumstances (does not understand that he/she may be hurt or may not be helped or cannot distinguish research from treatment); and/or,
- An inability to provide a logical rationale for participation/no participation in a study (cannot address risk/benefit-related reasons for or against participation in a study.

_____ Other- *Explain*

3. The following steps will be taken to document the determination of competency to consent.

__X___ A note to file will be written and filed in the study files and/or medical records to describe the consenting process. The note will include a description of methods used to determine capacity of the subject to consent. The note should also include the name of the person determining competency of the subject. May use the SOM CTO form Determination of Capacity to Consent.

_____ Other *Explain:*

4. When will subjects capacity to consent be assessed?

__X___ Prior to initial consenting process if there is a concern that the potential subject has a cognitive impairment. *Must be checked for all protocols.*

___X__ On a periodic basis throughout the study process if there is a concern that the potential subject has a cognitive impairment. . *Explain:* The patients in this study have the potential to become impaired due to their underlying medical condition worsening; due to the onset of seizure; due to other complications of medical or surgical treatment. Due to this potential, subjects will be evaluated each day by residents in the course of regular neurosurgical care, and any change in mental status will be recorded. If any further intervention is required for these patients, surrogate decision makers will be utilized as outlined above in accordance with Medical Center policy.

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?

Drug name: dexamethasone
Manufacturer: Roxanne Pharmaceuticals (current manufacturer, as used by UVA Health System, as of 11/2013)
IND# - SOM CTO letter on file—IND exempt

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?
N/A

3. What is the phase or stage of this study?

This is a Phase IIb study.
The study is not being used for changing the labeling or indication of the investigational drug, which will be used off-label in this study. The study is designed to test efficacy, but will not be used to provide physician labeling (i.e. Phase III study).

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?
Dexamethasone

2. Where will the subjects be seen for the administration/dispensing of the drug?
__X___ Inpatient Unit: *specify:__6 West; neurosurgical floor or Neurosurgical ICU___*

3. What dose will be utilized in this study?

Table 2. Proposed Dexamethasone Dosing Schedule

Dose	Duration	Total Doses
4mg q8h	3 days	9
4mg morning / 2mg midday / 2mg qHS	3 days	9
2mg q8h	3 days	9
2mg q12h	3 days	6
2mg qD	3 days	3

4. What will be the frequency of dosing in this study?

Table 2. Proposed Dexamethasone Dosing Schedule

Dose	Duration	Total Doses
4mg q8h	3 days	9
4mg morning / 2mg midday / 2mg qHS	3 days	9
2mg q8h	3 days	9
2mg q12h	3 days	6
2mg qD	3 days	3

5. What will be the duration of dosing in this study?

Table 2. Proposed Dexamethasone Dosing Schedule

Dose	Duration	Total Doses
4mg q8h	3 days	9
4mg morning / 2mg midday / 2mg qHS	3 days	9
2mg q8h	3 days	9
2mg q12h	3 days	6
2mg qD	3 days	3

Total days of treatment: 15

6. What route of administration will be utilized?

All patients able to take PO medication will be given PO tablet form of the medication. For patients unable to take PO medication due to mental status or other comorbidity, IV dexamethasone will be used until able to take PO medication or a feeding tube or PEG tube is placed, at which time PO medication will be dispensed per NG tube.

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?

_____ YES
___X__ NO- Drug will be prepared and/or administered per package insert

7a. Concentration

___X__ Standard
_____ Non- Standard- *specify*

7b. Diluents

___X__ Standard
_____ Non- Standard- *specify*

7c. Stability after prepared

__X___ Standard
_____ Non- Standard- *specify*

7d. Special storage requirements
___X__ Standard
_____ Non- Standard- *specify*

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? No

10. How will missed doses be handled?

Missed doses while inpatient will be recorded in the study database, but the dose schedule will not be adjusted to compensate for missed doses.

Compliance with the drug regimen will be confirmed through examination of the medication administration record while patients are hospitalized, and through clinical interview with the patient and care partner at all subsequent clinic visits. This data will be recorded as part of the study protocol.

11. Will a comparator (active or placebo) be utilized in the protocol? No

12. Does this study involve research on a drug, biologic, supplement or food additive? Yes

►IF YES, is this study investigator initiated?
Yes

13 Are you using a drug/supplement/ food additive in a manner not approved by the FDA? Yes

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

Dexamethasone is a synthetic glucocorticoid with minimal mineralocorticoid effects, which is 6.7 times as potent as prednisone, and 26.7 times as potent as hydrocortisone. It is commonly used in oncology patients as an anti-edema agent in CNS tumors and as a chemotherapeutic agent in hematologic malignancies such as multiple myeloma. The agent is also used for a wide range of other clinical purposes including some patients with adrenal insufficiency, glucocorticoid resistance, altitude sickness, pulmonary edema, and in obstetrics for fetal lung maturation.

The effect of dexamethasone on chronic subdural hematoma is thought to be through its effect on dissolution of clot membrane and decrease in neovascularization (7-9). Glucocorticoids block inflammatory mediators such as lymphokinins and prostaglandins, thus blocking neo-membrane and neo-capillary formation (2, 1, 8). These agents also induce secretion of plasminogen inhibitor, which reduces VEGF expression, a factor that has been found on external membranes of cSDH and is involved in angiogenesis and may extend the cycle of rebleeding and lysis that causes enlargement of cSDH (2, 1, 9). In a rat model, corticosteroid treatment has been shown to decrease the size of chronic SDH.

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

Corticosteroid treatment for cSDH has been proposed based on the anti-angiogenic properties of steroid treatment and its anti-inflammatory properties. This treatment strategy has been reported in retrospective case series and case reports in the literature (2,10-16). In the largest of these series, favorable results were seen in 71/73 patients (97.2%) exclusively managed with dexamethasone, and surgical drainage was required in 21.8% of patients initially treated with dexamethasone (2). In another series, pre-operative dexamethasone was associated with improved outcome in multivariate analysis, without increased incidence of complications (21).

No optimal dosing schedule for corticosteroid treatment of cSDH has been outlined in the literature (Table 1).

Table 1. Dosing Schedule of Dexamethasone Treatment for cSDH in Prior Studies

Study	Dexamethasone Dosing Schedule
Delgado-Lopez (2)	4mg q8h x 48-72h, then clinical re-assessment and if no surgery, taper 1mg per day to off
Sun (16)	Primary dexamethasone group: 4mg QID x 21 days Dex + Surgery group: 4mg QID, drainage within 48h, then dexamethasone taper to off over 2 weeks
Berghauser Pont (21)	4mg QID, followed by surgical drainage within 48h, then dexamethasone taper "in a pace dependent on the duration of preoperative use"
Rudiger (14)	4mg BID for 6 weeks

13c. Have there been any human deaths associated with this drug?

None have been reported

13d. In how many humans has this drug been used previously?

This drug is used in an estimated 5,000 neurosurgical patients per year in the U.S.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.

N/A

14. Do the following criteria apply?

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

The use of dexamethasone for the treatment of chronic subdural hematoma is not anticipated to materially change the safety for the overall use of this product in neurosurgical patient population.

___X_ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and

___X_ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)

15. Is this a post-marketing study? No

►IF YES is the study required to be done by the FDA?

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1a-1e) to describe your/central registry's plan to protect the identifiable data from improper use and disclosure.

1a. How will data be stored?

__X___ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.

1b. Will specimens be stored by the UVa study team?No

1c. Will any of the data be stored electronically by the UVa study team?Yes

►IF YES, will it include any HIPAA identifiers with health information or other highly sensitive data?

Yes

►IF YES, where will it be stored?

__X___ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

1d. Will any of the data be collected or stored in hard copy format by the UVa study team (*e.g.- on paper*) ? Yes

►IF YES, where will it be stored?

__X___ case report forms will be stored in a secure area with limited access.

__X__questionnaires/ surveys will be stored in a secure area with limited access.

1e. The following procedures will also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential.
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.
  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection. Identifiable data is considered to be "Highly Sensitive". A Limited Data Set is usually considered to be "Moderately Sensitive" and de-identified data is usually considered to be "Not Sensitive".
- If identifiable data (*data with health information and HIPAA identifiers*) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and UVa Institutional Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

- LIMIT- Limit the HIPAA identifiers to the minimal amount needed- e.g. use initials instead of name, use a code instead of initials, limit amount/type of health information collected, and collect and share only those items you state you will in this protocol.
- SECURE- Secure Highly Sensitive Data
  - Because single-use electronic devices and media, such as desktops, laptops, memory sticks, CDs, smartphones etc., can be easily lost or stolen, the University strictly limits the circumstances under which Highly Sensitive Data may be stored on them. In accordance with the University's Electronic Storage of Highly Sensitive Data Policy, you must obtain written approval from your Department AND VP or Dean prior to moving data to single use devices or media by using the Highly Sensitive Data Storage Request Form.
    - *You additionally are responsible for applying all security safeguards covered in that policy, including but not limited to password protecting and encrypting any document on a single access electronic device.*
    - *If you use your smartphone to send email and your phone is not managed was not purchased and/or set up for you by the Health System, you cannot send Highly Sensitive Data via email.*
      - *In addition, do not use Outlook Web to send your email if it contains sensitive data.*
      - *Also, you are not allowed to auto forward your email to outside email systems like Gmail or Yahoo.*
      - *Do not save any email attachment containing Highly Sensitive Data to a single use device.*
    - *You are allowed to access Highly Sensitive Data stored on the University or Health Systems network via a VPN, however you cannot download any of the information onto your desktop or laptop.*
    - *Store files containing Highly Sensitive Data on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the "F" and "O" managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive.*
    - *If data will be collected and/or viewed via a website, it is critical that the website and associated data file are set up in a highly secured manner. Do not attempt without assistance from:*
      University Side: ITCmicrosystems@virginia.edu
      Health System: Web Development Center: (434-243-6702)
  - Encrypt any electronic file containing Highly Sensitive Data that is not on a network drive specifically designated for this purpose. . *See encryption solutions guidance.*
  - Password protect any electronic device containing Highly Sensitive Data.
  - Lock up hard copies of Highly Sensitive Data.
- PROTECT- Protect Highly Sensitive Data
  - Do not leave a hard copy file open on your desk when not using it and secure your computer when not attended.
  - Have discussions in private.
  - If you lose Highly Sensitive Data, you must report it in accordance with the Information Security Incident Reporting Policy.

- Do not share Highly Sensitive Data with those not on the study team or those who do not have a need to know.
- Do not share with sponsor unless subject has already signed a consent form or IRB has approved waiver of consent.
- If faxing Highly Sensitive Data within UVa
  - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
  - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
- If faxing Highly Sensitive Data outside of UVa to the sponsor or CRO after the subject has signed consent:
  - the receiving fax machine is in a restricted-access location,
  - the intended recipient is clearly indicated,
  - the recipient has been alerted to the pending transmission and is available to pick it up immediately.
  - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
  - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
- Highly Sensitive Data may not be stored in a Drop Box.
- If you plan to store data in the Cloud, you must consult with UVa Information Technology Services (ITS) to verify all essential security measures are in place. If you have a contract to use the cloud, the contract must include required security measures as outlined by ITS.
- DO NOT email health information with name, medical record number or Social Security number to or from an email address that does not have an *HS in the address. May use subject initials if within the UVa HIPAA covered entity: The "UVA HIPAA covered entity" includes the hospital, health system, School of Medicine School of Nursing and the VP for Research Office.
- Be aware: PHI collected without consent/ HIPAA authorization will NOT be allowed to leave UVa in an identifiable form unless the disclosure is tracked with Health Information Services.
- Any Highly/Moderately Sensitive Data sent outside of UVa (e.g. to sponsor) that was obtained under a consent must be encrypted and password protected.
- If your electronic device is sent outside of UVa for repair, all institutional data, whether Highly Sensitive or not, must be either encrypted or removed.
- If transporting Highly/Moderately Sensitive Data in paper format from one UVa building to another, take the following steps to protect it:
  1. Put paper inside a closed container such as a briefcase, or sealed envelope to limit the chance of a losing a piece.
  2. Do not leave Highly Sensitive Data unattended in a public area if it is not locked up.

  - When the study is complete, all electronic files containing Highly/Moderately Sensitive Data must be stored on a network drive specifically designated for that purpose. They may not be stored on a single use device such as a CD.
- STOP, THINK and BE CAREFUL-
  - If this was your Highly Sensitive Data how would you want it protected?
  - There are significant monetary fines to the individual and the institution for loss or misuse of sensitive data.
  - Your job may also be on the line.

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

__X___ The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete.
This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes

This means that after the study is closed at UVa:

- *You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval*
- *You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)*
- *You cannot share your research data with another researcher outside of your study team without additional IRB approval*
- *Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.*

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints

16. Full face photographic images and any comparable images
17. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)