PROTOCOL TITLE:

Clinical Action of Curcumin/Turmeric In chronic Subdural hematoma recurrence (CACTIS)

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
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Is this a clinical trial under ICH-GCP E6? ☐ *Yes* ☒ *No*

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☐ *Yes* ☐ *No*

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser:
http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

Our long-term objective is to evaluate the efficacy of curcumin (CC) in preventing a recurrence of chronic subdural hematoma (cSDH) following surgical evacuation. Recurrence is defined as an increase in total hematoma volume on the operated side compared to a post-operative day one CT scan with persistent or recurrent neurological symptoms. We propose this pilot study to assess feasibility and obtain preliminary benefit assessment of the proposed therapeutic approach.

Objective 1: To determine if the use of CC treatment reduces the total hematoma cavity volume over a 6-month interval, compared to a post-subdural drain removal CT scan. This evaluation is expected to offer sufficient evidence for a larger definitive trial.

Objective 2: Study the effect of CC on interleukin-8 (IL-8)-induced disruption of endothelial permeability *in vitro* using human vascular endothelial cells.

Central hypothesis: CC treatment prevents the re-accumulation of cSDH, which may occur by inhibition of IL-8 and allowing resolution of the total hematoma cavity volume over six months.

2. Background

Chronic subdural hematomas (cSDH) are extra-axial fluid collections in the cranium that can result in brain compression and neurological decline. cSDH commonly occurs after traumatic brain injury (TBI); though, many times there is no history of trauma. The incidence of cSDH is expected to significantly rise, due to an increasing elderly population worldwide. This is a common and challenging neurosurgical problem due to their ability to recur requiring repeated surgical re-evacuation. Repeat surgery comes with additional morbidity as well as rising costs for both patients and hospitals. The literature reported recurrence rates ranging from 2.3% to 33%.[8,29,32,40]

We recently completed a retrospective review of 147 chronic unilateral, subdural hematomas and 75 chronic bilateral subdural hematomas at our institution from 2007-2014 (IRB#14-160). The data show that 15.65% of the unilateral group and 9.33% of the bilateral group showed recurrence.[17] Operative decompression is the treatment of choice; however, an effective therapy preventing recurrence of cSDH after surgical intervention has not yet been found. Our long-term goal is to develop a therapeutic approach focused on the prevention of cSDH recurrence after initial surgical intervention.

cSDH is characterized by encapsulation of the subdural hematoma within newly developed membranes mostly associated with aberrant neomembrane neovascularization through inflammatory processes. Current research efforts have been targeted at investigating the composition of cSDH fluid. Angiogenesis growth factors, inflammatory cytokines and matrix metalloproteinases (MMP) are believed to play a critical role in increased microvascular leakage and hemorrhage.[38] We previously showed that samples of subdural hematoma fluid (SDHF) from cSDH patients contained several molecules significantly upregulated compared to venous blood. These included stromal-derived growth factor-1 (SDF-1), vascular endothelial growth factor (VEGF), and metalloproteinase MMP-9. These results led to our search for the upstream regulators of these molecules that could be targets for cSDH therapy.

We found that the pro-angiogenic and pro-inflammatory cytokine **interleukin-8** (IL-8/CXCL8) was elevated by more than 300 times in SDHF but restricted to SDH, not systemically.[38,39] Frati et al. reported that increased levels of the inflammatory cytokines IL-6 and IL-8 were correlated with cSDH and possible key stimulators of inflammation and hemorrhage during cSDH progression.[7]

IL-8 is implicated in a wide variety of clinical disorders, including cancer, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and cystic fibrosis, which prompted an intensive search for neutralizers and inhibitors of this cytokine. Numerous investigations have identified curcumin as a

potent inhibitor of IL-8.[1,3,14] **Curcumin**, a polyphenolic compound derived from the dietary spice turmeric, possesses diverse pharmacologic effects, including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic activities. Various animal models and human studies proved that curcumin is extremely safe, even at very high doses.[11] Numerous research investigations identified the compound curcumin as a potent inhibitor of IL-8 production and signaling.[10] Thus, this could be regarded as a safe over-the counter remedy for targeting IL-8-initiated pathological conditions.[5]

"Some promising effects have been observed in patients with various pro-inflammatory diseases including cancer, cardiovascular disease, arthritis, uveitis, ulcerative proctitis, Crohn's disease, ulcerative colitis, irritable bowel disease, tropical pancreatitis, peptic ulcer, gastric ulcer, idiopathic orbital inflammatory pseudotumor, oral lichen planus, gastric inflammation, vitiligo, psoriasis, acute coronary syndrome, atherosclerosis, diabetes, diabetic nephropathy, diabetic microangiopathy, lupus nephritis, renal conditions, acquired immunodeficiency syndrome, β-thalassemia, biliary dyskinesia, Dejerine-Sottas disease, cholecystitis, and chronic bacterial prostatitis."[10] It has also been found to directly inhibit the production of the pro-inflammatory, and pro-angiogenic chemokine IL-8 (CXCL8), Vascular Endothelial Growth Factor (VEGF), and basic Fibroblast Growth Factor (bFGF). This discovery has led to additional research in the oncology field for potential clinical uses of this herb. With the current literature indicating the role of IL-8 in subdural hematoma expansion, our hope is to evaluate the role of curcumin in the prevention of cSDH expansion and recurrence.

Inflammatory Markers

Suzuki et al. and Stanisic et al. conducted independent studies investigating inflammatory markers found locally at the site of chronic subdural hematomas, as well as systemically through the peripheral venous blood. Both groups' papers concluded that the concentration of inflammatory markers is significantly elevated within the subdural hematoma cavity when compared to peripheral blood samples.[38,39] Suzuki et. al. measured IL-6 and IL-8 to be 10-times higher in the fluid of chronic subdural hematomas compared to subdural effusion patients.[1]

Stanisic et al. also investigated the concentration of both pro-inflammatory and anti-inflammatory cytokines in the chronic subdural hematoma fluid compared to the systemic circulation. The objective of his study was to demonstrate that not only are pro-inflammatory markers (IL-2R, IL-6, IL-7) elevated within the subdural fluid but that the ratio of pro-inflammatory to anti-inflammatory markers (IL-10, IL-13) is elevated within this subdural hematoma fluid as well. They concluded that there is a poorly coordinated innate immune response within the chronic subdural hematoma cavity, which leads to an abnormally increased inflammatory response. This ultimately leads to the formation and progression of chronic subdural hematomas.[38]

Frati et al. evaluated whether local inflammation within the subdural hematoma cavity was a risk factor for the recurrence of posttraumatic chronic subdural hematomas. Although the authors were more interested in measuring the inflammatory markers locally within the hematoma site; their conclusion that high levels of inflammatory cytokines (IL-6 and IL-8) were statistically correlated with recurrence of the hematoma is extremely relevant to our area of interest.[7]

A South Korean study chose to investigate the components of both the chronic subdural hematoma fluid as well as their outer membrane in 66 patients that underwent burr-hole hematoma drainage. They found a statistically significantly increase in the concentration of IL-6 within the hematoma fluid of patients that had a recurrence. In addition, they found a significantly stronger immune-histochemical staining of VEGF and bFGF within the outer membrane of hematomas that recurred compared to the non-recurrence group. This study demonstrated that IL-6 within the hematoma fluid and VEGF and bFGF in the outer membrane are direct risk factors for the recurrence of cSDH.[15]

Hidaka et al. conducted a study looking at CC effects on the production of IL-8, and ultimately, its impact on NF-kappaB activation and human pancreatic carcinoma cell growth. The authors found

that the production of IL-8 was inhibited by curcumin in a dose dependent manner. Additionally, it was found that CC inhibited IL-8 induced receptor internalization as well. These two findings were significant for the author's investigation into tumor cell growth. More relevant to our interest, it demonstrated that CC inhibits the inflammatory response of IL-8 through a decrease in its production and an inhibition of IL-8 induced receptor internalization.[14]

It should first be noted that IL-8 is a known angiogenic factor, and the previous papers mentioned above showed increased IL-8 within the cavity of chronic subdural hematomas.[7,38,39] CC has also been found to have anti-angiogenic properties as well. By proving curcumin's inhibitory effect on IL-8, current research has already suggested that CC is an anti-angiogenic molecule. Three additional papers investigated this anti-angiogenic activity directly. Bhandarkar et al. found that CC directly down regulates the activity of both VEGF as well as bFGF, while also inhibiting multiple signal transduction pathways that are involved in angiogenesis.[3] Another study, conducted in Boston by Arbiser et al. also found that CC significantly inhibited bFGF-mediated corneal neovascularization in mouse models.[1] The molecular mechanisms of curcumin's anti-angiogenic effects were investigated by Gururaj et al. who found CC to have a direct time-dependent and dose-dependent inhibition of VEGF at the level of gene expression. In their study; however, CC was directly injected into the intra-peritoneal cavity of mice. This was not only found to not be cytotoxic, but it also reduced ascites by 66% in mice with Ehrlich ascites tumor cells. Though this is just an initial mouse model, it may be one step closer towards understanding the non-cytotoxic effects of CC for future research.

Brain Injury

CC has demonstrated promising results in multiple studies related to brain injury including intraparenchymal hemorrhage, acute stroke, subarachnoid hemorrhage, and general injury to the blood-brain-barrier.[16,20] 6 hours following intracerebral hemorrhage in adult mice, curcumin was administered in clinically relevant doses of 75-300 mg/kg. After 72 hours, there was a reduction in hematoma size, decreased vasogenic edema secondary to a less damaged blood-brain-barrier, decreased inflammatory markers, and overall improved neurological outcome.[16] After discussing the role of T-lymphocytes in contributing inflammation and worsening neuronal injury, mouse models were used to demonstrate a suppression of T-lymphocyte infiltration in the brain after administration of curcumin. There was also a reduction in cerebral edema and improvement of neurological scores.[20] One study administered low dose (80mg/day) curcumin to healthy middle-aged adults (40-60 years of age), when compared to a placebo group. The CC group had lower levels of plasma triglyceride, salivary amylase levels, plasma beta amyloid protein concentrations (protein responsible for Alzheimer's disease and other forms of intracerebral hemorrhage), and other beneficial health effects.[5]

Alzheimer's Trial

Several studies evaluating the possible protective properties of CC in Alzheimer's disease have been published.[30] CC, commonly found in Indian spices, is hypothesized to be part of the low incidence of Alzheimer's disease in Indians. A study published by DiSilvestro et al. demonstrated that **80 mg of CC daily** decreased the plasma levels of beta-amyloid, the main component in the amyloid plaque found on histopathology of Alzheimer patients.[5] Currently, a phase II study (NCT01001637), using positive results from animal models, is following Alzheimer's patients for 6 months, with either a **2,000-3,000mg BID dose of curcumin** versus the placebo. Animal models have already demonstrated significantly reduced memory deficit with curcumin administration.[13,21] Much of their current research is at targeting a formulary form of CC that can cross the blood brain barrier. Fortunately, in our population of patients with chronic subdural hematomas, we assume that their blood brain barrier is leaky from the presence of inflammatory markers that contribute to the recurrence of the hematoma. Our capsule contains 270 mg of pure curcuminoids (curcumin) and 3mg of black pepper extract. The recommended serving size is 3 capsules a day. Therefore, the patients will receive **810mg of pure curcumin** and 9mg of black pepper extract (pepperine) per day.

Curcumin with Piperine

It was recently detected that combining CC with piperine (black pepper extract, also known as pepperine or BioPerine), a known inhibitor of hepatic and intestinal glucuronidation, enhances the serum concentration, extent of absorption and bioavailability of CC in both rats and humans.[35] Srinivasan wrote an exhaustive review of the physiological effects of piperine and found that previous reported concerns were based on questionable reports, and it is in fact safe for human consumption.[36] Myers et al demonstrated that gastric bleeding was no different than that from aspirin, and this was in higher doses of pepper consumption.[25] Therefore, CC supplement is now used in combination with the black pepper extract (Appendix 1).

Black pepper/piperine is listed under the FDA as being safe (Appendix 2).[23] The average amount of pepper consumed by a person during a day in the United States is 359 mg, which translates to 18-32 mg of piperine a day. Furthermore, rat trials show a daily intake of 5 to 20 times the average daily dose of humans produced no clinical symptoms. Furthermore, studies on acute, subacute, and chronic piperine toxicity show no abnormalities or clinical symptomatology, or significant blood chemistry data in laboratory animals. Black pepper extract has a high degree of safety being used nutritionally. The amount of piperine that is formulated in the curcumin capsules is several thousand times less than the LD_{50} established in mice and rats.[22] Our capsule contains 270 mg of pure curcuminoids (curcumin) and 3mg of black pepper extract. The recommended serving size is 3 capsules a day. Therefore, the patients will receive 810mg of pure curcumin and **9mg of black pepper extract** (pepperine) per day, which is less than the average amount of pepper consumed by a person daily in the United States.

CT Scans

The use of CT scans to evaluate the volume of hemorrhage in cSDH patients is the standard of care. At our institution, it is standard practice to obtain a minimum of three CT scans over the course of surgical management of a cSDH. The **first CT scan** is obtained pre-operatively to characterize the subdural and determine subsequent management. In patients who receive surgical evacuation, a **post-operative scan (second scan)** is performed to demonstrate adequate drainage of the fluid, improvement in midline shift, and to assess for new hemorrhages or strokes. If a subdural drain is placed intra-operatively, a **third scan** is obtained within 24-hours of subdural drain removal. One study on acute subdural hematomas (aSDH) reported an average of 4.3 CT studies per patient during their hospital stay.[34] There is extensive empirical evidence that strongly supports the correlation between pre-operative imaging and pre-and post-operative neurological data and the risk of rebleeding regardless of drain placement and removal.[12,26,27,33,41] Most researchers agree that the drain removal procedure is risky, but there is no clear consensus on what exactly defines this risk; therefore, a post-operative scan is felt to be advantageous to document the formation of new hemorrhage, hemorrhage as fragile brain tissue and vasculature may be disturbed.[4,33]

In a study by Stanisic et al. evaluating the use of CT imaging to predict postoperative recurrence of cSDH, the authors determined three predictors of recurrence: **preoperative volume of the hematoma**, CT density, and **residual total hematoma cavity volume** (fluid and pneumocephalus) based on post-subdural drain removal CT scan.[37] This group performed a pre-operative CT scan (**scan one**), a post-operative scan within 24 hours of surgery following drain removal (**scan two/three**), and **monthly interval** scans until complete disappearance of the fluid collection, for up to 7 months. **Relapse** was defined as increased total hematoma cavity volume on the operated side compared to a post-operative day 1 CT scan, with persistent or recurrent neurological symptoms. This group found that in patients with a pre-operative hematoma volume of less than **115cc**, the probability of no recurrence was 94.4%. In patients with a post-operative subdural drain removal scan that demonstrated a residual total hematoma cavity volume of less than **80cc**, the probability of no recurrence was 97.4%.

Interestingly, the group also found that in the patients who had complete disappearance of the residual cSDH, this could be seen by **120 days (4 months)**.

In another study evaluating 986 cSDH cases status post evacuation, their protocol included repeat CT scans 6 and 12 weeks after discharge to evaluate for and residual hematoma.[31] They defined recurrence of the cSDH, if the hematoma cavity volume increased within three months of surgery but no specific measurements were provided. All patients in this study were followed for three months following surgery. The **Markwalder grading score** (MGS) was used as a measure of patient's neurological status.

Lin et al. published an article on utilizing hematoma density to assess post-operative recurrence in cSDH patients.[19] In these patients, CT scans were completed 24 hours following surgery, similar to our institution, and on monthly intervals for up to 6 months and only discontinued if complete disappearance of subdural collection was observed.

Utilizing Stanisic et.al findings, our protocol will only include patients with a pre-operative hematoma volume of **115cc** or greater. Similar to this group, we will perform monthly interval CT scans until the total hematoma volume is measured to be less than **80cc**[37] our working definition of resolution. At this point, we will determine that the patient has met criteria for **resolution** of the cSDH and would not require further imaging. If the patient demonstrates a neurological change or increased volume, an earlier CT scan will be performed, regardless of volume size.

Conclusion

The current literature and our own preliminary data have demonstrated that there is local elevation of pro-inflammatory chemokines and pro-angiogenic factors within the subdural hematoma cavity of chronic subdural hematomas that are not found systemically. CXCL8 (IL-8) demonstrates both pro-inflammatory and pro-angiogenic properties. Curcumin has shown to directly inhibit the production and activity of CXCL-8 (IL-8) *in vitro* and *in vivo*, as well as down regulating the activity of VEGF and bFGF. These combined effects make CC an important anti-inflammatory and anti-angiogenic molecule that has the potential to reduce the recurrence rate of chronic subdural hematomas. We expect that CC will prevent/reduce persistent hemorrhage within the subdural hematoma cavity, by blocking IL-8-induced disruption of the blood vessels. Specifically, CC is expected to preserve blood vessel leakage and accumulation of blood in SDH cavity, by blocking destructive effect of IL-8 on the vascular endothelial tight junctions.

3. Study Design

This is a *double-blinded, randomized placebo-controlled pilot study*. The patients, neurosurgeons, nurses and clinical coordinators will be blinded except for the research pharmacists who will keep a key linking a code # on a bottle handed to the clinical coordinator and the patient's MRN #. The pill bottles handed to the clinical coordinator will be identical for placebo and CC.

Study Type: Interventional
Study Design: Randomized Treatment assignment
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigators, coordinators, nurses)
Primary Purpose: Treatment
Intervention:
1) Curcumin (turmeric extract), over the counter supplement (1 capsule/three times a day).
Producer Company: Oregon Wild Harvest

The dosage used for the patients is based on the amount recommended by the producer Company (and approved by FDA). According to the Company, each capsule contains: 270 mg of pure curcuminoids (curcumin) and 3 mg of black pepper extract. Recommended serving size is 3

capsules per day. In total, the patients will receive **810 mg** of pure curcumin and **9 mg** of black pepper extract (pepperine/BioPerine) per day.
The active Curcumin/Bioperine capsules will be over encapsulated with the orange size 00 vegetarian capsules so that they cannot be distinguished from the placebo capsules.

2) Placebo (1 capsule/three times a day).
Producer: Investigational Drug Services
IDS will prepare the placebo capsules by placing the cellulose directly into the orange size 00 vegetarian capsules so they are indistinguishable from the curcumin/bioperine pills.

- ## Inclusion and Exclusion Criteria

3.1. Eligibility Screening

All patients with unilateral cSDH that are being consented for evacuation during their hospital stay will be evaluated for eligibility screening. No history of head trauma is required.

3.2. Inclusion Exclusion Criteria:

3.2.1 Inclusion criteria

Chronic subdural hematoma (cSDH)

- Age of 18 years old or older
- Unilateral cSDH with no other intracranial injuries
    - Membranes with minimal hemorrhage may be included but no clear acute component should be evident
- Subdural volume ≥ 115cc
- MARWALDER GRADING SCALE [24]
    - Score of 0-2
- Patient or patient's POA available to sign consent
- Patient undergoes **surgical** evacuation of cSDH

3.2.2 Exclusion criteria

- Age < 18 years old
- Bilateral subdural hematomas
- Subdural volume < 115cc
- Acute subdural hematoma
- Patient does not undergo surgical evacuation
- Other evidence of intracranial injury (i.e. epidural hematoma, intraparenchymal hemorrhage, skull fractures, subarachnoid hemorrhage, hydrocephalus)
- Patient's family not available for consent and requires emergent surgical evacuation
- Previous intracranial surgery
- Recent head trauma (<1 week)

- Use of anti-coagulation (i.e. Coumadin, Heparin, Apixiban, and Rivaroxiban) or anti-platelets (Plavix) drugs, with the exception of Aspirin
- Known coagulopathy disorders
- Positive urine or serum pregnancy test in pre-menopausal female subjects, without a documented history of surgical sterilization; or currently breastfeeding

1.1.1.□.1. Since the nuclear group in an older population, the pregnancy test will be made in exceptional cases.

- Allergy to curcumin or turmeric.
- Allergy to black pepper
- Markwalder Grading Scale

1.1.1.□.1. Score: 3-4

- Baseline dementia (for more than 6 months).
    - Adult who cognitively impaired for more than 6 months will be excluded from the study, since this impairment might be due to other reasons than cSDH, such as dementia or cognitive impairment.

4. Number of Subjects

This is a single center pilot study. A total of 48 subjects will be recruited in this study.

24 patients will receive placebo pills, and 24 will receive Curcumin (CC) pills. Patients will be first stratified according to their pre-surgery hematoma volume. Randomization will be performed within each hematoma volume group (12 subjects per hematoma volume group) to ensure equal distribution between placebo and CC groups.

Study Timelines

- Duration of an individual subject's participation in taking CC or placebo will be for up to a maximum of 60 days, with follow-up at 6 months and 18 months
- Clinical follow-up with CT scans will be up to 6 months, depending on if residual total hematoma volume< 80cc
- Enrollment of subjects will continue for 2 years.
- Complete data analysis will be performed within 2 years.

cSDH patients will take one capsule three times a day for up to 60 days. Because maximum treatment duration is 60 days, IDS will dispense a total of 180 capsules. IDS will dispense this amount on two occasions to reduce waste and save cost for cases in which treatment may end earlyThey will undergo standard post-operative care in regard to imaging and clinical follow-up.

- Patients will begin taking placebo or CC ***within 24 hours*** post-operatively and able to take oral medication. It will then be continued TID.
- CT Imaging:
    - *Pre-operative CT SOC scan*
        - If the hematoma volume is < 115 cc, the patient will not be included in the study
    - *Post-operative day one CT SOC scan within 24 hours of surgery.*
    - *Post subdural drain removal SOC scan usually 1-2 days after surgery.*

        - If the residual total hematoma cavity volume is <80cc, the patient will be dropped from study, as the curcumin has not had time to influence the patient's reabsorption.
    - *During the SOC one week follow-up appointment without a CT scan*, the attending will decide on the need for a repeat CT scan in 4 weeks based on the patient's **post-subdural drain removal SOC scan**.
        - If the residual total hematoma cavity volume is **≥ 80cc**, the patient will receive an additional CT scan (SOC) for an appointment one month following the previous appointment (Approximately post-operative day 37)
        - If there is a decline in neurological exam or other clinical concern, the neurosurgeon may perform an earlier CT scan
    - This will continue on a monthly basis for 6 months, or until residual total hematoma cavity volume is < 80cc
        - **Resolution** will be defined as residual total hematoma cavity volume < 80cc
        - Patients with resolution of their hemorrhage will no longer require Tx or follow-up visits. Their pills will be returned and discarded.
          These patients will receive phone **call** follow-ups at 1-month, 6-month, and 18-month intervals

All radiographic imaging discussed here is our institution's standard of care for the management of SDH. If Tx discontinued, the patients will still be followed according to the schedule below

- Study Follow-Up **Phone Calls**
    - 1 month, 6 months, 18 months
        - Modified Ranking Scale (MRS) (Appendix 3)
        - Markwalder Grading Scale (Appendix 4)

5. Study Endpoints

5.1. Describe the primary and secondary study endpoints.

5.1.1. Primary: Change, rate of change, and time-to-resolution in total hematoma volume of cSDH compared to post-subdural drain scan of less than 80cc in post-surgical patients

5.1.2. Secondary: Recurrence rate of cSDH

5.1.3. Secondary: Markwalder and mRS progression.

5.1.4. Secondary: Rate of surgical intervention in CC and placebo groups.

5.1.5. Secondary: Rate of persistent or recurrent neurological symptoms in CC and placebo groups.

5.2. Safety Endpoints:

5.2.1. To assess the tolerability of CC in patients via frequency of any side effects, or adverse events as defined by the National Institute of Health's Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0)

5.2.2. Subject participation will be terminated if any reported adverse events, discomfort, or distress is detected.

6. Research Setting

This is a single center study that will take place at the University of New Mexico Hospital. New patients admitted directly to the UNM Neurosciences Intensive Care Unit (NSICU) as a transfer from

an outside hospital as well as patients admitted directly through the UNM Emergency Department (ED), with subdural hematomas will be identified and recruited as potential subjects. All surgical operations will take place in the main operating room (OR) at UNMH. The perioperative care of the enrolled patients, as well as the non-surgically managed patients will take place both in the NSICU as well as the Neurosurgical step-down unit.

Once patients have been discharged from the hospital, all follow-up appointments will take place in the Clinical Neurosciences Center located adjacent to UNMH. Patients will follow-up in the subdural clinic, staffed by **Dr. Howard Yonas**, Principal Investigator.

7. Resources Available

Dr. Howard Yonas is the chairman of the Department of Neurosurgery. He has been a part of the UNM faculty since 2005, and has significant experience with both the surgical/medical management of patients with subdural hematomas, as well as with oversight on research projects. Dr. Yonas is personally responsible for the development of the 24-bed Neurosciences ICU where neurosurgical patients are cared for, as well as the multidisciplinary Neurosciences center where patients are followed in an outpatient setting. **He will see all patients enrolled in the trial in his clinic.**

Dr. Yonas has participated in two clinical trials.

"Carotid Occlusion Surgery Study"
R01-NS421676 10/01/2001-
06/24/2010 Role: PI

"National Acute Brain Injury Study: Hypothermia II" (Multicenter Clinical Trial)
R01-NS43353 (PI: Guy Clifton, MD) 08/15/2002-06/30/2010
NIH/NINDS Role: Site PI

The other staff involved in the care of these patients includes Neurosurgery residents that have all received a medical degree and are currently training under the supervision of the attending physicians in the Department of Neurosurgery, midlevel providers (Nurse Practitioners and Physician Assistants) both in the NSICU and the step-down units, and resident physicians from other medical departments at UNMH that are rotating in the NSICU.

There is a resident physician from the department of Neurosurgery always present in the NSICU. All clinical data collected from patients is reviewed by a senior resident as well as an attending physicians both in the NSICU as well as within the Neurosurgical department. After review of the pertinent information (clinical exam, laboratory data, radiographs), the attending physicians makes the decision whether a patient requires surgical intervention or can be managed conservatively (i.e. medically with anti-epileptics and pain medications).

The Department of Neurosurgery has a group of clinical research coordinators and nurses that have all been trained on proper consenting techniques and are available to consent patients and assist with data collection for all studies for the department. They are on call 7 days a week from 6am to 10pm, which allows the coordinator and the PI to conduct consent and protocol initiation in a timely manner. The coordinators are also aware of the consent challenges with our specific population, as many times due to the degree of injury of the patient, the LAR must be contacted for consent.

Once the study begins, an informative lecture will be given to the Neurosurgery department providers (resident and attending physicians) as well as to the staff of the Neurosurgery research team, so that all team members are aware that the study is beginning, and what each of their roles in the study will be.

The department of neurosurgery mentor students from the school of medicine with their research requirements. In the event that we have a student acting as a research assistant with any part of the study, they will be formally added as a study team member and will complete all human subjects training requirements.

The laboratory research will be conducted by Dr. Tamara Roitbak's group. Dr. Roitbak, a Research Associate Professor in the Department of Neurosurgery, is an active investigator with expertise in cellular and molecular mechanisms of the regeneration following brain injury. Her research supported by the NIH R01 grant. As a study co-I, Roitbak will devote 30% of her time to research project described in the application.

- Proposed research analyses will be performed in the fully equipped laboratory and research facilities in the UNM BRaIN Center. UNM HSC Biostatistics Resource Facility provides a full assistance in data analysis and power calculations for all UNM investigators.
- The steps that will be taken to secure the data
    - Research nurse and/or research coordinator will remove all identifiers from the sample, and provide a specific code for a sample with date of surgery, and a unique identifier (i.e.: 16-252-01, 16-252-02, etc.)).
    - All other personal information about the patient (with appropriate coding number) will be confidentially kept by a research nurse.
- Data handling
    - Only the Research nurse and Research coordinator will have access to full patient information. A research team will receive the specimens with date of the surgery and appropriate coding (please see above).
- Data and Specimen storage
    - The patients' data will be stored by research Coordinator, until the data completion. Specimens will be transported on ice from the operating room to Dr. Roitbak's research lab. Specimens will be stored in Dr. Roitbak's laboratory freezer (-70^{o}C), until the completion of the study.
- Duration of storage: The data and specimens will be stored until study completion. A description of this study will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify subjects. At most, the Web site will include a summary of results

8. Prior Approvals

1. Signed departmental review is uploaded
2. Radiation Safety Form is uploaded
3. Biological Specimens attachment is upload.

9. Study Procedures

Patients who have symptomatic unilateral chronic subdural hematomas, with no acute component and do not meet the exclusion criteria, will be evaluated. At the time of consent for evacuation of the subdural hematoma, patients will also be consented for this trial by the research team. They will be instructed that they will be randomized to either the placebo group or the curcumin group. They will take one capsule three times a day for a maximum of 60 days. They will undergo standard post-operative care in regard to imaging and clinical follow-up.

Evaluation:

1. Patient evaluated by neurosurgery resident

2. Patient or POA consented by Neurosurgery resident for cSDH evacuation in the operating room.
3. Evaluated by research team for inclusion into trial within 48 hours of presentation to the Neurosurgery service
4. Consent patient or POA for trial participation

Interventions:

1. *Intra-operatively*, patient has samples sent to lab
    a. At least10 cc of subdural hematoma fluid will be collected during the initial and recurrence operative, along with 5 cc blood from an existing IV
    b. The SDH fluid and blood samples will be sent to Dr. Roitbak's lab and used in the experimental setup within 10-15 days of collection and in addition analyzed for inflammatory cytokines/chemokines.
2. *Presurgical randomization by stratified hematoma volume.* Presurgical hematoma volume randomization is important because recurrence of cSDH has been shown to be related to presurgical hematoma volume by Stanisic et al.[37] The hematoma volume and other CT characteristics are recorded as shown in **Table 1** below.
    a. Hematoma volume will be recorded and stratified into two groups according to hematoma volume: >140 ml and ≤140 ml. The process of stratification and subsequent randomization will be done by the IDS pharmacist who will conceal the randomization results from all study team members until after the results of the study have been analyzed.
    b. After the first patient is consented, we will record his or her hematoma cavity volume. All subjects will be assigned to a treatment group to receive either curcumin-containing or non-curcumin-containing capsules.
    c. For the next patient, we will first determine the hematoma cavity volume group; this patient's Tx assignment (CC or placebo) will be alternate to the immediately preceding patient. This process is repeated until all of the patients are enrolled.
3. The patients will start medication **within 24 hours after surgery**, or as soon as they are able to take oral medication
    a. 1 capsule three times a day (with breakfast, lunch, and dinner) for a maximum of 60 days or until resolution of subdural hematoma
    b. Resolution will be defined as residual total hematoma cavity volume < 80cc
        i. If the post-subdural drain removal scan demonstrates a residual total hematoma volume <80cc, the patient will not be included in the study sample; although, the patient may receive more than one dose of CC by the time of the CT scan.

- CT Imaging:
    - Pre-operative CT SOC scan-- If the hematoma volume is < 115 cc, the patient will not be included in the study
    - Post-operative day one CT SOC scan
    - Post subdural drain removal SOC scan--If the residual total hematoma cavity volume is <80cc, the patient will be removed from study, as the curcumin has not had time to influence the patient's reabsorption.
    - During the SOC 1 week follow-up appointment, the attending will decide on the need for a repeat CT scan in 4 weeks based on the patient's **post-subdural drain removal SOC scan**. The considerations for re-evacuation include: lack of resolution of the initial clot, an obvious increase in size of the clot, persistent headache, onset of seizures, or onset of new deficit or headache. These criteria will be used in all subsequent considerations for surgical re-evacuation.

- If the residual total hematoma volume is ≥ **80cc**, the patient will receive an additional CT scan (SOC) for an appointment one month following the previous appointment (Approximately post-operative day 37)
- If there is a decline in neurological exam or other clinical concern, the neurosurgeon may perform an earlier CT scan

- This will continue on a monthly basis for 6 months, or until residual total hematoma cavity volume is < 80cc
  - **Resolution** will be defined as residual total hematoma cavity volume < 80cc
  - Patients with resolution of their hemorrhage will no longer require follow-up visits. Their pills will be returned and discarded.
  - Patients who are no longer in the study will be **called** at 1 month, 6 months, and 18 month intervals

Table 1. CT Scan Variables on cSDH Characteristics and Quantitation

CT SCAN MEASUREMENTS			
Pre-operative: Scan #1			
Location of SDH (Left/Right)	CT Density (HU)	Midline shift at 3rd ventricle (mm)	Volume (cc)
Post-operative: POD#1 Scan			
Subdural Fluid Volume (cc)	Pneumocephalus Volume (cc)	Total Residual Cavity Volume (cc)	Midline shift at 3rd ventricle (mm)
Post-operative: Post-SDD removal Scan			
Subdural Fluid Volume (cc)	Pneumocephalus Volume (cc)	Total Residual Cavity Volume (cc)	Midline shift at 3rd ventricle (mm)
Post-operative: one week (staple removal)			
Subdural Fluid Volume (cc)	Pneumocephalus Volume (cc)	Total Residual Cavity Volume (cc)	Midline shift at 3rd ventricle (mm)
Post-operative: 4weeks			
Subdural Fluid Volume (cc)	Pneumocephalus Volume (cc)	Total Residual Cavity Volume (cc)	Midline shift at 3rd ventricle (mm)

Clinic Follow-up (Subdural clinic):

1. A subdural clinic has been established to see all subdural patients. Dr. Howard Yonas will evaluate ALL patients in the trial during their appointments. A research team member will also be present to help coordinate data collection, tracking of pills, measurements, and follow-up.
2. Patients will be seen **1 week** post-operatively for staple removal.
   a. Subdural volumetric measurements of remaining subdural fluid from last scan will be completed.
      i. Patients with a residual total hematoma cavity volume < 80cc will be instructed to discontinue the pills. Unused medication will be retrieved from the subjects and returned to IDS for destruction. They will not have additional neurosurgical imaging or follow-up required, unless deemed necessary by the neurosurgery attending.

1. They will continue to be followed by the study team with a 6 month and 18-month phone call

a. For patients with a residual total hematoma cavity volume ≥ 80cc, the neurosurgery attending will determine if the patient requires surgical re-evacuation for a 1 month follow-up in clinic with a repeat Head CT. The considerations for re-evacuation include: lack of resolution of the initial clot, an obvious increase in size of the clot, persistent headache, onset of seizures, or onset of new deficit or headache. These criteria will be used in all subsequent considerations for surgical re-evacuation.

ii. If there is a decline in neurological exam or other clinical concern, the neurosurgeon may perform an earlier CT scan. The patient will continue to take the placebo or CC three times a day.

3. Patients presenting for their 2nd clinic appointment (Approximately post-operative day #37):
   a. Repeat CT scan will be performed on the day or near the day of the appointment
   b. Subdural thickness measurements of remaining subdural fluid will be completed
      i. Patients with a residual total hematoma cavity volume < 80cc will be instructed to discontinue the pills. Unused medication will be retrieved from the patients and returned to IDS for destruction. They will not have additional neurosurgical imaging or follow-up required, unless deemed necessary by the neurosurgery attending.
         1. They will continue to be followed by the study team with a 6 month and 18-month phone call
      ii. For patients with a residual total hematoma cavity volume ≥ 80cc, the neurosurgery attending will determine if the patient requires surgical re-evacuation as previously described for a 1 month follow-up in clinic with a repeat Head CT. If there is a decline in neurological exam or other clinical concern, the neurosurgeon may perform an earlier CT scan. The patient will continue to take the placebo or CC three times a day.

4. Patients presenting for their 3nd clinic appointment (Approximately post-operative day #67):
   a. Repeat CT scan will be performed on the day or near the day of the appointment
   b. Subdural thickness measurements of remaining subdural fluid will be completed
      i. Patients with a residual total hematoma cavity volume < 80cc will be instructed to discontinue the pills. Unused medication will be retrieved from the patients and returned to IDS for destruction. They will not have additional neurosurgical imaging or follow-up required, unless deemed necessary by the neurosurgery attending.
         1. They will continue to be followed by the study team with a 6 month and 18-month phone call

      For patients with a residual total hematoma cavity volume ≥ 80cc, the neurosurgery attending will determine if the patient requires surgical re-evacuation as previously described for a 1 month follow-up in clinic with a repeat Head CT If there is a decline in neurological exam or other clinical concern, the neurosurgeon may perform an earlier CT scan.

5. Patients will not take CC pills or placebo longer than 60 days. If there are extra pills, they will be properly retrieved and returned to IDS for destruction.

All radiographic imaging discussed here is our institution's standard of care for the management of SDH. <u>If a patient is discontinued, they will still be followed by the research team until the end of the trial</u> (see below).

Follow-up outcome assessments (Modified Ranking Scale (MRS); Markwalder Grading Scale, [MGS]) will be obtained 1 month, 6 months, and 18 months following surgery for research. All data are coded

with a unique identifying number to maintain confidentiality. This exam assesses the patient's neurological status to predict additional progress and evaluate functional status. This exam will be conducted with the use of a structured interview (see attached MRS questionnaire) by phone or in person if the patient has a scheduled appointment by one of the researchers.

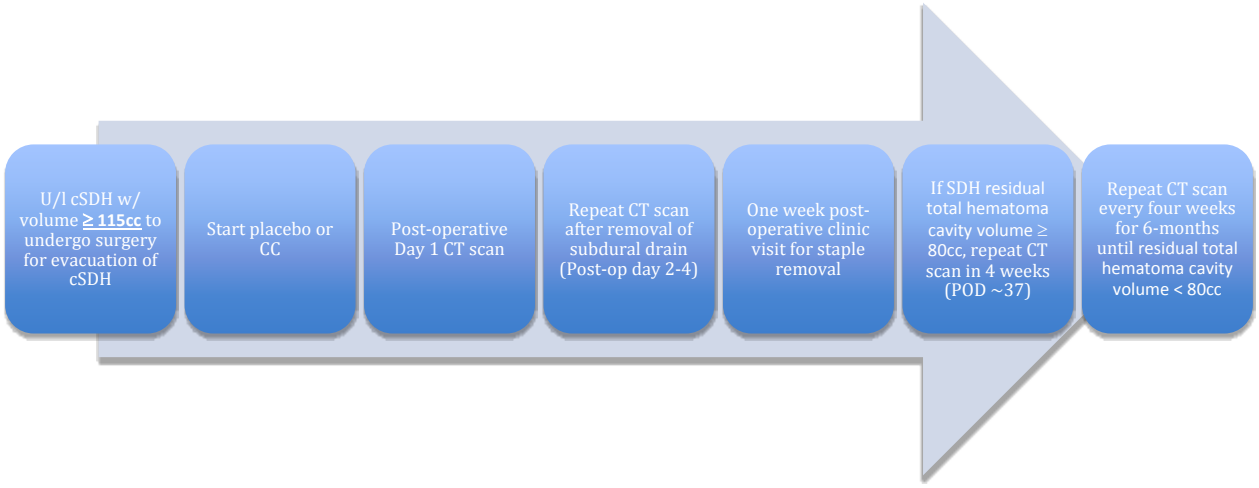
- Study Follow-Up Phone Calls
  - 1 month, 6 months, 18 months
    - Modified Rankin Scale (MRS)
    - Markwalder Grading Scale

Modified Rankin Scale (mRS)

Score	Degree of Disability
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

Markwalder Grading Scale

Mental Status	Neurologic Findings	Grade
normal	Normal	0
fully alert and conscious; may have mild symptoms such as headache	none or mild (reflex asymmetry – i.e. Pronator Drift)	1
drowsy or disoriented	variable neurologic deficits such as hemiparesis	2
stuporous but responds appropriately to noxious stimuli	severe focal signs such as hemiplegia	3
comatose, with absent motor responses to painful stimuli	decerebrate or decorticate posturing	4



Laboratory Analysis:
10 cc of subdural hematoma fluid will be collected during the initial and recurrence operative, along with 5 cc blood from an existing IV, the samples will be sent to Dr. Roitbak's lab and use in the experimental setup within 10-15 days of collection. They will be immediately spun down and frozen at -80C at the time of collection. The samples will also be analyzed for inflammatory mediators.

The objective is to study the effect of CC on IL-8-induced disruption of endothelial permeability. *In vitro* vascular permeability assay will be utilized to model characteristic for cSDH leakage from the abnormal vasculature. These experiments will be performed using commercially available primary human microvascular endothelial cells (Cell Biologics Company). These cells are well-characterized and routinely used in Dr. Roitbak's research. The cells will be grown as a monolayer and pre-incubated with 50 ng/mL IL-8 (this treatment disrupts endothelial junctions and increases their permeability).

In parallel with IL-8 treatment, the other group of cells will be incubated with subdural hematoma fluid (cSDHF) obtained from the cSDH patients:

1. Chronic subdural fluid removed during initial surgery (10 cc of fluid/per patient)
2. Chronic subdural fluid removed during Recurrence surgery (10 cc of fluid /per patient)

Subsequently, several concentrations of curcumin (ranging between 10-100 mM) will be added, and endothelial permeability before and after treatment will be evaluated. The dosage used in the cell culture experiments is based on the available literature, describing a dose-dependent inhibition of IL-8 signaling by curcumin (effective in 5-100 micromolar range). According to the literature on curcumin pharmacokinetics and bioavailability, after the oral administration of ~1g curcumin/pepperine in humans, the concentration of curcumin in blood plasma was detected in micromolar range. Therefore, concentration used in cell culture is relevant to the actual bioavailability of curcumin in human blood/tissues. The working hypothesis is that curcumin treatment will restore/support the integrity of the endothelium in vitro.

In addition, IL-8-treated and untreated cells will be collected and analyzed for the expression of key endothelial junction proteins (ZO-1, claudin, occludin, VE-cadherin), as well as key members of the major signaling pathways associated with endothelial integrity including Akt, PI3K, mTOR, and JAK/STAT pathways.

9. Data Analysis

A. Clinical Studies

1) (cSDH) Data to be recorded to address the primary and secondary aims of the study comparing the CC and placebo groups:

- Primary: Change, rate of change, and time-to-resolution in total hematoma volume of cSDH compared to post-subdural drain scan of less than 80cc in post-surgical patients.
- Secondary: Recurrence rate of cSDH
- Secondary: Markwalder and mRS progression.
- Secondary: Rate of surgical intervention in CC and placebo groups.
- *Secondary:* Rate of persistent or recurrent neurological symptoms in CC and placebo groups

Physician's decision making for re-evacuation will also be recorded. Examples include: lack of resolution of the initial clot, an obvious increase in size of the clot, persistent headache, onset of seizures, or onset of new deficit or headache.

To assess the tolerability of CC in patients via frequency of any side effect, or adverse events as defined by the Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0)

Statistical analysis:

This is a **pilot study** aiming to establish potential effect of CC on hematoma volume change as well as measurements and criteria for surgical intervention and cSDH recurrence. The sample size of 25 for each group is determined based on the patient population size and logistics of recruitment and will not reach the conventional statistical power of 80% or more unless the resolution rate of cSDH is 50% greater in CC than in placebo. To establish the effect size, we will compare CC and placebo groups by performing specific statistical analysis for each primary and secondary outcome: linear-mixed effects modes for the trajectory hematoma volume over the period of up to six month (change and rate of change); survival analysis for time-to-resolution (since patients will be "censored" in their follow-up); Fisher's exact test and logistic regression for rate of surgical intervention or recurrence (criteria to be developed) as well as the rates of exiting symptoms removal and new symptom occurrence. These analyses serve multiple purposes: establish CC effects compared to the placebo; identify determinants of the various endpoints, and pilot-test working definition of recurrence etc. We will also report descriptive statistics and estimation, using confidence interval of 75% (instead of 95% used for large trials). The confidence interval will be interpreted with regards to the minimum clinically important difference (MCID). Dr. Yiliang Zhu, PhD and Professor at the Division of Epidemiology, Biostatistics, and Preventive Medicine, Director of UNM CTSC Biostatistics, Epidemiology and Research Design Core, will serve as a co-investigator and oversee the statistical analysis and data interpretation. k

B. **Laboratory Studies.**

Experimental data on endothelial cell permeability after exposure to cSDH fluid at different concentrations of CC and the changes in protein expression will be quantified using Prism and GraphPad Prism software. Group comparisons using two-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test will be performed to detect significance of differences between control (no treatment), IL-8-treated, IL-8/CC-treated, cSDH fluid-treated, and cSDH-fluid/CC-treated samples. For more detailed statistical analysis, we will use mixed model repeated measures with Wald tests between groups, followed by Sidak's family-wise error rate correction for multiple comparisons within each experimental group.

Provisions to Monitor the Data to Ensure the Safety of Subjects

Safety will be assessed by DSMB (see below) and a multidisciplinary team of representatives from ICU nursing, research coordinators, investigators, and data management. A specific discussion will be initiated at this meeting to see if any involved party has seen any safety concerns related to an enrolled patient and openly discussed. All unanticipated adverse events will be reported to the HRRC for review. All study participants will be required to fill out a pill log (diary), indicating the amount and time each pill is consumed.

Data Safety Monitoring Plan (DSMP)

In addition to above meetings, the study team will have periodical Data Safety Monitoring Board meetings in regard to patient and data safety management. The board meeting will also be required to schedule a prompt meeting after any unexpected or serious adverse event is identified in regard to patient safety or data breach. A log of signed meeting minutes will be filed in the regulatory binder. If no unexpected or adverse events occur, the first DSMP meeting will occur after the first 5 enrolled patients in the study, followed then by meeting after every 10 patients enrolled. These meetings will consist of monitoring for any potential events as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0; Appendix 5) The board will make recommendations to the study team on whether or not the study should stop for any reasons, or proceed. Adverse events will include unexplained causes od diarrhea, gastrointestinal problems, or allergic reactions. The participation of a pharmacist on the DSMB board will help identify these events.

DSMB board members are as follows:

- William E. Rivers, DO – Assistant Professor, Dept. of Neurosurgery, UNM
- Omar Chohan, MD - Assistant Professor, Dept of Neurosurgery, UNM
- Jeremy Lewis, MD – Assistant Professor, Dept. of Neurosurgery, UNM
- Mikiko Yamada-Takeda, PharmD, MS, PhC – Assistant Professor, Dept. of Pharmacy Practice and Administrative Sciences, UNM

b. Withdrawal of Subjects

Participation in this study is completely voluntary. Patients will be able to withdraw from the study at any time. If the patient/LAR chooses to end participation in the research study protocol, they will continue to be followed by the neurosurgery team per standard of care.

During follow-up visits to the Neurosurgery outpatient clinic, patients that are found to be noncompliant with the scheduled study drug (either Curcumin or placebo) will be withdrawn from the research study without their consent. The patient will continue to be followed in the outpatient clinic based on the standard of care, and will no longer be administered the study drug. No tapering of study drug is required, but as stated in the previous section, the patient will continue to be followed based on the standard of care. Since patients that are noncompliant with the study drug are still followed in the outpatient clinic, with serial radiographs and neurologic examinations, the data will continue to be collected.

c. Data Management/Confidentiality

All subject data will be kept as private and confidential as possible. Data will be anonymized, a study number will be assigned to each participant, then the data will be entered and stored on the Research Electronic Data Capture (REDCap) database, which is widely used in the academic research Community. The REDCap is a HIPAA compliant database. The data will be stored for two years after completion of the project. Study subjects will be assigned a confidential, de-identified number that corresponds to their data. The numbers will be the HRPO study number, followed by their enrollment number (i.e.: 16-252-01, 16-252-02, etc.). The research coordinator will have the key for data, which are kept on a password encrypted computer, in a locked Neurosurgery Research office. Subject identifier keys will be destroyed at closure of the study. The data will be stored for 7 years time.

d. Data and Specimen Banking

The cSDHF specimens will be temporarily stored in the research laboratory (PI Roitbak, UNM BRaIN imaging center Building, 1101 Yale Blvd) and used in the experimental setup within 10-15 days after collection. The specimens will not be banked for a future use. The samples will be collected in the blood collection tubes and coded indicating the HRPO number and subject number (for instance: 16-252-01, 16-252-02,…)and date of collection. Only the research pharmacist will have a complete list of the patients and the information regarding the randomization, linking each sample with the individual patient.

e. Risks to Subjects

There are no known adverse risks or known drug interactions with curcumin and black pepper; therefore, the risk to the study subjects is minimal.[9,10,28] Except for the addition of the study drug/placebo, the management and follow-up of these patients is the same as the standard of care for all SDH patients seen by the UNM Neurosurgery department. The risks of surgery and radiation exposure from CT scans of the head are already well documented and are all SOC.

All radiographic imaging discussed here is our institution's standard of care for the management of SDH. If a patient is discontinued, they will still be followed by the research team until the end of the trial (see below).

The study drug curcumin (CC) is an active ingredient in the popular cooking spice turmeric. CC used for this study is concentrated into a single capsule. Numerous clinical trials have been performed on humans with varying doses of CC, including high doses of up to 1500mg daily, with little to no adverse effects .[9,10,28] Known possible adverse effects of the supplement include headache, skin rash, upset stomach, abdominal pain, nausea, and diarrhea, which were seen to resolve within 1-3 days, but no other adverse effects were identified up to doses of 8 grams.[2,6] One study even showed that single doses of 12g yielded no significant adverse events.[18] No significant prescription drug interactions have been observed with curcumin.[2]

Black pepper/piperdine is listed under the FDA as being safe (US. Pat. No. 5,536,506).[23] The average amount of pepper consumed by a person during a day in the United States is 359 mg, which translates to 18-32 mg of piperine a day. Furthermore, rat trials studying a daily intake of 5 to 20 times the average daily dose of humans produced no clinical symptoms (US. Pat. No. 5,536,506).[23] **Furthermore, acute, subacute, and chronic toxicity studies on piperine show no abnormalities or clinical symptomatology, or significant blood chemistry data in laboratory animals. Black pepper extract has a high degree of safety being used nutritionally.** The amount of piperine that is formulated in the curcumin capsules is many thousand times less than the LD_{50} established in mice and rats.

Patients should continue follow-up care with primary care physicians for all other medical problems.

f. Potential Benefits to Subjects

The benefits of curcumin, with regards to the purpose of this study, are unknown.

g. Recruitment Methods

All patients seen by the UNM department of Neurosurgery in the Emergency Department as well as direct transfers from an outside facility to the UNM Neurosciences ICU with a unilateral subdural hematoma will be possible study subjects. The Neurosurgery research team will screen each patient to determine the eligibility, then approach the patients (mRS 0-2) or their LAR, for enrollment into the study.

h. Provisions to Protect the Privacy Interests of Subjects

The patient/LAR will be approached in a private area to discuss study participation (hospital room, consultation room, or pre-operative area). Other than this initial interaction for the consent process, there will be no expected risk to privacy.

i. Economic Burden to Subjects

No cost will be assigned to the subjects for this research. The only addition made during this study from the standard of care for this patients' population is the study pill/placebo. The cost of these capsules is covered by the study, and the patients will not be financially responsible.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Study drug/placebo		X	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Standard surgical procedure	_____	☐	X
Pre-operative CT imaging	_____	☐	X
Post-operative CT imaging	_____	☐	X
Clinical follow-up in outpatient setting	_____	☐	X

j. Compensation

No plans for compensation

k. Compensation for Research-Related Injury

N/A

l. Consent Process

Consent will occur in either the patient's hospital room or with family in a consultation room, or in the pre-anesthesia area. Privacy is ensured by curtains or closing doors when available. The study will be discussed with the patient or LAR if the patient is unable to consent. Adequate time will be provided for the patient/LAR to consider participation. No pressure to participate will be introduced. If the patient or LAR wants additional time to consider participation that would delay the surgery, the patient will be excluded so as not to delay standard care. The initial consent is the only time that participation is required, ongoing consent will be maintained with adequate and on-going conversations with the patient/LAR and the research team. The patient or LAR will be asked to describe what is involved in the study to ensure adequate understanding of the study. HIPAA consent will be included in the consent process.

Subjects not fluent in English

N/A

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

cSDH is a slowly progressive bleed, which may cause altered mental status. Therefore, the physician might not be able to determine the exact time of onset. In this case, any patient with cSDH who is cognitively impaired for more than 6 months, will be excluded from the study; since this impairment might be due to other reasons such as dementia or cognitive impairment. If patients are cognitively impaired and unable to give their own consent to participate in the study due to their cerebrovascular accident; in this case, investigators will identify a LAR and because the patient is not thought to be able to consent for the operation, then the same party consenting for the surgical procedure (if applicable) will be used for consent for the study. All reasonable attempts will be made to ensure that this party is the LAR by asking and ensuring that the same party making medical decisions is making the decision whether to participate in the study. The treating physician will make this determination at the time of consenting the patient for surgery.

It will be explained to the patient/LAR that they have the right to refuse to take part and/or withdraw from this study at any time without penalty or loss of care. Their ongoing medical care will not be affected by the decision to take part or not take part in this study. Patients who decline to take part in this study will receive the standard of care treatment.

m. Documentation of Consent

Consent for the study will be obtained by one of the members of the Department of Neurosurgery clinical research coordinators or one of the investigators. The UNM HSC consent generator will be used.

n. Study Test Results/Incidental Findings

All study subjects will be followed in the outpatient neurosurgery clinic. During the clinic visit, the patients can be shown any of their CT scans, and the progression that has been made. This is currently the practice for all subdural patients. If the patient requires an additional surgical procedure if they underwent an initial craniotomy, or a surgical procedure after initially being managed conservatively, this information will be shared with the patient to allow proper consent for surgery and all of the additionally required steps.

o. Sharing Study Progress or Results with Subjects

No results will be shared with the subjects.

p. Inclusion of Vulnerable Populations

Patients enrolled in the study may be cognitively impaired and unable to provide informed consent; in this case, a legally authorized representative (LAR) will be appropriately identified and approached by a research coordinator to provide consent. These discussions will take place in a private setting where privacy and confidentiality can be maintained. It will be explained appropriately to the LAR that they have the right to refuse participation in the study and/or withdraw at any time without penalty or loss of care.

q. Community-Based Participatory Research

N/A

r. Research Involving American Indian/Native Populations

N/A

s. Transnational Research

N/A

t. Drugs or Devices

A. **Turmeric pills** to be used:

Wild harvest: Serving size: 3 capsules

Composition: 95% curcuminoids in 825 mg = 784 mg curcumin

5% curcuminoids in 525 mg = 26 mg

Pepperine: 9 mg

Each capsule contains: **~270 mg of pure curcuminoiods** and **3 mg of black pepper** extract.

Turmeric/pepperine extracts are in the vegetarian cellulose capsules with the same composition as placebo capsules

- The dose is chosen based on other clinical studies as well as the manufacturer's recommended dosage.
- If you refer to the in-vitro studies on cells, the curcumin concentration is based on the available scientific literature

B. **Placebo pills**: The placebo pill is a vegetarian cellulose capsule, with cellulose powder inside. The composition is cellulose and magnesium stearate. Produced by MHS Labs. Certificate of Manufacture provided.

Turmeric and placebo pills will be stored (at room temperature) and sorted in the standard pill bottles in the UNM Hospital Pharmacy.

For blinding purposes, both types of capsules (Turmeric and placebo) will be over-encapsulated in an empty, opaque, orange gelatin capsule shell.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

2. Describe the purpose for the review (e.g., screening):

3. Describe who will conducting the reviews (e.g., investigators, research staff):

4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☐ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☐ True

      ☐ Other justification:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☐ True

      ☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☐ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☒ Yes. Describe:

   ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   The use of PHI for screening involves no more than minimal risk, as we already have access to this information for clinical care of these patients. PHI that may be used/viewed for screening will not be retained in any way after the consent process has been completed. If the patient is determined to not be an eligible participant or declines consent, all PHI that may have been collected during screening will be destroyed immediately and will not be retained in and way. If the patient is determined to be eligible, the patient will be consented and will sign a HIPAA authorization at that time. Any PHI collected for screening purposes will be destroyed at the earliest time possible and will not be disclosed or re-used.

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?
   - ☐ All
   - ☐ Some. Explain:
2. Provide justification for <u>one</u> of the following:
   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?
   - ☐ Yes. Please attach a copy to your submission in Click.
   - ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

1. Which element(s) of consent do you wish to eliminate <u>and</u> why?
2. Which element(s) of consent do you wish to alter <u>and</u> why?

3. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

    b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

    c) The research could not practicably be carried out without the waiver or alteration:

    d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
    ☐ All
    ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
    a) The research involves no more than minimal risk to the subjects:

    b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

    c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)
Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization
Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

☐ True

☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

cSDH is a slowly progressive bleed, which may cause altered mental status. Therefore, the physician might not be able to determine the exact time of onset. In this case, any patient with a cSDH, who is cognitively impaired for more than 6 months, will be

excluded from the study; since this impairment might be due to other reasons such as dementia or cognitive impairment.

2. Describe how capacity to consent will be evaluated.

Again, due to the nature of the injury, some patients will be unable to consent for themselves. If the patient is not thought to be able to consent for the trial, then the same party consenting for the surgical procedure will be used for consent for the study. All reasonable attempts will be made to ensure that this party is the LAR by asking and ensuring that the same party making medical decisions is making the decision whether to participate in the study. The treating physician will make this determination at the time of consenting the patient for the surgical procedure.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

If the patient regains the ability to provide informed consent (i.e. above GCS 13), the study will be explained to them, and they will be asked to decide on their further participation. Patients are assessed daily for competence by the resident and attending neurosurgeon. This assessment will include a basic assessment of orientation as well as using the "repeat back" method (Cordasco Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices. Chapter 39, 2013) to assess whether the subject is competent to make a determination.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

During consent of the subject/LAR, we will use the teach back method to ensure understanding of all study related procedures. This method will be done with the participant, if the participant regains consciousness and is determined to able to consent by the attending physician.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

Assent will not be obtained.

Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

The risks to the study subjects are minimal, as the study drug curcumin (CC) is an active ingredient in the popular cooking spice turmeric. Also, the management and follow-up of these patients is the same as the standard of care for all SDH patients seen by the UNM Neurosurgery department.

6. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

Since there is no treatment for patients, with recurrent cSDH, other than the Standard of Care, we believe that Curcumin will be very effective in reducing the recurrence of previously evacuated chronic subdural hematomas.

7. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

   Please see protocol in section 15.

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