A Comparative Study of the Efficacy of Intralesional Sodium Thiosulfate Versus Intralesional Normal Saline for the Treatment of Dystrophic and Idiopathic Calcinosis Cutis, A Double-Blind Randomized Placebo-Controlled Trial

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A Comparative Study of the Efficacy of Intralesional Sodium Thiosulfate Versus Intralesional Normal Saline for the Treatment of Dystrophic and Idiopathic Calcinosis Cutis, A Double-Blind Randomized Placebo-Controlled Trial

1.0 Objectives*

1.1 The purpose of our research is to compare the effectiveness of 40mg/ml sodium thiosulfate (STS) solution to normal saline (0.9% sodium chloride) when injected intralesionally for the treatment of calcinosis cutis. Our specific aim is to assess the response of dystrophic and idiopathic calcinosis cutis to the injections of sodium thiosulfate in our patients.

1.2 Our hypothesis is that three injections of STS, each spaced one month apart, will significantly improve our patients' calcinosis cutis condition to a point where they are effectively clear or have a 2-point improvement in their Physician Global Assessment (PGA) scores when compared to normal saline.

2.0 Background*

2.1 Calcium plays an important role in the growth and differentiation of the skin.[1] As a result, dysregulation of calcium can have dermatologic consequences. One of these consequences results in a condition known as calcinosis cutis. This is an uncommon dermatologic condition in which calcium deposits are formed in the skin and result in cutaneous calcification. There are various types of this condition, including dystrophic, metastatic, iatrogenic, and idiopathic.[1,2] Our research, however, will be focused on dystrophic and idiopathic calcinosis cutis. These forms often present in areas of the skin that have been previously damaged, and these patients often have no fundamental metabolic irregularities in calcium regulation.[1] It is believed that the calcification develops when an associated disease causes tissue damage. This damage allows calcium to move into the affected area and crystallize.[1] Another line of thinking is that the acidity which follows cell damage may have an effect on local calcium inhibitory processes.[1] Dystrophic Calcinosis cutis is commonly associated with autoimmune connective tissue disorders such as scleroderma, dermatomyositis, and cutaneous lupus erythematosus.[1,2] Other etiologies may include panniculitis, genetic disorders, infections, neoplasms, and trauma[1].

2.2 There are a variety of potential treatments for dystrophic calcinosis cutis which depends upon factors such as size, location, and etiology. These treatments include surgical excision, bisphosphonates, warfarin, tumor necrosis factor inhibitors, among others[2]. However, these often have varying degrees of success and none of which are FDA-approved.[2] One studied treatment involves the drug sodium thiosulfate. Sodium thiosulfate (STS) has been used successfully in a number cases topically, intravenously (IV), and intralesionally by increasing the solubility of the cutaneous calcium deposits. There have been several case reports examining STS topically for several months.[3–7] Potential downsides to topical treatments are that they may not penetrate the skin deep enough to affect the calcifications, and patients must strictly adhere to the application directions. Additionally, STS has been used intravenously with success.[3,8,9] However, there have been cases of patients discontinuing IV STS due to its side effects of fatigue and nausea.[10] There have also been cases in which there was a lack of response to IV STS.[9,10]

2.3 We wish to examine STS intralesionally (IL) since this would allow for minimization of the side effects of the IV treatment, higher local concentrations than the topical approach, and easier accessibility of the affected site(s). Intralesional STS has been used in a number of cases to treat dystrophic calcinosis cutis with great success.[11–13] However, from the literature, there are currently no prospective studies which compare the efficacy of STS to normal saline which is the gap in knowledge that we are attempting to address.

Our prospective study will allow us to address this gap in knowledge by comparing the intralesional administration of STS to normal saline for the treatment of dystrophic and idiopathic calcinosis cutis lesions. If successful, this study will contribute significantly to demonstrating the efficacy of IL STS for dystrophic and idiopathic calcinosis cutis and could be a stepping stone for development of more effective treatments.

3.0 Inclusion and Exclusion Criteria*

3.1 Subjects will be screened in person at the UCF Health Clinic in Lake Nona. Subjects will be screened and evaluated in the clinic to verify diagnosis through history, physical findings, health records, and previous labs. Subjects who fit the diagnosis of dystrophic or idiopathic calcinosis cutis will be asked whether they wish to participate in the study. Subjects will <u>not</u> be recruited from a search of their medical records (see Section 22: Recruitment Methods). Female subjects who require a urine pregnancy test as part of their screening will be asked to give verbal informed consent for the test prior to the completion of screening.

3.2 Screening Criteria

- Inclusion Criteria:
    - Male or female adult 18 years of age or older
    - Must have health insurance will be eligible to participate
    - Must have a current diagnosis of dystrophic or idiopathic calcinosis cutis
    - Subjects must have at least 2 lesions of at least 2mm in size

- Exclusion Criteria:
    - Unable to read and speak English
    - Allergy to any component of the sodium thiosulfate solution
    - Adults unable to consent
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women
    - Women who are breastfeeding
    - Prisoners

4.0 Study-Wide Number of Subjects*

4.1. We plan on enrolling 12 subjects with the aim to accrue 10 subjects who successfully screen for eligibility for the study. This number was derived on consultation with Bee Nash.

5.0 Study-Wide Recruitment Methods*

5.1 Not applicable. This is not a multicenter research study and research will only be conducted at the UCF Health clinic in Lake Nona. Local recruitment methods are described in section 19.0 Setting.

6.0 Multi-Site Research*

6.1 Not applicable. This is not a multi-site research project. Research will only be conducted at the UCF Health clinic in Lake Nona.

7.0 Study Timelines*

7.1 Subjects are expected to participate in this study for a total of three months. During these three months, subjects will be required to come to UCF Health Clinic at 9975 Tavistock Lakes Blvd., Orlando, FL 32827 for a total of four appointments:

- Timeline:
  - Week 0 (Visit 1): 90 minutes
  - 48-hour post-treatment follow-up phone call: 5 minutes
  - Week 4 (Visit 2): 90 minutes
  - Week 8 (Visit 3): 90 minutes
  - Week 12 (Visit 4): 15 minutes
- Ten months is the anticipated length of time to recruit subjects
- The study is expected to be completed by April 2019.

8.0 Study Endpoints*

8.1 Study endpoints:

- Primary:
  - Change in size of study lesions
  - Change in Physician Global Assessment
  - Visual Analog Scale of pain of injection
- Secondary:
  - Adverse Events

8.2 Primary and secondary safety endpoints

- Primary safety endpoints: Serious adverse event due to IL STS, will be required to withdraw.
- Secondary safety endpoints:

- Intolerance to pain associated with injections, will be required to withdraw.
- Vasovagal reaction. If a subject develops a vasovagal reaction, he or she will be given the option to withdraw but will not be required to withdraw.
- If a subject experiences a mild to moderate adverse event he or she will be given the option to withdraw but will not be required to withdraw.

9.0 Procedures Involved*

9.1 Our study is prospective double-blind randomized placebo-controlled trial that seeks to compare STS to a placebo saline when injected intralesionally for the treatment of dystrophic or idiopathic calcinosis cutis.

9.2 Timeline

- Subject visits
  - The sodium thiosulfate and saline solution will be prepared the same day as the subject's baseline visit after consent to participate is obtained.

  - Baseline Visit
    - Minute 00-15:
    - Informed consent, HIPAA authorization, and screening and enrollment process.

  - Minute 15-30:
    - Obtain demographics and medical history via Demographics Form and Medical History Form (attached)
    - Selection of 2 lesions of dystrophic or idiopathic calcinosis cutis.
      - Note: The lesions must be at least 2mm in diameter and no larger than 2cm in diameter. If a lesion smaller than 2cm is not available then a 2 cm x 2 cm portion of a larger lesions will be used.
    - One lesion will be "Lesion A", and the other will be "Lesion B" for the entire study duration.
    - Lesions will be labeled with their corresponding letter 'A' and 'B' with a marker and photographed
    - Assessment of calcinosis cutis lesions via Case Report Form (see attached).
    - Administration of STS and normal saline.

  - Minute 30-90:
    - Monitoring of subject for adverse events
- 48-hour follow-up phone call:
  - Minute 0-5:
    - Brief phone call to assess for any adverse reactions

- 1-month (+/- 8 days) Follow-up
  - Minute 00-30:
    - Lesions will be labeled with their corresponding letter 'A' and 'B' with a marker and photographed
    - Assessment of calcinosis cutis via Case Report Form (attached)
    - Administration of STS and normal saline.
  - Minute 30-90:
    - Monitoring of subject for adverse events
    - Debrief of subject

- 2-month (+/- 8 days) Follow-up
  - Minute 00-30:
    - Lesions will be labeled with their corresponding letter 'A' and 'B' with a marker and photographed
    - Assessment of calcinosis cutis via Case Report Form (attached)
    - Administration of STS and normal saline
  - Minute 30-90:
    - Monitoring of subject for adverse events
    - Debrief of subject

- 3-month (+/- 8 days) Follow-up
  - Minute 00-15:
    - Lesions will be labeled with their corresponding letter 'A' and 'B' with a marker and photographed
    - Assessment of calcinosis cutis via Case Report Form (attached)

- During each visit subjects will be monitored for any adverse events and asked about any potential adverse events since the last visit. Any adverse events will be logged on the Adverse Events Form (see attached).
- Visit 1 will be followed with a 48-hour post-treatment phone call to assess for any adverse events.
- After all subjects have completed their participation, photographs of lesions will be reviewed by Dr. Sami who will fill out the Independent Observer Case Report Form (see attached) for each visit. He will be blinded as to which lesions received which treatment and at which visit in the study the lesions were photographed.

- Screening and consent
  - First, each subject will sit down with the principal investigator to discuss the study in depth and review the screening criteria. After all risks, benefits, alternatives, and questions have been discussed consent will be obtained.
  - After the informed consent form is signed, the eligibility screening portion of the case report form will then be filled out by the principal investigator with the research subject. If necessary, a pregnancy test will be performed.

- Solution preparation
    - 50 ml vials of sodium thiosulfate (250mg/ml) will be used for preparation of the treatment solution.
        - The solution from the bottle will be diluted in a ratio of 1 part sodium thiosulfate 250mg/ml to 5.25 parts sterile water to yield a 40mg/ml solution of sodium thiosulfate.[14] This is done to make the final solution as close to isotonic as possible.
    - 30 ml vials of sodium chloride 0.9% will be used for the control treatment.
    - The solutions will be drawn up in 1 cc syringes utilizing a 25g needle by Dr. Weinstein. The needle with then be replaced with a capped 30g ½ inch needle.
    - All solutions will be drawn up by Dr. David Weinstein the day of use and discarded immediately after use.
    - Treatment and control will be randomized once for the entire study and all subjects based upon a one-time flip of a coin as follows:
        - If coin flip is heads: all "A" lesions will receive STS and all "B" lesions will receive normal saline
        - If coin flip is tails: all "A" lesions will receive normal saline and all "B" lesions will receive STS
        - This result will be recorded on the Unblinded Treatment Document (See attached).
        - Dr. Weinstein will not be notified of the result until after completion of the study so as to keep him blinded.
    - The syringes will be labeled with an "A" or "B" label for blinding by Adam Foley, or Amelia Winter.

- Administration of study solutions
    - A volume of 0.1 ml/cm2 of normal saline or STS will be injected into each lesion. Therefore, a maximum of 0.4ml of 40mg/ml STS or 16mg of STS (given maximum size of 2 cm x 2 cm) will be used per visit per subject.
    - The same treatment lesion will be injected only with STS every injection and the same control lesion will be injected only with normal saline (0.9% sodium chloride) every injection. In other words, "Lesion A" will always be injected with solution A and "Lesion B" will always be injected with solution B.
    - Dr. Weinstein, a board-certified dermatologist, will be administering all injections of STS and normal saline to minimize risks for subjects.

- Disposal Protocol:
    - After use, needles will be disposed of in red harps container according to UCF Health policy
    - After use, urine samples will be disposed of in the toilet according to UCF Health policy

9.3 Risk Management:

- Subjects will be directly observed during the administration of the STS and normal saline for any adverse events. An anaphylaxis kit is available in clinic should any subject experience such an event. The principal investigator is certified in basic cardiopulmonary life support and an AED is present in the facility. Subjects will be provided with the phone number of the PI should any issues related to participation in the study arise.

- Sodium thiosulfate is currently FDA-approved for as an antidote in the treatment of cyanide poisoning. FDA phase III studies are currently being conducted for use in calciphylaxis.

- 0.9% Sodium chloride is currently FDA-approved for parenteral replenishment of fluid, diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.

- Sterile water is currently FDA-approved as a solvent or diluent vehicle for parenterally administered drugs or solutions and as a source of water for parenteral fluid replenishment after suitable additives are introduced.

- The following are the source documents (see attached):
    - Subject ID Assignment Log
    - Screening and Enrollment Log
    - Drug Accountability Log
    - Unblinded Treatment Document
    - Eligibility Form
    - Demographics Form
    - Medical History Form
    - Case Report Form
    - Independent Observer Case Report Form
    - Adverse Event Form
    - Photographs of study lesions
- Details regarding the storage of the above information is outlined in Section 11.3.

9.4 Data to be collected

- Age
- Gender
- Race
- Ethnicity
- Medical History
    - Past Medical and Surgical History
    - Medications

  - Allergies
  - Social History
    - Tobacco use
    - Alcohol use
  - Laboratory Results
- Size of lesions
- Visual Analog Scale for Pain (VAS Pain)
- Physician Global Assessment (PGA)
- Photographs will also be taken of all study lesions during every assessment and will be stored directly in the password protected HIPAA compliant network drive for clinical research at UCF Health. Though the photos will not contain any identifiers, subjects are potentially identifiable from the photos and thus they will be stored in the password protected HIPAA compliant network drive for clinical research at UCF Health.

10.0 Data and Specimen Banking*

10.1 There will be no data or specimen banking for future use.

11.0 Data Management* and Confidentiality

11.1 Data will be reported descriptively [mean and standard deviation; median (min-max) and frequency and percentage]. Interrater reliability of PGA will be conducted using Cohen's kappa statistic. As a second step, differences across times and between groups will be explored with non-parametric tests, such as Kruskal-Wallis test and the Mann Whitney U test. Statistical significance will be tested at $p<.05$.

The data will be analyzed for significant differences with aid of a statistician. The results of the data analysis will be graphed for each parameter.

11.2 For our study, we will recruit up to 12 adult male and female volunteers ages 18 years and older. This number is estimated from clinical knowledge of the cases that present to treatment on an annual basis at the research site. Furthermore, a review of the existing literature suggests that the targeted sample size is commensurate to other published studies.[3,4,13,5–12]

11.3 Data will be managed as follows:

- Data will be stored in the secure HIPAA-compliant database called REDCap.
- Unique identifiers will be created using sequential numbers (i.e. 1, 2, 4 etc.).
- No data collection instrument in REDCap will contain identifying information
- The Screening and Enrollment Log, Drug Accountability Log, Unblinded Treatment Document, Demographics Forms, Medical History Forms, Eligibility Forms Case Report Forms, Independent Observer Case Report Forms, Adverse

Event Forms (see attached documents) will all be stored in the regulatory binder in a locked drawer in a locked room at UCF Health. Only Dr. David Weinstein will have access to this locked drawer.

- Photographs will be taken with a UCF Health digital camera. The photographs will then be transferred to a folder on a password protected HIPAA compliant network drive for clinical research at UCF Health. After transfer of photographs to clinical research folder they will be deleted from the camera. Photographs will be labeled with subject ID number and visits number (i.e Subject 01 3-month)
- A subject ID assignment list (see attached document "Subject ID Assignment List") that links the subject name and contact information with their unique identifier will be stored in a separate folder in locked drawer in a locked room at UCF Health. Only Dr. David Weinstein will have access to this locked drawer.
- Identifying information such as the "Subject ID Assignment List" will only be accessed by the PI and co-PIs for initial entry. It is possible the identifiable information may be referenced if questionable data are detected during data analysis (e.g.: number out of range, missing data).
- The "Screening and Enrollment Log" and the "Subject ID assignment List" will both be disposed of in a HIPAA-compliant shred bin at the completion of the study.
- Informed consents and HIPAA authorizations will be stored in locked drawer in a locked room at UCF Health and kept for a minimum of six years after the conclusion of the study (per UCF data retention policies.)
- Only de-identified data will be used and exported for analysis.
- De-identified data and photographs will be stored for a minimum of five years after the conclusion of the study (per UCF data retention policies).

11.4 Data will be verified for correctness by 2 of the investigators after entry to REDCap.

11.5 Not applicable. See above section for how data will be handled study-wide as this is a single center, single site study.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

12.1 The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe is as follows:

- The principal investigator and statistician will review cumulative adverse event data after 5 out of 10 subjects have completed the study.
- If there are more severe adverse events in the treatment lesions compared to the control lesions with $p < 0.05$ then the study will be suspended immediately.

13.0 Withdrawal of Subjects*

13.1 Subjects will be withdrawn from the research without their consent if they become intolerant to the treatment and/or the researchers determine that they are too nervous, anxious to continue.

13.2 Procedures for orderly termination:

- Subjects may voluntarily terminate their participation in the research at any time by informing a member of the research team.
- A subject may partially withdraw from the study after any of the study visits if the subject is unable or unwilling to do the follow up visits.

13.3 Procedures for subject withdrawal:

- If a subject withdraws or is withdrawn from the study prior to completion, further data collection will be stopped. However, partial data already collected will be used for analysis.
- Orderly termination will proceed at the end of study period for all subjects.

14.0 Risks to Subjects*

14.1 There is no major anticipated risk associated with the study. However, potential risks to the subject include:

- Discomfort and minimal pain upon injection and infiltration of STS or normal saline.
- Minimal (<27%) risk of nausea and vomiting[15]
- Low risk of hypotension, headache, disorientation[15]
- Negligible bleeding or bruising
- Negligible risk of infection

The procedures in this research are known to hurt a pregnancy or fetus in the following ways:

Sodium Thiosulfate Injection is Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Sodium Thiosulfate Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no reported epidemiological studies of congenital anomalies in infants born to women treated with sodium thiosulfate during pregnancy. In animal studies, there are no teratogenic effects in offspring of hamsters treated during pregnancy with sodium thiosulfate in doses similar to those given intravenously to treat cyanide poisoning in humans. Other studies suggest that treatment with sodium thiosulfate ameliorates the teratogenic effects of maternal cyanide poisoning in hamsters. In other studies, sodium thiosulfate was not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day, respectively.

15.0 Potential Benefits to Subjects*

15.1 Potential benefits to subjects include:

- Possible improvement of cutaneous calcinosis lesions.

16.0 Vulnerable Populations*

16.1 This study does not involve individual who are vulnerable to coercion or undue influence.

17.0 Community-Based Participatory Research*

17.1 This is not community-based participatory research.

18.0 Sharing of Results with Subjects*

18.1 There are no plans to share results with subjects.

19.0 Setting

19.1 Research will be conducted at UCF Health:

- Potential subjects will be identified and recruited at both the UCF Health clinic in Lake Nona and the UCF Health clinic on Quadrangle blvd.
- Screening, enrollment and the initial/baseline study visit will take place athe UCF Health clinic in Lake Nona. Follow up study visits will take place at the UCF Health clinic in Lake Nona.
- There will not be a community advisory board.

20.0 Resources Available

20.1 Dr. Weinstein has significant prior experience conducting research, knowledge of the regulations and customs at UCF Health, and works regularly with patients performing dermatologic surgery. All injections will be administered by Dr. Weinstein. Dr. Sami has extensive experience conducting clinical research. In addition, the medical students involved in the project will be able to help significantly. Through the FIRE project Bee Nash will be able to assist with data analysis.

20.2 Resources available to conduct research:

- The study's small sample size (N=10) makes it likely that the required number of subjects will be recruited in less than 8 months. Drs. Weinstein and Sami combined see more than half this number of patients with calcinosis cutis annually. In addition, the rheumatologists at UCF Health see at least as many patients with calcinosis cutis. Finally, recruiting through the local dermatology society and advertising should supplement the numbers needed to complete the study.
- Research will be conducted during Dr. Weinstein's administrative time or on the weekend.
- The study will be will be conducted at the UCF Health Clinic, see section 19. Setting.
- While the chances of a research related injury are extremely rare, subjects will be required to have health insurance in order to participate in this study. Treatment for research related injury will be made available,

however costs associated with this treatment will be billed to the subject's insurance company. Costs not covered by the subject's insurance company will be the subject's responsibility.

- All individuals assisting in the research study will be provided a copy of the IRB-approved protocol and given the opportunity to meet with the principal investigator before recruitment begins. The principal investigator, Dr. Weinstein, will be responsible for informing all research staff of their research-related duties during a personal meeting or via phone or email. The contact information of the principal investigator and co-principal investigator will be distributed to all research staff and the subjects.

21.0 Prior Approvals

21.1 Approval from the medical director and the HIPAA privacy officer of UCF Health will be obtained prior to commencing research.

22.0 Recruitment Methods

22.1 The research team will start recruitment shortly after IRB approval and the sodium thiosulfate has been received. Patients with a diagnosis of calcinosis cutis will be recruited from the UCF Health Clinic during a patient's visit (medical records will not be searched for patients with a diagnosis of calcinosis cutis) and through advertising on the UCF Health website and within the UCF Health clinic.

22.2 The primary source of subjects will be patients at the UCF Health Clinic and people in the greater Orlando area. This represents a large pool of potential subjects from which to recruit.

22.3 Dr. Weinstein and Dr. Sami will rely on prior labs, pathology reports, and physical examination to determine if the participant has a diagnosis of calcinosis cutis. As stated, medical records will not be searched for patients with a diagnosis of calcinosis cutis.

22.4 An e-mail and within clinic advertisement may be used to recruit patients (see attached Advertisements). This is a small pararaph describing the study. This text may be displayed in the UCF Health clinic, to other providers at UCF Health or members of the local dermatology society. In addition, a similar small paragraph describing the study will be posted on the UCF Health website (see attached Advertisements).

22.5 Subjects will not be compensated for their time.

23.0 Local Number of Subjects

23.1 We plan to enroll approximately 12 subjects.

23.2 We anticipate most subjects that are enrolled to be successfully screened. There may be a few subjects that will fail screening due to failing urine pregnancy testing. Given this, it may be that 12 subjects need to be enrolled and screened to obtain 10 eligible subjects.

24.0 Provisions to Protect the Privacy Interests of Subjects

24.1 Subjects will be in the same general vicinity during the study and will be recruited from the UCF Health Clinic. Therefore, there will be the possibility that subjects may know and recognize each other.

24.2 Prior to enrollment subjects will be made aware of this possibility and if unacceptable, will be given the option to decline to participate.

24.3 All investigators will have access to all of the information collected on the subjects. The "Subject ID Assignment Log" will be kept in a separate folder so that investigators will only have access to identifiable information if needed for data entry or if there is a data discrepancy. Only de-identified data will be exported and used for data analysis.

25.0 Compensation for Research-Related Injury

25.1 While the chances of a research related injury are extremely rare, subjects will be required to have health insurance in order to participate in this study. Treatment for research related injury will be made available, however costs associated with this treatment will be billed to the subject's insurance company. Costs not covered by subject's insurance company will be the subject's responsibility.

26.0 Economic Burden to Subjects

26.1 Subjects have to give his or her time (approximately 5 hours) and bear any transportation costs (gas, tolls, etc.). If the subject's health insurance does not cover the costs for the treatment related injury, the subjects will be billed for the treatment. There are no other expected costs that subjects will incur as a result of participating in the study.

27.0 Consent Process

27.1 Consent process:

- The consent process will take place in person at the UCF Health clinic in Lake Nona.
- Subjects will be given the option of picking up the consent and HIPAA authorization prior to participation to discuss with their primary care physician, significant other, etc., to help minimize the possibility of

coercion or undue influence. Subjects will be able to wait however long they desire after obtaining the study information and before signing the consent and HIPAA authorization. However, if the study is completed before the subject chooses to sign the consent then they will not be allowed to participate.

- Subjects may voluntarily terminate their participation in the research at any time by informing a member of the research team. Other than the initial informed consent no other formal process will be done to document ongoing consent.
- The UCF "SOP: Informed Consent Process for Research (HRP-090)" will be followed.
- The consent process will be documented in writing on the Informed Consent and HIPAA Authorization. The investigator will describe the details of the study and answer any questions the subject may have about the study. Subjects will be given an informed consent and HIPAA authorization for the study and the primary investigator's contact information. Those subjects who express interest in the study will be required to sign the Informed Consent form and HIPAA authorization to ensure that there is no coercion in the study.

28.0 Process to Document Consent in Writing

28.1 The UCF "SOP: Written Documentation of Consent (HRP-091)" will be followed.

28.2 All subjects will be required to complete and sign the informed written consent document and HIPAA Authorization to ensure that there is no coercion in the study. The informed consent documents will be signed both by the subject and by the principal investigator (see attached "Informed Consent" and "HIPAA authorization").

29.0 Drugs or Devices

29.1 Sodium thiosulfate being used will be stored in a bag labeled "For Research" in a locked medication cabinet in a locked room at the UCF Health clinic in Lake Nona. This will only by accessible by authorized research personnel. The medication will only be used on research subjects by authorized study personnel. Logging of the drug inventory and administration will be kept on the Drug Accountability Log (see attached).

29.2 The sodium thiosulfate and normal saline solutions are not investigational drugs and are readily available FDA-approved medications.

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