**PROTOCOL TITLE:**

Rapid Elimination Procedure of Teriflunomide

**PRINCIPAL INVESTIGATOR:**

Alice Roberts, M.D.

USF Department of Neurology

813-974-5555

ARoberts@usf.edu

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**REVISION HISTORY**

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| **Revision #** | **Version Date** | **Summary of Changes** | **Consent Change?** |
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# Study Summary

1.1

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| --- | --- |
| **Study Title** | Rapid Elimination Procedure of Teriflunomide |
| **Study Design** | Non-randomized, two-period, two-treatment, single sequence PK interaction study. |
| **Primary Objective/Purpose** | To determine if colestipol hydrochloride tablets can accelerate the elimination of teriflunomide. |
| **Secondary Objective(s)/Purpose** | To collect information on the pattern of side effects with use of colestipol hydrochloride after teriflunomide administration and to determine the best duration of therapy needed for adequate elimination |
| **Research Intervention(s)/ Investigational Agent(s)** | Teriflunomide rapid elimination using colestipol hydrochloride. |
| **IND/IDE #** | N/A – IND Exempt |
| **ClinicalTrials.gov NCT#** | Pending |
| **Study Population** | Healthy volunteers 18-45 years of age with a BMI of 18-29 kg/m2 |
| **Sample Size** | 30 |
| **Study Duration for individual subjects** | 8 visits, 1 follow-up call for a total of 540 minutes over a 40-day period |
| **Study Specific Abbreviations/ Definitions** | N/A |

# Objectives

2.1 The primary objective is to determine if colestipol hydrochloride (HCL) tablets can accelerate the elimination of teriflunomide. The secondary objective is to collect information on the pattern of side effects with use of colestipol HCL after teriflunomide administration and to determine the best duration of therapy needed for adequate elimination.

2.2 We hypothesize that colestipol HCL will have the same elimination timing as cholestyramine (current approved elimination procedure).

# Background

3.1 Teriflunomide is a novel, once-daily, oral disease-modifying therapy approved for the treatment of relapsing forms of multiple sclerosis. Teriflunomide exerts its effect by selectively and reversibly inhibiting dihydro-orotate dehydrogenase, a mitochondrial enzyme required for de novo pyrimidine synthesis [1]. This enzyme inhibition results in an impairment of the proliferation of stimulated T and B lymphocytes owing to their need of de novo pyrimidine synthesis to undergo expansion. The salvage pathway for pyrimidine synthesis are relatively unaffected by teriflunomide therefore slowly dividing or resting cells are able to proceed with pyrimidine synthesis. Teriflunomide has a rapid absorption and is extensively bound to plasma protein (>99%). Teriflunomide is moderately metabolized and eliminated mainly through direct biliary excretion of unchanged drug via the feces. Given that it is highly protein bound and involved in enterohepatic recycling, teriflunomide has a long median terminal half-life of 19 days. This results in an extremely slow elimination from plasma, which on average takes 6-8 months but can take up to 2 years for teriflunomide plasma concentrations to reach a minimum level. If a participant needs an accelerated elimination of teriflunomide, the oral administration of cholestyramine, an anion-exchange resin, or activated charcoal can be administered [2]. This has been shown to be effective because cholestyramine and activated charcoal can bind to unbound teriflunomide forming insoluble complexes leading to these becoming sequestered in the small intestine and eventually excreted in feces. By preventing their reabsorption, this process results in the partial removal of unbound teriflunomide and bile acids from the enterohepatic circulation.

Colestipol hydrochloride is bile acid sequestrant, similar to cholestyramine [3]. Colestipol hydrochloride has the potential to exert a similar effect on unbound teriflunomide given its similarity to cholestyramine. Colestipol hydrochloride has the potential advantage over cholestyramine in its ease of administration given that it can be dosed as a daily or twice daily regimen where as cholestyramine is typically dosed as three times a day. Another potential advantage is that colestipol is available in an oral tablet formulation where as cholestyramine is supplied as an oral powder for suspension [3].

1. O’Connor PW et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303.

2. Miller A, Turpault S, Manguy-Vacheron Francoise. Rapid Elimination procedure of teriflunomide with cholestyramine or activated charcoal. Poster session presented as works in progress. The Fourth Cooperative Meeting of the Consortium of Multiple Sclerosis Centers and Americas Committee for Treatment and Research in Multiple Sclerosis; 2012 May 30-Jun 2; San Diego, CA.

3. Insull W Jr, et al. The effects of colestipol tablets compared with colestipol granules on plasma cholesterol and other lipids in moderately hypercholesterolemic patients. Atherosclerosis 1995 Jan 20; 112 (2): 223-35.

3.2 N/A

# Safety Endpoints

4.1 If any of the laboratory values (CBC/CMP safety labs) are greater than two times outside of the normal limits, the subject will be withdrawn. If three people are withdrawn for that reason, the study will be stopped.

# Study Interventions, Investigational Agents, and FDA-Regulated Products

5.1 The intervention under study is teriflunomide rapid elimination using colestipol hydrochloride.

5.2

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| --- | --- |
| **Devices** | **Drugs/Biologics** |
| FDA Approved Device – Approved Use | FDA Approved Drug/Biologic – Approved Use |
| FDA Approved Device – Unapproved Use | FDA Approved Drug/Biologic – Unapproved Use |
| Investigational Device – Non-Significant Risk | Investigational Drug/Biologics |
| Investigational Device – Significant Risk | Placebo |
| Humanitarian Use Device Exemption | Other Drugs/Biologics |
| Other Devices |  |

* If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section and attach as an appendix at the end of the protocol.

5.3 The pharmacy will order and deliver the teriflunomide and colestipol HCL to research staff on the approved list of authorized staff. Research staff will keep a drug accountability log of all intake and dispensations of the study drugs. Research staff has been trained on enrollment of patients and drug handling per the attached SOP. Subjects will be given the study drugs in person after verification of the subject ID, DOB, and name.

Teriflunomide is indicated for the treatment of patients with relapsing forms of multiple sclerosis. Colestipol HCL is indicated as adjunctive therapy to diet for the reduction of elevated serum total and LCL-C in patients with primary hypercholesterolemia who do not respond adequately to diet. Neither study drug are approved for use in health patients. If a participant needs an accelerated elimination of teriflunomide, the oral administration of cholestyramine, an anion-exchange resin, or activated charcoal can be administered.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug;

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product;

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product;

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50); and

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation).

The FDA has concurred with the study team’s assessment that the unapproved use of the study drugs meets the criteria for an IND exemption.

5.4 N/A

5.5 N/A

# Procedures Involved

6.1 This is a non-randomized, two-period, two-treatment, single sequence PK interaction study.

6.2

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| --- | --- |
| Audio/Video Recording | Physical Exam |
| Blinding | Radiation or Radiation-Producing Machines (e.g. X-ray, CT, etc.) |
| Control Group | Radioactive Materials (e.g. Radiopharmaceuticals) |
| Deception | Randomization |
| Focus Groups | Record, Chart, or Dataset Review |
| Follow-Up Call | Specimen Analysis |
| Interviews | Specimen Collection |
| New Innovative Practice/Therapy | Surveys and/or Questionnaires |
| New Investigational Procedure (e.g. a new surgical procedure) | Other Biomedical Procedures |

Study Flow Chart:

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Day 0  (Baseline) | Day 4  (± 2 Days) | Day 11  (± 2 days) | Day 18  (± 2 days) | Day 22  (±2 days) | Day 28  (±2 days) | Day 33  (±2 days) | Day  40  (± 5 days) | Day 50 |
| Informed consent | X |  |  |  |  |  |  |  |  |
| Inclusion/Exclusion criteria | X |  |  |  |  |  |  |  |  |
| Physical exam | X |  |  |  |  |  |  | X |  |
| Vital signs/pregnancy test | X | X | X | X | X | X |  | X |  |
| PK blood draw |  |  | X | X | X | X |  | X | X |
| CBC/CMP for safety | X |  | X |  |  |  |  | X |  |
| Dispense teriflunomide |  | X |  |  |  |  |  |  |  |
| Dispense colestipol hydrochloride |  |  |  | X |  |  |  |  |  |
| Review AEs/Medications |  | X | X | X | X | X | X | X | X |
| Review adherence | X | X | X | X | X | X | X |  | X |
| Follow-up call |  |  |  |  |  |  | X |  |  |

**Vital Signs**

Pulse, temperature, height/weight, blood pressure, and pulse. Blood pressure and pulse will be measured in the sitting position for all subjects.

**Pregnancy Testing**

Serum pregnancy tests will be carried out for women of child-bearing potential (WOCBP).

**CBC/CMP**

Safety labs will be drawn to review liver function and any other abnormalities that may lead the investigator to deem use of teriflunomide contraindicative and to follow-up at study conclusion for safety measures.

**Rapid Elimination Procedures**

Oral intake of cholestyramine or activated charcoal significantly accelerates the elimination of teriflunomide. The preferred rapid eliminationmedication is cholestyramine. Without using the rapid eliminationprocedure, it may take up to two years for teriflunomide plasma concentrations to reach acceptable low levels (≤ 0.02 μg/mL). All participants who discontinue teriflunomide early or in the case that the colestipol hydrochloride does not adequately eliminate teriflunomide based on blood levels (plasma concentration exceeding 0.02 μg/mL), the participant must be willing to undergo the rapid eliminationprocedure. This procedure must be carried out at the study site by the Principal Investigator.

The 11-day rapid eliminationprocedure must be initiated in all subjects who have

permanently discontinued teriflunomide. The recommended procedure is 8 grams

cholestyramine administered every 8 hours for 11 days. Alternatively, 4 grams of cholestyramine administered every8 hours for 11 days. Also, another alternative would be 50 grams oral activated charcoal powder administered every 12 hours for 11 days.

After treatment with either cholestyramine or activated charcoal, the teriflunomide plasma concentration will be measured. Feedback on plasma concentration above 0.02 μg/mL will be provided to all participants who meet this criterion. Both cholestyramine and activated charcoal may influence the absorption of estrogens and progestogens and reduce the effectiveness of oral contraceptives; therefore, the use of alternative contraceptive methods for women is recommended during the rapid elimination procedure. The contraindications of the rapid elimination medications will be completely reviewed by the Principal Investigator prior to the rapid elimination procedure.

**Screening/Baseline visit (120 minutes)**

At screening/baseline, informed consent will be obtained, demographics and medical history will be collected, inclusion and exclusion criteria will be assessed, vital signs will be taken, pregnancy test will be performed for all women, follicle FSH will be tested for women who are post-menopausal, CBC/CMP safety labs will be drawn, a physical exam will be performed, and subjects will be counseled on the importance of medication adherence.

**Visit 1 – Day 4 (90 minutes)**

Vital signs, adverse events and medication review, dispense teriflunomide, review labs, pregnancy test for WOCBP, review adherence.

**Visit 2 – Day 11 (60 minutes)**

Vital signs, adverse events and medication review, PK blood draw, pregnancy test for WOCBP, review adherence, CBC/CMP safety labs.

**Visit 3- Day 18 (90 minutes)**

Vital signs, adverse events and medication review, dispense colestipol hydrochloride, PK blood draw, pregnancy test for WOCBP, review adherence.

**Visit 4 – Day 22 (45 minutes)**

Vital signs, adverse events and medication review, PK blood draw, pregnancy test for WOCBP, review adherence.

**Visit 5- Day 28 (45 minutes)**

Vital signs, adverse events and medication review, PK blood draw, pregnancy test for WOCBP, review adherence.

**Follow-up call – Day 33 (15 minutes)**

Adverse events, medication, and adherence review.

**Visit 6 - Day 40 (60 minutes)**

Vital signs, physical exam, adverse events and medication review, PK blood draw, pregnancy test for WOCBP, CBC/CMP safety labs.

**Visit 7- Day 50 (15 minutes)**

PK blood draw, adverse events and medication review, review overall adherence/need for cholestyramine.

**Unscheduled visits**

Unscheduled visits will be arranged if the subject reports an adverse event that requires medical investigation.

6.3 N/A – there is no standard of care for healthy volunteers.

6.4 Patients will be screened for any contraindications (physical exam and lab work) to taking the included medications and evaluated per protocol inclusion/exclusion criteria. The risk to subjects in this trial will be minimized by compliance with inclusion/exclusion criteria, close clinical monitoring, avoidance of prohibited treatments, and adherence to investigator guidance regarding specific safety areas. If during the study, a female patient becomes pregnant or decides to attempt to become pregnant, or if a male patient decides to attempt to father a child, then she or he must stop the study medication and undergo the rapid elimination procedure. Female patients must not be breastfeeding or pregnant (as confirmed by serum pregnancy test) at the time of study entry and must agree to undergo serum pregnancy testing throughout the study at each clinic visit. In addition, a serum pregnancy testing should be conducted in case of an unexpected delay of menorrhea.

6.5 N/A

6.6 Blood samples will be collected via venipuncture standard practices. The samples will be immediately sent to Quest Diagnostics for processing. The samples will be stored at Quest until the results are reported to the study team. Samples will not be stored for future research and will not undergo genetic testing. The samples will be used to measure safety with CBC and CMP, pregnancy testing, follicle FSH, and for PK levels for analysis of elimination.

6.7 N/A

6.8 N/A

# Data and Specimen Storage for Future Research

7.1 N/A

7.2 N/A

7.3 N/A

# Sharing of Results with Subjects

8.1 N/A

# Study Timelines

9.1 Subjects will come into the office for 8 visits, and will have 1 phone call visit for a total of 9 hours. Unscheduled visits or a withdrawal visit will be scheduled as needed.

# Inclusion and Exclusion Criteria

10.1 Subjects will be prescreened prior to coming in for the screening/baseline visit. After consent, subjects will complete a medical history questionnaire and vital signs, a serum pregnancy test for WOCBP, and a blood sample will be taken to confirm eligibility.

10.2 Inclusion:

Participants having provided informed consent with signature on informed consent form: the informed consent process should be complete with full discussion of all requirements and possible risks.

Healthy volunteer (defined as free of concomitant medications and use of either treatment, as deemed by the Principal Investigator, is not contraindicated with any past medical history of the participant)

Aged 18–45 years, inclusive

Body Mass Index of 18–29 kg/m2 (body weight of 40–85 kg for women and 50–95 kg for men)

10.3 Exclusion:

1. Current smoker or past history as smoker.
2. Unable to provide informed consent to participate in the study Such as a mental condition rendering the participant unable to understand the nature, scope, and possible consequences of the study
3. Participant unlikely to comply with protocol as determined by Investigator
4. Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the participant at risk by participating in the study
5. Persistent significant or severe infection, either acute or chronic
6. Recent history of drug or alcohol abuse within that past 6 months (participants will be asked to refrain from alcohol and drug use during the course of the study)
7. Prior use of any investigational drug in the preceding 6 months
8. Liver function impairment or persisting elevations (confirmed by retest) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct bilirubin greater than 2x the upper limit of normal range (ULN).
9. Pregnant or breast-feeding women or those who plan to become pregnant during the study
10. Women of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy.
11. Participants wishing to parent children (be a partner in the conception of a child) during the course of the trial.
12. Participants with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia ***(confirmed by retest)***:
    * Hematocrit < 35% and/or
    * Absolute white blood cell count < ***3***000 cells/mm3 (μL) and/or
    * Platelet count < 150 000 cells/mm3 (μL) and/or- Absolute neutrophil ≤ 1500 cells/mm3 (μL)
13. Any known history of severe preexisting constipation
14. History of swallowing disorder or difficulty swallowing

10.4 Subjects will be withdrawn from the study if the investigator determines it is in the best interest of the subject after review of safety labs, adverse events, and medication changes. If the subject is lost to follow-up, he/she will also be withdrawn after attempts are made to bring the subject in for a withdrawal visit (if needed).

10.5 N/A

# Vulnerable Populations

11.1 N/A

# Local Number of Subjects

12.1 30 subjects will be recruited locally.

12.2 It is expected that 25 patients will be eligible to enter this study during the proposed timeframe. This sample size will be used for a pilot, PK level evaluation study and therefore is not powered.

# Recruitment Methods

13.1 Flyers will be posted around the USF community to recruit healthy subjects between 18 and 45 years of age. Subjects who are interested will be asked to contact the study team to complete a prescreen questionnaire.

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| --- | --- |
| Email | Online/Social Media Advertisement |
| Flyer | Record Review |
| Letter | Other |
| News Advertisement |  |

13.2

13.3 Potential subjects will be asked to contact the study team if interested in participating. No special or vulnerable populations will be recruited. While USF students may choose to participate, students are not the target population.

# Withdrawal of Subjects

14.1 Subjects will be withdrawn from the study if:

1. The Investigator considers it would be in the best interest of the subject (e.g. adverse events, intercurrent illness or onset of new clinically significant condition).
2. Female subject becomes pregnant.
3. Protocol violation which increases the risk to the subject.
4. Non-adherence to study medication regimen.
5. Use of any investigational drug other than the study medication.
6. Intake of prohibited medication.
7. Subject withdraws consent or is lost to follow-up.

14.2 The subject will be contacted immediately to schedule a withdrawal visit. If the subject cannot be reached on first attempt, second and third attempts to contact the subject via phone and email will be made.

14.3 If and when a subject withdraws from the study for any reason, all efforts will be made to complete and follow the participant through observations as thoroughly as possible. A final evaluation will be attempted in those willing to participate. Participants that have already taken any doses of teriflunomide will be asked to undergo the currently approved rapid elimination procedure (as outlined in 10.3.2) and will be notified if their values exceed 0.02 μg/mL after completion of the rapid elimination procedure.

# Risks to Subjects

15.1 Risks to this protocol include the potential harm that can be caused to subjects who become pregnant (or their partner) while taking teriflunomide. Teriflunomide is known to be teratogenic and can harm the growth of the fetus. Teriflunomide has also been known to cause diarrhea, nausea, increased liver enzymes, alopecia (hair loss/thinning), influenza, and paresthesia. During the duration of the study, participants should abstain from alcohol and drug use due to potential risk of the teriflunomide on liver function.  
  
Colestipol hydrochloride is generally regarded as safe but can cause gastrointestinal discomfort. Common side effects of the two medications include nausea, vomiting, diarrhea, and constipation. Due to the nature of colestipol hydrochloride, subjects who are taking concomitant medications, including oral contraceptives and over the counter vitamins, should administer these at least 1 hour before or 4 hours following the administration of the study drug.

Cholestyramine should not be used if the subject has a blockage in their digestive tract. Common side effects include nausea, stomach pain, loss of appetite, diarrhea, constipation, bloating or gas, irritation of the tongue, or itching/irritation around the rectal area. Subjects who are taking concomitant medications including oral contraceptives and over the counter vitamins should administer these at least 1 hour before or 4 hours following the administration of the study drug.

Risks associated with blood draws include bruising or minor pain at the puncture site.

There is a risk of breach of confidentiality, which will be mitigated as described in section 17.

15.2The effect of teriflunomide on human fetal development is unknown and may be potentially harmful based on results from animal studies. Therefore, all subjects must be fully informed as to this risk and provide written consent to not become pregnant or father a child during their participation in this study. If during the study, a female subject becomes pregnant or decides to attempt to become pregnant, or if a male subject decides to attempt to father a child, then she or he must stop the study medication and undergo the rapid elimination procedure.

Female participants must not be breast feeding or pregnant (as confirmed by serum pregnancy test) at the time of study entry and must agree to undergo serum pregnancy testing throughout the study at each clinic visit. In addition, a serum pregnancy test should be conducted in case of an unexpected delay of menorrhea.

Definition of “woman not of child-bearing potential”:

- Be post-menopausal (at least 2 years since last menses). Post-menopausal status must be

verified by a follicle FSH test at screening (Visit 1); or

- Be surgically sterilized (hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation). A woman of child-bearing potential (WOCBP) is any female who has experienced menarche and does not meet the criteria for “woman not of child-bearing potential”.

Women of child-bearing potential and male subjects must agree that they will take means to reduce reproductive risk by agreeing to use a double method of contraception. Acceptable methods of contraception are defined for this protocol as:

For male subjects:

- True abstinence: when this is in line with the preferred and usual lifestyle of the

subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)

- Male sterilization (with the appropriate post vasectomy documentation of the absence

of sperm in the ejaculate)

- Use of condoms throughout the study, in addition to spermicides is recommended.

For women of child-bearing potential:

- True abstinence: when this is in line with the preferred and usual lifestyle of the

subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)

-Highly effective oral contraceptives, such as biphasic and triphasic oral contraceptives

are considered adequate. Progestogene only pills or “mini pills” which have

demonstrated efficacy will be acceptable.

- Injectable hormones, hormonal implants, transdermal patches,

intrauterine device (IUD), intrauterine systems (IUS), or intravaginal ring

(NuvaRing) which have demonstrated efficacy comparable to high efficacy oral

contraceptives are adequate.

15.3 There may be a risk to the female partners of male subjects who become pregnant during the course of the study, as described in section 15.1. No other risks to others are anticipated.

# Potential Benefits to Subjects or Others

16.1 There is no expected direct benefit to subjects enrolled in this study.

16.2 If found to be efficacious, the results of this research may help patients with multiple sclerosis who take teriflunomide and need a rapid elimination of the drug with less side effects than the currently approved elimination procedure.

# Data Management and Confidentiality

17.1 Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). Non-parametric analyses will be used in situations where the variables are not normally distributed.

There will be no stopping rules based on statistical criteria as no interim analysis is planned. For all analyses, α will be set at 0.05. No correction for multiple comparisons is planned because this is a pilot study.

All subjects entered into the study at Baseline will be included in the safety analysis. The frequencies of AEs by type, body system and severity will be summarized. SAEs will be described in detail.

The quartile ranges will be reported for the teriflunomide concentrations at Day 28 and the average concentration decrease at Day 28 will be calculated with coefficients of variation. The decreasing trend of the teriflunomide concentrations will be illustrated over Day 22, Day 28, and Day 33.

17.2 Hard copy data including informed consents will be stored in the Principal Investigator’s locked office, in a locked storage cabinet. Individual subject data will be stored in a study binder, one for each subject, which will be stored in the locked storage cabinet. The binders and hard copy documents with the exception of the signed informed consents will be labelled with a unique subject ID. Binders will be removed from the cabinet as needed and will remain with a study team member at all times. Electronic data will be entered into a password protected file in REDCap. Only the study team will have access to the locked storage cabinet and the REDCap data.

17.3 All hard copy data will be verified against the data entered in REDCap on a weekly basis.

17.4 Identifiers include names, contact information (phone numbers, email addresses, mailing addresses), and dates will be collected. All data will be stored for a minimum of 5 years after the study is closed with the IRB, or after 6 years from the date of HIPAA authorization, whichever is longer. Hard copy data will be destroyed via secure shredding using a HIPAA compliant shredding method used by USF. Electronic data will be permanently deleted from REDCap. Confidential data and PHI will not be disclosed outside of the study team except as required by law or as allowed by the consent (e.g. with the USF IRB or those who monitor the study).

17.5

|  |  |
| --- | --- |
| Obtaining Signed Authorization | Waiver of HIPAA Authorization for Recruitment/Screening Purposes Only |
| Obtaining Online or Verbal Authorization (Alteration of HIPAA Authorization) | Data Use Agreement |
| Waiver of HIPAA Authorization for Entire Study | Business Associate Agreement |

Signed HIPAA authorization will be obtained via the informed consent process. During prescreening, verbal HIPAA authorization will be obtained over the phone prior to the collection of PHI. Identifiers collected via the phone screen will be entered directly into a prescreening form in REDCap, which is password protected. If the potential subject fails prescreening, identifiers will not be collected. If the potential subject declines to participate, identifiers will be destroyed upon declination. If the potential subject signs consent, their name and email address will be copied to a screening log in REDCap and removed from the prescreening form. Any remaining information on the prescreening form will be permanently deleted from REDCap when prescreening closes. PHI will not be reused/disclosed to any other person or entity except as required by law, for authorized oversight of the research, or for other research which use/disclosure of PHI would be permitted by the HIPAA privacy regulations. It is not practicable to obtain signed HIPAA authorization from potential subjects during prescreening as the prescreening will occur over the phone. Identifiable information collected during prescreening (names, email addresses) will only be collected if the potential subject meets the eligibility criteria. Health information will not be recorded during prescreening but will be reviewed to confirm eligibility.

# Provisions to Monitor the Data to Ensure the Safety of Subjects

18.1 N/A

18.2 Adverse events and safety labs will be reviewed at each visit by the Principal Investigator. Additionally, subjects will be instructed to call the study team to report new symptoms/adverse events. These adverse events will be recorded in the subject’s binder and in REDCap on cumulative adverse event log. If a serious adverse event is unresolved when a subject permanently discontinues the study, the subject will be followed until the event resolves or the clinical course is stabilized. A MedWatch form will be completed as necessary for serious adverse events.

An independent safety monitoring physician (Robert Moore, M.D.) will review safety labs and adverse events after the first 5 subjects are enrolled and then after the 15th and 30th subjects are enrolled. He will notify the study team if he determines that the study must stop for safety concerns. Dr. Moore will be charged with the responsibility of determining if the trial needs to be stopped based on lab criteria and data from any unexpected adverse events. These unexpected adverse events will be promptly reported to the independent safety monitoring physician.

Subjects will be withdrawn from the study if:

1. The Principal Investigator considers it would be in the best interests of the participant (e.g. adverse events, intercurrent illness or onset of new clinically significant condition)
2. Female participant becomes pregnant
3. Protocol violation resulting in a safety concern
4. Non-compliance to study medication regimen
5. Use of any investigational drug other than the study medication
6. Intake of prohibited medication
7. Subject withdraws consent or is lost to follow-up

The whole study will be stopped in cases where serious adverse events are experienced by 3 or more subjects and are not deemed unrelated to participation in the study by the Principal Investigator or the independent safety monitoring physician.

# Provisions to Protect the Privacy Interests of Subjects

19.1 All subject interactions will occur in a private room or lab setting. Subjects will be introduced to the various study team members by the Principal Investigator or study coordinator with whom they’ve already established a relationship through prescreening or the consent process.

19.2 The research team will obtain consent prior to receiving any information about subjects.

# Compensation for Research-Related Injury

20.1 There will be no compensation in the event of a research related injury.

# Subject Costs and Compensation

21.1 Subjects may incur some travel costs, which will be covered by the compensation.

21.2 Subjects will be given a $50 check in person at the end of each completed visit, with the exception of the follow-up phone call. Subjects will be mailed a $10 check after completion of the follow-up call. If a subject fails screening prior to labs being drawn, the subject will be compensated a prorated amount of $25. Potential subjects will not be compensated for the phone prescreen. Subjects who withdraw will receive payment for each visit they complete.

# Consent Process

22.1

|  |  |
| --- | --- |
| Obtaining Signed Consent (Subject or Legally Authorized Representative) | Obtaining Consent Online (Waiver of Written Documentation of Consent) |
| Obtaining Signed Parental Permission | Obtaining Verbal Consent (Waiver of Written Documentation of Consent) |
| Obtaining Signed Assent for Children or Adults Unable to Consent | Waiving Consent and/or Parental Permission (Waiver of Consent Process) |
| Obtaining Verbal Assent for Children or Adults Unable to Consent | Waiving Assent/Assent is Not Appropriate |

22.2 The consent process will take place in a private patient room in the USF Morsani Center for Advanced Health Care. Potential subjects will be sent the consent via email prior to their screening visit to review the consent at home. Subjects will be asked to review the consent again when they arrive for the screening visit, and to sign when all questions have been asked and answered. Significant consent changes will result in reconsent. Only the Principal Investigator and study coordinator will obtain consent. Potential subjects will be reminded of their rights before signing the consent.

22.3 Verbal consent will be obtained for the phone prescreening portion of the study only. The prescreening portion of the study is limited to a questionnaire which presents minimal risk to potential subjects. Written consent is not normally required for this type of questionnaire. The study coordinator will conduct the phone screen in a private office. If the potential subject would like to review the verbal consent prior to the prescreening call, the verbal consent document will be sent to the potential subject via email for review. All questions will be addressed prior to administration of the questionnaire. Potential subjects will be reminded of their rights before being asked to agree to participate in the prescreen.

22.4 N/A

22.5 N/A

22.6 N/A

22.7 N/A

# Setting

23.1 The prescreen and follow-up call will be conducted over the phone. The study coordinator will complete these calls in the study team’s private offices in the USF Morsani Center for Advanced Health Care. All in person procedures will be performed in private patient rooms in the USF Morsani Center for Advanced Health Care.