Discontinuation of levothyroxine therapy for patients with subclinical hypothyroidism: a pilot randomized, double-blinded, placebo-controlled study

Randomized Clinical Trial (RCT) protocol
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Principal Investigator (PI):
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Aim. Evaluate the feasibility of LT4 discontinuation among Veterans with SCH and determine the changes in quality-of-life measures, treatment burden, and adverse events.

Design: Double-blind, placebo-controlled randomized clinical trial
Performance site: CAVHS
Participants: Fifty veterans with LT4-treated SCH will be randomized to either (1) continue current dose of LT4 [pre-study dose] or (2) placebo. Up to 150 veterans will need to sign consent and HIPAA authorization to reach 50 randomized participants due to the anticipated screen failure rate. The screen failure rate accounts for participants whose baseline lab results (TSH, FT4 and LDL) are out of study range. Participants will be identified from CDW/Strategic Management (Aim 1) and referrals from CAVHS providers (including Primary Care or Endocrine clinic providers).
Exclusion Criteria: (1) TSH > 10 mIU/L (at any point), (2) LT4 dose more than 75 mcg daily, (3) use of antithyroid medications, amiodarone, tyrosine kinase inhibitors or lithium, (4) history of thyroidectomy or radioactive iodine therapy, (5) LT4 suppressive therapy for thyroid cancer, goiter or inflammation, (6) pregnancy or plans for pregnancy in the next 6 months, (7) an unstable medical condition that would jeopardize safety or interfere with study participation, (8) hospitalization for major illness within the previous 4 weeks, (9) severe hypothyroidism-related symptoms, (10) strong family history of hypothyroidism, (11) severe dyslipidemia, (12) acute coronary artery syndrome, acute myocarditis, or pancarditis or stroke within the previous 12 months, (13) Grade IV New York Heart Association (NYHA) heart failure, (14) receiving services from hospice, (15) lack of decision-making capacity, (16) terminal medical condition for which life expectancy would be less than 6 months, (17) not willing to stop LT4, (18) self-reported non-adherence to LT4 therapy and (19) abnormal TSH at time of screening for participation (assessed during Baseline Visit). Pregnancy testing will be performed for females of child-bearing potential that sign consent to participate in the study. The results will be reviewed prior to randomization.
Recruitment: We will send an **IRB-approved opt-out letter** to eligible veterans identified from CDW/Strategic Management or referral from CAVHS provider. The Principal Investigator (PI) has presented the study background, goals, and procedures to endocrinologists and primary care clinicians at CAVHS, answered questions, and got feedback from them (Development phase). A post-presentation poll of primary care physicians showed that 75% felt that LT4 discontinuation was acceptable in patients with SCH and 97% were comfortable with randomization of their eligible patients in the study. All endocrinologists felt that LT4 discontinuation was acceptable in patients with SCH and were comfortable with randomization of their eligible patients in the study. Clinicians were informed that Veterans under their care may be invited to participate and that those Veterans may want to discuss participation with their clinicians prior to enrolling. Before beginning to recruit, we will repeat the presentation to CAVHS clinicians who might prescribe LT4, including primary care, medicine, and endocrinology service clinicians, to refresh their memories and ensure that we reach clinicians new to CAVHS. In addition, an email with materials describing the study will be sent to clinicians who miss the presentation. Clinicians will be invited to contact the PI if they have questions or concerns about the study. The PI will utilize the Medicine and Primary Care quarterly conference to update clinicians. Study staff will send up to 100 IRB-approved opt-out letters weekly until all eligible veterans identified are sent the letter or 50 veterans are randomized (whichever occurs first). The pool of potential participants will be identified from CDW/Strategic Management and referrals from CAVHS providers. Women and minorities will be included in the study in proportion to their presence among CAVHS patients. We will submit and get approval for a **telephone script**. The designated study staff will call potential participants, with varying lengths of LT4 therapy, that do not opt-out (after at least two weeks from the mail date of the opt-out letter) and use the IRB-approved telephone script to guide the conversation.
Consenting: Written ICF and HIPAA will be obtained by the designated study staff prior to any study activities.
Intervention: (1) Continue current dose of LT4 [control or "sham discontinuation"] or (2) placebo [intervention or "real discontinuation"]

Randomization Scheme: 1:1, a randomized block design will be implemented to ensure group sizes are equal. Block sizes of 2, 4, and 6 will be used. In addition, randomization will be stratified by participant's pre-study dose of LT4.
Blinded Person(s): PI, Co-Investigators (Drs. Owen, Drummond), Research Coordinator/Study Staff (SC), Participant, participant's other clinicians (routine care), Biostatistician, Safety Monitor
Unblinded Person(s): Terri Dodds (Co-Investigator and Research Pharmacist), Jasmine Nichols (Research Staff and Research Pharmacy), Dustin Thompson (Research Staff and Pharmacist)
Study Medication Blinding Procedure: The brand of LT4 to be used in this study will be Synthroid® tablets of 25 mcg, 50 mcg, and 75 mcg (AbbVie Inc). The study drugs (LT4 and placebo) will be sourced, assembled, and packaged by the CAVHS Research Pharmacy. Over-encapsulation will be achieved using a capsule filler and will ensure that capsules are kept as small as possible for the ease of swallowing (DB capsules gelatin size AA, color: White Opaque, manufacturer: Capsugel).
Study Medication Dosing: Participants will be instructed to start the study medication the day after randomization. The study medication will be taken orally once a day. A two-month supply of study medication will be provided to the participant at (1) Baseline, (2) around the time of Clinic Follow-up 1, and (3) around the time of Telephone Visit 3 (Month 4). Study medication may also be provided (in-person or by mail) at an unscheduled visit for reasons such as loss of study medication or resupply.
Source of Information: CAVHS veterans
Use of Information: Evaluate the feasibility of LT4 discontinuation among veterans with SCH and determine changes in quality-of-life measures, blood lipids and adverse events.
Data Collected: (1**) Baseline Visit**: ICF, HIPAA, medical history, demographics, Vital signs (blood pressure and pulse, height and weight), study questionnaires (ThyPRO Hypothyroid symptoms and Tiredness scales, EQ-5D ThyPRO-39) and blood sample collection (TSH, FT4, lipids). (2) **Telephone Visit 1** (Month 1 +/- 3 days): Adverse event assessment and study medication compliance assessment. (3) **Clinic Follow-up 1** (6-8 weeks post randomization): Vital signs (blood pressure and pulse, weight), study questionnaires (ThyPRO Hypothyroid symptoms and Tiredness scales, EQ-5D), study medication compliance assessment, adverse event assessment and blood sample collection (TSH, FT4, TPO antibodies). (4) **Telephone Visit 2** (Month 3 +/- 3 days): Adverse event assessment and study medication compliance assessment. (5) **Telephone Visit 3** (Month 4 +/- 3 days): Adverse event assessment and study medication compliance assessment. (6) **Telephone Visit 4** (Month 5 +/- 3 days): Adverse event assessment and study medication compliance assessment. (7) **Clinic Follow-up 2** (Month 6 +/- 3 days): Vital signs (blood pressure and pulse, weight), study questionnaires (ThyPRO Hypothyroid symptoms and Tiredness scales, EQ-5D, ThyPRO-39, End of Study survey), study medication compliance assessment, assessment of integrity of blinding, disclosure of study medication assignment to participant, blood sample collection (TSH, FT4, blood lipids), duration of LT4 therapy and return to usual care plan. (8) **Unscheduled Visit:** an unscheduled visit(s) may be performed during the study. The unscheduled visit may be completed by telephone or in-person. Possible reasons for an unscheduled visit include safety assessment (such as lab collection for assessment of possible adverse event), repeat lab collection (test error or result confirmation), early termination (participant, Investigator, or joint decision) and/or study medication resupply.
Planned Analysis: Initial data analysis will include descriptive statistics for all variables, including assessment of potential outliers and the extent of missing data. If the missing data rate is small, < 5%, and found to be at random, then complete case analyses will be performed; otherwise, multiple imputation strategies will be explored. Data will be presented as frequencies for categorical variables and means (standard deviations) for continuous variables. We will compare characteristics between groups using t-tests for quantitative variables and chi-square tests for categorical variables. For the primary outcome, intervention feasibility, we will calculate participants' willingness to enter the trial (percent of eligible Veterans approached who consented to participate), recruitment rate (number of patients randomized divided by the length of the recruitment period, i.e., from the date that recruitment opened to the date of the last randomization). These measures will shed light on the anticipated acceptability of LT4 discontinuation. Finally, we will calculate completion rate for each arm. Secondary outcomes include changes from baseline to 6 months in the ThyPRO Hypothyroid Symptoms and Tiredness scores, EQ-5D, ThyPRO-39 and blood lipids. We will also assess changes in weight, body mass index, blood pressure,

and pulse. Analysis of covariance (ANCOVA) models will be employed to analyze these outcomes. Baseline measures and gender will be included in the models as covariates. A one-sided t-test will be used to determine whether the mean ThyPRO Hypothyroid Symptoms and Tiredness scores for the real discontinuation group differ from the mean ThyPRO Hypothyroid Symptoms and Tiredness scores of the sham discontinuation group by no more than 14 points. An α-level of 0.05 will be used to determine the statistical significance of the non-inferiority test for each ThyPRO domain. Failure to reject the null hypothesis will suggest that the QoL measures in the real discontinuation group, on average, are more than 14 points worse than in the sham discontinuation group. This will be considered as evidence against our conjecture that discontinuation does not negatively affect the QoL of patients with SCH. In addition, analyses comparing groups with respect to adverse event rates will be performed using chi-square tests. Analyses will be based on the intention-to-treat principle. Statistical analyses will be done using SAS 9.4 (SAS Institute, Cary, NC).

Additional details Analysis Plan: We will add a Biostatistician to the project. They will be hired through an IPA to work on the project. The Biostatistician will be sent the data set by encrypted email and will use computer software on their laptop (non-VA) to complete the analysis. No name, date of birth or SSN will be included in the data set for analysis. Those data points will remain within the VA protected environment.

Sample size estimates: The overarching goals of this pilot trial are to assess the feasibility of a subsequent, full-scale effectiveness trial and to obtain preliminary estimates of effect sizes. Thus, the pilot needs to be large enough to be informative about the feasibility of recruitment/retention and research procedures and to provide enough information on the efficacy of the intervention to justify and inform the planning of a full-scale trial. The primary endpoints of the full-scale RCT will be the ThyPRO Hypothyroid Symptoms scale and Tiredness scale scores. With an estimated standard deviation of 20 for ThyPRO hypothyroid scale score[52], from a study of patients with autoimmune hypothyroidism, a sample size of 23 Veterans per group will allow us to achieve 80% power using a 5% α-level to determine statistical significance for a one-sided t-test; accounting for a drop-out rate of less than 10%,[8,53] a final sample size of 50 patients will be required. This sample size is adequate both to assess feasibility and to obtain preliminary data on effect sizes.

Participant Compensation: Participants will be provided compensation for time and travel expenses as a result of participating in the study. The payments will be distributed as follows: (1) $50 for completion of Baseline Visit, (2) $50 for completion of Clinic Follow-up 1 (Month 2), (3) $50 for completion of Clinic Follow-up 2 (Month 6), and (4) $100 for completion of all study activities and End of Study survey. The participant will be paid within 4-6 weeks after each clinic visit. Payment will be issued by check or by electronic transfer of funds according to local medical center procedures. The participant name, SSN, address and date of visit are required to process the funds. An Internal Revenue Service (IRS) Form 1099 will be generated using the participant's SSN. On a case-by-case basis, the PI may authorize additional compensation to cover the cost of transportation (public transportation or gas mileage estimate).

Compliance and Withdrawal: We will provide an **IRB-approved pill diary** to all study participants. The study team will assess study medication compliance throughout the study. The pill diary may be reviewed at the follow-up clinic visits. Study medication compliance will be considered good if the participant reports taking study medication 80-100% of the time. **Participants may decide not to continue the study medication (LT4 or placebo) at any time. Additionally, the PI may decide not to continue the study medication for an individual (for example, following lab results). We will assist the participant to ensure that appropriate medication, if any, is started at the time of study medication discontinuation. If this occurs, the participant will be asked if they will continue the study (including follow-up visits, blood collection and study questionnaires) without continuing the study medication. If the participant agrees, they will be followed per protocol. If the participant does not agree, they will be classified as withdrawn from the study. We will document this occurrence, reason for discontinuation of study medication and participant decision to continue participation in the study (visits, blood collection and study questionnaires). Participants may agree to all or some of the study procedures.** We will instruct participants who discontinue the study

medication to dispose of any unused study medication in the manner in which they usually dispose of expired medications or offer to have them return the unused study medication to CAVHS. Participants may withdraw from the study at any time. Withdrawal by the participant will be defined as any participant that informs the study team that they do not wish to continue the study medication, do not wish to allow any further collection of data, and do not wish to have any further contact with the study team. If they do so, they will be considered withdrawn voluntarily from the study. We will document the circumstance(s) and reason(s) for participant withdrawal. The PI may also withdraw participants from the study. This may occur in the event of inter-current illness, adverse events, protocol violations, non-compliance, or administrative reasons. We will assist the participant to ensure that appropriate medication is started at the time of withdrawal. We will instruct participants who withdraw (or are withdrawn) from the study to dispose of any unused study medication in the manner in which they usually dispose of expired medications or offer to have them return the unused study medication to CAVHS. Participants withdrawn from the study will not be replaced. To avoid breaking the blind, results of Visit 1 (Month 2) laboratory tests will not be published in CPRS but will be recorded in the Veterans Information Systems and Technology Architecture (VISTA), which is not used by clinicians for lab review. These lab results will be reviewed by Unblinded Personnel.

Randomization Lab Criteria: Baseline lab results (TSH, FT4 and lipid profile) will be reviewed prior to randomization by the Investigator or SC. To qualify for randomization, TSH and FT4 must be within normal reference range and LDL must be ≤190 mg/dL. Normal reference range for TSH: 0.54 – 5.6 mIU/mL. Normal reference range for FT4: 0.47 – 1.41 ng/dL.

Study Medication Discontinuation Criteria: The Unblinded Personnel will notify Blinded Study Personnel (SC) if a participant develops OH or hyperthyroidism. At which point, the SC will be unblinded. Results will be communicated to participants and treating physicians by Unblinded Study Personnel and/or SC. The participant will be followed per protocol (following discontinuation of study medication) unless they decide to withdraw from the study at the time of study medication discontinuation. Lab criteria for study medication discontinuation: (1) TSH > 10 mIU/mL or (2) TSH < 0.34 mIU/mL or (3) FT4 < 0.47 ng/mL or (4) FT4 > 1.41 ng/mL. Study medication will be discontinued if any of the criteria are met. Unblinded Study Personnel will maintain a document for each participant with the Month 2 lab results. The document details the criteria for study medication discontinuation and process of notification. The document will be stored in the Unblinded Study Personnel binder in the Research Pharmacy office (a locked, private office) inside the Outpatient Pharmacy area (locked, private area). The SC will collect a copy of the document from Unblinded Study Personnel once the participant completes the study. The copy will be maintained in the participant folder in a locked file cabinet in a private office. The PI will not be alerted to study medication discontinuation. She may inadvertently become aware of study medication discontinuation, but she will not be informed of the reason (hypothyroidism or hyperthyroidism at Month 2) in order to maintain the blind through the planned analysis. Study medication may also be discontinued in the case of early termination (participant decision to withdraw, Investigator decision to withdraw or joint decision). In this case, the PI may be alerted to study medication discontinuation and study medication assignment.

Safety Monitor: A safety monitor (CAVHS provider) will be designated for the project. They will serve in the dual role of Safety Monitor and Pharmacy Compliance Monitor. A log will be maintained on the S drive detailing adverse events, including occurrence of hypothyroidism or hyperthyroidism at Month 2. The log will be completed by the SC. The Safety Monitor will be granted access to the log on the S drive. They will monitor for occurrence of significant adverse events at pre-specified timepoints (at least monthly) and ensure that the pharmacy is properly conducting the study per protocol. Scheduled monitor visits will be recorded and documented in the pharmacy regulatory binder.

Safety Considerations

Participants randomized to continuing LT4 treatment will continue to face side effects associated with chronic LT4 use, usually side effects indicative of excessive dosage (exogenous hyperthyroidism). Such effects include flushing, sweating, weight loss, tremor, restlessness, excitability, insomnia, angina pain, cardiac arrhythmias, palpitations, tachycardia, diarrhea, muscle cramps, muscle weakness, menstrual irregularities, and heat intolerance. Although, we do not anticipate any side-effects of continuing LT4 for participants who were already taking it as part of their usual care, at the baseline visit we will exclude participants with thyroid function test results suggestive of exogenous hyperthyroidism. We will also exclude patients who were not previously adherent to their LT4 treatment. This is a safety measure to avoid the possibility of developing exogenous hyperthyroidism for a patient who had normal thyroid labs at the baseline visit as a result of not receiving consistent LT4 therapy previously. All participants will have thyroid function tests 6-8 weeks after their initial visit, which is the recommended time to assess the effects of LT4 changes, and at 6 months post-randomization. If hyperthyroidism is confirmed, participants will be required to stop the trial medication and will be referred to their clinicians for treatment.

As with any medication, allergic reactions are a possibility. Allergy to LT4 is extremely rare and very unlikely to occur in patients who have been taking this medication chronically. Participants will have already been taking LT4 prior to enrollment in the study. If assigned to the LT4 group, the participant will continue the pre-study dose of LT4 throughout the study. Participants will be advised to notify the PI or research coordinator if they experience a significant rash, wheezing or other allergy symptoms.

LT4 interacts with the following drugs: anticoagulants, anti-convulsants, anti-arrhythmics, antidiabetics, beta-blockers, antidepressants, sympathomimetics, cardiac glycosides, antineoplastics, nonsteroidal anti-inflammatory drugs, sex hormones, lipid regulating drugs, and general anesthetics. However, it should be noted that interactions are generally weak and have very limited clinical relevance for the treatment of SCH with LT4. If Veterans' LT4-prescribers have concerns about their participation in the RCT, they will be invited to contact the PI.

The risks involved with discontinuation of LT4 (participants allocated to placebo) include development or worsening of hypothyroidism-related symptoms such as weight gain, fatigue, cold intolerance, body aches, muscle weakness, edema, depression, constipation, hair loss, dry skin, brittle nails, menstrual abnormalities, neck pain/discomfort, memory trouble and cognition issues. In patients with SCH, these clinical manifestations are usually mild. However, given the evidence that LT4 therapy does not confer important hypothyroid-symptom-related benefits for patients with SCH, it is unlikely that the participants who discontinue LT4 will experience the onset or worsening of hypothyroidism-related symptoms. Participants will be informed of this risk and the array of hypothyroidism-related symptoms. We will be monitoring for these side effects during the clinic visits and monthly phone calls and participants will be instructed to notify the PI or research coordinator if they experience these symptoms. Participants may return to the medication they were using before the study, at any time and for any reason. The PI will also discontinue study medication if ongoing treatment becomes inappropriate for the participant.

Fluctuating thyroid hormone levels may be harmful to a fetus. Because of this risk, women who are pregnant or plan to become pregnant are not eligible to take part in this study. We will ask women of child-bearing potential to use birth control for the duration of the study. Acceptable methods of birth control are: (1) hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants, (2) barrier methods, such as a condom or diaphragm, used with spermicide (a foam, cream, or gel that kills sperm), (3) intrauterine devices, and (4) abstinence (no sex). Women will be instructed to

notify the study team immediately if they miss a period or think they might be pregnant during the study. The PI may ask for permission to collect information about the outcome of the pregnancy.

There is a physical risk from blood collection. We plan to collect blood for research purposes three times during the study. We may collect additional blood, if needed, for safety assessment or repeat lab. The amount of blood collected will not exceed 17 mL per study collection. Possible risks of a blood draw include pain, bruising and/or infection, nausea, dizziness, and syncope. Both discomfort and bruising should disappear in a few days. The blood sample will be collected in the CAVHS Outpatient Lab in accordance with best practices to minimize any risks of possible adverse events. All personnel involved in the testing of blood samples will follow all needed safety and data security protocols. The risk associated with the blood collection for research purposes is not greater than the usual risk associated with standard of care.

There is a psychological risk that may be associated with the collection of quality-of-life information from RCT participants. The Veterans may be unaware of the extent to which they are experiencing symptoms, such as depression or memory loss. However, the study questions are similar to those encountered in clinical care and we have sought to use only the necessary measures that would have relevance for the participants. The questionnaires are self-administered, and the participants can skip questions that make them uncomfortable.

The clinical trial will be double blinded. Participant blinding to treatment allocation will be ensured through use of matched capsules for LT4 and placebo. However, when participants complete the clinical trial, they will be informed of whether they were allocated to LT4 or placebo and will be advised to discuss this with their usual (non-study) clinicians. In addition, there will be immediate response to requests for unblinding from clinicians if needed for optimal clinical care. A CPRS Research Note will have been written by the research coordinator describing the study procedures and listing emergency contact information. In the event that unblinding is needed for optimal clinical care, an attempt will be made to maintain blinding of the research team.

Full details of all adverse events of special interest (new atrial fibrillation, fractures, acute myocardial infarction, stroke, acute coronary syndrome, heart failure, mortality) including the nature of the event, relationship to study drug and outcome will be recorded. Adverse events of special interest will be monitored and followed up until satisfactory resolution or stabilization. All adverse events will be assessed for seriousness. Serious adverse events will also be assessed for causality, expectedness, and severity. This assessment will be carried out by the PI or designated Investigator. If the study demonstrates a convincing pattern of serious adverse events with either LT4 or placebo (LT4 discontinuation), this would be an important endpoint in its own right. If an association of adverse events is noted with either LT4 or placebo allocation, this would require careful consideration as to whether it is ethical and appropriate to continue with the trial. Adverse events will be recorded at all visits and telephone contacts. Participants will be informed of potential adverse events and advised to contact the study team if needed. Adverse events, adverse drug reactions, unexpected adverse reactions, serious adverse reactions, or suspected unexpected serious adverse events will be recorded, notified, assessed, reported, analyzed, and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations. The PI may withdraw patients from the study and refer them to their clinicians, who would be notified of the participant's study withdrawal, in the event of inter-current illness or adverse events.

A safety monitor will be designated for the project. They will be a CAVHS provider with medical knowledge and training sufficient to enable review of adverse events and identify any safety concerns for the project. A log documenting all adverse events, including hypothyroidism and hyperthyroidism at Month 2, will be maintained on the secure S drive behind the VA firewall by the SC. The safety monitor

will review the log at pre-specified timepoints (at least monthly). They will be blinded to the study medication assignment.

Consent Plan

Written ICF and HIPAA will be obtained by the study personnel prior to any study activities for the RCT. The ICF and HIPAA will be maintained in a separate folder, in a locked file cabinet in the research coordinator's office. The consent form will be reviewed with eligible veterans in a private room at CAVHS. The PI and/or research coordinator will conduct the consent discussion in-person. The eligible veteran will be given time to ask questions. All questions will be answered before the consent form is signed. The person conducting the consent discussion will ask the eligible Veteran questions during the consent discussion to ensure that the patient understands that participation is voluntary, treatment is available without participation in the study, the study purpose, study activities, and study medication schedule. The PI and/or research coordinator will ensure that the patient is able to understand the consent and to give informed consent for participation in the study.

Written, informed consent and HIPAA will be obtained from all eligible Veterans that voluntarily wish to participate in the study. A copy of the ICF and HIPAA authorization will be given to the participant. All consent forms will be in English. If the eligible Veteran cannot understand English, he/she will not be enrolled in the study.

Data Management

Adequate qualified staff are available for this research. PI is Dr. Spyridoula Maraka. She is an endocrinology physician and clinician researcher at CAVHS.

Strategic management service will send data via secure VA email with a password-protected database. Data will be stored on VINCI, secure S drive project folder assigned to the PI for this project and, possibly, REDCap. The servers can only be accessed by assigned VA personnel from behind the VA firewall. REDCap is the VA version for research and is not outside the VA protected environment. Additionally, data sets will be sent by encrypted email to the Biostatistician. They will use software on their laptop (non-VA) to complete the planned analysis. These data sets will not include name, date of birth or SSN. The Biostatistician will be hired through an IPA and will complete and maintain all required CAVHS research training and documentation. We will not grant access to the biostatistician until IRB approval of the personnel. They will use the data sets for the approved analysis only. The original data sets will be maintained with the electronic research records behind the VA firewall.

Study personnel will only access the data needed for completion of their work assignments. No study data will be stored on local hard drives. The PI will ensure that access to data is removed for any research staff member that leaves the study or no longer requires the access to the data for completion of work assignment.

The regulatory files will be maintained electronically. The submission documents for the CAVHS Institutional Review Board (IRB) and Research and Development (R&D) Committee will be maintained on IRB Net. No physical logbooks will be generated or kept for this study. All study logs will be maintained electronically on the HSR&D drive assigned to the PI for this study and/or the research file (S: drive) created for the PI of this study. An electronic storage form will be submitted with the initial project submission.

Paper source documents will be created at the study visits. The source documents will be submitted to the CAVHS IRB and R&D Committee for review with the initial project submission. Any updates to the source documents will be submitted to the CAVHS IRB prior to implementation. Paper source documents will be stored in the participant binders in locked file cabinets in the Coordinator's office at CAVHS.

Participants (RCT) will be assigned a unique study ID at signature of ICF and HIPAA authorization. Data collection forms (study questionnaires, study medication compliance diary, adverse event logs, source documents) will use the unique study ID. Names and social security numbers will not be used on the data collection forms.

All research staff members will maintain current privacy training. The data will only be used for the IRB-approved research. Modifications to the research plan will be submitted to the CAVHS IRB prior to implementation unless required for the immediate safety of the participant.

Study documents will be retained in accordance with the VA Records Control Schedule DAA-0015-2015-0004 (or the current VA Records Control Schedule at the time of study completion). The current schedule requires that research records be maintained for 6 years following the end of the fiscal year after completion of the research project. Upon study closure, hard copy records will be surrendered to Research Administration for storage until destruction.

Any talks or papers about this study will not identify the participant by name or other individually identifiable information. The information collected for this study will be kept confidential. A copy of the ICF and HIPAA authorization will be placed in the participant's medical per local policy. The information and biospecimens collected as part of this study will not be used or distributed for future research studies.

This project does not have a Data Safety Monitoring Board. It will use a **data and safety monitoring plan** to ensure (1) that the risk/benefit ratio does not change during the study, (2) that all study procedures are followed as written in the protocol and (3) that the confidentiality of research subjects is maintained. The PI or SC will be in touch with RCT participants by telephone at least monthly. Participants' safety (health status and side effects, if any) will be assessed during these calls, during clinic visits and, if necessary, during unscheduled visit/contact. Participants will be evaluated clinically via vital sign measurements and thyroid function blood tests 6-8 weeks post randomization, 6 months post randomization and, if necessary, during unscheduled visit/contact. In addition, responses to quality-of-life questionnaires will be reviewed for possible significant deterioration. Participants' blood lipids will also be assessed at baseline, 6 months post randomization and, if necessary, during unscheduled visit/contact. As described above, the SC will report adverse events and unanticipated problems to the PI or designated Investigator for assessment of relatedness to the study and seriousness. Serious adverse events will also be assessed for causality, expectedness, and severity by the PI or designated Investigator. Adverse events, adverse drug reactions, unexpected adverse reactions, serious adverse reactions, or suspected unexpected serious adverse events will be recorded, notified, assessed, reported, analyzed, and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations. Adverse events will be reported to the IRB per local policy and regulations. The PI and study staff plan to meet weekly to review all events observed or reported during the study as well as to review the recruitment and enrollment processes. These meetings will have documented meeting notes/minutes that will be disseminated to all study staff. A safety monitor will be designated for the project.

Quality Assurance

The primary responsibility for data quality will be performed by the PI. The PI will provide the medical knowledge (endocrinology) for the project. Designated research personnel will assist the PI with all regulatory submissions for the project.

Dissemination of Results and Publication Policy

Results of this study will be used for publications on indexed journals. The publications will not contain any identifiable information that could be linked to a participant.

Publications from this research will be made available to the public through the National Library of Medicine PubMed Central website within one year after the date of publication per the guidance provided on the ORD website.

A Limited Dataset (LDS) will be created and shared pursuant to a Data Use Agreement (DUA) appropriately limiting use of the dataset and prohibiting the recipient from identifying or re-identifying (or taking steps to identify or re-identify) any individual whose data are included in the dataset.

Electronic files containing final datasets will be made available to the public upon written request. Requests for access to the final datasets will be reviewed by the PI and a determination will be made within 30 days. Access to the final dataset may be granted under a written agreement between other Federal or academic institutions. Final datasets will be maintained locally until enterprise-level resources become available for long-term storage and access.

Final datasets will include a limited dataset to enable validation of results. The data that will be shared will include the variables used to conduct the analyses which underlie conclusions drawn and presented in publications resulting from this research.

Ethics

This project will comply with all VA regulations and research policies. The PI does not have any financial conflict of interest to declare for this project. The study is funded (award number HX003268-01A1).