



Manual of Procedures (MOP)

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1. Protocol Summary

Title	The Testosterone Trials
Protocol Number	808676
Study Design	Randomized, placebo-controlled, double-blind study of five coordinated trials
Study Duration	Six years
Study Centers	Multi-center set of trials involving 12 clinical sites geographically distributed across the United States
Objectives	The primary specific aims are to test the hypotheses that testosterone treatment of elderly men whose serum testosterone concentrations are unequivocally low – and who have symptoms and/or objectively measured abnormalities in at least one of five areas that could be due to low testosterone (physical or sexual function, vitality, cognition, and anemia) – will result in more favorable changes in those abnormalities than placebo treatment.
Number of Participants	800
Diagnosis and Main Inclusion Criteria	A constellation of conditions that occur as men age will be studied: mobility disability, decreased libido, low vitality, reduced memory performance, as well as anemia, all of which could be at least partially the result of low testosterone. Primary entry criteria will be age ≥ 65 years, an unequivocally low testosterone concentration (< 275 ng/dL in the morning, twice), and symptoms and objective manifestations of mobility disability, low libido, or low vitality.
Study Product, Dose, Route, Regimen	AndroGel [®] , testosterone in an alcohol-water gel, will be administered transdermally in doses from 5 to 10 grams per day, as necessary to maintain the serum testosterone concentration within the range of normal for young men.
Duration of administration	AndroGel or placebo will be administered to each participant for 12 months.
Reference therapy	The effects of AndroGel on the primary and secondary end points will be compared to effects of placebo on these end points.
Statistical Methodology	The primary end points for each of the five trials (Physical and Sexual Function, Vitality, Cognitive Function and Anemia) will be analyzed separately by random effects models for each specific trial.

2. Study Overview

2.A. Objectives

The primary specific aims of the coordinated set of randomized, placebo-controlled clinical trials are to test the hypotheses that testosterone treatment of elderly men whose serum testosterone concentrations are unequivocally low – and who have symptoms and/or objectively measured abnormalities that could be due to low testosterone (physical or sexual function, vitality, cognition, or anemia) – will result in more favorable changes in those abnormalities than placebo treatment. The trials are highly coordinated, but each trial has its own primary, secondary, and exploratory specific aims.

2.B. Description

Each of the twelve participating clinical centers will plan to enroll approximately 67 men aged 65 and older, to establish the baseline cohort of 800 participants. The T Trial sites will strive to include a racially and ethnically diverse group of men.

2.C. Study Organization

2.C.1. Clinical Sites

Twelve (12) clinical sites are responsible for recruiting, enrolling and following T Trial study participants according to the protocol and established procedures. Key clinical site staff includes the Principal Investigator (PI) Co-Investigator (Co-I), Study Manager, Nurse or Nurse Practitioner, Research Coordinator (RC), Recruiter/Scheduler, and Lab Technician. The roles of the research staff vary among institutions and may include some or all of the study responsibilities. It is the responsibility of all members of the study team to adhere to the study protocol and Manual of Procedures (MOP). The participating clinical sites are:

Site #	Site	Location
11	Albert Einstein College of Medicine	New York, NY
12	Baylor College of Medicine	Houston, TX
13	Boston University	Boston, MA
14	Northwestern University	Chicago, IL
15	University of Alabama at Birmingham	Birmingham, AL
16	University of California at Los Angeles	Torrance, CA
17	University of California at San Diego	San Diego, CA
18	University of Florida	Gainesville, FL
19	University of Minnesota	Minneapolis, MN
20	University of Pittsburgh	Pittsburgh, PA
21	VA Puget Sound Health Care System	Seattle, WA
22	Yale University	New Haven, CT

2.C.2. Laboratory and Reading Centers

CENTRAL LABORATORY & READING CENTERS

Central Biochemistry Laboratory	Quest Laboratories, Van Nuys, CA
Interactive Voice Response Services (IVRS)	Criterion, Inc., Saratoga Springs, NY
Investigational Drug Service (IDS)	University of Pennsylvania, Philadelphia, PA
Lymphoblastoid Cell Line Core	Cedars-Sinai Medical Center, Los Angeles, CA
Cognitive Function Testing Center	Wake Forest University School of Medicine Winston-Salem, NC
Prostate Biopsy Reading Center	Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA
Clinical Monitoring Services	KAI Research, Inc., Rockville, MD

2.C.3. Data Coordinating Center

The University of Pennsylvania, School of Medicine, in Philadelphia, PA, serves as the administrative center for the research network. The Center for Clinical Epidemiology and Biostatistics and the Clinical Research Computing Unit (CRCU) function as the Data Coordinating Center (DCC) for the study in providing comprehensive regulatory oversight, research management, tools and technology for this clinical trial.

2.C.4. Sponsors

The National Institute on Aging (NIA), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) and Abbott Laboratories, Abbott Park, Illinois, are the sponsors of the study.

2.C.4.a). FDA and IND Status

The Food and Drug Administration (FDA) will oversee the trial. It has been assigned Investigational New Drug (IND) # 104707.

2.C.5. Clinical Site Responsibilities

Clinical site investigators and staff will participate in planning and implementing all trial research activities and are responsible for all direct interactions with study participants in recruiting, enrolling and following study participants. The trial will require significant effort at the clinical site in administering the many assessments, procedures and questionnaires that comprise the clinical visits. Specific expertise and/or training will be required in the areas of assessing medical problems, physical function testing, cognitive function testing, and using the data management system. The Principal Investigator is responsible for the overall study conduct and all site related activities.

2.C.6. Training

A minimum of two site staff members should attend the initial training session and subsequent sessions conducted over the course of the study. All members of the site staff should read the protocol, Case Report Forms (CRFs) and Manual of Procedures (MOP) in preparation for the start of the study.

As roles and responsibilities will vary among sites, delegation of responsibility for the conduct of study procedures such as administration of informed consent, drawing blood, conducting the physical function test, and administration of cognitive function tests should be clearly defined and documented on the Staff Delegation of Responsibilities Log.

When a staff member leaves the study team, or a new staff member joins the study team, a new delegation log must be completed and sent to the DCC. The DCC should be notified anytime a staff member leaves the study so they can be removed from distribution lists and so that any access they have to T Trial tools can be removed.

One or two staff members should be designated as the Lead Trainer at each site. This person will be responsible for ensuring that T Trial procedures are performed only by appropriately trained staff members. In addition, the Lead Trainer will oversee training of all staff members as well as new staff.

Two clinical site staff members should attend all data management system (DMS) training sessions. They in turn will serve as a resource for new users, as needed. All users of the DMS will be required to perform the required skills listed on the Data Management Certification Checklist (DMCERT).

The DCC will provide all training materials and checklists for documentation of training. In addition, the DCC will provide webinar training and make training materials available to clinical site staff members via the website. Each clinical site is responsible to maintain training files for each staff member of The T Trial study and be able to provide these materials for review by the DCC or during a site monitoring visit.

2.C.7. **Communication**

2.C.7.a). **Distribution Lists**

Distribution lists will be used to communicate with clinical sites and to distribute study documents. The DCC will manage the access of study members to the list tool. If the clinical site staff changes or requires different access to a particular list, a site staff member should contact the DCC to provide complete information about the access required for a particular individual. The following list includes the Testosterone Trial lists that have been established to date:

ttrial-rr@lists.upenn.edu	Recruitment and Retention Committee members
ttrial-rc@lists.upenn.edu	Research Coordinators
ttrial-sitepi@lists.upenn.edu	Principal Investigators
ttrial-steering@lists.upenn.edu	Steering Committee members
ttrial-anc@lists.upenn.edu	Ancillary Studies Committee
ttrial-dci@lists.upenn.edu	Data Collection Instruments Committee
ttrial-op@lists.upenn.edu	Operations Committee
ttrial-qa@lists.upenn.edu	Quality Assurance Committee
ttrial-cv@lists.upenn.edu	Cardiovascular Committee
ttrial-ivr@lists.upenn.edu	Interactive Voice Response System Committee
ttrial-lab@lists.upenn.edu	Laboratory Committee
ttrial-urology@lists.upenn.edu	Clinical Site Urologists
ttrial-cog@lists.upenn.edu	Cognitive Function Testers and Wake Forest
ttrial-pjm@lists.upenn.edu	DCC Project Managers

ttrial-dataentry@lists.upenn.edu

T Trial data entry personnel

ttrial-qa@lists.upenn.edu

T Trial QA committee

2.C.7.b). **Email**

DCC personnel will also use email to send documents and current information to T Trial study members. Email lists and individual addresses will be used to send meeting information and documents to site staff. DCC staff members are easily accessible by email and will reply to questions and requests for information as soon as possible.

2.C.7.c). **Contact List**

A contact list will be developed and revised regularly to provide clinical site staff members with current email and phone contact information for all DCC, laboratory, and reading center personnel.

2.C.7.d). **Web Landing Page**

A web landing page will provide all T Trial members with one interface from which to access study news, calendar, documents, case report forms, the data management system and tools for entering study data and all other relevant study information. The public section of the website will be made available to potential participants to obtain information about the trial. The private section of the website will require a username and password in order to provide a secure environment from which to access study documents and reports.

The address of the web landing page is: <http://www.ttrial.org>

2.C.7.e). **Helpdesk**

The T Trial DCC will operate a helpdesk to assist users in accessing the data management system. The DCC will staff the helpdesk Monday through Friday from 9 AM to 5 PM (Eastern). Assistance from the DCC helpdesk is focused on access to tools and technology to enter study data. The helpdesk contact information is listed below:

Phone: (215) 573-4623

Email: crcuhelp@mail.med.upenn.edu

Fax: (215) 573-6262

3. **Recruitment**

3.A. **Methods**

A wide variety of methods will be used to inform and recruit men into The Testosterone Trial. The Recruitment and Retention Committee will evaluate and adapt techniques that have been used successfully by network sites and work collaboratively to employ selected methods at all sites. In addition, sites may employ techniques they have used successfully in the past. They include the following:

- **Mass Mailings.** Many types of lists have been used successfully to target mass mailings by zip code, including retirement communities, retired employee groups (military, unions), and graduates of local universities of appropriate graduating classes printed centrally for economy of scale and distributed locally.

- **Local Presentations.** Investigators and staff have been successful by talking to local physicians at medical grand rounds and other local medical meetings, so they are aware of the trial when participants ask. Talks to lay groups at senior centers may also yield participants. Two slide presentations have been developed to describe the study; one will address medical/professional groups and the other will be directed to older men.
- **Radio Ads.** Sites have highlighted their success with radio advertisements in this demographic.
- **Direct recruitment at residential facilities for the elderly.**
- **Providing transportation.** Given the age of the participants in this study, we have planned for transportation - drivers or taxis - for participants who need it.
- **Competition among sites.** Monthly conference calls with a representative from each site will review recruitment reports to share successful recruiting methods and solve problems.
- **National and Local Media.** National media, including network television, newspapers and magazines, are quite interested in testosterone and have featured previous studies conducted by several of the investigators in this study.
- **ClinicalTrials.gov.** The study is listed on the NIH web site, ClinicalTrials.gov.

ClinicalTrials.gov Identifier:	NCT00799617
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3.B. Eligibility Criteria

The list below summarizes the study eligibility criteria. As it includes a wide variety of medical conditions, some may require further evaluation by the Principal Investigator or designated study physician. If there is confusion about an individual participant's status or concern about a person's suitability for the trial, the site staff should consult the PI and the DCC for guidance. Eligibility data are collected between Prescreening and Screening Visit 2. After SV2 all data will be evaluated for eligibility in specific trials. During the trial informed consent process at the baseline visit, specific trial eligibility and interest are used in alignment to enroll and randomize a participant into at least one, or more than one, trial.

3.B.1. Inclusion Criteria

Inclusion criteria:

- Men ≥ 65 years old
- Total serum testosterone concentration ≥ 100 and < 275 ng/dL (SV1) and ≥ 100 and < 300 ng/dL (SV2) at 7 -10 AM at each of two screening visits. The average of the 2 T levels must be < 275 ng/dL.

Note: T levels less than 100 at SV1 or SV2 must be evaluated by a physician for continued screening eligibility.

3.B.2. Exclusion criteria:

3.B.2.a). Alcohol/substance abuse

- Alcohol or substance abuse within the past year (based on self-report)

3.B.2.b). Blood Pressure and Body Mass Index

- Body mass index (BMI) > 37 kg/m²

- Hypertension defined as blood pressure of >160 mmHg systolic and/or >100 mm Hg diastolic blood pressure

3.B.2.c). Diagnosed illnesses

- Angina not controlled by treatment
- Kidney disease requiring dialysis
- Known skin intolerance to alcohol or allergy to any of the ingredients of testosterone gel
- Myocardial infarction within 3 months before entry
- NYHA class III or IV congestive heart failure
- Severe pulmonary disease that precludes physical function tests
- Skin conditions at the testosterone gel application site, such as ulcer, erosion, lichenification, inflammation, or generalized skin conditions such as psoriasis or eczema that might affect testosterone absorption or tolerability of the testosterone gel
- Sleep apnea, diagnosed but untreated
- Stroke within the previous 3 months

3.B.2.d). Labs and test scores

- Severe lower urinary tract symptoms (score of >19) by the International Prostate Symptom Score questionnaire
- TSH value > 7.5 mIU/L
- Hemoglobin <10 g/dL or >16.0 g/dL. Subjects who have hemoglobin level below 10 g/dL will be referred to their primary care providers for evaluation of anemia.
- Serum creatinine >2.2 mg/dL
- ALT 3x upper limit of normal
- Hemoglobin A1c >8.5%
- Mini Mental State Exam (MMSE) Score <24
- We will exclude men who have major psychiatric disorders, including major depression (PHQ-9 score >14), mania, hypomania, psychosis, schizophrenia or schizoaffective disorders, that are untreated, unstable, have resulted in hospitalization or medication change within the previous three months, or would result in inability to complete the trial efficacy parameters. Subjects whose disorders have been stable while being treated for more than three months are eligible.

3.B.2.e). Language

- Ability to speak and understand English

Several standard forms in use in the T Trial have been validated in Spanish and are available for use in the study. However, not *all* forms are available in Spanish and several forms are being administered by the Interactive Voice Response (IVR) System in English only. In order to be as inclusive as possible and still maintain standard methods for collecting all data, we will have to exclude men who speak Spanish (or any other language) exclusively, and are unable to read and respond to questionnaires in English. Participants who enroll in the study

must be able to interact with the study instruments in English.

It must be noted on the cognitive function test booklet if English is not the participant's first language.

3.B.2.f). Medications

- Drugs that affect serum testosterone concentration, (eg, testosterone, androstenedione, DHEA, estrogens, GnRH analogs, spironolactone, and ketoconazole) within the previous three months.
- rhGH or megestrol acetate within the previous three months.
- Anti-depressant medication that has been introduced within the past three months. (Subjects with diagnosed depression who have been stable for more than three months while taking anti-depressant medication are eligible.)
- Prednisone (dose of greater than 5 mg daily) use daily for more than two weeks, or equivalent doses of other glucocorticoids for more than two weeks during the previous three months.
- Opiate abuse within the past three months. Subjects who are using opiate analgesics intermittently for relief of chronic pain at doses that do not exceed the equivalent of 20 mg methadone daily will be included. The following doses of opiate analgesics are considered equivalent:
 - Methadone 20 mg
 - Hydrocodone 30 mg
 - Oxycodone 30 mg
 - Morphine sulfate 30 mg
 - Codeine sulfate 200 mg

3.B.2.g). Prostate and other cancers

- Diagnosed prostate cancer or prostatic intraepithelial neoplasia (PIN) or, by the Prostate Cancer Risk Calculator, a >35% risk of having overall prostate cancer or >7% risk of having high grade prostate cancer.
- Diagnosis, or treatment for cancer, within the past 3 years; with the exception of nonmelanotic skin cancer

3.B.3. Inclusion and Exclusion Criteria by Trial

Each trial has its own eligibility requirements that must be met in order to participate. In addition, a man must indicate that he agrees to participate in the specific trial when he signs the consent form.

As of October 2012, approval for amendment 15/16, men must be eligible for either the Bone or CV ancillary studies, in addition to one of the main trials listed below (physical, sexual or vitality) in order to be enrolled in the T Trial. Eligibility assessment details for these trials are included in the Bone and CV study MOPs.

3.B.3.a). Physical Function Trial

Inclusion criteria: symptomatic mobility disability, defined by

- Self-reported difficulty in walking one-quarter mile and/or
- Self-reported difficulty climbing a flight of stairs
- Walking speed <1.2 m/sec on the 6-minute walk test

Exclusion criteria:

- Not ambulatory
- Other conditions affecting mobility of sufficient severity that testosterone is unlikely to improve, including neurological conditions (stroke, multiple sclerosis) and severe disabling arthritis of the lower extremity, joints, or back

3.B.3.b). Sexual Function Trial

Inclusion criteria:

- Decreased libido, defined by a score of ≤ 20 on the DISF-M-II SR questionnaire
- Sexual partner willing to have sexual intercourse \geq twice/month

Exclusion criteria:

- Medical or nonmedical reasons that would preclude sexual activity (e.g., penile deformity, Peyronie's disease, pelvic surgery for bladder cancer)
- Severe peripheral vascular disease associated with an absence of pedal pulses
- Autonomic neuropathy based on assessment

3.B.3.c). Vitality Trial

Inclusion Criteria:

- Decreased energy, self-reported
- Low vitality, defined by a score <40 on the FACIT-Fatigue Scale

3.B.3.d). Anemia Trial

Inclusion Criterion:

- Hemoglobin concentration <13.5 g/dL, the lower limit of normal for the central laboratory

Exclusion Criterion:

- Hemoglobin <10.0 g/dL

3.B.4. Cognition Trial

Cognitive function tests will be performed in all men in all trials, so there will be no specific inclusion or exclusion criteria for this Trial

During the informed consent process, participants will be asked for permission to audio-tape the testing sessions. Participants may refuse and continue to participate in the study. This is done for quality control purposes at the Wake Forest University (WFU) Cognitive Function Reading Center. Recordings will be erased after scoring is completed.

3.C. Pre-screening Process

Pre-screening may occur in person at a health fair or during a presentation at a senior center, but it is anticipated that it will occur primarily when a potential participant calls the clinical site contact number to inquire about the trial based on information in the study brochure or from other media.

Clinical site personnel will respond to participant inquiries about the trial by completing the Prescreening [PSCR] form.

3.C.1. Initial Eligibility Assessment [PSCR]

The first prescreening consent question (#1) must be asked in order to collect and save prescreening data. The first pre-screening question is; “Do I have your permission to collect and record this information?” If your IRB has instructed you to read a prescreening consent form or script, you must do this before completing the rest of the form.

Potential participants will be asked several questions about medical history that indicate preliminary eligibility for the trial. Follow the directions after each question to determine preliminary eligibility.

Bookmark the NHLBI Body Mass Index (BMI) calculator in order to quickly calculate the BMI and inform a participant if he is eligible to proceed to the next screening step.

<http://www.nhlbisupport.com/bmi/bmicalc.htm>

If a participant responds to any item that renders him INELIGIBLE (see form), complete the last question on the form (Is the participant eligible to proceed to Screening Visit 1?) to indicate this status.

If a participant responds to a question that defers eligibility such as having knee replacement surgery in the last 6 months, ask him to call back when the appropriate amount of time has passed. Ask the open-ended question about medical conditions or physical limitations that would prevent full trial participation.

If a participant is eligible based on the responses to the questions on the Prescreening form, he should be scheduled for Screening Visit 1.

Record complete contact information in order to schedule and remind participants about the Screening Visit 1 appointment. Instruct participants to fast (consume nothing but water after midnight) before the morning appointment for the blood draw.

The data collected on this form must be entered into the T Trial PRESCREENING Data Management System (DMS).

Participants may be re-screened at this phase. This may happen if they have been deferred as described above or it was determined that they were ineligible during a previous screening visit. Men who are pre-screened again for the trial should be assigned a new pre-screening number. This re-screening status should also be indicated on the PRSC form.

3.C.2. Assigning Pre-screening Number

Prescreening ID numbers will be generated by the electronic Data Management System (DMS). A series of unique numbers will be listed each time you enter a new PSCR form into the DMS. Select the next available (unassigned) number and transcribe it onto the Prescreen (PSCR) form in order to

link the form with the data. If this participant proceeds to Screening Visit 1, you will assign a Participant Identification (PID) number from your site specific, preprinted PID LOG. Site specific PID logs are located on the T Trial website. These two numbers will be linked via the Standard Visit Form (SCVST1).

4. Informed Consent Administration and Protocol Implementation

4.A. Informed Consent Requirements

Prior to answering questions on the pre-screening survey, the participant will be asked for his permission to collect data. A pre-screening consent form or script should be developed to ensure uniformity in the informed consent process.

If a participant proceeds to Screening Visit 1, the first step is to obtain informed consent during Screening Visit #1. This must be done before drawing blood or collecting any study data. The consent form signed at this time is for the tests and questionnaires at Screening Visits #1 and #2 only. If eligible, a separate consent form will be administered for the trial.

Each clinical site is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB), and State Department of Health requirements. The informed consent form must be obtained (signed and dated by the participant) prior to initiation of study related activity. Specifically, the following must be accomplished during the informed consent process:

- The participant must be informed that participation in the study is voluntary and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed that the study involves research.
- The participant must be informed of any alternative procedures.
- The participant must be informed of any reasonable foreseeable risks.
- The participant must be informed of any benefits from the research.
- An outline of safeguards to protect participant confidentiality must be included, as well as an indication of which parties are allowed to review the record and of the participant's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if they decide to enroll.
- The participant must be informed of his right to have questions answered at any time and of whom to contact for answers or in the event of research-related injury.
- The participant must be informed that he will be notified of any safety-related changes in the protocol that might affect his willingness to continue in the study.
- The participant must be informed as to whether or not any compensation will be offered for participation in the study and whether any medical treatments are available, and if so, what they consist of.
- The participant must be provided with a HIPAA authorization to sign, either as a part of the informed consent or as a stand-alone document to be presented at the time of consent, which details all potential risks of disclosure and individuals and organizations who may have access to participant research data.

4.B. Administration of Informed Consent

The Coordinator will provide the potential participant with a copy of the Informed Consent Form so that he can read and consider participation in the T Trial study. (You may consider sending a blank form to the participant in the mail so that he may read in before the scheduled Baseline Visit.)

The informed consent form should be reviewed in a setting where the participant is able to make a free choice without coercion and undue influence. Ample time should be provided for a participant to thoroughly read and process the information. Because the enrollment process of this study must occur in a limited time period, it is important that the study staff be particularly mindful of time influence during the administration of the informed consent and not allow time limits to unduly effect how they administer the informed consent or convey study information. The Coordinator should review the consent with the participant and answer any questions. The participant should be made aware of his/her responsibilities throughout the Treatment and Follow-up phases of the trial. The importance of treatment compliance and continued follow-up should be stressed. This is balanced with a discussion of the effect of participant withdrawal on the study.

If the participant expresses uncertainty about participation or indicates a need to delay in making a decision about participating, the RC should suspend consent process and ask the participant to contact the clinical site staff if he would like to resume the process. It is helpful to explain the visit schedule to the potential participant so that he can assess the time commitment involved in consenting to the study.

The Informed Consent Form must be signed and personally dated by the participant and the person “obtaining consent”. A participant should not be asked to sign the consent statement if he has any doubts about enrolling or if the staff believes he does not understand what his participation would involve. Under no circumstance is study information to be collected from the participant or study procedures performed for the specific purpose of the trial before the participant has signed the informed consent form.

During the informed consent process, participants will be asked for permission to audio-tape the testing sessions. Participants may refuse and continue to participate in the study. This is done for quality control purposes at the Wake Forest University (WFU) Cognitive Function Reading Center. Recordings will be erased after scoring is completed.

4.B.1. Documenting Informed Consent

The Coordinator will maintain the original consent document in the participant’s confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the participant. A second copy of all informed consent(s) should be made as a back up and stored together in the “study-confidential file.” In addition, a signed/dated progress note must be made in each participant’s research file documenting that the informed consent was obtained before conducting any study procedures.

Participants will be asked to sign a consent form for screening visits 1 and 2, the trial consent form, a pharmacogenetics consent form and a separate form for each ancillary study associated with the trial.

To ensure confidentiality, the Coordinator will not send copies of the informed consent form(s) signed by the participant to the DCC or keep any copies of the informed consent form with the case report forms (CRFs).

4.C. HIPAA

Participants must sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization in addition to the Screening and Trial Informed Consent Forms. The HIPAA Authorization may or may not be incorporated into the T Trial consent depending on the policy of the clinical site. However, if the HIPAA language is incorporated into the Informed Consent Form, the regulation mandates that it be submitted to the IRB for prior approval. This form describes both the kinds of health information collected in this study and also all of the disclosures of health information that will be made. The form must also list parties to whom disclosures of personal health information will be made.

4.D. Confidentiality

Extensive efforts will be made to ensure and maintain participant confidentiality, except as may be required by law. All identifying information must be maintained in a secure area at all times and must never appear on CRFs. Consent form(s) must be maintained in a separate folder from original CRFs. If source documentation must be made available for data audits, copies of the source documents should be forwarded to the DCC with only Participant ID number visible and personal information obscured.

The DCC staff has access to the Participant ID number for data management purposes. All communication between the DCC staff and the clinical site staff regarding participant data occurs via the Participant ID number only.

A Certificate of Confidentiality (CoC) has been obtained from the NIA by the DCC that encompasses all participating clinical sites. This certificate ensures that researchers cannot be forced to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative or other proceedings.

5. Data Management

5.A. Collecting data

T Trial data are obtained through interviews, self-report, laboratory tests and targeted evaluations. The participant should be reassured that confidentiality is maintained on all collected data, throughout the course of the study. Participants should be urged to use their “best estimate” rather than leaving a question unanswered. However, exercise caution that you do not paraphrase or answer questions on the participants’ behalf. The data collected should adhere to the following general rules:

- Print legibly and clearly on all study documents – Case Report Forms (CRFs), Source Documents, Lab Forms, etc.
- Always use a ballpoint pen with **black or blue ink**. Do **NOT** use pencil or multi-colored ink (green, red, etc).
- Do not use erasers or correction fluid.
- If an error is made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be clearly initialed and dated. The correct response *may* be circled for clarification, if necessary.

- Dates **must** match any source or supportive chart, lab, or evaluative documentation. The approved format for collecting dates is Month / Day / Year. If only partial dates are available, write in the known data and supply “01” for the missing information. For example, if a participant answers “June of 2009”, but cannot recall the exact day, enter 06 / **01** / 2009.
- Times are collected in *standard* (12-Hour AM & PM) and *military* (24-Hour) clock formats. The CRFs will specify which collection method is being utilized. If only a partial time is available, write in the known data and supply “01” for the unknown units of time. For example, if a participant answers “a little after 4PM”, but cannot remember the exact amount of minutes, enter 04:01 PM (12-Hour) or 16:01 (24-Hour) clock.
- Always use participants’ initials, not full name on CRFs or any other information that is submitted (electronically or copied and sent) to the DCC. In cases where participant has no middle initial, use an “X”.
- Provide signature and date as required on forms.
- Avoid using abbreviations when collecting and entering data.
- Be clear, concise, and to the point when completing CRFs, writing comments, or providing additional / supportive information.
- Do not write comments in the margins or on the reverse side of the CRFs.
- Completely fill in study information at the top right corner of each CRF.
- Questions should not be left unanswered. If a participant chooses to leave a question blank, write “ND per participant’s choice”, date and initial next to the blank question. When data queries are issued for missing data fields, one can respond appropriately by referencing the CRFs.
- Even though medical / chart information may contradict participants’ response, do not alter participant responses on the participant completed CRFs.
- Site staff will review all CRFs for inconsistencies and missing information **before** the participant leaves the area, and will attempt to collect any missing data.
- A **FORM NAME** is located in a box in the bottom right corner of the CRF pages; this is an abbreviation of the form name and is used in structuring the form layout within Oracle™ Clinical Remote Data Capture (RDC).
- Each CRF is dated and identified with a version number, located in the bottom left corner. This number is important should a CRF become revised at a later date. Note the version number and date of each form, should it change for any reason you will be notified.

When soliciting information from the participant, attempt to get a reasonable answer from the participant; if their answer is unclear, incomplete or irrelevant, it is acceptable to repeat the question, refocus and redirect the participant, and use “probing techniques”. However, do not lead the participant or attempt to answer on their behalf.

Some samples of “probing techniques” are:

- **Basic Probe:** Repeat the question to get the participant back on track; this technique can be used when the participant is “going off on a tangent”.

- **Explanatory Probe:** Used to get clearer understanding by completing the incomplete statements of the participant. The questioner asks questions like, “Can you give me an example of that?” or “Can you explain that?”.
- **Focused Probe:** Used to get particular understanding about a topic. For example, “What type of ... did you use?”
- **Silent Probe:** The questioner maintains silence and waits for the participant to break silence. This type of technique is generally useful when the participant is taking a lot of time to respond or is hesitant to respond.
- **Drawing Out:** Used when the participant has stopped and is not responding. The questioner restates or rephrases the last question or topic (ergo: “So, the question was...” or “What else can you tell me about...”), which helps the participant start talking again.

5.B. Identifying and acquiring Case Report Forms (CRFs)

Case Report Forms (CRFs) can be obtained directly from a hyperlink on the Main Landing page by accessing the Study Documents section of the T Trial website. CRFs are available as Adobe Portable Document Files (pdf) in visit packets or as single forms.

- Site Staff are responsible to print CRF packets for participants.
- **NOTE:** It is not recommended that Site Staff print complete CRF visit packets for each participant at the time of enrollment (e.g. full set of CRFs from Prescreening through Month 24). Rather, the staff should print only a few packets in advance of the participant’s current or impending visit. This method will:
- Ensure that all CRF packets printed represent the current version of the approved CRFs.
- Reduce wasted paper by potentially replacing newer versions of forms with older versions.
- The DCC will notify the Clinical Centers of CRF revisions which include changes to old CRFs and the introduction of new CRFs. The DCC will instruct the staff how to incorporate CRF changes into the study and how updates will impact the Data Management System (DMS) during the standing Research Coordinator teleconferences.
- Along with CRFs the Main Landing Page will also house Administrative forms, which are supplied to provide additional information and supporting documentation of the day-to-day study functions.
- **NOTE:** Administrative forms are not entered into the database.

5.C. Case Report Form Completion Guidelines

Case Report Forms for the T TRIAL Study can be:

- Participant Completed
- Site Staff Completed
- A combination of the above

5.C.1. Participant Completed CRFs

- “Participant Completed” forms are completed by the participant either during their clinic visit or at home via the Interactive Voice Response System (IVRS).
- During the completion of the CRFs at the clinic, if a participant makes any mistakes they should be instructed to draw a line across the error response, initial and date next to the error to

indicate who made the error correction and provide the date the correction was made. The correct response should be written legibly above or near the original response.

- If the Site Staff believes that the participant may have trouble reading the CRFs, the staff member may read the questions to the participant but should not answer or complete the CRFs on behalf of the participant.
- When the participant completes the CRFs, the staff member will check the forms for completeness. After the CRFs are reviewed, forms should be entered into the data management system within 48 hours.

5.C.2. **Site Staff Completed CRFs**

- Site Staff Completed CRFs are administered to the participant by the appropriate questioner by interviewing the participant, or gathering the information from study measures (e.g., anthropometry, medication review, etc).
- Use the probing techniques described in section 5.A. to garner further information.
- Site Staff will ask the participant to elaborate or reconsider an incomplete or inappropriate answer without leading the participant or influencing the content of the answer (creating bias in the participants answer).
- Be mindful of sensitive or painful issues for the participant and exercise sensitivity when asking questions.
- Reassure the participant regarding the confidentiality of their response and explain the importance of the question if the participant seems hesitant.
- If information can be obtained from study methods – Blood Pressure, Hip Measurements, Waist Measurements, Lab Device, etc – make certain that all answers are completed.
- Upon completion, check forms for legibility prior to performing data entry.

5.C.3. **Review of Completed CRFs**

Site Staff will complete the following.

- Review all CRFs for legibility, accuracy, and completeness prior to entry into Oracle™ Clinical Remote Data Capture (RDC).
- All CRFs should be entered into DMS within 48 hours of being received or collected by Site Staff.
- Correct any errors with a single line in **blue or black ink**, enter the correct information on the CRF, and initial and date the change. Any changes made in RDC should be reflected on the paper CRFs and vice versa. The CRF-to-database records should be identical and act as a secondary audit trail system.

5.D. **General Directions for Competing Study-Specific Case Report Forms (CRFs)**

This section will outline the different types of study-specific CRFs:

- Prescreening CRF
- Administrative Forms
- Data Entry CRFs

5.D.1. Prescreening CRF

The Prescreening form is used to determine preliminary eligibility for entrance into the trial screening process.

- Those participants who successfully pass the prescreening process will be able to progress to the next step in the screening process.
- Those participants who do not successfully pass the prescreening process will not be able to progress to the next step in the screening process.
- Prescreening form should be filled out when a potential participant contacts the Study Site. The Prescreening form should be entered into the data management system as soon as possible, ideally within 2 days.
- The prescreening data can be found in the Oracle™ Clinical “study” book labeled T TRIAL_PRESCREEN. See the T TRIAL User’s Manual for more information.

5.D.2. Administrative Forms

- Administrative forms are designed to manage different aspects of study administration, - Screening, Contact, etc. and are not data collection points but are useful in the day-to-day operations of the study.
- Administrative forms are not entered into RDC.
- Some of the administrative forms contain private and confidential participant information – such as name, address, contact numbers, etc – and must be locked in a secure location. Forms that contains Protected Health Information (PHI) should never be submitted to the DCC.

5.D.3. Data Entry CRFs

Refer to the T Trial User’s Manual:

Data Entry CRFs represent those forms that are completed by Site Staff and / or the participant, and are entered into RDC. These forms are used to gather valuable Primary and Secondary Endpoint data, safety data, and efficacy data. It is vital to ensure that all questions are answered in their entirety before entry into RDC.

5.E. Description of Study Tests and Questionnaires

The following is a brief description of the study tests in the specific trials (vitality, physical, sexual, cognitive) and the overall study. The cognitive questionnaires (TMT, BVRT, Card Rotation, 3MSE, WMS-R-LM-II- verbal memory paragraph recall) are described in detail in the Cognitive Function Training Manual of Procedures provided by Wake Forest.

5.E.1. General Tests

IPSS

The International Prostate Symptom Score (IPSS) is an 8 question (7 symptom questions + 1 quality of life question) written screening tool used to screen for, rapidly diagnose, track the symptoms of, and suggest management of the symptoms of the disease Benign Prostatic Hyperplasia (BPH). The IPSS was designed to be self-administered by the participant, with speed and ease in mind.

This test will be done at Screening Visit 2, Baseline, Month 3 and 12 and as needed

whenever a participant reports worsening of urinary symptoms such as incomplete emptying, weak stream, frequency, etc. **A Screening Visit 2 score that is >19 will exclude a participant from the study.**

During the treatment phase, the IPSS total score will be monitored for changes, relative to the baseline score. An increase in score > 5 points or to an absolute score of > 19, above the baseline value will lead to urologic consultation. The Principal Investigator will be informed by the DCC that this change has occurred and must arrange for the participant to consult with the study urologist or his own urologist. The urologist may request information about the participants' treatment arm and lab tests over the course of study participation; these will be provided to the urologist by the DCC.

FALLS

The Falls scale will be used to measure a baseline number of falls that participants experience and then will be used as a follow up measurement of the number of falls participants experience over the course of the trial.

The FALLS scale is administered to all participants at baseline and at months 3, 6, 9 and 12.

**Participant
Impression of
Change Questions**

These questions are used to monitor the participants' baseline impressions, and subsequent changes in impression, of their overall health status (all trials), walking ability (for the physical function trial), sexual desire (for the sexual function trial), energy level (for the vitality trial), and memory (for the cognitive function trial).

After Screening Visit 2, participants will respond to all questions about their baseline impression in all 5 areas: general health, physical, sexual, vitality and cognitive. At months 3, 6, 9 and 12, participants will answer the general health and cognitive questions as well as the questions that reflect the trial in which they are participating. Participants will answer these questions using the IVR system.

**The 6 Minute Walk
Test**

The object of this test is for a participant to walk as far as he can, on a flat surface, in 6 minutes. The 6 minute walk test will be conducted at Screening Visit 2, baseline, and months 3, 6, 9 and 12; in all study participants.

PF-10

PF-10 is a 10 item physical functioning scale focused on activities of daily living. It is done by participants in the Physical Function trial only; at Baseline, Months 3, 6, 9, and 12.

5.E.2. Sexual Function Tests

UCLA Sexual Diary

UCLA Sexual Diary, also known as the Psychosexual Daily Questionnaire is a self-reporting questionnaire with components to assess sexual desire, enjoyment, performance and activity, as well as positive and negative mood.

After Screening Visit 2, all men who may be eligible for the trial will complete the entire diary for 7 consecutive days between SV 2 and the scheduled baseline visit. This will serve as the baseline measure.

After the baseline visit, only men in the Sexual function trial will complete the entire

diary for 7 consecutive days after the clinical visit at Months 3, 6, 9, and 12. However, all of the men in the trial will complete only Question #4 of the diary for 7 consecutive days at Months 3, 6, 9, and 12.

This questionnaire will be completed using the Interactive Voice Response (IVR) System. Once the diary is begun, it must be completed daily over the next 6 consecutive days. This can be monitored on the IVR webboard.

<https://upenn.criteriuminc.com/>

IIEF The IIEF is the International Index of Erectile Function Questionnaire, which asks questions about the effect of erection problems on the participant's sex life, over the past 4 weeks. This will be completed only by those participants enrolled in the sexual function trial at baseline and months 3, 6, 9, and 12.

DISF-M The Derogatis Interview for Sexual Functioning – Male Questionnaire is a self-report survey of sexual thoughts and activities during the last 30 days. This will be completed only by those participants enrolled in the Sexual function trial at baseline and months 3, 6, 9, and 12.

5.E.3. Vitality Tests

FACIT- F is the Functional Assessment of Chronic Illness Therapy scale for Fatigue, specifically designed to measure feelings of tiredness. **The short version (13 statements) of the FACIT-F is being used in this study. This questionnaire will be completed by Interactive Voice response (IVR). All participants will complete the FACIT- Fatigue scale after Screening Visit 2, and at months 3, 6, 9, and 12.**

PHQ-9 The Patient Health Questionnaire-9 (PHQ-9) is a self-report version of the Primary Care Evaluation of Mental Disorders for use in primary care with 9 questions. The PHQ-9 will be conducted at screening visit 2, on paper, to screen for depression. Those participants who have a score > 14 will be excluded from the study. All participants will complete the PHQ-9, via IVR, after screening visit 2 and at months 3, 6, 9, and 12.

PANAS The Positive Affect Negative Affect Schedule (PANAS) is a psychometric scale developed to measure the largely independent constructs of positive and negative affect both as states and traits. All participants will complete the PANAS, via IVR, after screening visit 2 and at months 3, 6, 9, and 12.

SF-36 The Short Form (36) Health Survey is a survey of participant health. The SF-36 is commonly used in **health economics** as a variable in the **quality-adjusted life year** calculation to determine the **cost-effectiveness** of a health treatment. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health.

The entire SF-36 will be conducted by all participants at the baseline visit. Data collected at the

baseline visit will be collected on a paper form. Thereafter, the SF-36 vitality subscale, which consists of 4 questions, will be conducted only by those enrolled in the vitality trial, via IVR, after baseline, and at month 3, 6, 9, and 12.

5.E.4. Cognitive Function Tests

MMSE The Mini-Mental State Examination (MMSE) or Folstein test is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in **medicine** to screen for **dementia**. It is also used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment.

This test is done once only at Screening Visit 2. A score of less than 24 will exclude a potential participant.

6. Screening and Enrollment

This section outlines the activities, evaluations, and procedures for the visits that occur from Prescreening thru Randomization.

6.A. Summary of Activities, Evaluations, and Procedures

6.A.1. Visit Schedule and Windows

Study Visit	Visit #	Type	Window
PRESCREENING CONTACT		Phone	3 months
SCREEN VISIT 1	1	Clinic site	4 months
SCREEN VISIT 2	2	Clinic site	
BASELINE	3	Clinic site	
MONTH 1	4	Clinic site	+ or – 7 days
MONTH 2	5	Clinic site	+ or – 7 days
MONTH 3	6	Clinic site	+ or – 7 days
MONTH 4	7	Phone	+ or – 14 days
MONTH 5	8	Phone	+ or – 14 days
MONTH 6	9	Clinic site	+ or – 14 days
MONTH 7	10	Phone	+ or – 14 days
MONTH 8	11	Phone	+ or – 14 days
MONTH 9	12	Clinic site	+ or – 14 days
MONTH 10	13	Phone	+ or – 14 days
MONTH 11	14	Phone	+ or – 14 days
MONTH 12	15	Clinic site	+ or – 14 days
MONTH 18	16	Clinic site	+ or – 30 days
MONTH 24	17	Phone	+ or – 14 days

As of September of 2011 we have extended the window from telephone screen to SV1 from 60 days to 3 months and extended the window from SV1 to baseline visit from 90 days to four months.

The interval between Prescreening and Screening Visit 1 (SV1) is now 12 weeks or 3 months. The interval between Screening Visit 1 and the Baseline Visit is 16 weeks or 4 months. The date of the baseline visit is the anniversary date, upon which all subsequent visits and visit windows are determined.

Month 1, 2, 3 – plus/minus 7 days

Month 6, 9, 12 - plus/minus 14 days

Month 18 - plus/minus 30 days

Phone contacts at Months 4, 5, 7, 8, 10, 11, 24 - plus/minus 14 days

Every effort should be made to enroll men within the scheduled visit window for the study visit. If a participant cannot be enrolled within the study visit window time frame, then a protocol deviation form must be completed and submitted to the DCC. If such deviations need to be submitted to the site's IRB, then the form should be simultaneously submitted to the DCC and the site's IRB.

The protocol deviation/ violation form is an administrative form which can be found on the T Trial website, ttrial.org. The form is not entered into the data management system.

6.A.2. Missed Study Visits

At Months 1 and 2, a visit will be considered missed, and thus cannot be completed, if it occurs within the opening of the next visit window. For example, if the visit window opens for the Month 2 visit on the 23rd, the month 1 visit must occur by the 22nd. If the Month 1 visit does not occur by the 22nd, it will be considered a missed visit. In the case of a missed visit, complete the MISS visit CRF which can be found as a PRN form on the TTRIAL website, ttrial.org. The MISS CRF should be entered into the DMS.

For Month 3, a visit will be considered missed if it does not occur by 45 days after the end of the visit window around the 3 month anniversary date. The Month 3 visit has a 1 week window on either side. A Month 3 visit must occur within 45 days after the of the visit window.

For Months 6, 9 and 12 a visit will be considered missed if it is 45 days after the 2 week window of the target date. For example, if the target date for a 6 month visit is the 1st, the 2 week visit window ends on the 14th, if the visit does not occur 45 days after the 14th, it will be considered missed (roughly the 29th of the following month). In this case a MISS form must be completed and entered into the DMS.

6.A.3. Participant Visit Schedule Report

The DMS has a feature to generate a Participant Visit Schedule Report to provide guidance to the staff and participant about the schedule of study visits and telephone contacts that will occur after the baseline visit. This schedule is generated by Participant ID# and is accessed through the DMS tab on the website. See example below.

The visit schedule for participants is based upon the start date of drug which is entered on the DOSE log. Sites will not be able to generate a visit schedule until this date and dose are entered onto a participant's dose log.

				Participant ID: 101234 Participant Initials: CHH
Participant's Date of Randomization:		11/02/2009		
Participant's Kit Number:		(Drug Kit #)		
Participant's Cognitive Function Packet:		ABC		
Participant's Trials:		Physical Function Sexual Function		
Visit Name	Open Window	Target Date	Close Window	Comments
Month 1 – Clinic Visit	11/25/009	12/02/2009	12/09/2009	
Month 2 – Clinic Visit	12/25/2009	01//02/2010	01/09/2010	
Month 3 – Clinic Visit	01/25/2010	02/02/2010	02/09/2010	
Month 4 – Telephone Visit	2/17/2010	03/02/2010	3/16/2010	
Month 5 – Telephone Visit	03/19/2010	04/02/2010	04/16/2010	

6.A.4. Cardiovascular Substudy Visit Schedule Report

Men enrolled in the CV substudy will have a baseline visit followed by a CT scan at separate visit. Participant should not begin using gel until the CT scan has been completed; this scan should be scheduled within **2 weeks** of the baseline visit. The coordinator should receive confirmation that the CT scan has been completed by the CT technologist or department contact and then promptly contact the participant and instruct him to begin applying gel. The baseline visit should occur as usual for men in the CT substudy and gel should be distributed but men should be instructed not to use the gel until after the CT scan. **The DOSE log should not be completed until after the scan has been conducted. The DOSE log should be started after the scan has taken place and the participant has been called and told to begin using gel.** Record on the DOSE log the date a man started using gel. In some cases this may be the date he was called and in other cases it may be a day later, depending on any information the participant may provide at the time of the phone call. Once the DOSE log has been entered with a start date of gel listed it will be possible to generate a visit schedule for men in the CV substudy which will be about 2 weeks later than the baseline visit.

6.A.5. Bone Substudy Visit Schedule Report

Men who are enrolled in the bone study will have a baseline visit followed by a QCT scan (the DXA scan is done prior to the QCT and before the baseline visit since it is an eligibility criteria for the bone trial) potentially at a separate visit from the baseline visit. Participants should not be using gel until the QCT scan has been performed. Once a QCT scan has been performed either call the participant, or tell them in person that they can begin using gel. This should be recorded as the start date on the DOSE log for the participant. If a participant informs you that he started gel prior to his scan, still complete the DOSE log with the start date but be sure to complete a protocol deviation that gel was started prior to the scan. This should be submitted to the DCC and, depending on local reporting requirements at your institution, your IRB. The QCT must be performed within 2 weeks of the baseline visit. Any scans outside of 2 weeks should elicit a protocol deviation which should be sent to the DCC.

6.A.6. Physical Function Enrollment- Changes to Eligibility Criteria

When the T Trial initially began the enrollment gait speed for the physical function trial was <1 m/s. This was changed in August of 2011 to <1.2 m/s, at which time the DCC sent lists to individual sites of the men who were already randomized who would now qualify for the physical function trial. In order to enroll these men in the physical function trial men should sign either the original baseline consent form, indicating participation in the physical function trial, or an addendum consent form. Randomized men can be entered into the physical function trial, after they have already been randomized, anywhere from month 1 all the way to month 24.

When entering randomized men into the physical function trial DO NOT change their RAND Form to indicate enrollment in the physical function trial, instead enter the form labeled REASSESS and mark enrolled in physical function trial. This will enable the DCC to monitor randomized men who are subsequently enrolled into the physical function trial.

The DCC also sent lists to sites of men who were excluded from enrollment into the T Trial only because they were not eligible for a single individual trial who became eligible for physical function with the criteria change in gait speed. If these men were seen for an SV1 and an SV2 within the past 6 months, they may be called and asked if they would like to come in for a baseline visit and be randomized. If men had an SV2 or an SV2 and SV1 which are over 6 months old, these men will require an SV3 visit to be completed before they can be consented and randomized. The sv3 procedure will work exactly as detailed in section 6.A.11. After clearing an SV3 visit, these men can be randomized to the physical function trial. Men who fall into this category will be tracked separately by the DCC for enrollment into the physical function trial.

6.A.7. Sexual Function Trial Enrollment

In February of 2012 the sexual function trial met its' enrollment goal while the other 2 main trials, physical function and vitality, were still busy enrolling. At that time an amendment was submitted, amendment 11, which specified men could only be enrolled in the sexual function trial if they were eligible for one or both of the other trials; vitality and physical function. In January of 2013 all 3 of the main trials completed enrollment. In February of 2013 we submitted amendment 18, which specified men can enroll in the sexual function trial if they are eligible for either bone, cv or both. Since men were turned away in the past year if they were only eligible for sexual function, the Steering Committee decided these men could be re-contacted and have an SV3 visit to see if they were still eligible. Lists of men who were excluded because they were only eligible for sexual function, and were seen in the past year, were sent to the sites. Sites should follow the procedures outlined in section 6.A.13 of the MOP to follow up with these men.

6.A.8. Telephone Pre-screening

Potential participants will call the site in response to advertisements, or other recruitment materials, and will be asked for consent to collect information. If the potential participant agrees, the pre-screening questionnaire should be completed in order to determine preliminary study eligibility. Potential participants will be asked if they are 65 or older, general questions about their eligibility for the trials and medical history questions. Answers to these questions will determine eligibility for the next screening visit. The steps below should be completed during pre-screening.

1. Prescreening consent, if required
2. Prescreening questionnaire
3. Prescreening Eligibility Determination
4. Data Entry

6.A.8.a). Telephone Prescreening Preparation

The following materials are needed to conduct the Telephone Prescreening visit:

- Telephone
- List of potential participants
- Telephone Prescreening Script
- Telephone Prescreening Case Report Form (CRF)

6.A.8.b). Telephone Prescreening Conduct

Study Coordinator / Clinic Staff / Research Assistant:

- Greet the participant and explain the study following the Telephone Prescreening Script
- Ask for permission to ask, collect, and enter information for prescreening purposes. If required, read the pre-screening consent to the participant over the phone and mark that they concurred with the terms.
- Ask the Prescreening questions in the order in which they appear on the form. This will inform decisions about exclusion criteria if it becomes necessary to re-evaluate these criteria.
- Ask questions on Telephone Prescreening CRF:
- If a response indicates that a participant is not eligible, do not proceed with completing the rest of the prescreening CRF. Provide an explanation why he is ineligible and thank him for his time.
- Ask question on the BONE PSCR CRF. If a participant is not eligible for the bone trial, as of October 2012, they cannot continue further in the screening process. Thank them for their time and end the call.
- Complete the form by answering the last question: "Is this participant eligible to proceed to Screening Visit 1?"
- **IMPORTANT NOTE:** It is essential to ask questions 5 and 5a at prescreening contact. These are the physical function trial eligibility questions and they are only asked during this prescreening visit. Be sure to ask both of these questions and record the answers on the source CRF and in the DMS.
- If participant is eligible, collect contact information on the administrative form (CONTACT) and schedule his Screening Visit 1.
- If participant indicates on the pre-screening form (PSCR) that he was diagnosed in the past 3 years with nonmelanoma skin cancer this should be noted as it will need to be reviewed at Screening Visit 1. Any diagnosis or treatment for other cancers within the last 3 years is exclusionary and these men should be schedule for SV1.
- When calling for the day is complete, begin making participant screening visit binders for those participants who have been scheduled

- Coordinate with site staff regarding upcoming scheduled visits of potentially eligible participants

Data Entry and Discrepancy Management (Must be a certified study coordinator/clinic staff/research assistant)

Review the Prescreening (PSCR) CRF:

- If the participant is eligible, enter the prescreening data into the Data Management System (DMS). For eligible participants there are several required fields that must be entered into the database: questions 1, 2, 21 and 22 and the physical function question, 5 and 5a These questions indicate that the participant is eligible to proceed to Screening Visit 1.
- If questions 5, 5a, 6, and 7 are all answered negatively, the participant is **not** eligible for any of the three (3) trials because he does not meet inclusion criteria for any of the trials. Enter the responses to questions 1, 2, 5, 5a, 6, 7, and 21.
- If the participant is ineligible, enter the criterion that renders the participant ineligible. If the participant is ineligible there are 6 required fields that must be entered into the database; questions 1,2,5, 5a, 21, and whichever question renders the participant ineligible for the study. This will allow data to be reported on ineligibility.
- Note that participants who report cancer treatment (question 20) must be evaluated during SV1 to assess their overall health status and ability to participate in the trial for 2 years.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure Data Management System (DMS) as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab utilizing a screening number
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

6.A.9. Screening Visit 1

During SV1, participants will come to the clinical site and the screening informed consent process will be conducted. Information collected at this visit will be used to determine preliminary trial eligibility. After signing the consent form, blood will be drawn and information will be collected about medical history, and demographic data. Blood drawn at this visit must be between 7 – 10 AM. Participants must be in the fasting state, which is defined as drinking water only after midnight of the night before the clinical visit. The following activities will occur at Screening Visit 1:

1. Screening Informed Consent
2. Fasting Venipuncture – T Level & PSA (Reflex) & Metabolic Panel (Reflex)
3. Demographic Data Collected (DEMO)
4. Brief Medical History and Medications (MHX1)
5. NCI Prostate Risk Calculation (RISK)
6. Screening Eligibility Determination (SCVST1E)
7. Data Entry
8. Data Discrepancy Management

Screening Visit 1 Preparation

The following materials are needed to conduct the Screening Visit 1:

- IRB Approved Screening Informed Consent
- Screening Visit 1 form packet
- Venipuncture equipment and barcoded / labeled vials for research collection samples
- Contact the participant to review the fasting requirements

Drawing and Processing Blood

Important: Blood must be drawn between 7 AM and 10 AM for both screening visits, the baseline visit and all follow-up visits. Participants must be in the fasting state for **all** blood draws. Fasting is defined as drinking only water after midnight of the night before a clinical visit that requires drawing blood. If the blood draw happens to take place after 10AM contact the DCC. If the draw is past 10:30 then a protocol deviation will definitely need to be submitted.

If a participant has not been fasting for a blood draw, it is recommended that the clinical site staff schedule another appointment to have a fasting blood specimen drawn. This may mean asking the participant to return to the clinical site or to make other arrangements to have a fasting sample drawn as soon as possible. This could include making a home visit or providing transportation to the site for collection of the sample. Depending on the time, distance and reliability factors, each site should evaluate the likelihood of losing contact with a participant versus collecting a non-fasting specimen.

Quest labs recommend that blood is centrifuged within 30 – 60 minutes of being drawn. (See Quest lab manual for additional information.) It may not be possible to do this within 60 minutes if blood is drawn off site. The following guidelines must be followed when processing blood:

- a. Blood drawn at SV1 and SV2 should be centrifuged **within one hour** if possible. If this is not possible, it must be done within four (4) hours.
- b. Blood drawn at the baseline visit to the 12 month visit **must be centrifuged within one (1) hour.**

Unscheduled Blood Draw

If a participant lab test result requires a repeat blood draw because the initial specimen cannot be used or because it must be repeated to confirm the safety of medical follow-up, two steps must be taken. The site must complete the **Unscheduled Blood Draw (UNSC)** form and enter it into the DMS.

In addition, the site must complete an Unscheduled Visit requisition form and submit it to Quest with the replicates to track the testing of redrawn specimens. Indicate a retest on the Quest Unscheduled Visit requisition form by writing the word 'RETEST' on the top right section of the form. It is important that the sample be marked as a RETEST so that it will be noted as such when it enters the Quest and the DCC system.

Screening Visit 1 Conduct

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and invite him to a private room for the consent process
- Present and review the study screening informed consent with the participant and address any questions and / or concerns the participant might have concerning the study or the study visits.

Document in the participant binder that screening consent was obtained and note any questions that the participant may have had

- Assign the participant a Participant Identification Number (PID) using the Participant Log
- Collect any administrative data – address, contact information, etc – and store in the participant’s binder. This binder must be stored in a secure location.
- Collect demographic information
- Complete the bone trial eligibility and the CV eligibility CRFs. For more details on the CV and Bone eligibility please refer to the Bone and CV appendices
- Notify the phlebotomist (if applicable) after the completion of the screening consent process, informing them that the participant is ready to have blood drawn.

Phlebotomist (May be certified study coordinator or in-patient staff)

- Have the Screen Visit 1 Venipuncture lab kit from Quest Labs ready
- Confirm that the participant has been fasting
- Test at this visit: T Level. (A reflex PSA and Metabolic Panel will be done if the T level is eligible.)
- Calcium will be checked for the bone trial eligibility
- Through eGFR the kidney function will be checked for eligibility in the CV trial
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped.
- The certified phlebotomist (or study coordinator) will oversee all procedures related to the samples and storage / shipping of these samples to the Quest Lab
- Keep an inventory of the shipments

Study Coordinator / Clinic Staff / Research Assistant

- Copy the answers to the physical function questions, question #'s 5 and 5a, from the PSCR CRF onto the screening visit 1 standard visit form, SCVST1.
- DO NOT ask the participant the questions about physical function difficulty (question 5 and 5a) again. Transcribe the answers from prescreening onto the screening visit 1 form.
- Obtain abbreviated medical history.
- If a participant reported at pre-screening that he was treated for cancer within the past three years, the participant should be questioned further about the type of cancer, type and length of treatment. Men will be excluded from the study if they were diagnosed with, or treated for, cancer in the past 3 years with the exception of nonmelanotic skin cancer. These should be reviewed by the study clinician prior to enrollment.
- If a participant indicated at pre-screening that he had been treated for bladder cancer in the past, and this is confirmed again on the Screening visit 1 CRF (SCVST1), the study physician should determine if this was a pelvic surgery which involved retro-pubic dissection. If there was a retro-pubic dissection then this participant will not be eligible for the sexual function trial.

- If a participant indicated at pre-screening that he was treated for non-melanoma skin cancer in the past or some other type of cancer, they should be assessed by a clinician at SV 1 and more information should be gained about when he was diagnosed and treated in order to determine eligibility.
- Review the participant's binder prior to his departure and confirm that the participant has completed all procedures for this visit
- Based on the procedures for this visit, evaluate the participant's continuing eligibility:
- If participant is ineligible – provide an explanation why he is ineligible and thank him for his time
- If participant is eligible pending serum results – explain to the participant that they will be contacted about study eligibility when test results are received in 7 - 14 days
- Schedule tentatively eligible participants for Screening Visit 2
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab within 48 hours
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

6.A.9.a). Prostate Cancer Risk Calculation (RISK)

The Prostate Cancer Risk Calculator will be used to calculate a prediction of a man's risk of both overall and high-grade prostate cancer. The RISK form is used to collect the relevant data to make this assessment.

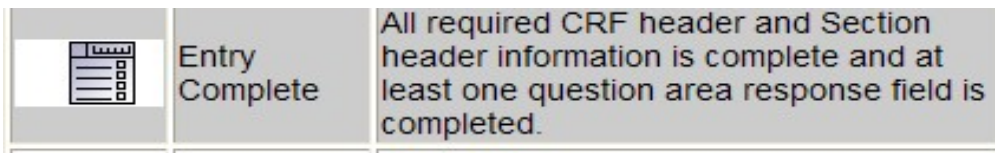
Complete questions 1 – 7 of the RISK form by interviewing the participant and using only the response categories provided on this form. All questions must be answered. If a participant is unable to answer about his family history of prostate cancer [question # 3], check the 'No' reply.

For the purpose of making this evaluation only, the DRE is assumed to be normal [question #4]. (The DRE will be done at Screening Visit 2.)

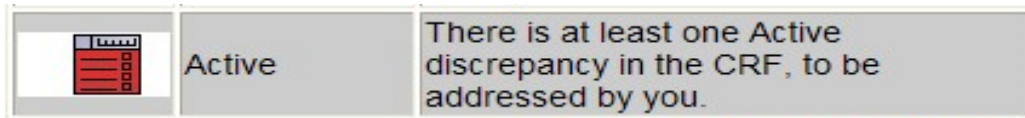
Important Note: Enter the RISK form into the DMS **within 2 days of receiving confirmation** from Quest that the T result is in the eligible range (100 – 274) and that the reflex PSA test has been done. (The actual T and PSA results will be indicated as 'BLINDED.') Choose the '**Save Complete**' option after entering the responses from questions 1 through 7. Do NOT enter the RISK form for men who are ineligible due to T level.

The T and PSA values will be adjusted within the DMS and used to calculate cancer risk. The results of these calculations will be saved in the DMS and indicated to the clinical site as follows.

After saving the form ('Save Complete') it will appear as a completed form in the DMS.



The form will remain unchanged until the lab data have been imported and the risk calculations have been processed in the DMS. This will typically take 2 to 3 days. The response to question #8 will be completed by the DMS based on the risk calculation results. The results will be shown as 'Eligible' or 'Ineligible.' When this has been done, the form will turn from white to red, indicating a change of status that must be addressed.



This is the visual cue to the site staff to open the RISK form and resolve the discrepancy by acknowledging the participant status in question #8 and actively checking the status box in question #9. This is the overt acknowledgement that the coordinator has completed the prostate cancer risk evaluation and is aware of the cancer risk eligibility status.

Note: If after 2 weeks from the date of the blood draw for SV1, the expected lab results have not been received, the RISK form will turn red. This visual cue will be displayed as 'Lab results pending' when the RISK form is opened for review. Site staff should contact the DCC which will start an investigation of the missing data with Quest.

The final step in documenting this evaluation is to transcribe the information from the bottom of the RISK form displayed in the DMS onto the paper copy of the form in the participant binder. It is also good practice to date and initial this step at the bottom of the form as this is a very important eligibility criterion.

- The eligible range is defined as < 30% risk of having overall prostate cancer **and** <7% risk of having high grade prostate cancer.
- If the results of the Prostate Cancer Risk Calculator are **outside of the eligible range**, the participant will not be eligible to continue in the screening process and the specific values will *not* be reported to the clinical site staff or the participant. The DCC will provide a template letter to the sites which can be customized and sent to the participant, informing him that he is not eligible for the trial.
- If the results by the Prostate Cancer Risk Calculator are within the **eligible** range, a participant will be eligible to continue in the screening process. The specific values will *not* be reported to the clinical site staff or the participant.

Please Note: If for some reason the prostate RISK form is entered correctly, for example a man reveals a history of prostate cancer after the form has been completed or indicates he is taking Finasteride and forgot to mention this at the time of the SV1, the RISK form can be updated and will re-calculate. Simply enter the RISK form and update the information on the form. The validation/calculation procedure embedded in the RISK form runs nightly, thus the newly calculated eligibility status will appear the morning after the form has been changed.

6.A.9.b). T, PSA and Chemistry Panel Results

After Screening Visit 1, Quest will send a report to the clinical site designee (via fax) confirming that the T test was completed. However, the results may not be visible to clinical site staff. If the T result is within the eligible range, the Quest report will indicate 'BLINDED' in the result column. If the T level is outside of the eligibility range (< 100 or ≥ 275), the report **will** specify the T result. This information can be discussed with men who are not eligible.

A report of the reflex PSA result will also be shown as 'BLINDED' in the result column.

The chemistry panel results will be visible. At this time, the creatinine and ALT results must be evaluated based on the eligibility criteria and recorded on the SCVST1E form.

- Creatinine >2.2 mg/dL and eGFR calculation
- ALT $> 3x$ upper limit of normal
- eGFR less than $60\text{ml}/\text{min}/1.73\text{m}^2$ (exclusion criteria for the T Trial CV substudy only)

6.A.10. Screening Visit 2 (SV2)

At Screening Visit 2 another blood sample for testosterone eligibility level will be drawn.

Blood must be drawn between 7 AM and 10 AM. Participants must be in the fasting state for all blood draws. Fasting is defined as drinking only water after midnight of the night before a clinical visit that requires drawing blood. Blood drawn at SV2 should be centrifuged within one hour if possible. If this is not possible, it must be done within four (4) hours.

Anthropometric measures, urinalysis, and a Digital Rectal Exam (DRE) will be done. The DRE should be performed by a member of the research team who has experience conducting DREs. The examiner should not be a medical student or other inexperienced student. It can be conducted by a nurse practitioner provided he/she is experienced and has been properly trained.

A small amount of urine is needed for urinalysis. If a participant is unable to provide a urine sample, he is still eligible to continue in the screening process. You may encourage the participant to drink water and ask him to try to provide the urine sample later in this visit.

The screening tests for the 3 trials (physical, sexual, and vitality) will all be conducted as well as screening tests for dementia and depression. The following activities will occur during Screening Visit 2:

- Fasting Venipuncture – T Level, CBC, HgbA1c, TSH
- Blood Pressure
- Medical History (MHX2) and Medications (CMED)
- Urinalysis
- Weight, Height, Waist and Hip Measurement
- Digital Rectal Exam (DRE)
- International Prostate Symptom Score (IPSS)
- 6-Minute Walk Test (WALK)
- Derogatis Inventory of Sexual Function Male (DISF-M-II)

- MMSE
- PHQ-9 (This test must be scored and evaluated promptly with regard to the total score and the response to question #9, suicide ideation. A score of >14 is ineligible.)
- Study Eligibility Determination (ELIG)
- Interactive Voice Response (IVR) System Instructions and Practice Test
- Interactive Voice Response (IVR) Forms:
 - a) PANAS (IVR)
 - b) PHQ-9 (IVR)
 - c) FACIT-F (IVR)
 - d) Global Impression Baseline Measure – General (1) and Trial Specific (4) (IVR)
 - e) UCLA Sex Diary – entire diary (IVR)

Screening Visit 2 Preparation

The following must be reviewed before Screening Visit 2:

- Confirm that the participant is eligible to participate in the study based on the lab tests, medical history data collected and prostate cancer risk assessment made at SV1.
- Contact the participant to review the fasting requirements and remind him to bring the medications that he is currently taking or a list of these medications that includes the dose and frequency

The following materials will be needed for the Screening Visit 2:

- Screening Visit 2 study form Booklet
- Calibrated Blood Pressure Monitor and Cuffs
- Calibrated Metric Scale
- Metric Stadiometer
- Metric Tape Measure (Anthropometric Measures)
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Telephone for the participant to use for Interactive Voice Response (IVR) system training

Screening Visit 2 Conduct

Screening Visit 2 (SV2) is the final step in evaluating trial eligibility. The second T level is measured and specific trial eligibility tests are conducted at this visit. Concomitant medications are documented. Participants are also instructed in use of the Interactive Voice Response (IVR) system so that they are able to use the system from home (when eligibility is confirmed after SV2) to complete questionnaires.

6.A.10.a). Interactive Voice Response (IVR) System

Participants will be registered to the IVR System web board during SV2. This involves entering some information (PID #, DOB, and PIN number) so that the IVR system will recognize the ID number as valid when a participant calls. A test run of the IVR system will be done during SV2 to teach participants how to use the system. The PANAS form will be used for instructional purposes but the data will not be part of the valid data system. A separate ID number will be generated for the

practice PANAS call. This ID number will be used one time, during the practice PANAS call, and will not be used again during the course of the study. The separate test call ID number begins with a 95. The results of the PANAS test call can be reviewed on the webboard by clicking on the Test Call icon on the participant registration page of the webboard.

The Criterium webboard link is located on the T Trial website under the Collaborating Centers tab.

 [Criterium Inc: Webboard System](https://upenn.criteriuminc.com/)
<https://upenn.criteriuminc.com/>

After completing the PANAS the participant should be asked if he has any questions or had difficulty using the IVR system. He will then use his PID number and DOB to log into the actual IVR system and complete the FACIT. The FACIT scale is completed during the SV2 visit by the participant with the coordinator out of the room or nearby for assistance. The score from the FACIT scale will be populated on the webboard after the participant completes the scale.

If a participant is not eligible, based on screening visit 1 and 2 activities, for the physical function trial or the sexual function trial and he has a FACIT score at SV2 of ≥ 40 then he is not eligible to participate in the T Trial because he is not eligible for any of the subtrials. The participant should be terminated from the webboard system by entering a termination date on the participant's ID page and the man should be thanked for his time. If the man is still eligible at the end of SV2 he will be given IVR instructions and copies of all of the surveys he will need to complete after the SV2 visit.

If a man is eligible, based on repeat T level and other data collected during SV2, the site staff will contact the participant and instruct him to complete the IVR questionnaires. He will begin with the UCLA diary and complete it daily for 7 consecutive days and complete the remaining questionnaires on day 8.

IMPORTANT NOTE: While completion of 7 consecutive days of diary data is ideal, men will have 14 days to complete 7 days of diary data, once it is initiated. It is only after these 14 days have passed, or 7 days have been completed, whichever comes first, that the vitality questionnaires will be made available in the IVR system. At Screening Visit 2, you should instruct the participant not to begin the IVR testing until he is notified by the clinical site staff.

Once it is determined that a participant is eligible to proceed to the baseline visit, call the participant and tell him to begin the IVR. Remind the man of his PID# and have him write it down on the front of his IVR booklet so that he has it on hand for each of his calls.

If a participant is not eligible after SV2, he will not complete the IVR questionnaires. At that time the site staff must return to the IVR web board and enter a 'Termination Date' for that participant so that the IVR system closes that case.

The following forms are completed by **all** participants after SV2 Complete UCLA Sex Diary for 7 consecutive days. Participants will have a total of 14 days to complete the diary.

- PANAS
- PHQ-9
- Baseline impression questions in 4 specific categories and 1 general category.
- Remember that the FACIT-F is completed by all men at SV2.

After these forms are complete, the baseline visit can be scheduled. Note that the IVR system requires the use of a touch-tone telephone. Inquire if the participant has a touch-tone phone and if he does not, arrange for him to get one. A cell phone may also be used to access the IVR system.

The following list is a brief summary of IVR preparatory steps. Complete details are found in the IVR manual. Register the participant with the IVR system using the web board. You can also monitor the progress of form completion on the webboard.

1. Provide and review the forms and instruction sheet for using the IVR system to the participant.
2. Using a telephone in a quiet area, assist the participant in answering the sample questions.

Instruct the participant to take the IVR paper forms home with him and that he will be contacted by the site staff in 1 to 2 weeks regarding the need to complete the forms in the IVR system.

3. Quest will inform sites via fax about a participant's eligibility after SV2 based on T level. If the T level is eligible, the coordinator should check all of the eligibility data collected at SV2. It is essential to review the data entered on the ELIG2 form which will indicate if the mean of the 2 testosterone values is eligible (i.e. mean T level <275). Upon this confirmation, the coordinator should contact the participant and instruct him to complete the IVR forms. Reminder calls can also be set up in the Criterium system by entering the participant's phone number, if he has consented to have it released to Criterium, into the webboard. Reminder calls will then come daily unless the man has already completed his survey by the time of the scheduled call.
4. From the time that the FACIT is completed there will be a window of 30 days at which time the participant must either be terminated in the IVR system, if he is not eligible, or he must begin the IVR (i.e. start the first day of the UCLA diary). After 30 days from the FACIT, if the participant has not begun the UCLA diary the days of data will begin to appear as missing.
5. A participant should begin answering the IVR forms, starting with the sexual diary, on the same day (or the following day) of eligibility notification.
6. Questionnaires should be completed in the order in which they are described in the IVR manual. The sexual function diary should be completed over the first 14 days, if not faster, i.e. within 7 days, followed by the rest of the forms after the 14 days.
 - Provide printed copies of the UCLA Diary, FACIT-F, PANAS, PHQ-9 and the baseline impression questions for the participant to use as a visual cue when using the IVR system at home. These materials are available on the website.
 - The score of the FACIT-Fatigue scale will be viewable on the IVR web board shortly after it has been completed by the participant at SV2. The total score on the FACIT at this time must be less than 40 in order for a participant to be included in the Vitality Trial. This summary score must be recorded from the web board to the source document and checked when completing the Eligibility (ELIG) form in order to determine eligibility for the Vitality Trial.
 - REMEMBER: For men who are enrolled in the vitality study there is a vitality specific questionnaire which needs to be completed after the baseline visit. This is the only IVR

questionnaire which appears between baseline and month 1. This form can also be completed in clinic, after the baseline visit, if a site thinks that is easier.

- After the baseline visit and each clinic site visit, the coordinator must enter the date of that visit into the visit field to make the IVR system accessible to the participant for 30 days after the clinic visit date.
- The clinical site staff is responsible to monitor the daily Criterium participant status reports, sent daily by email at 3 PM Eastern. The coordinator should contact participants who appear on the report of missing days of IVR data.

6.A.10.b). T, CBC and Urinalysis Results

After Screening Visit 2, Quest will send a report to the clinical site designee (via fax) confirming that the T test was completed. If the T result is within the eligible range, the Quest report will indicate 'BLINDED' in the result column. If the T level is outside of the eligibility range (< 100 or > 300), the report **will** specify the T result.

At this time, the hemoglobin, HgbA1C and TSH results must be evaluated based on the eligibility criteria.

- Hemoglobin < 10g/dL or > 16.0 g/dL
- Hemoglobin A1C > 8.5%
- TSH > 7.5 mIU/L

SV2 Testing

Completing the tests and questionnaires at SV2 will require the coordinated effort of site staff certified or designated to perform certain functions. Note that the DRE, 6 Minute Walk and cognitive function tests should be conducted by the appropriately qualified personnel. The roles below may be shared by several individuals at the site.

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for SV2.
- Notify the phlebotomist that the participant is ready for the blood draw

Phlebotomist

- Have the Screen Visit 2 Venipuncture lab kit from Quest Labs ready
- Confirm that the participant has been fasting.
- Tests at this visit: T Level, CBC, TSH, Hgb A1c.
- Collect blood, process, and label as described in the MOP.
- Notify staff that the participant is ready to continue the visit.
- Take the samples to be processed / stored / shipped as outlined in the MOP.
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab.
- Keep an inventory of the shipments.

Study Coordinator / Clinic Staff / Research Assistant

- If applicable, review any questions the participant may have regarding the study screening process, informed consent, or any other questions the participant may have regarding study conduct.
- Complete the participant's medical history on the (MHX2) form. Check the status of eligibility criteria and consult with the study physician/investigator in cases of questionable responses or conflicting information.
- Note that the responses to questions about diabetes may require medical assessment at the clinical site of pedal pulses, peripheral neuropathy, and orthostatic hypotension (defined as fall in systolic BP by 30 mmHg or diastolic BP by 20 mmHg from lying to standing) by a study physician who is experienced in this evaluation. This review may lead to trial ineligibility if one of these conditions is uncovered.
- Document the participant's medications from the containers or a list of concomitant medications by listing them on the CONMED form. (When this form is entered into the DMS ineligible medications will be indicated on the screen. Note that the usage time frame is an important part of eligibility determination for concomitant medications.) Compare this information to the exclusionary medications listed on the ELIG2 form. They are:
 - Testosterone and medications that affect serum testosterone concentration **except 5 alpha reductase inhibitors such as finasteride and dutasteride**
 - rhGH or megestrol acetate
 - Anti-depressant medication
 - Anti-psychotic medication
 - Prednisone or other glucocorticoids
 - Opiates
- Collect urine sample, process, and label as described in the Quest Laboratory MOP.
- Take the sample to be processed / stored / shipped as outlined in the Quest MOP.
- Prepare the sample for shipping to Quest Lab.
- Keep an inventory of the shipments.
- Record the clinical weight and height in metric measurements.
- Measure and record the pulse and blood pressure twice. These measures can be consecutive; it is not necessary to have more than a brief (1 – 2 minute) rest period between them.
- If the average of either the systolic blood pressure is >160 mmHg or the diastolic blood pressure is >100 mmHg then the participant is ineligible.
- If a participant comes into the visit and reveals he normally takes medicine to control hypertension but he did not take it before this visit the blood pressure reading for this participant can be rescheduled. The participant may be brought in for another visit between the SV2 and baseline visit at which time blood pressure will be taken and recorded in the box at the bottom of the ANTH form.
- Record the waist and hip measurements using a metric measuring tape.

- Bone Trial- eligibility DXA scan can be performed at this visit or at an unscheduled visit at some point between SV2 and baseline. The scan can also be completed at the baseline visit but prior to drawing blood or randomizing the participant since this is an eligibility criteria. For more details please see the Bone MOP.
- CV Trial- eligibility for the trial will be assessed and the CVELIG CRF completed at this visit
- Note: For sites only participating in the CV trial a BUN and creatinine clearance needs to be done within 30 days of the CT scan for the participant. This can be added to the SV2 visit or performed as an unscheduled visit between SV2 and baseline.

Physician / Registered Nurse Practitioner (or designee)

- Instruct the participant to complete the IPSS form.
- Perform the Digital Rectal Exam and record the results on the (SCVST2) form.
- Notify staff that the participant is ready to continue with the visit
- Digital Rectal Examination (DRE):
 - If a prostate nodule is found during the DRE at SV2, the site staff should do the following:
 1. Suspend screening activities and refer the participant to the site urologist.
 2. Contact the site urologist within a few weeks to determine the outcome of the evaluation.
 3. If a biopsy was done that showed prostate cancer or prostatic intraepithelial neoplasia, the participant is ***ineligible*** to proceed further.
 4. If a biopsy was done that showed no cancer or prostatic intraepithelial neoplasia, the participant is ***eligible*** to proceed.
 5. If the participant did not have a biopsy, he is ***ineligible*** to proceed. [Some men will be told to have a biopsy but will decide they do not want to have a biopsy.]

Physical Function Specialist (or certified designee)

- Have the participant perform the 6-minute walk and record the associated data.
- Notify staff that the participant is ready to continue with the visit.

Cognitive Function Specialist (or certified designee)

- Conduct the MMSE and record the data on the [MMSE] study form.
- Notify staff that the participant is ready to continue with the visit.

Sexual Function Testing

- Read the instructions on the DISF-M form to the participant and ask him to record his responses on the [DISF] form.
- Notify staff that the participant is ready to continue with the visit.

Study Coordinator / Clinic Staff / Research Assistant

- Read the instructions on the PHQ-9 form to the participant and ask him to record his responses on the (PHQ9) form. This form will be repeated by IVR after SV2, if eligible.
- Review the PHQ-9 form by checking the total and the response to the suicide question. If the participant has a score of >14, the participant is ineligible and should be provided with

resources for referral. Each site should develop a plan to address the needs of participants in terms of this evaluation.

- Review the participant's binder prior to the participant leaving the clinic, and confirm that the participant has completed all forms and procedures for this visit.
- Begin confirming the criteria on the Eligibility CRF. At this time all of the required information will not be available, though it will accumulate over the course of the next week to ten days. As test results and questionnaire scores become known, continue to check the data against the eligibility criteria (ELIG2) to assess eligibility status.
- If the participant is ineligible – provide an explanation why he is ineligible and thank him for his time.
- If the participant is potentially eligible – tentatively schedule the Baseline Visit, informing the participant that the appointment will be confirmed after lab results and other tests and questionnaires have been received and reviewed.
- Complete all necessary CRFs.

Data Entry and Discrepancy Management

- Review all CRFs for completeness before beginning data entry, and refer any CRF questions to the study coordinator / clinic staff / research assistant. Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide.
- Enter the data for the participant in the appropriate visit tab.
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies.

6.A.10.c). Eligibility 2 (ELIG2)

After receiving 2 blinded testosterone results, at SV1 and SV2, from Quest, complete question #2 on the ELIG2 CRF and indicate –yes, the participant is eligible to proceed to baseline. Once the ELIG2 form is saved as 'Complete' it will calculate a mean of these 2 testosterone values. If the mean is eligible, <275ng/dL, then the answer to question #2 will remain yes and a discrepancy will NOT be generated. This indicates that you can proceed with randomization. If the mean is >275 ng/dL, then the participant's mean is not eligible and he is not eligible for the trial. In cases where the testosterone mean is ineligible the following discrepancy message will appear on the ELIG2 form:

'The T result(s) for this subject are out of range. This subject is not eligible.'

Please confirm the man is ineligible on the ELIG2 form and call the participant to let him know he is ineligible. Also terminate the man from the IVR system.

In some cases the testosterone level from screening visit 2 will not yet be in the DMS for calculation. In this case the form will generate a discrepancy, when saved complete, stating that not all T levels are available. In this case the testosterone values should be in the system within 2-4 days. Validation will run on the ELIG2 form nightly, so as soon as the value is present in the system a mean will be calculated and the ELIG2 form will populate.

It is not possible to randomize a man who has an ineligible T level, from either SV1 or SV2, or who has an ineligible average from the two screening visits.

6.A.11. Screening Process for T Levels <100

Men with a testosterone level < 100 ng/dL at SV1 or SV2 will be evaluated by the study physician or referred to an endocrinologist for the measures described below.

Assessment of the following laboratory test results, in combination, will inform the physician of the need for further testing by MRI.

- serum LH > 9.3 mIU/mL
- total T4 < 4.5 µg/dL
- prolactin >30 ng/mL
- cortisol <10 µg/dL
- repeat testosterone

These five (5) additional tests will require a 10 cc venous blood draw. Blood must be drawn between 7 – 10 AM. Participants must be fasting which is defined as drinking only water after midnight on the night before the blood draw.

- a. Men will be excluded who have a sellar mass >1 cm by an MRI scan of the head, in the absence of an elevated LH level.
- b. Men will be excluded who have a history of mumps orchitis, castration, Klinefelter’s syndrome or chemotherapy with an elevated LH level.
- c. Clinical site staff must document that the participant has been told that standard medical treatment for a serum testosterone concentration < 100 ng/dL, is testosterone replacement, yet there is a 50% chance he would receive placebo for one year if he participates in The Testosterone Trial.

The participant’s insurance company will be billed for the additional laboratory or procedural assessments associated with evaluating low T. If medical insurance will not pay for these tests, the study will provide assistance with these expenses.

See protocol section 4.3.1, Evaluation of T Level < 100, for additional information.

6.A.12. Rescreening

A man who was deemed ineligible at any point prior to randomization may be rescreened to determine eligibility according to the following guidelines:

- Must occur 6 months after the SV1 date
- Will encompass all activities from prescreening through SV2
- Can only be conducted once on a given participant

A new PSCR ID must be assigned to the participant. If the participant is eligible beyond the PSCR visit then a new PID number is assigned as if this is a new participant. There is a section on both the prescreening [PSCR] CRF and the screening visit 1 eligibility CRF [SCVST1E], to indicate that the participant is a rescreen.

For men who are excluded for conditions which are variable (blood pressure or BMI) the participant should be encouraged to see his PCP or lose weight however the 6 month time frame still applies for re-screening.

Men who are excluded for a borderline TSH value should be encouraged to go see their PCP and have their lab values drawn again for initiation of clinical treatment or they may start treatment for the elevated TSH via the T Trial clinic staff. The site should measure TSH at a local laboratory about two months after starting thyroxine treatment for hypothyroidism to know if they have treated the man with the right dose or if the man's PCP has treated him with the correct dose.

Once the site thinks that the dose is the right dose, the TSH MUST be repeated via Quest and the T Trial. This value is the one that will determine if the subject qualifies on the basis of TSH. The re-testing via Quest can be done at a minimum, 6 months after the participant has started treatment.

Management of Quest Lab Records for Rescreens

In order for Quest to know that a person is being rescreened and results do not revert back to the former PID with the same DOB and initials:

- Write 'Ppt. RESTART' in the participant section of the Quest lab requisition form so that Quest recognizes that this is a rescreen.

The DMS will link the old PSCR and PID with the new PSCR and PID.

6.A.13. Screening Visit 3 (SV3)

Procedures for Subjects Who Were Screened Prior to June 2010- the change in testosterone entry level, men who were screened prior to the change in BMI criteria September 2010, men who were seen prior to the physical function change in August 2011 and men who were seen between February 2012 and March 2013 the time when the sexual function trial was not active. The SV3 visit applies only to the following screenees

If a subject was screened more than six months before enrollment, the following safety assessments must be repeated:

- CBC
- chemistry battery
- PSA
- prostate risk history
- other history relative to diseases that exclude (see below)
- Testosterone does **not** have to be repeated.

For all subjects screened before changes to the enrollment criteria were made , the maximum time allowable from screening to enrollment will be extended from 12 weeks to **nine** months.

- 1. SV1 tests required if 6 months have elapsed since SV1**
 - a. Lab tests: PSA (results blinded) and chemistry panel (results NOT blinded)
 - b. Prostate cancer risk calculation (using T level from the SV1 and PSA from SV3)
 - c. Forms: 1) RISK, 2) MEDHX1, 3) SCVST1E 4) SCVST1
- 2. SV2 tests required if 6 months have elapsed since SV2**
 - a. Lab tests: CBC, HbA1C, TSH

- b. Concomitant medications
- c. Anthropometry (BMI, BP and waist circumference?)
- d. IPSS
- e. DRE
- f. MMSE
- g. Forms: 1) SCVST2, 2) MEDHX2, 3) ELIG2

6.A.14. Baseline and Randomization

At this visit the entire study, including the rationale, assessments, treatments, and potential risks, will be explained to the eligible participants. Participants will be given the option of participating in one or more of the physical, sexual or vitality trials, if they qualify. This information is recorded on the Randomization (RAND) form. All participants will be enrolled in the cognitive and anemia trials if they sign the consent form and agree to participate in the study.

The baseline visit must be conducted within **16 weeks** of SV1. The procedures listed below will be conducted at the baseline visit. If necessary this visit can be separated over 2 days, but it is preferred that baseline visit procedures and randomization are conducted on the same day. For men who enroll in the Bone Trial or the CV Trial, scans can be completed on the day of the baseline visit, if it is approved by a sites IRB and included within the consent form, or they may be completed within 2 weeks' time of the baseline visit. Please refer to the CV and Bone Trial Appendices for more details.

The baseline visit procedures and questionnaires should follow the sequence below in that the study should be explained and the informed consent form must be signed first. After this step is completed, the coordinator should complete all of the forms required for randomization and enter them into the data management system, while the participant is completing the baseline tests and forms. The procedures and questionnaires can vary in the order in which they are completed and that works best for the participant and the staff. The important feature is that consent is done first and that the essential data are entered from several forms in order to make the eligibility determination and randomization assignment. In this way, all of the baseline assessments will be conducted and data will be available in the DMS for eligibility determination and randomization to occur and study drug distribution and instruction can be completed as the last step of the visit.

- | | |
|--|--|
| 1. T Trial Informed Consent | 15. <i>SF-36 (FULL)</i> |
| 2. Genetics Informed Consent | 16. <i>DISF-M-II</i> |
| 3. Fasting Venipuncture – T Level, PSA, FSH & LH,
60 ml whole blood, 10 ml plasma | 17. <i>IIEF</i> |
| 4. 10 ml urine collection | 18. <i>BVRT</i> |
| 5. Concomitant Medication | 19. <i>Card Rotation</i> |
| 6. Clinical Weight | 20. <i>TMT</i> |
| 7. Waist and Hip Measurement | 21. <i>Pre-existing Medical Conditions (PREMED)</i> |
| 8. Blood Pressure | 22. <i>Data entry for eligibility determination (ELIG2)
and randomization (RAND)</i> |
| 9. IPSS | 23. <i>Gel instruction and review</i> |
| 10. 6-Minute Walk Test | 24. <i>Data Import Review – Venipuncture Results,
Urinalysis, and IVR Results</i> |
| 11. Verbal Memory Paragraph Recall (WMS-R-LM-II) | 25. <i>Data Entry</i> |
| 12. <i>FALLS</i> | 26. <i>Data Discrepancy Management</i> |
| 13. <i>Modified MMSE (3MSE)</i> | |
| 14. <i>MAC-Q</i> | |

Randomization and Baseline Visit Preparation

Determining eligibility is a pivotal step in the T Trial. It requires the integration of a great deal of information and should be performed by someone at the site who has a thorough understanding of the criteria and the protocol. The ELIG2, STVSTB and the RAND forms must be entered into the DMS during the course of this visit in order to be able to successfully enroll a participant and distribute the study drug. The RAND form requires the signature of the Principal Investigator.

The following must be performed prior to the Baseline visit:

- Review the medical history from SV1 and SV2 to assess eligibility based the criteria listed on the ELIG2 form
- Review the lab results from SV 1 and SV2 to assess eligibility based on T Level or other lab exclusion criteria
- If all eligibility criteria are met, contact the participant to confirm their Baseline visit appointment
- If all eligibility criteria are not met, contact the participant prior to their tentative visit date and explain the study criteria in as reassuring a manner as possible, and thank them for their participation
- Contact the participant to review the fasting requirements

The following materials are needed to conduct the Baseline visit:

- Baseline study form Booklet
- Calibrated Blood Pressure Cuff
- Calibrated Metric Scale for height and weight
- Metric Tape Measure (Anthropometric Measures)
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Dispensing Log for Gel
- Calibrated Scale for weighing gel pumps

Randomization and Baseline Visit Conduct

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for the baseline visit
- Present and review the Trial Informed Consent
- Note the trials for which the participant is eligible and has agreed to participate in, so that future visits can be structured around the consented trial requirements
- Address any questions and / or concerns the participant might have about the study or the study visits
- Notify the phlebotomist that the participant is ready for their blood draw

Phlebotomist

- Have the Baseline Venipuncture lab kit from Quest Labs ready

- Confirm that the participant has been fasting.
- Tests at this visit: T Level, FSH & LH, PSA, additional 60 ml whole blood, 10 ml plasma
- Blood drawn at the baseline visit to the 12 month visit **must be centrifuged within one (1) hour.**
- Collect blood, process, and label as described in the Quest MOP.
- Notify staff that the participant is ready to continue the visit.
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP.
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Keep an inventory of the shipments.

6.A.14.a). Randomization Data Entry

- Before the participant arrives, enter the Eligibility (ELIG2) form and resolve all discrepancies in the data management system
- Important! Complete and enter the **Baseline Standard Visit (STVSTB)** form in the DMS before the **Randomization (RAND)** form. This must be done in this order for randomization to occur.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab
- Record the Gel Supply Number provided by the data management system – this number will be used to dispense the gel pump-bottle prior to the participant leaving the clinic
- Record the Cognitive Function Packet Randomization assignment number on the RAND CRF
- Have the RAND CRF signed by the PI

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP
- Record the clinical weight in metric measurements
- Record the waist and hip measurements using a metric measuring tape
- Record the blood pressure
- Review the participant's medications for any changes. Inquire if they have experienced any medication changes since their last visit
- Complete the SF-36 (Full) and record the data on the provided study form
- Complete the IPSS and record the results on the provided study form
- Record pre-existing medical conditions on the PREMED form. This information will be used to provide a benchmark for changes (worsening) in pre-existing conditions reported as adverse events.

Physical Function Testing

- Have all participants perform the 6-minute walk test and record the associated data
- Complete the FALLS on the provided study form

Cognitive Function Testing

- Perform the 3MSE and record the data on the provided study form.
- Perform the WMS-R-LM-II and record the data on the provided study form.
- Perform the MAC-Q and record the data on the provided study form.
- Perform the BVRT and record the data on the provided study form.
- Perform the Card Rotation and record the data on the provided study form.
- Perform the TMT and record the data on the provided study form.

Vitality Testing- Vitality Trial Participants Only

- Provide participant with the SF 36 paper forms and remind him to complete them via IVR after the baseline visit- he should call in right after the visit

Sexual Function Testing – Sexual Function Trial Participants only

- Ask the participant to complete the DISF-M-II and the IIEF forms and record the data on the provided study forms.

6.A.14.b). Confirming Eligibility

Information that is essential to determine trial eligibility is collected and entered into the data management system over the course of the screening visits and the baseline visit. The ELIG2 form consolidates the information from lab results, medical history data and questionnaires to confirm eligibility. Use the ELIG Worksheet to assess each inclusion and exclusion criteria before entering the ELIG2 and RAND forms into the DMS.

If it is determined, after a man has been randomized, that he was not eligible for one of the sub-trials (sexual, physical or vitality) in which he was entered contact the DCC. One of the project managers at the DCC will complete a data change request form and the back end tables of the RAND form will be modified to reflect the change. The project manager will then instruct the site to update the RAND form so it is correct. After this is completed the IVR webboard should be updated so the participant hears the correct surveys when calling in to the system. A protocol deviation should be completed in this case and sent to the DCC. The protocol deviation may need to be submitted to your local IRB; this will depend on your institution's reporting policies.

6.A.14.c). Final Review before Completing the Baseline Visit

- Review the participant's binder before leaving the clinic, and confirm that the participant has completed all procedures for this visit.
- Schedule the Month 1 visit
- Register vitality trial participant to the IVR system to complete the SF-36 vitality subscale, associated with the baseline visit.
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant

- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days as described in the MOP
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

7. Study Intervention

7.A. Androgel

The study drug, AndroGel®, will be supplied by Solvay Pharmaceuticals, Marietta, GA. It contains 1% testosterone in an alcohol-water gel and is FDA-approved for treatment of low testosterone in men. Solvay will provide AndroGel in pumps, which deliver 1.25 g of gel per depression. Solvay will provide identical pumps with placebo gel. Androgel or placebo will be supplied to participants at the end of the baseline visit.

7.B. Safe use of study drug

AndroGel or placebo will be applied to the shoulders, upper arms or abdomen once a day at the same time to dry, intact skin. Participants will be instructed to wash their hands after application and to let the gel dry before dressing and to refrain from showering, swimming, or bathing for 5 hours after the gel has been applied. It is important to instruct participants not to have contact with women or children while the gel is wet to avoid transfer of the drug to them. Participants will be taught how to apply the gel and written instructions and precautions will be provided. At each visit, the staff should review the process of depressing the pump and remind the participants to only use their specified dose of the gel.

7.B.1. Dose Adjustment

The initial dose of AndroGel will be 5 g (containing 50 mg of testosterone) once a day. The serum testosterone concentration will be measured monthly for the first three months, and then at months 6, 9 and 12. If the testosterone concentration is not between 500 and 800 ng/dL at any time point, the dose will be increased or decreased by increments of 1.25-3.75 g/day, up to a maximum of 15 g/day. If the serum testosterone concentration is >800 ng/dL following two consecutive reductions in Androgel dose, treatment will be discontinued. Men who have several dose adjustments may also eventually be decreased to a dose of 0 depressions.

To maintain blinding when the dose of a participant in the testosterone group needs to be changed, an unblinded DCC staff member will instruct the clinical trial site personnel to change that participant's dose and also instruct that the dose (i.e., amount of gel) of a participant in the placebo group be changed.

The placebo participant will be selected based on the following characteristics:

- T level drawn on the same date or within a few days
- Matching Visit (e.g., Month 1 for the T participant and Month 1 for the placebo participant)
- Different trial site, if possible

Likewise, if testosterone treatment needs to be discontinued because the serum testosterone concentration is too high despite two dose adjustments (see above), a participant in the placebo group will also be identified to discontinue gel use.

The DCC will notify sites of dose adjustments via email and also through the ALERT form in the DMS. The email message will indicate whether a dose increase or decrease is required and will instruct the staff to complete the ALERT form in the DMS. The ALERT form will appear red and will remain as an active discrepancy until the site acknowledges the dose adjustment.

The DOSE log should also be updated to indicate that a DOSE change was initiated. A stop date should be recorded for the previous dose and a start date should be filled in for the new dose based on the dose adjustment initiated. Men who are alerted to stop gel, or are reduced to 0 depressions, should have the ALERT form completed and a start date for 0 depressions should be entered onto the DOSE log. The 0 dose will remain active until a participant is notified to resume treatment.

Men who are reduced to 0 depressions, or who have 2 consecutive reductions and require a third, can be re-tested after 2 weeks have passed in order to determine if they are eligible to re-start gel use. Two weeks from the stop date, men may have an unscheduled T test conducted through Quest. This should be on the unscheduled requisition form and marked as a RETEST. If the man has a value below 500, then he may restart gel use. This notification will be sent to the site via the ALERT form at which time the dose of 0 depressions should be ended on the DOSE log and a new start date line started for the new dose.

Men who stop gel use because of medical complications (heart attack, stroke, erythrocytosis, prostate cancer) will not have the option of restarting gel. These men will have the stop date entered on their DOSE log as well as all gel collected and the treatment stop (bottom portion) of the COMP form completed.

7.B.1.a). Dose Adjustment for T > 1500

Dose adjustments for serum testosterone concentrations > 1500 ng/dL are considered exceptions to the normal dose adjustment schema. Serum testosterone concentrations that are unusually high suggest the possibility of laboratory error or artifact due to antecubital fossa skin contamination with the testosterone gel. In such situations, lowering the AndroGel dose would be inappropriate, so determining if the value is accurate or represents an artifact is important. If a subject has a serum testosterone concentration >1500 ng/dL at any visit, the following steps will be taken:

- The DCC will confirm that the central laboratory, Quest, has repeated the assay.
- If the result of the second assay is ≤ 1500 ng/dL, the DCC will implement the usual protocol for AndroGel dose adjustment using the second value as the basis for the adjustment. The gel dosage would be decreased by 3 depressions, per the protocol.

If the result of the second assay is >1500 ng/dL, the DCC will do the following:

- Notify the site to ask the subject to return for a repeat measurement of serum testosterone and also to re-instruct the subject over the phone of the need to avoid skin contamination at the antecubital fossa.

- The subject should be told to apply the gel principally to abdomen and flanks, as well as the shoulders, but not the arm. The subject should also be reminded to wash his hands thoroughly after application of the gel.
- Schedule the participant for an unscheduled visit and at the time of the visit, application technique can be observed using placebo gel. The phlebotomist should be reminded not to touch the bare skin of the arm above the antecubital fossa.
- Simultaneously, the DCC will identify a subject in the placebo group at the same time point in the trial and instruct the site to ask the participant to return for a repeat serum testosterone measurement and to give him the same instructions.
- The usual dose adjustment protocol will then be implemented based upon the results of the unscheduled blood draw.
- Notifications of dose adjustments and repeat blood draws will be sent to the sites via email and the ALERT form.
- Send all blood to Quest via the unscheduled visit requisition form and mark them as RETEST on the unscheduled visit requisition form.
- Be sure to complete the unscheduled visit (UNSC) form in the DMS as well as resolve discrepancies in the ALERT form and update the DOSE log, if necessary.

7.B.1.b). Dose Adjustment Based on Hemoglobin

If a participant's hemoglobin concentration is found to be greater than or equal to 17.5 g/dL and the man has a testosterone (T level) in the normal range, 500-800 ng/dL, then the site will be instructed to retest the participant's hemoglobin within 30 days. This notification will be sent to the site's Principle Investigator as well as the site RC. If the Hgb is still elevated then the participant will be referred to an unblinded physician for evaluation, and potential treatment, of erythrocytosis.

If a participant's hemoglobin concentration is found to be greater than or equal to 17.5 g/dL and the man has a testosterone (T level) that is below the normal range, the site will be instructed via the ALERT form, and an email from the DCC, notifying the site to retest the participant's Hgb within 30 days. No dose increase will be made until the results of the Hgb are returned. Depending on the follow up Hgb, completed within 30 days the site may be instructed to increase the participant's dose or to refer for assessment of erythrocytosis.

If a participant's hemoglobin concentration is found to be greater than or equal to 17.5 g/dL and the T level is above the normal range, the site will be instructed via email from the DCC and the ALERT form to decrease the man's dose and repeat the T level and the Hgb within 45 days. Based on the repeat values the site may be instructed to decrease the man's dose again and/or refer him for evaluation.

A placebo participant will be matched to the active participant (see criteria above) for a repeat hemoglobin and potential subsequent dose reduction.

All retest of hemoglobin should be sent to Quest on the unscheduled visit form and be marked as RETEST.

7.B.2. Estimated Days of Use for Pump Bottle

<i>Estimated Dose Chart</i>	
2.5gm/day (2 depressions/day)	30 days per bottle (4 bottles for 3 months)
5gm/day (4 depressions/day)	15 days per bottle (7 bottles for 3 months)
7.5gm/day (6 depressions/day)	10 days per bottle (10 bottles for 3 months)
10gm/day (8depressions/day)	7.5 days per bottle (13 bottles for 3 months)
15gm/day(10 depressions/day)	5 days per bottle (19 bottles for 3 months)

At the start dose of 4 depressions per day, a single pump bottle of either gel or placebo should last a participant 15 days. The table above indicates how long a bottle should last if the dose is decreased by 2 depressions, increased by 2 depressions or if the dose is increased to the maximum allowable dose of 15 grams per day or 10 depressions.

7.C. Distribution, Tracking, and Compliance Evaluation

7.C.1. Distribution of Gel Pumps

Androgel pumps containing active and placebo gels will be supplied by abbvie to the Investigational Drug Service (IDS) at the University of Pennsylvania, which is the central pharmacy for the study. The IDS will then supply labeled, packaged pumps to the research pharmacists, or other designated IDS contact, at each of the 12 sites.

Blinded, tamper-sealed treatment kits containing a 3-month supply of testosterone or placebo, will be shipped to each site and stored securely. Each kit will be labeled with a specific randomization number, which will be repeated on each individually-labeled pump bottle. The initial set of pumps will be dispensed to the study participant only after randomization has taken place. Additional blinded and tamper-sealed sets of pumps will be provided to the sites in 3-month increments as refills, labeled for the individual study participant, after randomization has taken place. If sites require refills in increments other than every 3 months they may contact the IDS at Penn for resupply. Depending upon the participants dose, i.e. if there are increases, the Penn IDS will ship additional bottles to the site so that participants do not run out of gel between visits. The weight of these bottles, as well as the number of the bottles, should be recorded on the comments section of the DOSE log from the previous visit.

7.C.1.a). Preparing Gel Pump Bottles

1. Dispense the gel starter kit based on the participant’s Gel Supply Number provided during the randomization step. The kit number is recorded on the Randomization (RAND) form. The starter kit includes 7 pump bottles which is a 3 month supply.
2. The pumps must be weighed before the gel bottles are dispensed to the participant. This initial weight of all of the pumps will be used to monitor participant compliance. This information is recorded on the Drug Distribution (DIST) form.
3. Before dispensing Testosterone or placebo pump bottles to the participant, perform the following steps to weigh the pumps:
 - remove the plastic caps
 - weigh all of the pump bottles together *without the caps*

- record the weight of the pump bottles on the Drug Distribution (DIST) CRF (the average weight of one full pump bottle is about 127 grams). All the pump bottles should be weighed together. If your scale can only accommodate 1 pump bottle at a time then please sum the weights of the pump bottles.
 - When drug is being dispensed, complete line # 2 of the DIST log only.
 - When drug is being returned, complete line #1 of the DIST log only.
 - When drug is being dispensed AND returned, complete both lines of the DIST log.
 - Do not round the weight of the pump bottles. Drop all decimal places and record the weight of the pump bottles.
 - Replace the caps.
4. Each pump bottle must be primed before use. Demonstrate how to prime the pump using the first bottle in the starter kit, by depressing the pump completely 3 times and discarding the contents. Note that these priming actuations may or may not dispense any gel. There is no need to wear gloves for priming the pump. The pump discharge can be pointed to a folded paper towel or trash bin. A biohazard bin should be made available. The coordinator should wear gloves if he/she assists the participant in applying the gel.

Once a pump has been primed, through 3 depressions of the pump, it will provide 60 true depressions. Each depression provides 1.25 grams of testosterone. Beyond 60 depressions the pump may supply gel but it will not be the full 1.25 grams. Instruct participants to depress the pump fully but not to struggle with the pump to retrieve gel. There will be about 5 grams of gel remaining in the bottle, which the participant will not be able to retrieve by depressing the pump.

5. Instruct participants that they should prime each pump once, just before they start using that pump bottle for the first time. Priming should not be done in advance as this may cause the capillary tube inside the bottle to become dry and clogged.
6. Instruct participants to maintain the kit (bag and its contents) at room temperature in a dry location, pulling one pump bottle at a time from the bag for use as needed. The empty pump bottle should be returned to the bag for safe keeping when a new pump bottle is started. Together, the used and unused pump bottles contained in the bag (ie. "kit") should be returned at each visit.
7. When a participant returns for his follow up visits he must be reminded to bring all of the used and unused pumps bottles with him at each visit. (The weight of an empty pump bottle is about 44 grams.) The used and unused pump bottles will then be weighed together without caps. This value will be recorded on the DIST CRF in 2 ways:
- Number of Pump Bottles Returned and
 - Amount Returned in grams
 - This information should be recorded on Line #1 of the DIST log.
 - If participant reports that he missed doses during the time between visits, this information should be recorded on the DIST log.

- The DOSE log should be used to record starts and stops of gel use for prolonged periods of time (roughly 2-3 weeks or more) while the DIST log will be used to capture missed doses or stops which take place over shorter periods of time

7.C.1.b). Scales

The pan size of the scale will determine if all 10 pump bottles can be weighed together or separately. A scale that can accommodate all 10 pump bottles has a pan size that is approximately 6" X 7". A smaller scale is portable and can be transported easily to participant visit sites. If using a scale that is available at the clinical site that cannot accommodate 10 bottles, each bottle must be weighed individually(or a few at a time) and then totaled for entry onto the Drug Distribution Form (DIST) column "Quantity Dispensed in gms" on line 2 of the table at the bottom of the form. The same method of measurement will be used for returns, and redistributions.

Initial Dose Instructions

Each full pump depression delivers 1.25 g of testosterone. The chart below indicates the number of pump depressions per dose.

Daily Dose	Number of Pump Depressions
5 g	4 (once daily) Initial dose for all participants
6.25 g	5 (once daily)
7.5 g	6 (once daily)
8.75 g	7 (once daily)
10g	8 (once daily)
15g	10 (once daily)

The initial dose of testosterone gel for all participants is **5 grams** (containing 50 mg of testosterone) once a day. This is **4 pump depressions**.

Instruct participants to use this amount every day. At this dose, each pump bottle will last for 15 treatment days.

Review the instructions for applying the gel. Instruct the participant to apply gel every morning to the upper arms, shoulders or abdomen. Gel should be applied every day, even on the day of study visits, in the same manner. Provide instructions for the participant to take home with him, which provides additional information about applying the gel properly.

(Inform the participant that when traveling the gel can be taken on an airplane as it meets the liquid volume requirements.)

7.C.2. Case Report Form to Note after Weighing Bottles- DIST Log

Below is a picture of the Distribution log (DIST) CRF. This CRF will be completed at baseline visit (line #2 only) when the starter kit is distributed to the T Trial participant. At baseline weigh the entire starter kit. Place all of the starter kit bottles, with caps, on the scale and record the weight of the starter kit on line #2. Also include the number of bottles dispensed, the starting number of depressions, the date and the kit number.

[DIST]

Line Number	Date (mm/dd/yyyy)	Kit Number	Number of Bottles Dispensed	Daily Number of Depressions	Quantity Dispensed in gms	Dispensed By	Number of Bottles Returned	Amount Returned in gms	Comments
1			<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A			
2							<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	

At months 1 and 2 sites will enter line #1 of the DIST log. Weight all bottles (used and unused) together, with the caps on, and record the weight of returned gel on Line #1 of the log. Also note the date, kit number and the number of bottles returned. If a man returns fewer bottles than expected, you can make a note about this in the comments section of the log. Do not enter line #2 of the log unless, for some reason, drug is also being dispensed at this visit. It is possible, if a man is at a high dose, that interim bottles may need to be sent out at this visit. In that case follow the same procedure as for the baseline visit and record the number, weight and date of the interim supply on line #2. Make a note in the comment section that this is an interim supply.

At months 3, 6 and 9 men will be returning gel and gel will be distributed, so both lines 1 and 2 will be completed. Weigh all bottles, used and unused, and record the weight and date on line 1 of the DIST log. On line #2 you will record the weight of the resupply kit for the corresponding month along with the number of depressions the participant is currently using.

If a man has a dose increase and needs an interim supply of bottles these should be weighed and sent out to the participant between the 3 month visit intervals. Within the comment section of line 2 of the DIST log which was completed for the visit prior to the bottles being sent (for example bottles sent at month 5 will be recorded in the comment section, line #2, of the 3 month DIST log) record the number of bottles, weight and date the interim supply was sent.

At month 12 you will collect gel from men and follow the procedure described above for weighing all returned bottles. At month 12 line #1 will be the only line completed.

7.C.3. Compliance Reminders and Review

Compliance with gel use is an essential aspect of the T Trial. At every in person visit men will be asked about gel use and compliance. Review the Gel Use Instruction Sheet with participants at each visit (below). This sheet should also be used to send out to participants when a man has a dose change (increase or decrease). A man should also be notified via phone of his dose changes. Once the dose change has been verified, via a phone call with the participant, update the DOSE log.

During in person visits compliance conversations are easier to initiate because gel bottles will be returned and weighed (months 1,2,3,6,9 and 12). At certain in person visits, drug will also be collected and dispensed (month 3,6 and 9).

If something seems odd, or it is apparent that a man is not using the correct gel dose, i.e. the weight of bottles are not what would be expected at current dose, have a conversation with the participant about using the gel and missed doses. Record missed doses in the comments section of the DIST log.

During the phone visits (month 4, 5, 7,8,10 and 11) it is still imperative that RCs inquire about compliance. Below is some sample dialogue to use while reviewing the Gel Use Instructions with the participant. (Can also be found on standard visit CRF forms for months 4, 5, 7,8,10 and 11).

“You are currently at X dose and I want to remind you to use the gel and apply it to your body every day. Remember to apply the gel to your shoulders, upper arms or stomach in the morning. Do not apply the gel to your chest or to broken skin. When you are applying the gel, fully depress the pump all the way down, X times.”

“Do you have any questions about gel application? Have you been having any problems applying the gel to your body? “

For men who recently had a dose reduction, per the DOSE log:

“I know you recently had a dose reduction, down to X depressions, but I want to remind you how important it is to continue to use the gel at this exact dose every day. This dose is specific to you and has been tailored to your lab values so please continue to use the gel at this dose, daily, unless you hear differently.”

GEL USE INSTRUCTIONS

Same Time Each Day...

Apply gel at the **same time each day** (*preferably every morning*) to clean, dry, intact skin.

Shower/Bathe FIRST...

If you take a bath or shower in the morning, use the gel **after** your bath or shower. Make sure your skin is **completely dry before applying** the gel.

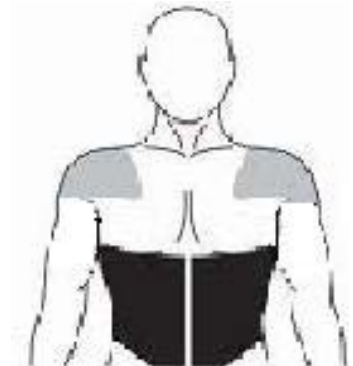
Fully Depress the Pump...

Fully depress the pump the appropriate number of times to deliver the daily dose.

For your dose, fully depress the pump _____ times.

Apply To...

Apply gel to healthy, normal skin on your shoulders, upper arms or stomach. Think of the area that would be covered by a short sleeve T shirt.



Precautions...

Wash your hands with soap and water right away after application to reduce the chance that the gel will spread from your hands to other people. Once your hands are washed and the application site is covered with clothing, there is little risk of transferring testosterone to someone else's skin due to bodily contact. If **you expect direct skin contact with someone else**, you should wash your application site(s) with soap and water before that encounter.

Let the gel dry for a few minutes **before you dress**.

Allow the gel to dry completely before smoking or going near an open flame.

Wait 5 to 6 hours before showering or swimming.

Never share your gel with anyone.

Keep the gel out of the reach of children.

Even on the day that you are scheduled for a return study visit or blood test, apply gel when you usually do.

Pump Bottle Instructions

- Prime each pump bottle once before use by depressing the pump completely 3 times and throwing away the contents. (Priming the pump may not actually dispense any gel, but that is OK.)
- Do not prime all of the pump bottles at once. Prime the pump only before you start using a new bottle.
- Keep the empty pump bottles to return on your next visit.



IMPORTANT NOTE! When you first notice that after you have been using a pump bottle for a week or more, that depressing the plunger does not give as much gel as in the first week of use, put that bottle aside and begin using the next full pump bottle. This ensures that you get an accurate dose with each application.

Do's and Don'ts:

➤ Do....

- Apply the gel every day
- Apply the gel to shoulders, upper arms, or stomach
- Apply the gel in the morning
- Apply the gel at about the same time each day
- Fully depress the pump
- Depress the pump one time for each dose. For example, if your dose is 4, depress the pump 4 times
- Save the used bottles and bottle caps for return to the clinical site at each visit.
- Return all bottles (used and unused) at each clinical visit.

➤ Do not

- Apply gel to broken skin
- Apply gel to your chest
- Apply gel to wet skin
- Apply gel to your penis or scrotum
- Share your gel
- Depress the pump more than the number of times that you have been instructed
- Try to get the last drop of gel from a pump bottle; once depressing the plunger no longer delivers as much gel as it did when you first started using that pump bottle, begin using a new one
- Throw away any of pump bottles
- Change your dose unless instructed to by study staff

Caution: This product is limited by Federal Law to investigational use only.

MD (or designee) Signature: _____ **Date:** _____

(For additional information, please see the complete Information & Instruction for Use Booklet.)

It is also very important that men come to their T Trial visits with all of their bottles, used and unused. When calling a participant to remind him of his visit also remind the man to gather all used and unused bottles and bring them to his visit. Labels can also be made and added to the bottles which say in bold letters, **DO NOT THROW AWAY AFTER USE. RETURN TO CLINIC.**

To calculate compliance use the following equation:

$$\left(\frac{\text{Testosterone Gel Weight Used}}{\text{Testosterone Gel Weight Supposed to be Used}} \right) \times 100$$

The gel used will come from the difference between gel dispensed at the previous visit and the gel returned. To determine that amount of gel that should be used, use the DOSE log to calculate amount of gel used daily based on current number of depressions.

Example:

month 1 - date 8/23 - amount 1129.3 to month 2 - 9/20 amount returned 951.4
actual used = 177.9 gms

based on DOSE log

8/23 to 8/27 = dose is 4 per day , 5 x 5 days = 25 gm

8/28 to 9/20 = dose increased to 5 , 6.25 x 24 days = 150

supposed used = 175 Total

177.9/175 = 101 %

7.C.4. Label on Kits/Pump Bottles

Labeling on treatment kits – SAMPLE

<p>T-TRIAL IND#104,707</p> <p>KIT #: _____ Use before: MM/YYYY</p> <p>ASSIGNED TO: _____ ID# _____</p> <p>CONTENTS: Testosterone Study Gel “1%” (10mg/mL or 0mg/mL): (2) bottles 88mL each.</p> <p>Sponsors: <i>National Institute on Aging & Solvay Pharmaceuticals Inc.</i></p> <p>Caution: <i>New Drug Limited by Federal (USA) Law to Investigational Use Only.</i></p>	<p>T-TRIAL</p> <p>KIT # _____</p> <p>Use before: MM/YYYY</p> <p>Testosterone Study Gel “1%” (10mg/mL or 0mg/mL) (2) bottles 88mL each</p> <p><i>Detach and affix to pharmacy worksheet before dispensing.</i></p>
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Labeling on individual bottles:

Name: _____

Date: _____ ID# _____

Apply __ depressions to skin once daily as directed.

Testosterone/Placebo 1% topical gel 88g
Store at room temp (59-86F) and out of reach of children. For use only by the person for whom prescribed. Limited by Federal (USA) law to investigational use.

Site:
Physician:
Phone:
VISIT #:
Kit #:



7.D. Blinding and Unblinding

The staff at the DCC will have access to treatment assignment and all lab values in order to safely monitor and adjust T levels. All site staff and investigators will be blinded to treatment assignment and relevant lab values, except when medical evaluation requires referral or consultation. The DCC will notify the Principal Investigator at the site when a medical safety situation requires consultation or referral that may result in unblinding.

To maintain blinding when the dose of a participant in the testosterone group must be adjusted, a DCC staff member will instruct the designated site personnel to change that participant’s dose. Also, the DCC staff member will instruct the clinical site personnel that the dose (i.e., number of pump depressions) of a participant in the placebo group must be changed as well. This participant may be at the same or at a different clinical site.

There is no foreseeable medical reason that a treating physician must know if a man is taking testosterone or placebo, because this knowledge would not change the treatment of any known disease. Therefore, there is no reason to break the blind in case of a medical emergency. If, in the unforeseen situation an emergency room

physician thinks that testosterone could be causing or exacerbating a participant's emergency medical condition, the physician could tell that man to discontinue using the gel until the site PI can be contacted.

7.D.1. Monitoring Hemoglobin Levels

Hemoglobin levels will be assessed at months 3, 6, 9, and 12 after baseline, to monitor men for erythrocytosis. If a participant has a hemoglobin level greater than or equal to 17.5g/dL, the hemoglobin level must be repeated as soon as possible.

The DCC will notify sites that a hemoglobin level must be repeated via the ALERT CRF. An email will be sent to the site informing the staff that they must check the ALERT form in the DMS for a repeat lab value. In addition, the ALERT form will turn red in the DMS to indicate that action is required on the form.

Repeated lab tests should be sent to Quest via the Unscheduled Visit requisition form and marked as a RETEST of labs from the visit with which they were associated (refer to section 6.A.5-unscheduled blood draw and the Quest MOP).

If a man exhibits a hemoglobin level greater than or equal to 17.5 g/dL on the repeated lab test, he will have a dose reduction and potentially be referred to an unblinded study physician by the study PI. (For more specific details on adjustment and repeat process with T level and Hgb please refer to section 7B1b above).

The DCC will notify the site via email and the ALERT form in the DMS which will indicate the need for a referral for assessment of erythrocytosis. The participant will be evaluated, treated and monitored as appropriate, based on the recommendations of the consulting physician. If the condition does not improve, i.e. hemoglobin value does not return to normal after dose reduction and treatment for erythrocytosis, treatment will be discontinued. The site PI will be responsible for following-up on the participant's status and communicating with the consulting physician.

7.D.2. Monitoring PSA Levels

Study participant's PSA level will also be monitored. PSA will be measured at 3, 12 and 18 months after the baseline. An increase in PSA of an increment greater than or equal to 1.0 ng/mL, above the corrected baseline PSA value, will lead to a repeat PSA and potential participant referral to a study urologist, if the PSA remains elevated after repeat. The site will be notified to repeat the participant's PSA via an email and the ALERT form which will appear red, noting need for action, in the DMS. All men, using active or placebo gel, will be monitored for changes in PSA.

If the PSA increase of 1 or more is confirmed, the participant will be referred to the blinded study urologist. The urologist may request information from the DCC that reveals treatment assignment as well as all lab values but will not initially be unblinded unless they request this information from the DCC. The DCC will monitor PSA values and alert the study PI, via email that a study participant must be referred to the study urologist. The urologist will evaluate the participant and may consider performing a prostate biopsy. If prostate cancer is found, the gel treatment will be stopped.

7.D.2.a). Monitoring IPSS Scores

If the IPSS score, which is measured at the Month 3 and Month 12 visits, is increased by 5 points or more from the baseline score or the absolute score is greater than 19 at any time after the baseline

visit, the DCC will notify the site via the DMS. The IPSS forms for that participant will turn red within the data management system indicating there is something the coordinator needs to monitor or resolve.

If the IPSS score increase by > 5 point from baseline or to an absolute score of > 19 the site should contact the participant and review medications that affect urine flow rates and evaluate the participant for prostatitis. If a cause is found, it should be treated. If no cause is found, treatment with an alpha blocker should be considered. This follow up should be completed by the PI or site physician and should occur as soon as possible. During this time the participant may remain on treatment.

After 1 month the IPSS should be re-administered to the participant. The IPSS can be found in the PRN tab of the T Trial DMS. If the score has decreased below the thresholds listed above no further follow up is needed and the next IPSS will be administered per the protocol. If the participant's score remains elevated after treatment with an antibiotic for prostatitis or prescription of an alpha blocker then the man should be referred to a study urologist.

The urologist should remain blinded unless there is a specific request made of unblinding. Request for unblinding should be made to the DCC if warranted. The urologist will treat the participant and the IPSS will be administered after 1 month. If after treatment by a urologist the IPSS has not decreased below the above threshold the man should stop taking gel. If his IPSS score has decreased then he may continue on gel.

At baseline if a man has an IPSS score >19 or 5 points greater than his SV2 score then he should follow the same guidelines as above but he should not be given a gel kit/ start using gel until his IPSS score has decreased. After treatment at baseline any man with an elevated score at baseline may retake the IPSS 1 month later. Provided it has reduced appropriately, the man may be given gel. The visit schedule for men in these situations will be adjusted based on the date that start taking gel which will be reflected on the DOSE log and in the participant's visit schedule.

7.D.3. Androgel Dose Adjustment Schema

7.D.3.a). Starting Dose

At the baseline visit all men will be instructed to use 5g (4 pump depressions) of testosterone or placebo gel. One (1) depression of the pump delivers 1.25 g of testosterone or placebo gel. The maximum allowable dose in the trial is 15.0 g, which is 10 pump bottle depressions of testosterone or placebo gel. A participant will never be told to use more than 15.0 g or 10 pump bottle depressions per day.

Encourage each participant to maintain the pump bottles in the original bag and to bring all bottles, used and unused to each visit. When weighing bottles it is important to keep the bottle weights in mind, as well as the participant's dose, so that a quick calculation of compliance can be made. If compliance appears to be low, discuss this with the participant and record missed doses in the comments section of the DIST log.

If a man consistently forgets to return bottles, have a conversation with him about how you can help him to remember to bring these back (reminder calls, labels, tote bag, etc.)/

7.D.3.b). Dose Adjustment

The dose adjustment schema is based on serum testosterone concentration levels which are measured at Months 1, 2, 3, 6, 9 and 12. The target testosterone level throughout trial is 500-800 ng/dL.

If serum testosterone levels are <500 ng/dL or >800 ng/dL during the course of the trial, the dose will be either increased by 1.25 – 2.50 g (1 to 2 depressions) per day or decreased by 1.25-3.75 (1 to 3 depressions) per day.

The DCC will monitor unblinded T levels and inform site staff members via email about the need for dose adjustment. The following schema will be used to determine the dose adjustment:

	Dose Change	Increase in # of Depressions	Placebo Arm Dose Adjustment
If serum T Level <500 ng/dL	+ 1.25 g/day	+ 1 more depression/day	The database will randomly select a participant in the placebo arm. This participant will be matched by study visit and date of corresponding blood draw as closely as is possible.
	+ 2.50 g/day	+ 2 more depressions/day	

	Dose Change	Decrease in # of Depressions	Placebo Arm Dose Adjustment
If serum T Level >800 ng/dL	- 1.25 g/day	1 fewer depression/day	The database will randomly select a participant in the placebo arm. This participant will be matched by study visit and date of corresponding blood draw as closely as is possible.
	- 2.50 g/day	2 fewer depressions/day	
	-3.75 g/day	3 fewer depressions/day	

The Dose Change Notification Log (DOSE) form must be completed to indicate that the dose change was acknowledged by the site staff and communicated to the subject. This log should be filled out with initial starting dose and date and then updated each time there is a dose adjustment.

In addition, the visit at which the dose adjustment was made needs to be marked on the DOSE log as it is possible there could be more than one dose adjustment associated with a monthly visit date. Be sure to update the participant’s DOSE log after you call him and instruct him to change his dose. If man says he will not be able to change his dose for a day or 2 note that as the start date of the new dose on the DOSE log and not the date you called the participant.

The ALERT form will notify sites when a dose adjustment needs to be made and this form will remain red until it has been updated to acknowledge that a change has been made.

Notify the participant over the phone of his new dose and be sure to mail him an updated gel usage sheet with his new dose recorded on the sheet.

8. Evaluations and Follow-Up

This section will outline the summary of activities, evaluations, and procedures for all of the visits that occur from Month 1 thru Month 24.

8.A. Summary of Activities, Evaluations, and Procedures

8.A.1. Treatment Month 1 and 2

Clinical site visits at Months 1 and 2 are focused primarily on evaluating how participants are adjusting to gel use, if they are using it properly and if they are having adverse events. The visit window around each of these study visits is one week. Blood drawn at this visit must be between 7 – 10 AM. Fasting (after midnight of the previous evening) is also essential for this visit.

Avoiding Contamination When Drawing Blood

Important Note: It is important to avoid cross-contamination of the venipuncture site from the gel application site. Before drawing blood, the phlebotomist should ask the participant if he has applied the gel to his arm. If so, avoid touching that part of his arm when drawing blood and do not allow clothing that has touched that part of the arm to touch the venipuncture site. The phlebotomist should also cleanse the skin thoroughly.

The following activities will occur at Month 1 and 2 visits:

- a. Venipuncture – for T Level and storage of whole blood and plasma
- b. 10 ml urine
- c. Adverse Events / Recent Medical Events
- d. Concomitant Medication
- e. Medication Compliance
- f. Gel Instruction & Review
- g. Lab Data Review – Venipuncture Results
- h. Data Entry and Data Discrepancy Management should be completed within 1-2 weeks.

TREATMENT MONTH 1 AND 2 PREPARATION

Before the Month 1 or Month 2 visit:

Call the participant to remind him of the appointment. Remind him of the following:

- apply gel as usual, even on the day of the study visit
- bring in used and unused pump bottles for weighing (the entire kit or bag)
- do not eat anything for 8 hours prior to the study visit because there will be a blood draw.
- take AM medications with water prior to coming in for the visit (if applicable).
- bring in all medications currently taking, especially any medications that are newly started (e.g. since the prior visit).

The following materials are needed to conduct the Treatment Month 1 and 2 visit:

- Treatment Month 1 or 2 study form booklet
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Calibrated scale for weighing the pump bottles.

Treatment Month 1 and 2 Conduct

At this visit the participant should bring in their used and unused pump bottles. The pump bottles will be weighed and the gel application instructions will be reviewed with the participant. Blood and plasma will be collected to monitor if a dose adjustment is needed.

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for today's visit
- Notify the phlebotomist that the participant is ready for his blood draw

Phlebotomist

- Have the Treatment Month 1 or 2 Venipuncture lab kit from Quest ready
- Confirm that the participant has been fasting.
- Tests at this Visit: T Level, 20 ml whole blood, 10 ml plasma
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP
- Review the participant's medications for any changes. Inquire if he has had any medication changes since his last visit. Record this information on the SVTM1 or SVTM2 CRF. If there has been a change in medication (i.e. change in dose, a medication has stopped, or a new one has started) update the CMED log.
- Review the participant's adverse events / current medical events. Inquire if they have had any recent health events. Record on the STVM1/2 CRF. Also update the participant's AE log if necessary.
- Have the participant complete the cardiovascular symptom questionnaire, (CVSYM). Be sure to inquire if the participant has informed his health care provider (HCP) of any new CV symptoms or any change in symptoms since the last visit. If the participant indicates he has not contacted his HCP, and he consented to have his HCP contacted, follow up with the participant's HCP after the visit.
- Complete the cardiovascular events CRF (CVENTS)
- Notify staff that the participant is ready to continue the visit
- Review the participant's Gel Usage and Compliance. Ask the participant when he last applied the gel. Note the date and the time of the last application on CFR DIST.
- Weigh the pump bottles (all returned; used and unused). When weighing the pump bottles: weigh without the caps. Record the number of pump bottles returned on the DIST CRF in the

column “Number of Bottles Returned” and the total weight in the column “Amount Returned in gms”. **(Line #1)**

[DIST]

Line Number	Date (mm/dd/yyyy)	Kit Number	Number of Bottles Dispensed	Daily Number of Depressions	Quantity Dispensed in gms	Dispensed By	Number of Bottles Returned	Amount Returned in gms	Comments
1			<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A			
2							<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	

- Review the instructions for applying the gel, reminding the participant that he should depress the pump fully for each dose. Remind the participant to start a new bottle when the pump no longer fully depresses and to return the empty bottle to the bag for safe keeping when a new bottle is started. Together, the used and unused pump bottles contained in the bag (ie. “kit”) should be returned at each visit.
- Provide a hand out for the participant to reinforce safe use of gel.
- Review the participant’s binder prior to the participant leaving the clinic, and confirm that he has completed all procedures for this visit
- Schedule the Treatment Month 2 or 3 visit
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant
- Follow up with the participant’s HCP if they indicated a change or new CV symptoms and have not informed their HCP. If the participant does not have an HCP schedule a follow up visit for that participant.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User’s Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days
- Review and respond to any IVR discrepancies
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

8.A.2. Treatment Month 3

At this visit the physical, sexual and vitality testing will be conducted depending upon which trials the participant is enrolled. Some of the tests specific to the trials will be conducted by IVR after the participant has left the clinic. All participants, in all of the trials, will conduct the IVR general global impression of change question and the cognitive global impression of change question. All participants will also complete the PHQ-9, PANAS, FACIT, and UCLA sexual diary question #4 via IVR. All other IVR procedures will be dictated by the trial in which the participant is enrolled. The medication will be dispensed for the next 3 months. Blood drawn at this visit must be between 7 –

10 AM. Fasting (after midnight of the previous evening) is also essential for this visit. The following activities will occur at the Month 3 visit:

Before the Month 3 visit:

Call the participant to remind him of the appointment. Remind him of the following:

- apply gel as usual, even on the day of the study visit
- bring in used and unused pump bottles for weighing (the entire kit or bag)
- do not eat anything for 8 hours prior to the study visit because there will be a blood draw.
- take AM medications with water prior to coming in for the visit (if applicable).
- bring in all medications currently taking, especially any medications that are newly started (e.g. since the prior visit).

The following materials are needed to conduct the Treatment Month 3 visit:

- Treatment Month 3 study form booklet
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Calibrated scale for weighing the Androgel pumps
- Calibrated Blood Pressure Cuff
- Calibrated Metric Scale for weight
- Metric Tape Measure (Anthropometric Measures)

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for today's visit
- Notify the phlebotomist that the participant is ready for their blood draw

Phlebotomist

- Have the Treatment Month 3 Venipuncture lab kit from Quest ready
- Confirm that the participant has been fasting.
- Tests at this Visit: T Level, PSA, Hct/Hgb: 30 ml whole blood, 10 ml plasma
- Additional serum (60mL), plasma (10mL), and urine (10mL) will be collected and stored
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP

- Review the participant's medications for any changes. Inquire if they have experienced any medication changes since their last visit. Record this information on the SVTM3 CRF. Also be sure to update the CMED log.
- Review the participant's adverse events / current medical events. Inquire if they have had any recent health events. Record on the STVM3 CRF. Also update the participant's AE log if necessary.
- Have the participant complete the cardiovascular symptom questionnaire, (CVSYM). Be sure to inquire if the participant has informed his health care provider (HCP) of any new CV symptoms or any change in symptoms since the last visit. If the participant indicates he has not contacted his HCP, and he consented to have his HCP contacted, follow up with the participant's HCP after the visit. Refer to the T Trial Cardiovascular MOP for further details.
- Complete the cardiovascular events CRF (CVENTS) Refer to the T Trial CV MOP for more detailed information on how events and procedures will be tracked in the DMS and followed up.
- Notify staff that the participant is ready to continue the visit
- Review the participant's Gel Usage and Compliance. Ask the participant when he last applied the gel. Note the date and the time of last application on DIST CRF. .
- Weigh the pump bottles (all returned; used and unused). When weighing the pump bottles: weigh without the caps. Record the number of pump bottles returned on the DIST CRF in the column "Number of Bottles Returned" and the total weight in the column "Amount Returned in gms".
- Dispense Gel for the next 3 months and record on the DIST CRF. Remind the participant to start a new bottle when the pump no longer fully depresses and to return the empty bottle to the bag for safe keeping when a new bottle is started. Together, the used and unused pump bottles contained in the bag (ie. "kit") should be returned at each visit.
- Review the instructions for applying the Gel, reminding the participant that he should depress the pump fully for each dose. Provide a hand out for the participant to reinforce safe use of the gel.
- Record the clinical weight in metric measurements
- Measure and record the pulse and blood pressure twice. These measures can be consecutive; it is not necessary to have more than a brief (1 – 2 minute) rest period between them.
- Record the waist and hip measurements using a metric measuring tape

Physician / Registered Nurse Practitioner (or designee)

- Instruct the participant to complete the IPSS form. An increase of >5 points should result in a review of medications that may affect the participant's urine flow. Furthermore and evaluation for prostatitis should be performed and an alpha blocker prescription may be considered.
- Perform the Digital Rectal Exam and record the results on the (SCVST2) form. If a nodule is uncovered refer to section for more details related to referral to the study urologist.
- If prostate nodule is uncovered during the exam refer to section 6.A.3.e for details on follow up procedures
- Notify staff that the participant is ready to continue with the visit

Study Coordinator / Clinic Staff / Research Assistant

- Have the participant complete the FALLS on the provided form
- Provide participant with the IVR forms for the following common IVR tests completed by all participants
- PANAS
- PHQ-9
- PF 10
- Participant Global Impression of Change (PGIC) Questions- general questions
- Participant Global Impression of Change (PGIC) Questions- cognitive questions
- Participant Global Impression of change questions specific to physical function
- Remind the participant to complete the IVR as soon as possible
- Men may start the IVR right after their month 3 visit and will have 45 days to complete the month 3 questionnaires

The following are the tests performed at this visit which are specific to the different trials:

Physical Function Testing- Completed by all men (conducted by staff trained in physical function assessments):

- Have the participant complete the 6 minute walk test

Sexual Function Testing complete by all men (conducted by staff member trained in sexual function assessments):

- UCLA sexual function Questionnaire- all men complete question #4 via IVR after the month 3 visit is complete

Sexual Function Testing- specific to the sexual function trial participants:

- UCLA sexual function questionnaire in its entirety- to be completed by IVR after the month 3 visit
- IIEF
- DISF-M-II SR
- Participant Global Impression of change (PGIC) questions- sexual function specific questions – completed by IVR after the month 3 visit is complete

Vitality Function Testing- completed by all men(conducted by staff member trained in vitality assessments):

- FACIT fatigue scale- completed via IVR after the month 3 visit

Vitality Function Testing- specific to men enrolled in the vitality trial:

- SF-36 scale completed by IVR after the month 3 visit
- Participant Global Impression of Change (PGIC) questions-vitality specific questions- completed via IVR after the month 3 visit

Visit Wrap up- Study Coordinator / Clinic Staff / Research Assistant

- Remind the participant of the tests that need to be completed via IVR and provide the participant with copies of the IVR forms they will need to complete at home following the month 3 visit
- Review the participant’s binder prior to the participant leaving the clinic, and confirm that he has completed all procedures for this visit
- Schedule the Treatment Month 4 visit
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant
- Follow up with the participant’s HCP if they indicated a change or new CV symptoms and have not informed their HCP. If the participant does not have an HCP schedule a follow up visit for that participant.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User’s Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days

[DIST]

Line Number	Date (mm/dd/yyyy)	Kit Number	Number of Bottles Dispensed	Daily Number of Depressions	Quantity Dispensed in gms	Dispensed By	Number of Bottles Returned	Amount Returned in gms	Comments
1			<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A			
2							<input type="checkbox"/> ₉₉ N/A	<input type="checkbox"/> ₉₉ N/A	

- Weigh the pump bottles (all returned; used and unused). When weighing the pump bottles: weigh without the caps. Record the number of pump bottles returned on the DIST CRF in the column “Number of Bottles Returned” and the total weight in the column “Amount Returned in gms”. **(Line #1)**
- Get a month 3 resupply kit for the participant and weight the pump bottles (entire kit) with the caps on. Record the number of bottles in the DIST log in the section “marked number of bottles dispensed” in grams **(Line #2)**. Mark the current number of depressions the participant is taking
- Review and respond to any IVR discrepancies. Be sure to check that the participant is completing the correct IVR tests in the appropriate window of time.
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

8.A.2.a). Monitoring Abnormal Values at Follow Up Visits

PHQ-9:

The PHQ-9 is administered via IVR after the initial test for inclusion at SV2. The PHQ9 is conducted for follow up at baseline ad months 3,6,9 and 12. The site PI and coordinator will be notified through an automatic alert system via Criterium if a participant answers the “thoughts of suicide” question in an affirmative manner. If a site is notified please take the following actions:

- The site PI or his/her designate will reach the patient by phone or in person to discuss the results and encourage the patient to seek appropriate care.
- The patient will be asked for permission to share the result with the

patient's primary physician and will be given the name and contact numbers for local resources available to help (such as a crisis center, psychosocial service group, name of a psychiatrist, etc).

Sites may use the T trial CONTACT sheet to collect information about primary care physicians or family members/ additional contacts in case the site cannot get a hold of the participant.

The consent form from baseline will also document if the site has permission to contact the participant's primary care physician and the physician's contact information should be on file if CV symptoms arise (please CV EVENTS MOP for more details)

8.A.3. Treatment Month 4 and 5:

The treatment month 4 and month 5 visits will be conducted over the phone and will focus on adverse events, concomitant medications and gel use and instructions.

The following materials are needed to conduct the Treatment Month 4 and 5 visits:

- Phone
- Participant CRF booklet month 4/5
- Review gel use and inquire about compliance with current dose (cross check DOSE log)

Study Coordinator / Clinic Staff / Research Assistant

- Call the participant and ask them if they have experienced any new adverse events or if any existing conditions have changed since their last visit. Record this information on the STVM4/STVM5 CRF.
- Ask the participant if they have begun taking any new medications since their last visit, stopped any medications or changed their previous dosage. Record this information on the STVM4/STVM5 CRF and update the participant's CMED log.
- Go over the instructions for using the testosterone gel with the participant again and remind them to use their specified dosage each day and apply it in the same manner.
- Schedule the month 5 or the month 6, in clinic visit, with the participant.

8.A.4. Treatment Month 6:

At this visit the physical, sexual and vitality testing will be conducted depending upon which trials the participant is enrolled. Some of the tests specific to the trials will be conducted by IVR after the participant has left the clinic. All participants, in all of the trials, will conduct the IVR general global impression of change question and the cognitive global impression of change question. The PHQ-9 and PANAS will also be conducted by all participants via IVR. All other IVR procedures will be dictated by the trial in which the participant is enrolled. The cognitive function battery of tests will also be conducted at this visit (BVRT, Card Rotations, WMS-R LM II, and the Trial Making tests. These tests will require that the staff member certified in cognitive function training be present for this participant visit. The medication will be dispensed for the next 3 months. Blood drawn at this visit

must be between 7 – 10 AM. Fasting (after midnight of the previous evening) is also essential for this visit. The following activities will occur at the Month 6 visit:

Before the Month 6 Visit:

- Call the participant to remind him of the appointment.
- apply gel as usual, even on the day of the study visit
- bring in used and unused pump bottles for weighing (the entire kit or bag)
- do not eat anything for 8 hours prior to the study visit because there will be a blood draw.
- take AM medications with water prior to coming in for the visit (if applicable).
- bring in all medications currently taking, especially any medications that are newly started (e.g. since the prior visit).

The following materials are needed to conduct the Treatment Month 6 visit:

- Treatment Month 6 study form booklet
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Calibrated scale for weighing the Androgel pumps
- Calibrated Blood Pressure Cuff
- Calibrated Metric Scale for weight
- Metric Tape Measure (Anthropometric Measures)

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for today's visit
- Notify the phlebotomist that the participant is ready for their blood draw

Phlebotomist

- Have the Treatment Month 6 Venipuncture lab kit from Quest Labs ready
- Confirm that the participant has been fasting.
- Tests at this Visit: T Level, PSA, Hct/Hgb: 30 ml whole blood, 10 ml plasma
- Additional serum (60mL), plasma (10mL), and urine (10mL) will be collected and stored
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP

- Review the participant's medications for any changes. Inquire if he has experienced any medication changes since his last visit. Record this information on the SVTM6 CRF. Also be sure to update the CMED log.
- Review the participant's adverse events / current medical events. Inquire if he has had any recent health events. Record on the STVM6 CRF. Also update the participant's AE log if necessary.
- Have the participant complete the cardiovascular symptom questionnaire, (CVSYM). Be sure to inquire if the participant has informed his health care provider (HCP) of any new CV symptoms or any change in symptoms since the last visit. If the participant reports symptoms and indicates he has not contacted his HCP, and he consented to have his HCP contacted, follow up with the participant's HCP after the visit. Refer to the T Trial Cardiovascular MOP for further details.
- Complete the cardiovascular events CRF (CVENTS) Refer to the T Trial CV MOP for more detailed information on how events and procedures will be tracked in the DMS and followed up.
- Notify staff that the participant is ready to continue the visit
- Review the participant's Gel Usage and Compliance. Ask the participant when he applied last applied the gel. Note the date and the time of last application on CFR DIST.
- Weigh the pumps bottles (all used and unused). When weighing the pumps: weigh the pumps without the caps. Record the number of bottles and the total weight of all of the pumps returned o the DIST CRF
- If required, dispense gel for the next 3 months and record on the DIST CRF. Remind the participant to start a new bottle when the pump no longer fully depresses and to return the empty bottle to the bag for safe keeping when a new bottle is started. Together, the used and unused pump bottles contained in the bag (ie. "kit") should be returned at each visit.
- Review the instructions for applying the gel, reminding the participant that he should depress the pump fully for each dose.
- Provide a hand out for the participant to reinforce safe use of gel.
- Record the clinical weight in metric measurements
- Measure and record the pulse and blood pressure twice. These measures can be consecutive; it is not necessary to have more than a brief (1 – 2 minute) rest period between them.
- Record the waist and hip measurements using a metric measuring tape

Study Coordinator / Clinic Staff / Research Assistant- Participant CRF completion:

- Have the participant complete the FALLS on the provided form
- Provide participant with the IVR forms for the following common IVR tests completed by all participants
- PANAS
- PHQ-9
- PF 10
- Participant impression of change question specific to physical function
- Participant Global Impression of Change (PGIC) Questions- general questions

- Participant Global Impression of Change (PGIC) Questions- cognitive questions

The following are the tests performed at this visit which are specific to the different trials:

Cognitive Function Testing (conducted by staff certified in cognitive function testing):

- Perform the WMS-R-LM-II and record the data on the provided study form
- Perform the MAC-Q and record the data on the provided study form
- Perform the BVRT and record the data on the provided study form
- Perform the Card Rotation and record the data on the provided study form
- Perform the TMT and record the data on the provided study form

Physical Function Testing- Completed by all men (conducted by staff trained in physical function assessments):

- Have the participant complete the 6 minute walk test

Sexual Function Testing complete by all men (conducted by staff member trained in sexual function assessments):

- UCLA sexual function Questionnaire- all men complete question #4 via IVR after the month 6 visit is complete

Sexual Function Testing- specific to the sexual function trial participants:

- UCLA sexual function questionnaire in its entirety- to be completed by IVR after the month 6 visit
- IIEF
- DISF-M-II SR
- Participant Global Impression of change (PGIC) questions- sexual function specific questions – completed by IVR after the month 6 visit is complete

Vitality Function Testing- completed by all men(conducted by staff member trained in vitality assessments):

- FACIT fatigue scale- completed via IVR after the month 6 visit

Vitality Function Testing- specific to men enrolled in the vitality trial:

- SF-36 scale completed by IVR after the month 6 visit
- Participant Global Impression of Change (PGIC) questions-vitality specific questions- completed via IVR after the month 6 visit

Visit Wrap up- Study Coordinator / Clinic Staff / Research Assistant

- Remind the participant of the tests that need to be completed via IVR and provide the participant with copies of the IVR forms they will need to complete at home following the month 6 visit
- Review the participant's binder prior to the participant leaving the clinic, and confirm that he has completed all procedures for this visit
- Schedule the Treatment Month 7 visit

- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant
- Follow up with the participant's HCP if they indicated a change or new CV symptoms and have not informed their HCP. If the participant does not have an HCP schedule a follow up visit for that participant.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days
- Review and respond to any IVR discrepancies. Be sure to check that the participant is completing the correct IVR tests in the appropriate window of time.
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

8.A.5. Treatment Months 7 and 8:

The treatment month 7 and month 8 visits will be conducted over the phone and will focus on adverse events, concomitant medications and gel use and instructions.

The following materials are needed to conduct the Treatment Month 7 and 8 visits:

- Phone
- Participant CRF booklet month 7/8
- Review gel use and inquire about compliance with current dose (cross check DOSE log)

Study Coordinator / Clinic Staff / Research Assistant

- Call the participant and ask them if they have experienced any new adverse events or if any existing conditions have changed since their last visit. Record this information on the STVM7/STVM8 CRF.
- Ask the participant if they have begun taking any new medications since their last visit, stopped any medications or changed their previous dosage. Record this information on the STVM7/STVM8 CRF and update the participant's CMED log.
- Go over the instructions for using the testosterone gel with the participant again and remind them to use their specified dosage each day and apply it in the same manner.
- Schedule the month 8 and the month 9 (clinic visit) with the participant over the phone.

8.A.6. Treatment Month 9:

This visit is very similar to the month 3 study visit. At this visit the physical, sexual and vitality testing will be conducted depending upon which trials the participant is enrolled. Some of the tests specific to the trials will be conducted by IVR after the participant has left the clinic. All participants, in all of the trials, will conduct the IVR general global impression of change question and the cognitive global impression of change question. All participants will also complete the PHQ-9 and

the PANAS via IVR. All other IVR procedures will be dictated by the trial in which the participant is enrolled. The cognitive function testing will not be conducted at this study visit. A three month medication supply may need to be dispensed at this visit depending on prior dose adjustments and/or gel use. Blood drawn at this visit must be between 7 – 10 AM. Fasting (after midnight of the previous evening) is also essential for this visit. The following activities will occur at the Month 9 visit:

Before the Month 9 Visit:

- Call the participant to remind him of the appointment.
- apply gel as usual, even on the day of the study visit
- bring in used and unused pump bottles for weighing (the entire kit or bag)
- do not eat anything for 8 hours prior to the study visit because there will be a blood draw.
- take AM medications with water prior to coming in for the visit (if applicable).
- bring in all medications currently taking, especially any medications that are newly started (e.g. since the prior visit).

The following materials are needed to conduct the Treatment Month 9 visit:

- Treatment Month 9 study form booklet
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Calibrated scale for weighing the Androgel pumps
- Calibrated Blood Pressure Cuff
- Calibrated Metric Scale for weight
- Metric Tape Measure (Anthropometric Measures)

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for today's visit
- Notify the phlebotomist that the participant is ready for their blood draw

Phlebotomist

- Have the Treatment Month 9 Venipuncture lab kit from Quest Labs ready
- Confirm that the participant has been fasting.
- Test at this Visit: T Level, PSA, Hct/Hgb: 30 ml whole blood, 10 ml plasma
- Additional serum (60mL), plasma (10mL), and urine (10mL) will be collected and stored
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP
- Review the participant's medications for any changes. Inquire if they have experienced any medication changes since their last visit. Record this information on the SVTM9 CRF. Also be sure to update the CMED log.
- Review the participant's adverse events / current medical events. Inquire if they have had any recent health events. Record on the STVM9 CRF. Also update the participant's AE log if necessary.
- Have the participant complete the cardiovascular symptom questionnaire, (CVSYM). If the participant reports any new symptoms be sure to inquire if the participant has informed his health care provider (HCP) of any new CV symptoms or any change in symptoms since the last visit. If the participant indicates he has not contacted his HCP, and he consented to have his HCP contacted, follow up with the participant's HCP after the visit. Refer to the T Trial Cardiovascular MOP for further details.
- Complete the cardiovascular events CRF (CVENTS) Refer to the T Trial CV MOP for more detailed information on how events and procedures will be tracked in the DMS and followed up.
- Notify staff that the participant is ready to continue the visit
- Review the participant's Gel Usage and Compliance. Ask the participant when he applied last applied the gel. Note the date and the time of last application on CFR DIST.
- Weigh the pumps bottles (all used and unused). When weighing the pumps: weigh the pumps without the caps. Record the number of bottles and the total weight of all of the pumps returned o the DIST CRF
- If required, dispense gel for the next 3 months and record on the DIST CRF. Remind the participant to start a new bottle when the pump no longer fully depresses and to return the empty bottle to the bag for safe keeping when a new bottle is started. Together, the used and unused pump bottles contained in the bag (ie. "kit") should be returned at each visit.
- Review the instructions for applying the gel, reminding the participant that he should depress the pump fully for each dose.
- Provide a hand out for the participant to reinforce safe use of gel.
- Record the clinical weight in metric measurements
- Measure and record the pulse and blood pressure twice. These measures can be consecutive; it is not necessary to have more than a brief (1 – 2 minute) rest period between them.
- Record the waist and hip measurements using a metric measuring tape

Study Coordinator / Clinic Staff / Research Assistant- Form completion section:

- Have the participant complete the FALLS on the provided form
- Provide participant with the IVR forms for the following common IVR tests completed by all participants
- PANAS
- PHQ-9
- PF 10

- Participant Impression of change question specific to physical function
- Participant Global Impression of Change (PGIC) Questions- general questions
- Participant Global Impression of Change (PGIC) Questions- cognitive questions

The following are the tests performed at this visit which are specific to the different trials:

Physical Function Testing- Completed by all men (conducted by staff trained in physical function assessments):

- Have the participant complete the 6 minute walk test

Sexual Function Testing complete by all men (conducted by staff member trained in sexual function assessments):

- UCLA sexual function Questionnaire- all men complete question #4 via IVR after the month 9 visit is complete

Sexual Function Testing- specific to the sexual function trial participants:

- UCLA sexual function questionnaire in its entirety- to be completed by IVR after the month 9 visit
- IIEF
- DISF-M-II SR
- Participant Global Impression of change (PGIC) questions- sexual function specific questions – completed by IVR after the month 9 visit is complete

Vitality Function Testing- completed by all men(conducted by staff member trained in vitality assessments):

- FACIT fatigue scale- completed via IVR after the month 9 visit

Vitality Function Testing- specific to men enrolled in the vitality trial:

- SF-36 scale completed by IVR after the month 9 visit
- Participant Global Impression of Change (PGIC) questions-vitality specific questions- completed via IVR after the month 9 visit

Visit Wrap up- Study Coordinator / Clinic Staff / Research Assistant

- Remind the participant of the tests that need to be completed via IVR and provide the participant with copies of the IVR forms they will need to complete at home following the month 9 visit
- Review the participant's binder prior to the participant leaving the clinic, and confirm that he has completed all procedures for this visit
- Schedule the Treatment Month 10 visit
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant

- Follow up with the participant's HCP if they indicated a change or new CV symptoms and have not informed their HCP. If the participant does not have an HCP schedule a follow up visit for that participant.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days
- Review and respond to any IVR discrepancies. Be sure to check that the participant is completing the correct IVR tests in the appropriate window of time.
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

8.A.7. Treatment Months 10 and 11:

The treatment month 10 and month 11 visits will be conducted over the phone and will focus on adverse events, concomitant medications and gel use and instructions.

The following materials are needed to conduct the Treatment Month 10 and 11 visits:

- Phone
- Participant CRF booklet month 10/11
- Review gel use and inquire about compliance with current dose (cross check DOSE log)

Study Coordinator / Clinic Staff / Research Assistant

- Call the participant and ask them if they have experienced any new adverse events or if any existing conditions have changed since their last visit. Record this information on the STVM10/STVM11 CRF. If necessary record this information on the participant's AE log.
- Ask the participant if they have begun taking any new medications since their last visit, stopped any medications or changed their previous dosage. Record this information on the STVM10/STVM11 CRF and update the participant's CMED log.
- Go over the instructions for using the testosterone gel with the participant again and remind them to use their specified dosage each day and apply it in the same manner.
- Schedule the month 11 and the month 12 (in clinic visit) with the participant over the phone.

8.A.8. Treatment Month 12

At this visit the physical, sexual and vitality testing will be conducted depending upon which trials the participant is enrolled. Some of the tests specific to the trials will be conducted by IVR after the participant has left the clinic. All participants, in all of the trials, will conduct the IVR general global impression of change question and the cognitive global impression of change question. The PHQ-9 and PANAS will also be conducted by all participants via IVR. All other IVR procedures will be dictated by the trial in which the participant is enrolled. The cognitive function battery of tests will also be conducted at this visit (BVRT, Card Rotations, WMS-R LM II, and the Trial Making tests).

These tests will require that the staff member certified in cognitive function training be present for this participant visit. Blood drawn at this visit must be between 7 – 10 AM. Fasting (after midnight of

the previous evening) is also essential for this visit. The following activities will occur at the Month 12 visit:

Before the Month twelve visit:

- Call participant to remind him of the appointment.

Remind him of the following:

- apply gel as usual, even on the day of the study visit
- bring in all (used and unused) pump bottles for weighing. Reinforce the importance of returning all pump bottles dispensed over the prior 12 months since this visit is the end of the study “treatment” phase of the study.
- do not eat anything for 8 hours prior to the study v-visit because there will be a blood draw.
- take AM medications with water prior to coming in for the visit (if applicable).
- bring in all medications currently taking, especially any medications that are newly started (e.g. since the prior visit).

The following materials are needed to conduct the Treatment Month 12 visit:

- Treatment Month 12 study form booklet
- Venipuncture equipment and barcoded / labeled vials for research sample collection
- Calibrated scale for weighing the Androgel pumps
- Calibrated Blood Pressure Cuff
- Calibrated Metric Scale for weight
- Metric Tape Measure (Anthropometric Measures)

Study Coordinator / Clinic Staff / Research Assistant

- Greet the participant and explain the procedures for today’s visit
- Notify the phlebotomist that the participant is ready for their blood draw

Phlebotomist

- Have the Treatment Month 12 Venipuncture lab kit from Quest Labs ready
- Confirm that the participant has been fasting.
- Test at this Visit: T Level, HgbA1c, PSA, Hct/Hgb: 32 ml whole blood, 10 ml plasma
- Additional serum (60mL), plasma (10mL), and urine (10mL) will be collected and stored
- Collect blood, process, and label as described in the Quest MOP
- Notify staff that the participant is ready to continue the visit
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments

Physician / Registered Nurse Practitioner (or designee)

- Instruct the participant to complete the IPSS form.
- Perform the Digital Rectal Exam and record the results on the (STVM12) form.
- Notify staff that the participant is ready to continue with the visit

Study Coordinator / Clinic Staff / Research Assistant

- Collect 10 ml of urine, process, and label as described in the Quest MOP
- Review the participant's medications for any changes. Inquire if they have experienced any medication changes since their last visit. Record this information on the SVTM6 CRF. Also be sure to update the CMED log.
- Review the participant's adverse events / current medical events. Inquire if they have had any recent health events. Record on the STVM12 CRF. Also update the participant's AE log if necessary.
- Have the participant complete the cardiovascular symptom questionnaire, (CVSYM). Be sure to inquire if the participant has informed his health care provider (HCP) of any new CV symptoms or any change in symptoms since the last visit. If the participant reports symptoms and indicates he has not contacted his HCP, and he consented to have his HCP contacted, follow up with the participant's HCP after the visit. Refer to the T Trial Cardiovascular MOP for further details.
- Complete the cardiovascular events CRF (CVENTS) Refer to the T Trial CV MOP for more detailed information on how events and procedures will be tracked in the DMS and followed up.
- Review the participant's Gel Usage and Compliance. Ask the participant, "when was the last time you applied the gel?" Note the date and the time of last application on CFR DIST.
- Weigh the used and unused gel pumps. When weighing the pumps: weigh the pump bottles without the caps. Record the pump numbers and the total weight of all of the pump bottles dispensed at the visit. Record the weight on the DIST CRF
- Record the clinical weight in metric measurements
- Measure and record the pulse and blood pressure twice. These measures can be consecutive; it is not necessary to have more than a brief (1 – 2 minute) rest period between them.
- Record the waist and hip measurements using a metric measuring tape

Study Coordinator / Clinic Staff / Research Assistant- Participant CRF completion:

- Have the participant complete the FALLS on the provided form
- Provide participant with the IVR forms for the following common IVR tests completed by all participants
- PANAS
- PHQ-9
- PF 10
- Participant Impression of Change question specific to Physical function
- Participant Global Impression of Change (PGIC) Questions- general questions
- Participant Global Impression of Change (PGIC) Questions- cognitive questions

The following are the tests performed at this visit which are specific to the different trials:

Cognitive Function Testing (conducted by staff certified in cognitive function testing):

- Perform the 3MSE and record the data on the provided study form
- Perform the WMS-R-LM-II and record the data on the provided study form
- Perform the MAC-Q and record the data on the provided study form
- Perform the BVRT and record the data on the provided study form
- Perform the Card Rotation and record the data on the provided study form
- Perform the TMT and record the data on the provided study form

Physical Function Testing- Completed by all men (conducted by staff trained in physical function assessments):

- Have the participant complete the 6 minute walk test

Sexual Function Testing complete by all men (conducted by staff member trained in sexual function assessments):

- UCLA sexual function Questionnaire- all men complete question #4 via IVR after the month 3 visit is complete

Sexual Function Testing- specific to the sexual function trial participants:

- UCLA sexual function questionnaire in its entirety- to be completed by IVR after the month 12 visit
- IIEF
- DISF-M-II SR
- Participant Global Impression of change (PGIC) questions- sexual function specific questions – completed by IVR after the month 3 visit is complete

Vitality Function Testing- completed by all men(conducted by staff member trained in vitality assessments):

- FACIT fatigue scale- completed via IVR after the month 12 visit

Vitality Function Testing- specific to men enrolled in the vitality trial:

- SF-36 scale completed by IVR after the month 12 visit
- Participant Global Impression of Change (PGIC) questions-vitality specific questions- completed via IVR after the month 12 visit

Visit Wrap up- Study Coordinator / Clinic Staff / Research Assistant

- Remind the participant of the tests that need to be completed via IVR and provide the participant with copies of the IVR forms they will need to complete at home following the month 12 visit
- Review the participant's binder prior to the participant leaving the clinic, and confirm that he has completed all procedures for this visit
- Schedule the Month 18 visit
- Complete all necessary CRFs

Data Entry and Discrepancy Management

- Review all CRFs for completeness prior to beginning data entry, refer any CRF questions to the study coordinator / clinic staff / research assistant
- Follow up with the participant's HCP if they indicated a change or new CV symptoms and have not informed their HCP. If the participant does not have an HCP schedule a follow up visit for that participant.
- Navigate to the T Trial Main Landing page via an Internet Explorer or a Netscape browser and login to the secure DMS as described in the User's Guide
- Enter the data for the participant in the appropriate visit tab
- Review and respond to any Out of Range discrepancies for lab results within 5 to 7 days
- Review and respond to any IVR discrepancies. Be sure to check that the participant is completing the correct IVR tests in the appropriate window of time.
- Review any online discrepancies for the participant that may have been triggered by the data entry process and, if applicable, address the discrepancies

8.A.9. Treatment Month 18

This is a post treatment visit which can be conducted in person or over the phone while the subject is in their home.

Study Coordinator / Clinic Staff / Research Assistant

- If in clinic, have the phlebotomist prepare the Quest Month 18 Venipuncture kit
- 15 mL of serum will be collected for PSA testing
- Collect blood, process, and label as described in the Quest MOP
- Take the samples to be processed / stored / shipped as outlined in the Quest MOP
- Oversee all procedures related to the samples and storage / shipping of these samples to Quest Lab
- Notify Quest that a shipment has been sent either via fax or by email
- Keep an inventory of the shipments
- Serum collection can also be conducted with the Quest Month 18 Venipuncture kit at home.
- Ask the participant if he has experienced any new adverse events or if any existing conditions have changed since his month 12 visit. Record this information on the STVM18 CRF and update the participant's adverse event log.

8.A.10. Treatment Month 24

This post treatment visit will be conducted over the phone.

Study Coordinator / Clinic Staff / Research Assistant

- Call the participant and ask them if they have experienced any new adverse events or if any existing conditions have changed since their last visit. Record this information on the STVM24 CRF and update the participant's adverse event log.
- Complete the COMP form with the study end date- ask participant which arm of the trial they think they were randomized to

- Thank the participant for their time and remind them that this will be their last trial visit/contact.
- Concomitant Medications

8.B. Identifying and Collecting Concomitant Medication Data

Medication names – specifically those prescribed by a physician or those obtained over-the-counter (OTC) – will be recorded for every participant enrolled into the T Trial. If a participant is eligible after Screening Visit 1, he should be instructed to bring either 1) a list of their prescription and OTC, or 2) the actual prescription and OTC bottles to Screening Visit 2. If the participant does not bring a list or their medication bottles to SV2, Site Staff will need to obtain the participant’s medication history via interview before the baseline visit as there are exclusionary medications that must be evaluated.

In the interest of knowing this information sooner, the coordinator can inquire about concomitant medications at SV1, though it unknown at this time if the participant is eligible to continue in the screening process. The Medication Reference Tool in the DMS tab of the website, must be used to evaluate exclusionary medications. (For details on installing the medication reference tool on your computer please refer to the Data Management System (DMS) User’s Guide).

Drug generic or brand names can be entered into the Medication Reference Tool and will generate a unique drug code. The drug code should then be entered into the CMED form within the DMS. When codes are entered into the CMED CRF the name and class of the drug will automatically populate when the form is saved complete. Drugs which **may** be exclusionary, based on their drug class, not drug name, will be flagged in red indicating there is a discrepancy.

To determine if a medication is allowable for entry into the study, enter the name into the Medication Reference Tool provided through the DMS. General exclusionary drug categories will appear as a red alert and may require additional investigation by the RC to determine, based on protocol criteria such as drug class and dose, if the drug is an exclusion.

If determined that a drug is exclusionary, please list this in the source file.

All medications that a participant is on at the start of the study (e.g. collected at SV2 and reviewed at Baseline for changes prior to randomization) must be listed on the CMED CRF with the Drug Code (obtained from the Medication Reference Tool), Medication Name, Dose, Unit, Frequency and Route. The Start Date must be entered as completely as possible and must be a date that is prior to randomization for all drugs that the participant is on at the time of the baseline visit. PRN drugs should be included.

Preexisting medications will be tracked at each follow up visit and all changes should be entered on the CMED CRF (stop date, dose changes, frequency, etc.) If there is dose, route or frequency change to a preexisting medication, enter a stop date for the prior medication and list the change as a new drug on the CMED CRF.

All participants should be queried at each visit for new medications that have been taken since the prior visit. These will be recorded on the CMED CRF. The reason for the new medication will most likely correspond to an adverse event. Always query participants about the purpose of the medication and record the corresponding reason on the AE CRF.

All discrepancies on the CMED CRF should be resolved. In resolving the discrepancy the site staff should indicate whether the participant is eligible or ineligible based on their drug/medication use.

Example: Participant reports they were using testosterone intermittently for 3 weeks a few years ago.

- Type testosterone into the medication reference tool to generate the code for the medication.
- Once the code is generated enter the code onto the CMED form along with the sequence number.
- Save the form complete and the name of drug and the class will appear
- Testosterone is potentially an exclusionary medication, depending upon the time frame of use, and the medication and class will flag red to indicate that it should be reviewed by the PI and study team as a possible exclusionary medication.

At the remaining visits a participant's continuing medication history will be reviewed for changes in medication use, any new medications, or any medications that have been discontinued. Record all relevant information on the CMED form. The following standard questions should be asked at each follow-up visit:

"Have you started taking any new medications since your last visit on [date]?"

"Have you changed the dose or stopped taking any of the medications that you used to take?"

Inquire about the reason for starting a new medication or changing/discontinuing a previous medication. This may indicate a change in health status that should be reflected on the AE form or may be recorded in the source file.

EXAMPLE: Asthma- If a participant indicates that he has begun using an inhaled steroid because of a diagnosis of asthma, the medication should be recorded on the CMED form and the corresponding [asthma] diagnosis should be included on the AE form.

8.C. Using DMS Tools for Concomitant Medications

For step-by-step directions for accessing the Medication Reference tool, refer to the T TRIAL User's Manual.

The Medication Reference Tool utilizes the National Drug Data File (NDDF):

- National Drug Data File Plus (NDDF) issued by First Data Bank will be used to code all Concomitant Medication (CMED) drug codes that are collected as CMED data on CMED CRFs.
- The NDDF encompasses medications approved by the U.S. Food and Drug Administration (FDA), and information on commonly-used over-the-counter and alternative therapy agents such as herbals, nutraceuticals and dietary supplements.
- The NDDF provides a comprehensive set of drug database elements that allow for flexibility in searching the drug thesaurus while enhancing the integrity and uniformity of drug reporting and review.
- The current version of the NDDF was released in 2nd Quarter of 2009, and is updated quarterly.
- The CRCU has designed and implemented a user friendly Medication Reference Tool available on the T Trial Main Landing Page, which can be used to search the drug index by Brand or Generic Name for all medications contained within the NDDF.
- The associated medication codes provided by the NDDF are used to standardize data collection and reporting by providing an electronic means for cataloging and analyzing medications used during the course and duration of the T Trial study
- If a drug does not appear within the drug dictionary and you are not able to obtain a code for it you may be able to get the code if the drug is split into its two components at their respective doses. However, this change for data entry should be noted within the source document.

8.D. Completion of Enrollment in sub-Trial

Each of the individual sub-trials (sexual, physical, vitality) have their own specific sample sizes. Once the samples size, or target enrollment for an individual trial has been reached, men can no longer be enrolled in that trial alone. For example, once the sexual function trial meets its enrollment goal, men who are only eligible for the sexual function trial will no longer be enrolled in the Trial/ they will no longer be eligible to participate. However, men who are eligible for the sexual function trial, and are eligible for another trial as well; either physical, vitality or both, may be randomized and enrolled in all the trials in which they are eligible.

9. Safety Reporting

This section describes the requirements and processes for reporting adverse events and unanticipated problems that occur during the study to the Data Coordinating Center (DCC). It incorporates recommendations from the National Institute on Aging (NIA), and those provided by the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) and also describe the Food and Drug Administration (FDA) reporting requirements. The DCC is obligated to ensure that researchers comply with the standard reporting procedures. Clinical trial investigators funded by NIA are obligated under federal regulations to appropriately inform the DCC and local IRB of serious adverse events and unanticipated problems. The DCC is required to notify the external study sites, DSMB, Steering Committee, NIA and FDA and is required to ensure that the appropriate procedures are in place to support this reporting.

9.A. Adverse Event (AE) Definitions

Definitions are per the January 2007 Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events, Office on Human Research Protection (OHRP) Guidance. <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>. The requirements and processes for reporting adverse events are described in the corresponding NIH Guidelines.

Adverse Event (AE): An AE is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to the participant's participation in the research.

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, external adverse events are those adverse events experienced by participants enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by participants enrolled by the investigator(s) at that institution.

Serious Adverse Event (SAE): An SAE is any AE that is:

- a. fatal
- b. life-threatening
- c. requires or prolongs hospital stay
- d. results in persistent or significant disability or incapacity
- e. results in congenital anomalies or birth defects
- f. an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.

9.B. Collecting Adverse Event Information

The research team is obligated to monitor participants so that their participation in the clinical trial is as safe as it can be.

Coordinators should seek information about adverse events at each study visit and record it on the Standard Visit form for the corresponding month. Adverse event collection will begin following the baseline visit as this constitutes enrollment in the trial. In conjunction with the reporting on the monthly standard visit form, adverse events will be recorded on the Adverse Event [AE] case report form at each clinic visit. This information may also be reported between scheduled study visits via participant phone calls or other unscheduled study visits or assessments if the participant reports health related problems or concerns. The study period during which adverse events must be reported is defined as the period from initiation of the study procedures to the end of the treatment follow up.

Participants will be encouraged to contact the investigator, at the conclusion of the trial, if subsequent events occur which the participant, or the participant's physician, believes may be related to participation in the research study.

Site staff will collect information about pre-existing conditions at the baseline visit and use this information to track changes in these conditions over the course of the trial, beginning at the Month 1 follow-up visit.

A **preexisting condition** is defined as a condition existing at the time that the research consent was signed and should only be recorded as an adverse event if the frequency, character, or intensity of the condition worsens during the study. The Adverse Event CRF includes a column to indicate if a preexisting health condition is present at the start of the trial. At the Baseline Visit, the coordinator should ask the participant the following question, "Do you have any pre-existing health conditions or problems?" This information should be recorded on the AE CRF and indicated as a pre-existing condition by checking the box in that column. This form should be referenced at each contact thereafter during the course of the trial.

At all follow-up visits, adverse event information should be elicited from participants by asking the following questions:

1. Have you had changes in pre-existing conditions since your last clinical visit on [date]?
2. Have you had any **new** symptoms, illnesses or injuries since your last clinical visit on [date]?

The information recorded should be based on the signs or symptoms reported and detected during the study visit with the participant. Coordinators must collect complete information about adverse events from participants to enable proper coding. This includes the following:

- Descriptive text and key words of the event
- Assessment of the event severity (grade)
- Indication if the event is serious and type
- Relationship to study drug
- Start date and end date (if applicable)

All recorded adverse events should be followed until resolution or stabilization. Adverse events will be categorized according to the corresponding MedDRA code at the DCC for reporting purposes.

9.B.1. Specific Adverse Events Categories

Most adverse events will be reported directly from the participant. However, there are several categories that the site staff should note in particular.

Gel Use

In the course of reviewing proper use of the gel, inquire if the participant has had any skin problems at the site of gel application. If so, inquire about the skin changes and if it seems warranted ask the participant to show you the gel application site. This may be helpful in assessing the seriousness of the problem.

Laboratory values

Any abnormal laboratory result must be reviewed and addressed by the investigator. A value that is only slightly out of range still may be relevant; thus, it is important for a qualified individual to assess the clinical significance of reported lab values. The Principal Investigator should sign the laboratory reports received at the site and recommend appropriate follow-up as needed. These are not recorded on the AE log but noted in the source file and on the assessment sheets (such as the CVADM form for example).

Other medical information

A participant may report that he had a medical test or procedure. If so, inquire as to why this was done as it may reveal pertinent information.

In addition, if a participant reports starting a new medication, it may also indicate a new diagnosis or a change in a pre-existing medical condition that should be discussed and documented on the AE form.

9.B.1.a). Recording AE Information

Record concise, complete information about each reported event on the AE form. (Use the source document to provide additional information about the event, if necessary.) This includes the severity (defined as extent of medical treatment required and interference with daily living activities), relationship to study drug, relatedness to a pre-existing condition, duration of the event (onset and resolution), and action taken in response (use of therapies).

Examples:

When gathering information and documenting adverse events in the source file the following conventions should be used:

1. Describe event then location – (e.g. rash on face or rash on shoulders which could be the gel application site)
2. Start date (onset)
3. End date (resolved or continuing)
4. Related to a preexisting condition
5. Treatment for the event (including medication, soaks, creams, etc.)

6. Doctor seen
7. Any other information that may be significant

9.C. Severity and Seriousness of the Adverse Event

The scale below indicates the correspondence between grade and seriousness of a particular event.

Severity	Seriousness
Mild AE; did not require treatment	SAE if required or prolonged hospitalization
Moderate AE; resolved with treatment	SAE if required or prolonged hospitalization
Severe AE; inability to perform normal activities; required professional medical attention	SAE if required or prolonged hospitalization
Life-threatening or permanently disabling	SAE
Fatal AE	SAE

9.C.1. Relatedness

The potential event relationship to the study intervention is described below:

- Not related: event is clearly not related to the intervention
- Possibly related: event may be related to the intervention
- Related: event is clearly related to the intervention

The determination of relatedness for Serious Events must be made by the Investigator.

9.D. Serious Adverse Event (SAE) Reporting

All SAEs must be reported to the DCC (by email or fax) within 24 hours of first knowledge of the event. An expedited report of an SAE will in turn be submitted to the independent safety monitoring body and the NIA within 48 hours of the event being reported to the DCC Principal Investigator or as specified in the Data and Safety Monitoring Plan. The DCC will be responsible for reporting the SAE to the study sponsor. The study investigator should keep a copy of the SAE forms on file at the study site. IRB's should be notified of an SAE within 10 working days.

The expedited SAE report (captured on the SAE reporting form) should be followed by a detailed, written report, within 48 hours, and captured on the Serious Adverse Event Reporting Form. In conjunction with the Serious Adverse Event Reporting form Medwatch 3500A forms should also be submitted.

The follow up SAE report should include a copy of the completed and signed Serious Adverse Event Form and any other diagnostic information that will assist in understanding of the event. In most cases the follow up diagnostic information will include medical records. Follow up information may be required and requested. When all of the essential information has been documented, the DCC will submit the Medwatch form 3500A to the FDA if it is determined that the event meets FDA reporting requirements.

FDA\Medwatch\Instructions for Completing Form FDA 3500A.htm

<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf>

9.D.1. SAE Reporting Timeline

Clinical sites and the DCC are responsible to adhere to the following timeline:

- The clinical site should inform the DCC of an SAE (via fax or email) within 24 hours of first knowledge of the event. This can be sent via the SAE reporting form which can be found on the ttrial website, ttrial.org, or via a partially completed MedWatch form. Within 24 hours of knowledge of the event be sure to provide the DCC with as much information as possible.
- The DCC will inform the sponsor within 24 hours of receipt from the site.
- The clinical site Principal Investigator should complete the Medwatch 3500A form. This form should be completed and sent to the DCC with all of the relevant information as soon as possible, within 5 days.
- The clinical site IRB should be notified within 10 working days unless site specific IRB's indicate events should be reported sooner.
- The DCC will provide the FDA with a complete Medwatch Form 3500A as soon as possible. Unexpected, life threatening or fatal SAE's will be reported to the FDA within 7 days; other SAE's will be reported to the FDA within 15 days if the SAE is considered related to study drug and unexpected or if it is considered related but occurring at a higher than normal frequency.

9.E. Unanticipated Problem (UP) Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- **unexpected** (in terms of nature, severity, or frequency) given the research procedures that are described in the IRB-approved research protocol and informed consent document;
- **related or possibly related to participation in the research**; possibly related means that there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research.
- **suggests that the research places participants or others at a greater risk of harm** (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.
- The majority of adverse events are not unanticipated problems. Some adverse events, but not all, are unanticipated problems.

9.E.1. UP Example

Medication errors and procedural mishaps are examples of Unanticipated Problems. The following is an example of an unanticipated problem (UP) that is not an adverse event but that must be reported to the IRB, appropriate institutional officials, and OHRP.

Example: As a result of a tracking error at the medical center a participant is given the wrong medication kit. This error was discovered by the site coordinator after the participant left the clinical center, necessitating a return visit for the participant. The investigational pharmacy made a prompt investigation of the incident and immediately replaced the medication kit with the correct kit. The participant resumed taking the correct medication within 5 days of the error.

This constitutes an unanticipated problem for the institution where the error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed participant at a greater risk of physical harm than was previously known or recognized.

9.E.2. Filing an Unanticipated Problem Report

A form entitled Procedural and Unanticipated Problem [PUP] Report is used to describe any unanticipated problems/incidents. All relevant information should be included on the PUP form and it should be entered into the DMS within 48 hours of first knowledge of a problem. If the unanticipated problem is also an adverse event, complete the AE reporting form to document any corresponding adverse event information related to this problem.

9.F. Medical Consultation

A physician at each site should be identified who will serve as an independent consultant to assess matters of participant safety and health. If a medical adverse event occurs that requires prompt intervention, such as a change in PSA or hemoglobin level to the safety thresholds defined in the protocol, an independent urologist or other physician (internist or hematologist) must be consulted to assess treatment needs and continued participation in the trial. In order to make this evaluation, this physician will have access to results from all lab data and will make a formal consultation report and recommendation to the Principal Investigator at the clinical trial site. The responsibility of ensuring that referrals are made and participants are evaluated appropriately will fall upon the Principal Investigator at each of the sites.

10. Study Compliance

10.A. Protocol Deviations

Any deviation from the approved protocol will be considered a protocol deviation.

Any deviation from the protocol requires an IRB approved protocol waiver prior to implementation except as described below. The waiver will describe the nature of the deviation and a rationale for its implementation. If the protocol waiver is approved by the IRB, the deviation from the approved protocol may be implemented on a one-time basis only.

A deviation to eliminate a hazard or otherwise protect the life or well-being of a participant may be implemented immediately, and it should be reported to the IRB and study Sponsor as soon as possible.

10.A.1. Guidelines for Reporting Protocol Deviations/Violations

The Investigator must notify the DCC Principal Investigator if a major protocol deviation/violation occurs, describing the nature of the deviation and the justification for its implementation. This should be sent to the DCC project managers via fax or email on the T Trial protocol deviation/violation form. The DCC Principal Investigator will contact the Chair of the Steering Committee and the NIA Project Officer to jointly decide on the appropriate mechanism (letter, conference call, and meeting) to address the deviation/violation, if it is major. Failure to report a protocol deviation in a timely manner will be considered a compliance issue.

Examples of Major Deviations/Violations

- Failure to obtain informed consent (i.e., no documentation of informed consent or informed consent was obtained after initiation of study procedures)
- Informed consent obtained by someone not approved to obtain consent for the protocol

- Use of invalid consent form (i.e., consent form without IRB approval stamp, or outdated/expired consent form)
- Enrollment of a participant who is ineligible for the study
- Performing a research procedure not in the approved protocol
- Failure to report serious adverse event to sponsor/DCC
- Study medication dispensing or dosing error
- Failure to follow the approved study protocol that affects participant safety or data integrity (e.g., failure to properly schedule study visits or failure to perform laboratory tests)
- Continuing research activities after IRB approval has expired
- Use of recruitment procedures that have not been approved by the IRB
- Participant giving study medication to a third-party
- Enrolling significantly more participants than approved in the IRB protocol

The protocol deviation/violation form is an administrative form used to track and describe all protocol deviations and violations that occur. Minor deviations can be defined as instances of failure to follow the approved study protocol that do not affect participant safety such as a follow-up study visit conducted outside of required timeframe. These forms should be available for review during site monitoring visits.

10.B. Missed Study Visits

If a participant does not keep a scheduled appointment, within the established window of its due date (refer to section 6.A.2.b.), the missed visit must be attempted and/or rescheduled as soon as possible to complete the testing required for that visit and to query the participant about his health status.

To minimize the occurrence of missed appointments, the participant will be provided with the following reminders when appropriate:

- Written schedule of visits during the baseline exam with reminder at each contact
- Printed card with date of next visit or contact (when appropriate)
- Advance notification of next visit (at least one week prior)
- Phone call reminder within 1 to 2 days prior to the scheduled visit
- Letter via postal mail if other methods of communication fail

If a follow-up contact cannot be completed within the time window allowed, the contact should be scheduled and completed before the window date of the next study contact. If the contact cannot be completed before the window date of the next contact, the contact must be considered missed, and the Missed Visit Case Report Form (MISS) must be completed and entered into the DMS.

When a participant misses a follow-up contact, the research coordinator should stress the importance of collecting follow-up data. When a participant misses multiple follow-up contacts, the PI may consider withdrawing the participant from the study.

10.C. Participant Status and Study/Treatment Stop Form (COMP)

It is the objective of the study to collect complete data on all enrolled participants for the two years during which they are in the trial. As such, sites should be as flexible as possible when working with participants to meet their scheduling needs.

During the consent process, review the visits schedule with the participant to prepare him for the expectations over the course of the study. Discuss potential problems with the schedule and timing of the visits. Review the visit schedule throughout the course of the trial and reiterate the importance of keeping appointments and contacting the coordinator if other arrangements need to be made.

The intent-to-treat analysis of the study means that participants will be asked to continue to provide complete data for study visits even if the participant is no longer using the gel.

Participants who enroll in the study will be asked to complete all study visits, even if they stop using gel on their own or are instructed to discontinue gel use because of complications (e.g., erythrocytosis or prostate cancer, heart attack). The site staff should discuss this aspect of follow-up with participants and explain to them the intent to treat design.

If a man is instructed to discontinue gel use, or he decides to stop using gel on his own, sites must complete the study/treatment stop form (COMP). For men who stop treatment the bottom half of the COMP form should be completed. The top half of the COMP form should be left blank, as the man has not withdrawn from the study. The date of treatment stop and the reason for treatment stop should be recorded on this form. The treatment stop section of the COMP form should be completed for men who will continue to come to all study visits but will no longer be taking study gel. If the participant stopped due to an SAE or AE please be sure to record this on the AE log. The DOSE log should also be updated with the visit at which treatment was stopped.

If a man decides to restart gel after stopping, record this date on the COMP form. Also, if a man restarts, update the DOSE log with the new start date and dose.

If a man misses several doses of gel due to hospitalization, vacation, etc. this is not considered a treatment stop and restart. The missed doses should be recorded at the next study visit on the participant's DIST log. There is a column on the DIST log for number of missed doses since the previous visit.

10.D. Study Stop and Close Out Visit

If a man refuses to continue using gel and will not return for any follow-up visits, the COMP form should be completed as a Stop Study/ complete the top portion of the form. This indicates the participant has withdrawn from the T Trial. If the man indicates he does not want to continue, a visit should be scheduled to close out the participant and collect gel.

The month 12 visit should be used as the close out visit for the participant and gel should be collected. It should be noted on all source documents that this is not a month 12 visit but actually a close out visit for the participant. On the month 12 standard visit form mark yes, this is a termination visits. During a normal month 12 visit this question will be marked as no.

Sites should attempt to collect all of the data for the month 12 visit but as this is a very long visit we recognize some men may refuse and it may not be possible in all cases. Safety data, such as labs, IPSS, DRE, AE and medical history questionnaires should be collected first. Next the site should focus on primary endpoint data for the Trial overall, such as the WALK test, and any primary endpoint data that can be collected for the specific trials in

which the man was enrolled. It is imperative that sites collect the gel and update the DOSE and DIST logs for the participant.

11. Quality Control Procedures

11.A. Data Reporting and Study Management

A set of standard reports will be developed to describe study activities that include accrual, study progress, compliance tracking, demographics, safety information and data quality. These reports will be developed using Oracle Reports and provided to investigators, NIA, the DSMB and designated committees as appropriate.

Data Management: The DCC provides overall coordination, logistical support, and implementation for all aspects of the study protocol including data collection, data processing, tracking of participant recruitment, tracking of specimens, training, quality assurance, and statistical analysis. The Clinical Research Computing Unit (CRCU), through its clinical data management, project management, and software systems developments, places into the field and maintains a state-of-the-art www-based data system that accommodates all scientific study data, and permits tracking and coordination of all T Trial activities.

11.B. Training and Certification

11.B.1. DMS Training and Certification

All study team members at the sites who will be conducting data entry will be identified and documented on the site delegation logs. People at the sites who are delegated to conduct data entry will go through a training and certification process before being given access to the Oracle Clinical Remote Data Capture System.

Data entry personnel will submit a formal data management system access request for to the DCC. This form will be reviewed, signed and processed by the DCC staff. After sending in an access form site personnel will be contacted with a date and time to attend a data entry webinar which will go over principles of data integrity, data entry and walk them through the data management system. After attending a data entry training session site personnel will be emailed a username and password which allows them access to the T Trial training data management system (DMS). They will also be sent mock data packets to enter in to the training data management system.

Once site personnel have completed entering the mock data they will contact the DCC so that their test data can be scored. A complete paper CRF to data entered CRF comparison is then conducted and if the error rate for data entry is greater than .05% the site personnel will be retrained and given additional data to enter. If the error rate is less than .05%, site personnel will receive an email with a certificate signifying their certification to enter data into the T Trial production data management system. At that time their username and password permission will be changed granting them access to enter data into the live system and revoking their access to the training data base.

Data integrity and use of the data management system will be tracked through the audit trail in the electronic data capture system. When changes are made to the data within the system it will be tracked via personnel's usernames and passwords.

11.B.2. Data Quality Control Procedures

The data quality control procedures are a multi-faceted approach involving:

- on-line edit checks
- electronic and manual data review
- queries and data updates
- audits
- regular monitoring by the T Trial QA committee of reports/ monitoring and attendance
- site monitoring visits conducted by KAI

11.B.3. Cognitive Function Training

Sites will be certified in cognitive function training through the Wake Forest group. Sites will practice the cognitive function testing on people at their site and record the testing. The tapes will then be sent to the Wake Forest group for scoring. Sites will receive notification of certification in cognitive function testing from the Wake Forest group. Certification is valid for 6 months at which time cognitive technicians will need to be re-certified.

11.C. Site Monitoring/Visits

Site Monitoring Visits will be conducted by KAI, Inc. the contracted CRO. These visits will be conducted as follows:

Visit Plan

KAI will conduct monitoring at all active sites according to the following plan:

- 1. To ensure that all subjects are consented appropriately**
 - KAI will review 100% of the Informed Consent Forms (ICFs) to ensure that all subjects are consented prior to study related procedures being performed and that the consent process is properly documented.
 - KAI will also review separate and optional ICFs for the first 600 men consenting to additional 10 mL of blood being drawn for development of lymphoblastoid samples.
 - KAI will confirm that the appropriate version of ICF is used and that it is approved by the local IRB/ethics committee.
- 2. To ensure that all subjects meet Protocol Inclusion and Exclusion criteria**
 - KAI will review source documentation to ensure that all enrolled subjects meet the inclusion and exclusion criteria, and adequate source documentation are provided to validate their eligibility.
- 3. To ensure that the site is compliant with the study protocol**
 - KAI will verify the data recorded on relevant paper Case Report Forms (CRFs) against the source documents and assess each site's compliance with all requirements of the protocol.
 - KAI will document any areas of deficiency and in conjunction with the Sponsor determine whether there will need to be additional records reviewed.
- 4. To ensure that all Investigational Products (IP) are transported, stored, accounted for, dispensed, and disposed of per protocol requirements**
 - KAI will review all relevant documentation (e.g. temperature logs, IP accountability logs/dispensation records) to ensure that the IP is stored and disposed of (when applicable)

per protocol requirements, that the quantity dispensed and on site are accounted for throughout the study.

5. To ensure that the study follows GCP/ICH guidelines in conducting the clinical trial

- KAI will monitor the overall documentation practices of each site to ensure that all data recorded on the CRFs can be verified against the source documents and collected in a manner that protects subjects' rights, integrity and confidentiality.
- KAI will review the regulatory binder to ensure that the Essential Documents are current and maintained throughout the study.

Timing of KAI monitoring visits

- KAI will conduct approximately 10 site monitoring visits over five years at each site for this study:

YEAR 1

- An Initial Site Visit will be conducted after the second subject has been enrolled
- Two- three day Interim Monitoring Visits will occur during the first year of the enrollment phase, when approximately 6-10 subjects and 16-20 subjects have been enrolled, respectively.

YEARS 2, 3 & 4

- Two-two day Interim Monitoring Visits will occur each year during the second, third and fourth years of the study. The frequency will be determined by accrual rates.

YEAR 5

- A one day Close-Out Visit will be conducted after the last subject completes the study at each site.

MISCELLANEOUS

- In addition to the above visits, additional For Cause Interim Monitoring Visits will be conducted as needed when specific problems are identified. Problems related to randomization, drug distribution, data quality and site performance are reasons for additional monitoring visits.

Main objectives of the monitoring visits

Initial Site Visit

- Meet with the project team
- Provide overall assessment of the clinical and research facility
- Evaluate study drug storage security and distribution
- Review regulatory documents
- Evaluate data management and documentation practices
- Review 100% of available data

Interim Monitoring Visits

- Review the Informed Consent Forms of all screened subjects
- Review drug storage and distribution records

- Review all eligibility, safety data, primary end point data, and adverse event report of all subjects enrolled
- Review the entire study chart of 10% of the subjects enrolled

Note: The Sponsor may request additional or fewer visits or specific monitoring assignments as needed over the course of the study. KAI may recommend that additional or fewer visits be conducted as well.

Reports

Study Monitoring Reports will be submitted to the Sponsor within 10 business days after the completion of the visit.

Site Study Staff

The Monitor will request that the PI at each site be physically present for the exit interview for each visit. If this is not possible, the exit interview can be conducted over the phone while the Monitor is on site. The Monitor will request the availability of all other relevant study staff during the visit for consultation as needed.

12. Study Completion and Closeout Procedures

KAI will conduct site visits at the end of the study. The Main objectives of the close-out visit are to:

Close-Out Visit

- Review all drug storage, distribution and reconciliation records
- Assure that all outstanding data queries have been resolved
- Assess appropriate storage of research records
- Review final report

13. Appendices

13.A. Lab Test Schedule

	Testosterone Trial - Lab test schedule									
All Subjects Real time testing	SV 1	SV 2	Base	1	2	3	6	9	12	18
CBC without differential		X								
Chemistry panel	X (reflex)								X	
Urinalysis		X								
FSH & LH			X							
PSA	X (reflex)		X			X			X	X
TSH		X								
Serum T Total	X	X	X	X	X	X	X	X	X	
HgbA1C		X							X	
Hgb/Hct			X			X	X	X	X	
DHT			X			X	X	X	X	
Storage - blood & urine			X	X	X	X	X	X	X	
X = Blinded results										