PROTOCOL TITLE: Perioperative Testosterone Replacement Therapy Improves Outcomes: A Pilot Safety and Feasibility Study

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	9/30/2020	Additions to sample size, power calculation, and data safety sections. In particular, interim analysis plan was elaborated on.
2	5/17/2021	Adding stipulation to ICF and Protocol that digital rectal exam will be Optional and determined to be needed by study physician

3	10/28/2021	Clarifying that self-reported questionnaires are used to determine quality of life before and after surgery
4	1/27/2022	Removing exclusion criteria for patients who are undergoing chemotherapy and/or radiation therapy pre- or post-operatively
5	3/31/2022	Addition of topical testosterone gel as a route of administration for patients undergoing testosterone replacement therapy.
6	6/29/2022	Added time windows, made sure eligibility checklist aligned with approved form, changed data storage information, changed pharmacy preference, added frailty measures
7	01/11/2023	Broaden form of testosterone to also include all topical brands (i.e. Testim, etc.) of equivalent dosage
8	11/16/2023	Alter study timeline to allow the Surgery Day visit to serve as the second confirmatory test for low testosterone
9	03/21/2024	Clarify protocol if screening PSA is elevated. Added exclusionary criteria to indicate elevated PSA at time of screening requires additional workup
10	8/30/2024	Extending the study timeline to allow follow-up visits 60 days before or after the 3 month follow-up visit date to reflect and align with the current clinical practice.

Table of Contents

1. Study Summary

Study Title	Perioperative Testosterone Replacement Therapy Improves Outcomes: A Pilot Safety and Feasibility Study
Study Design	Male patients already scheduled for a major surgery that will require an overnight stay in the hospital will be asked to participate in this study if they meet the inclusion criteria. Testosterone (T) and related hormones will be measured before surgery. Low T patients will be asked to participate in the intervention arm, where they will receive testosterone injections (i.e. cypionate, enanthate) or topical testosterone gel (i.e. AndroGel, Testim) for 3 months. Normal T patients will be asked to participate in the control arm, where no testosterone replacement is given. Frailty will be measured by Fried criteria before surgery and 3-months postoperatively. Quality of life questionnaires will be given both preoperatively and at 3-months postoperatively
Primary Objective	Examine safety and feasibility of preoperative testosterone replacement and determine if such replacement significantly affects quality of life perioperatively
Secondary Objective(s)	Perioperative outcomes, such as decreased length of hospital stay, complications, and mortality. Change in frailty phenotype during course of study, ICU admissions, discharge disposition (to home, to home with services, to facility), unplanned readmissions, and mortality
Research Intervention(s)/Interactions	Testosterone replacement in one trial arm
Study Population	Hypogonadal men undergoing major urologic surgery
Sample Size	124 (62 in each arm)
Study Duration for individual participants	From the time patients decide on surgery until 3 months post-operatively (4-5 months)

Study Specific Abbreviations/ Definitions	Testosterone (T), Testosterone Replacement (TR)
Funding Source (if any)	Department

2.Objectives

The purpose of this study is to examine the safety and feasibility of perioperative testosterone replacement (TR) therapy in hypogonadal male patients undergoing major operations. It is our hypothesis that hypogonadal patients who undergo testosterone replacement, as determined by objective criteria detailed below, will have improved quality of life and perioperative outcomes, such as decreased length of hospital stay, complications, and mortality. If proven correct, it is our supposition that testosterone (T) level testing and replacement should be incorporated into the perioperative treatment decision-making process in patients.

3. Background

Frailty is a global phenotype which indicates decrease in physical and mental reserve and is a strong predictor of post-operative complications and mortality.[1] Frailty has been demonstrated to be a “global phenotype” of decreased reserve with resultant vulnerability and poor outcomes. Though variably defined, geriatricians define frailty as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes. Previous literature has demonstrated that frailty is associated with decreased psychological and physical quality of life in elderly patients.[2,3] There is a remarkable paucity of data in the surgical literature about frailty in surgical patients. Fried criteria is a widely adopted frailty measurement, and Makary et al. found that elderly frail patients were 2.54 times more likely to suffer post-surgical complications, 1.69 times more likely to stay longer at the hospital and 20.48 times more likely to be discharged to a skilled or assisted living facility.[1,4] In a study of cardiac patients undergoing surgical intervention, Lee et al. found that frail patients had 1.8 times risk of dying in-hospital and identified frailty as an independent risk factor for midterm survival post-operatively.[5] Though, not specific to surgical patients, the literature has demonstrated an association between frailty and decreased quality of life in elderly patients.[2,3]

Testosterone is an important biomarker in physical strength and functioning, and low testosterone is associated with frailty phenotype. Testosterone deficiency in aging men has been associated with a variety of impactful outcomes and diseases. Low testosterone has been associated with metabolic syndrome and type II diabetes. Previous literature has suggested that

low total testosterone and free testosterone may have an association with frailty, sarcopenia and diminished muscle mass, limitations on mobility, and diminished overall physical function.[6nd] Additionally, while its relationship with cardiovascular disease remains ill-defined in the literature, some studies suggest that low testosterone increases cardiovascular morbidity.[9] Furthermore, hypogonadism has been associated with lower quality of life in elderly men.[10,11]

A previous study at our institution showed that low free testosterone and frailty combined are predictive of overall survival after major surgery. In addition, hypogonadism in older men has been associated with lower quality of life.[10] some studies have suggested that testosterone replacement may improve quality of life in hypogonadal men, but this has not been well established in surgical patients.[11ts.]

Testosterone replacement has been shown to have beneficial effects on hypogonadal patient populations. One study reported that, in combination with exercise therapy, testosterone replacement was associated with decreased muscle wasting and increased functional capacity.[14] Though once thought to pose increased risk of cardiovascular events, more recent literature has indicated that this relationship may be beneficial rather than harmful.[9] A study by Argalious et al. provided evidence that testosterone replacement therapy poses no increased mortality or risk of cardiovascular morbidity for patients undergoing noncardiac surgeries.[15] One randomized controlled trial reported that, among their cohort of frail men, patients receiving testosterone replacement increased lean body mass and decreased adipose mass compared to those who received placebo. In addition, the authors reported improved physical function among these patients, though the difference was not significantly greater than that of the placebo group. Furthermore, testosterone replacement patients reported improved somatic and sexual symptom scores compared to placebo.[16] Other studies have suggested that testosterone replacement improves physical and psychological quality of life in hypogonadal men.[10] **Given the positive effects of testosterone replacement on muscle mass and physical function in hypogonadal men, we hypothesize that testosterone replacement may be safe and provide benefit in improving quality of life. In addition, testosterone replacement may play a role in diminishing frailty and its influence on perioperative morbidity.** The purpose of our study is to investigate the safety and feasibility of testosterone replacement therapy administered to hypogonadal patients undergoing a major surgery.

Male patients already scheduled for a major surgery that will require an overnight stay at Emory University Hospital will be asked to participate in this study if they meet the inclusion criteria. Testosterone (T) and related hormones will be measured before surgery. Low T patients will be asked to participate in the intervention arm, where they will receive testosterone injections (i.e. cypionate, enanthate) or topical testosterone (i.e. AndroGel, Testim) for 3 months. Normal T patients will be asked to participate in the control arm, where

no testosterone replacement (TR) is given. Frailty will be measured by Fried criteria before surgery and 3-month postoperatively. Quality of life questionnaires will be given both preoperatively and 3-month postoperatively. Follow up visits, study-related labs, frailty measurements, and questionnaires will be done at 90 days (+/-) 60 days.

Other outcome measures will include complications, intensive care unit admissions, and length of hospital stay, discharge disposition, unplanned readmission, and 90-day mortality. We hope to demonstrate that perioperative testosterone replacement therapy is a safe treatment for improving quality of life and frailty phenotype and will reduce the risk of adverse postoperative outcomes.

4. Study Endpoints

Outcome measurements:

1. Changes in quality of life before and after surgery using self-reported questionnaires
2. Change in frailty phenotype before and after surgery (Fried Criteria)[4]
3. Major Complications (Clavien-Dindo IIIb and above): within 90 days of surgery
4. Minor Complications (Clavien-Dindo IIIa and below) within 90 days of surgery
5. ICU admission
6. Hospital Length of Stay
7. Discharge disposition (to home, to home with services, to facility)
8. Unplanned readmissions: within 90 days of surgery
9. Mortality: within 90 days of surgery
10. Testosterone Level

Safety Endpoints

1. Complete Blood Count (CBC)
2. PSA
3. CRP, ESR, LDH
4. Protein (total), Albumin

5. Study Intervention/Investigational Agent

Description of intervention: Depending on the desired route of testosterone administration, hypogonadal patients will be taught to self-administer weekly 75-100mg testosterone cypionate intramuscular injections or topical testosterone (i.e. 40.5 mg Androgel 1.62% daily [two pumps; one to each upper arm/shoulder in the morning] or Testim 50mg/5g [1%]

gel, one tube daily - half a tube per arm, every morning). Patients who elect for topical testosterone will be counseled on the risk of interpersonal transference and the subsequent need to cover the upper arms/shoulders upon gel application. Testosterone replacement will only be used in patients that test below the normal total testosterone level on two separate days. As testosterone is being used therapeutically according to FDA approval, IDS will not be involved in this study. Testosterone injections and topical gels are both standard of care for testosterone replacement in hypogonadal men. Therefore, IND exemption will not be requested. The medication will be dispensed by the pharmacy of choice on patient's record. The pharmacy will follow its own SOPs as required. The principal investigator or health care providers on his/her research team will provide the medicine to the patient and teach how to properly self-administer treatments. The number of vials and amount of testosterone gel dispensed by the pharmacy, as well as the number/amount distributed to each patient will be carefully recorded in the study binder and data sheet in an excel sheet that is password protected and behind the Emory firewall on HIPAA compliant share drive that can only be accessed by the study team. Patients will receive standard of care surgery.

6. Procedures Involved

Male patients 18 years and older scheduled for major urologic surgery requiring overnight hospitalization will be encouraged to participate in the study after they meet study participation criteria. If interested, patients will be consented for the study and testosterone related measures, biochemical measures, and objective measurements of frailty will be obtained preoperatively. Following determination of a low total testosterone level based on initial preoperative labs, patients will be notified if their testosterone is normal (>300ng/dL) or low (<300ng/dL). If low, patients will be ordered a second testosterone test for confirmation. This second testosterone test can occur before surgery or the surgery day. Thistest can serve as Low T confirmation. If normal on the second reading, patients will enter the control arm. If low again on the second reading (<300ng/dL), patients will enter the experimental arm and receive testosterone replacement therapy perioperatively. Patients in the experimental arm patients will receive weekly 75-100mg testosterone intramuscular injections (i.e. cypionate, enanthate) or dose equivalent topical testosterone gel (i.e. daily 40.5 mg Androgel 1.62%, Testim 50mg (1%) gel) that they are taught to self-administer. A medication diary will be provided. The goal total testosterone level for patients in the treatment group should be the midpoint of the normal range (within the middle tertile). Patients will continue testosterone replacement injections/testosterone gel and follow-up laboratory draws until their 3-month follow up appointment. Outcome measures will be collected postoperatively as listed above. This will involve searching through patient charts and filling in information in the study excel sheet.

Additionally, quality of life measures will be collected at the post-operative visits, though these are optional. Forms will be collected and stored in a binder. Survey scores will be entered in the study excel sheet. The measures of frailty and testosterone-related and biochemical measures will be completed per eligible patient. Patients with normal T levels will undergo the same frailty, testosterone, and quality of life measurements both preoperatively and postoperatively.

Quality of life Measures (PROMIS Global Health-10)--OPTIONAL:

1. Physical function
2. Overall Quality of Life
3. Physical health
4. Mood
5. Ability to Participate in Social Roles and Activities
6. Pain and Fatigue

Measures of Frailty (Fried Criteria)[4]

1. Comorbidity scales
    a. ASA (American Society of Anesthesiologists)
    b. CCI (Charlson Comorbidity Index)
2. Measures of activity
    a. Eastern Cooperative Oncology Group Performance Status (ECOG)
    b. Minnesota Leisure Time Activities Questionnaire – Short Form
3. Physical tests of strength/speed
    a. Grip strength
    b. Walking test
    c. Chair stands
    d. 10 ft. Timed Get-Up and Go
4. Nutritional status:
    a. Shrinking (weight loss): self-reported unintentional weight loss ≥ 10 pounds (lbs) in last year
5. Anatomic features
    a. Patient imaging will be examined to look at anatomic features associated with frailty

Testosterone Related and Biochemical measures

1. Laboratory Draws
    a. Testosterone (Total and Free)
    b. CBC

c. CRP, ESR, LDH
d. Protein (total), Albumin
e. Serum Cr, eGFR as measured by MDRD formula
f. LH, DHEA, SHBG
g. PSA

2. Physical Examination
    a. Digital Rectal Exam (optional)

The following are ways to minimize risks: careful chart review and patient history ensuring strict adherence to inclusion and exclusion criteria. Standard of care labs and exams will be performed prior to beginning and during the course of testosterone replacement therapy including measurement of PSA and drawing complete blood count. Additionally, a digital rectal exam may be required for certain patients and will be determined by the physician. Elevated PSA (>4 ng/mL) at the time of screening without complete evaluation in the last year will exclude the patient from the study to allow for a full workup at the discretion of the treating surgeon. Patients will receive standard of care surgical treatment as well as monitoring of patients for 90 days after surgery for any complications of surgery or adverse events from testosterone replacement.

Study Calendar

Tests and Observations	Screening and Consenting Visit (+/- 3 days)	Low T confirmation	Day of Surgery (+/- 1 day)	90 Day Follow-Up Visit(+/- 60 days)
Frailty Tests and Quality of Life Survey	**x**		**x**	**x**
Testosterone (Total and Free)	**x**	**X*** **	**X*** **	**x**
CBC, CRP, ESR, LDH, Protein (total), Albumin, Serum Cr, eGFR as measured by MDRD formula, LH,	**x**		**x***	**x**
DHEA, SHBG, PSA				

Digital Rectal Exam	**x****			
Post-Operative Outcome Measures				**x**

*PSA not needed at this laboratory draw

**Physician will assess patient's medical need for Digital Rectal Exam

***Either the "Low T Confirmation" or "Day of Surgery" can serve as the low T confirmation test to determine if the patient will be prescribed testosterone

7. Data Banking

All patient data collected during this study will be gathered from the patient medical record during the day of visit or recorded on survey forms we administer to patients. Data on each patient will be kept in a secure, password protected excel spreadsheet only accessible by study team stored behind Emory firewall on HIPPA compliant share drive. Surveys, informed consent forms, and withdrawal forms will be kept in a binder in the urology research unit, which requires passcode for entry. Patient information will be de-identified. Dr. Master, Dr. Ogan, Dr. Mehta and clinical research coordinators they employ will have access to the excel sheet. Data will include quality of life scores, frailty scores, laboratory values, surgical details, and perioperative outcomes.

8. Sharing of Results with Participants

There are no plans to share results with participants.

9. Study Timelines

Describe:

- The duration of an individual participant's participation in the study is expected to be 4 to 5 months. The duration anticipated to enroll all study participants is 1 -2 years.
- The estimated date for the investigators to complete this study is November 1, 2024.

10. Inclusion and Exclusion Criteria

Subject Eligibility:

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

Inclusion criteria:

1. Patients 18 years and older
2. Patients scheduled for major surgery requiring an overnight hospital stay
3. Patient willing to do study's preoperative and postoperative assessment tools

Exclusion criteria:

1. History of prostatectomy with detectable PSA
2. History of prostate radiation/chemotherapy treatment and has experienced bounce or rise in PSA
3. Elevated PSA at time of screening without complete evaluation in last year
4. History of orchiectomy, or are scheduled to undergo orchiectomy
5. Undergoing hormone replacement therapy currently or history of testosterone use within last year
6. History of solitary or undescended testis
7. History of pituitary disorders
8. History of thromboembolic events in last year
9. Hematocrit >55%
10. Uncontrolled congestive heart failure
11. Special populations: Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women and prisoners

11. Local Number of Participants

All of the recruited patients will be locally accrued. Following guidelines for pilot studies, the sample size of this study is set at 124, with 62 in each arm. This allows us to account for 20% chances of dropouts, lost to follow-up and exclusions and still provides a 80% power for the main trial with an estimated 0.2 standardized difference.[18] We will conduct an interim analysis at the mid-point of the study accrual to re-evaluate the sample power calculations and the results of primary outcomes based on existing data. The decision to continue with accrual will be based on this interim analysis.

12. Recruitment Methods

Participants will consist of individuals who are seen in Urology clinics at Emory University Hospital as patients. Participants may be identified by review of medical records or physician referral. Partial HIPAA waiver will be requested from the IRB for this purpose. After an investigator introduces the study to the participant, the consent form may be given in person, mailed, emailed, or sent to the participant through Epic or the Emory Patient Portal. The study team will follow up with the participant through the methods of communication listed above, by phone, and/or in person to communicate with the participant about the study. The participant will be given time to read the consent form and ask questions. A member of the study team will reach out to the participant to make sure the participant understands all aspects of the study and the participant is ready to sign the consent documentation. The participant may sign the consent forms in a private setting at Emory. Also, the participant has the option to consent by mail. Subjects with LEP may be enrolled and study team members will use Emory IRB approved short forms to conduct the consent process. Participants will not receive any payment or reimbursement for this study.

13. Withdrawal of Participants

Participants with a hematocrit laboratory value of >54% at any of the study scheduled laboratory visits will be withdrawn from the study without their consent. In addition, patients who have a hypersensitivity reaction to testosterone injection or topical testosterone therapy will be withdrawn without their consent. Participation in this study is completely voluntary and participants can withdraw at any time without any consequences. Participants can also be withdrawn from the study without their consent if their safety is at risk. This is unanticipated for this study. The revocation form specifies the procedures for participants withdrawing from the study.

14. Risks to Participants

The expected incidence of postoperative adverse events attributable to testosterone replacement therapy is expected to be low. Known side effects of testosterone replacement include dermatologic (rash, pain, erythema, edema, and itching at site of injection or gel application), gastrointestinal/metabolic (diarrhea, nausea, abdominal pain, increased appetite, weight gain), cardiovascular (hot flush, hypertension), genitourinary (lower urinary tract symptoms, prostatitis), hematologic (polycythemia, increased hematocrit), pulmonary side effects (cough while injecting) and mood side effects (mood swings, increased aggression or irritability).

Risk of developing elevated hematocrit has been demonstrated in the literature; however, whether this correlates to any clinical significance is not well known. Studies have suggested that testosterone replacement may increase the value around 2%.[19] Subjects will be monitored for change in hematocrit. If patients experience hematocrit lab value of greater than 54%, this is considered unsafe and patients will be excluded from further testosterone replacement. Development of erythrocytosis has been reported in up to 10% of patients using TR.[15,19,22] The effect of testosterone replacement therapy on prostate cancer remains unclear.[23 re] Though concerns over testosterone replacement and a potential association with development of deep vein thrombosis or cardiovascular disease have been proposed, the recent evidence suggested TR therapy may not increase risk of these conditions.[9,15,26,27] In particular, one recent study provided evidence that testosterone replacement therapy poses no increased mortality or risk of cardiovascular morbidity for patients undergoing non-cardiac surgeries.[15] In addition to these risks, the patient's personal health information could potentially be at risk due to the chart review needed for study eligibility screening as well as to access laboratory values and reports on the patient's outcomes. The chart will be accessed by members of the study team; thus, the subjects will be at risks associated with this.

There would be minimal risks for patients in the control group.

15. Potential Benefits to Participants

Participants in the testosterone replacement group are expected to experience a direct benefit. Testosterone replacement therapy has been shown to be beneficial for hypogonadal patients. Studies have demonstrated that frail patients undergoing testosterone replacement therapy have increased lean body mass and decreased adipose mass, and have improved physical functions, somatic and sexual symptom scores.[16] Testosterone replacement therapy can also stimulate bone formation and may decrease the risk of fracture.[23] We expect that all patients receiving testosterone replacement will receive these benefits throughout the duration of their treatment course. Upon termination of the treatment, we would expect this benefit to be diminished shortly after. We expect that testosterone replacement will increase quality of life and physical function by an amount easily noticeable to the patient and well-reflected by survey scores.

There would be no direct benefit for participants in the control group.

16. Data Management and Confidentiality

Statistical Analysis:

To determine the feasibility of the testosterone replacement therapy, changes in quality of life in the intervention arm will be compared to minimal meaningful differences seen in literature and control arm.[28,29] Other post-operative outcomes, including changes in frailty phenotype

and 90 day major complications seen in the intervention arm will be evaluated against the control arm. Analyses will be performed with SAS version 9.3 with a p-value cut off at 0.05 (SAS Institute, Cary, NC).

Sample size

Following guidelines for pilot studies, the sample size of this study is set at 124, with 62 in each arm. This allows us to account for 20% chances of dropouts, losses to follow-up and exclusions while still providing a 80% power for the main trial with an estimated 0.20 standardized difference.[18] This sample size calculation was done with quality of life measures in mind. This also fit well with the goal of determining if the treatment is safe, which should be observable and detectable with this number of patients. We will plan to conduct statistical analysis at the interim of our study.

Interim analysis: We will be concerned with quality of measures at this point, and about rates of adverse events (including DVT and elevated hematocrit). A preliminary/interim analysis will be conducted in order to establish a "go/no-go" assessment based on incidence of DVT and elevated hematocrit in enrolled subject population. Interim point is defined by half of enrollment in each arm of the study. With total 62 patients in analytical cohort we have 0.80 probability of observing at-least one DVT incidence in control arm. This analysis will help to establish the incidence of DVT in this population and we will re-assess sample size requirements to determine the exact number of additional patients needed to be enrolled.

Data Safety

We will conduct an interim analysis at the mid-point of the study to evaluate the sample power calculations and the results of primary outcomes based on existing data as well as review safety endpoints. Patient surveys will be stored in a binder in the password-locked urology research unit. Patient data will be entered into a password protected shared excel sheet that the research team can access to input data. Data will be de-identified when sent to statistician. The investigators, as well as the clinical research coordinators who lead the project will have access to the data and binder.

17. Provisions to Monitor the Data to Ensure the Safety of Participants

The Urology team will provide oversight for the conduct of this study by conducting periodic QA/QC. These will be conducted with the study coordinator every 3-6 months and proper documentation will be maintained as per Urology SOP. Complete source documentation review will be performed to ensure ALCOA++ guidelines and applicable Winship and CRU SOP compliance. There is no dose escalation planned for this study. The procedures to assure data integrity and protocol adherence are standard of care

procedures for this study. Regular data verification and protocol adherence will take place in real time. The standard of care labs will be collected, and the PI will review and analyze the results in real time. All data will be recorded, and all adverse events will be graded and reported in real time using the CTCAE criteria for evaluation. The oversight of the study team will be carried out by the PI reviewing data in real time and results being discussed at the GU working group meetings as necessary. The evaluation of testosterone and labs is standard of care. The study team will not need to be trained on study procedures because there are no new procedures being done that are not part of the standard of care.

Our team plans to conduct interim analysis (when we reach half our planned total enrollment number for each arm) of primary outcomes and safety endpoints. During this time, we will monitor rates of DVT and hematocrit laboratory values of >54%. Careful assessment of cause of any adverse events will be performed. Though patients undergoing operations are at risk for DVT at baseline, multivariate analysis will be performed to determine the relationship of testosterone replacement therapy to development of DVT. Analysis will control for preoperative characteristics and patient demographics such as age, BMI, gender, race, smoking status, past medical history (diagnoses of hypertension, renal failure, diabetes mellitus, etc.), and the type of procedure the patient undergoes; however, it will still be difficult to conclude that a difference in DVT rate between groups is due to the testosterone replacement therapy. Clinical judgement by the PIs will be performed, in concert with these analyses, to ensure that this therapy is proving safe for our patients. During our interim analysis (and throughout the trial) discussion and reach consensus about 1) whether an adverse event was related to TR, and 2) whether or not to proceed, for each patient who experiences an adverse event. Patients with elevated hematocrit will be withdrawn from the study. We will plan to conduct statistical analysis at the interim of our study about rates of adverse events (including DVT and elevated hematocrit). Because our patients may be at risk for DVTs due to other characteristics (such as undergoing surgery), it will be difficult to determine cause of DVTs. Thus, we will plan to use these statistical analysis in concert with clinical judgement by our physicians and other team members to ensure that our patients are done no unnecessary risk or harm.

18. Provisions to Protect the Privacy Interests of Participants

All actions described in HIPAA section of consent form will be taken to protect the privacy of participants. The study will be explained to participants and they will have the opportunity to ask as many questions as necessary to feel comfortable consenting to participate in the study.

19. Economic Burden to Participants

There are no additional costs that participants will be responsible for if they participate in this research study.

20. Consent Process

Participants may be identified by review of medical records or physician referral. After an investigator introduces the study to the participant, the consent form may be given in person, mailed, emailed, or sent to the participant through PowerChart or the Emory Patient Portal. The study information, such as the consent form, may be sent to the patient using an encrypted email. The study team will follow up with the participant through the methods of communication listed above, by phone, Emory licensed Zoom, and/or in person to communicate with the participant about the study. The study team member will confirm with the participant that they received all pages of the consent form. The participant will be given time to read the consent form and ask questions. A member of the study team will reach out to the participant to make sure the participant understands all aspects of the study and the participant is ready to sign the consent documentation. Identity of each participant will be confirmed prior to consent. The informed consent discussion can take place in person or via phone or Emory licensed Zoom. The consent process may take place in the ways described below.

1. The participant may sign the consent form in a private setting at Emory.
2. The participant may print the consent form at home and sign with a wet ink signature. The participant can send the consent form back to the study team using the following methods:

   2a. The participant will scan and send the signature pages of the consent form back to the study team via email

   2b. The participant may take pictures of the signature pages of the consent form and send it back to the study team via email

   2c. The participant can mail the wet ink signed pages of the consent form to the study team.

Participants will be given a copy of the consent form. Participants with LEP may be enrolled and study team members will use Emory IRB approved short forms to conduct the consent process. There will be a translator present when the study team enrolls a participant with LEP.

21. Setting

Subjects will be identified prior to surgery. They may be consented in a clinic setting or by mail.

22. Resources Available

There are hundreds of urology procedures necessitating overnight stay (major procedure) each year. Within a year of recruiting, the goal of 50 male patients willing to undergo testosterone replacement for symptomatic hypogonadism prior to surgery is feasible. In addition, picking 50 normal testosterone controls will be feasible and is expected to happen quickly. 33% of one full time research coordinator's effort will be devoted to this trial annually. Medical and psychological resources that participants might need as a result of an unanticipated consequences of the human research are available at Emory. A dedicated clinical research team will be available to assist in proper conduct of this research study. There will be extensive documentation of training for study personnel. This will be documented on training forms, delegation of authority forms, the 1572, and other documents. Training is ongoing and will be updated as needed.

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