1. Project Title:
A Randomized Double Blinded Placebo Controlled Trial between Anastrozole and Clomiphene to Evaluate Improvement in Hypogonadal Symptoms and Erectile Function Using ADAM, IIEF, and EHS Validated Scales

2. Investigator(s):

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A. STUDY BACKGROUND AND PURPOSE

Symptomatic hypogonadism occurs in 5.6% in men ages 30-79 years.[1] Low testosterone has known associations with diabetes, metabolic syndrome, hypercholesterolemia, osteoporosis, obesity, and overall mortality.[2,3] It has been shown that administration of testosterone can improve but not completely reverse many of these conditions.[4,5] Despite these trends, patients most commonly present for hypogonadism with lack of energy, diminished libido, loss of motivation, cantankerous mood, sleepiness after lunch and inability to concentrate in 62%, 56%, 44%, 42%, and 42% of patients, respectively.[6,7]

Aromatase inhibitors (AI) and selective estrogen receptor modifiers (SERMS) increase testosterone production through stimulation of the hypothalamic pituitary axis. Despite their known efficacy, easy oral administration, and safety profiles, use of these medications is uncommon, likely to due to off label use. While these drugs both reduce the feedback inhibition of estrogen on the pituitary, SERMs cause an increase in serum estradiol, whereas AIs reduce estradiol levels. Using these medications, we can obtain therapeutic testosterone levels with either an increase or decrease in estradiol levels.

While use of these medications to increase serum testosterone in hypogonadal men is established, there is a lack of randomized controlled trials which correlate improved testosterone levels with symptomatic improvement in hypogonadal symptoms. Furthermore, the few studies do not use widely accepted and validated symptom scores that are designed for male hypogonadal symptoms and erectile function, such as the Androgen Deficiency in Ageing Males (ADAM) questionnaire, the International Index of Erectile Function (IIEF) questionnaire, and the Erection Hardness

Scale (EHS). The ADAM questionnaire is a ten question survey with "yes" or "no" answers. It questions mood, energy and sexual function. A positive result on the ADAM questionnaire is defined as an affirmative answer (‘‘yes’’) to either questions “Do you have a decreased sex drive/libido?” or “Are your erections less strong?” or any three other questions. It has been validated internationally to evaluate for male hypogonadism[8] and expanded to a quantitative score for each question.[9] The IIEF questionnaire is a fifteen question survey with a score of 0-5 for each question that examines four domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction. This questionnaire has been internationally validated in a multitude of languages.[10] The Erectile Hardness Scale EHS is a validated self-administered one item scale used to assess erection hardness.[11] Another widely accepted and tested score is the Sexual Encounter Profile (SEP). This survey incorporates five “yes” or “no” questions evaluating successful and satisfactory intercourse with the most frequently used one through three. These three questions focus on erectile function.

To date there are only two placebo controlled randomized studies on AI to evaluate for symptomatic relief of hypogonadism. One study by Love et al randomized patients to placebo or an escalating dose of letrozole. This study used Symptom Checklist-90, Groninger Intellegence Test, and the Dutch Personality Questionaire, all of which are specifically psychological questionnaires only validated within the Dutch population. None of these questionnaires evaluated sexual function.[12] Another study by Leder et al randomized patients to placebo versus anastrozole 1mg daily versus anastrozole 1 mg twice weekly. This study used MOS Short-Form Health Survey and International Index of Erectile Function (IIEF) in elderly men. This study did not show significant change in these out comes for this elderly population.[13] Because this study only included men aged 62-74, this study is not generalizable to younger men in their 30's, 40's and 50's with hypogonadal symptoms. A third prospective study randomized patients to differing doses of testosterone gel with or without anastrozole. This study was not blinded or placebo controlled. It used a health related quality of life questionnaire that was previously validated in prostate cancer patients undergoing androgen deprivation therapy. This study by Finkelstein et al demonstrated worsening of sexual function in the anastrozole group and an improvement in the testosterone gel only groups. Because of the correlation they found with decreased estradiol levels and worsening libido, they concluded that estrogen is important for male sexual function.[14] This study introduced this controversial conclusion which contradicts traditional thinking that testosterone is the main determinate of male sexual function. As previously mentioned, this study was not blinded or placebo controlled.

While there is only one randomized double blinded placebo controlled study using clomiphene, there are other small cohort and retrospective studies which suggest clinical improvement in hypogonadal symptoms with use of SERMs. The one randomized controlled trial by Guay et al compared hypogonadal men with erectile dysfunction using placebo or clomiphene 50 mg three times a week. This study used unvalidated questionnaires and only included seventeen men. While it did not show a change in sexual function of the whole study group, the younger half of the study population did have improved sexual function outcomes corresponding with increased testosterone level. These findings suggest a relationship between increasing testosterone levels and symptomatic sexual function improvement in younger males only.[15] A few other small cohort studies (non randomized or placebo controlled), prospective and retrospective, show symptomatic improvement in hypogonadal symptoms in men treated with clomiphene. Improvements are noted with erectile function,[16] and ADAM scores.[17-19]

The current men’s health literature lacks high level evidence using widely accepted and validated questionnaires to evaluate the improvement of symptoms with SERMs or AIs. Also recent controversial evidence suggests an important role of estrogen in male sexual function,[14] though this has not been thoroughly corroborated with further clinical studies. The goal of our study to perform a double blinded randomized placebo controlled trial to determine the reduction in hypogonadal symptoms with clomiphene, a SERM, and anastrozole, an AI. This reduction in symptoms will be correlated with an increase in morning serum testosterone. Because of the different mechanisms of clomiphene and anastrozole, we will also be able to correlate the reduction in hypogonadal symptoms to see what role, if any, estradiol might have in male sexual function. This study will be performed as a cross over study.

Hypothesis

We hypothesize that administration of AI and SERMs with both increase serum testosterone from baseline in association with symptomatic relief of hypogonadal symptoms regardless of estradiol levels.

B. STUDY DESIGN

- 36 patients enrolled
- Statistical Assumptions are:
    - Average IIEF score baseline pre treatment will be estimated to be at 10 points. As previously demonstrated.[20]
    - A conservative estimate for meaningful improvement in symptoms in IIEF score will be by 4 points. We therefore expect after treatment IIEF scores to be on average 14 points.[20]
    - Alpha error = 0.05
    - 85% power on a one tailed test and for a cross over study.
    - Previous validation of IIFE score reveals a standard deviation of approximately 4.[10]
    - For this power and to find this effect, we will need 30 patients.
    - Assuming a 20% drop out rate we will need to recruit 36 patients.

- Half life of clomiphene is 5-7 days. Half life of anastrozole is 50 hours. After stopping the each medication and after four half lives, 90% of the drug will be eliminated from the patient's system, and after approximately 28 days and 8.3 days 90% of clomiphene and anastrozole will be eliminated, respectively. We will be assessing response to medication after eight weeks, and there should not be any effect from the previous 8 weeks drug administration.

- Primary outcome:
    Improvement in IIEF score by 4 points after 8 weeks of treatment as compared to placebo.

- Secondary Outcome
    - Percent of men with normalized Testosterone of >350 after 8 weeks of treatment.
    - Serum morning Testosterone, Free Testosterone, Luteinizing Hormone, Follicular Stimulating Hormone, Estradiol, Insulin-Like Growth Factor-3
    - Change in baseline Testosterone, Free Testosterone, Luteinizing Hormone, Follicular Stimulating Hormone, Estradiol, Insulin-Like Growth Factor-3 after 8 weeks of treatment.
    - ADAM score, EHS score, IIEF score, SEP Q1-3.
    - Change in ADAM, EHS, and SEP Q1-3 scores from baseline after 8 weeks of treatment.

Men will be incentivized to come to each clinic appointment with $20 dollars at the end of each appointment. If they complete the study they will be able to earn $100.

- Men will be incentivized to not use phosphodiesterase inhibitors (Viagra, Levitra, Cialis) throughout the study by giving them three 100mg tablets of Viagra, or an equivalent, per month of the study for a total of twelve 100 mg tablets. The Viagra will be purchased by the research group and be given, free of charge, to patients who complete the study.

Inclusion Criteria:

1. Men age 18-70
2. Baseline morning Testosterone 150-350 ng/dL x2
3. LH 1.5-9.2 miU/mL, FSH 1.6-8.0 miU/mL, Prolactin 4-15 ng/mL
4. Positive ADAM score. A positive score is when an affirmative answer (''yes'') to either questions "Do you have a decreased sex drive/libido?" or "Are your erections less strong?" or any three other questions.[10]
5. BMI <40
6. SHIM score >7 and <21. Patients are allowed to be taking phosphodieserase 5 inhibitors (i.e. Viagra, Levitra, Cialis) at baseline, however we will ask them to do the SHIM survey as if they were not taking this medication.
7. Men must attempt to have at least four sexual encounters over each of the eight-week periods
8. Men willing not to take phosphdiesterase 5 inhibitors throughout the entire study

Exclusion Criteria:

1. Current or previous history of prostate cancer
2. Previous or current androgen deprivation therapy for prostate cancer,
3. Past surgical history of prostatectomy.
4. History of testicular cancer.
5. History of DVT's or blood dyscrasia
6. History of breast cancer
7. Men with past or current treatment for erectile dysfunction including MUSE, intracavernosal injections, penile prosthesis. Men not on treatment or men who are on phosphodiesterase inhibitors will be allowed to be in the study but must stop their use at the screening visit.
8. Chronic opiod use
9. Use of steroids within the past 3 months, including prednisone and/or cortisone injections, and inhaled steroids. Topical steroid cream is acceptable.
10. History of or current use of anabolic steroids, i.e. testosterone, (or any analog of testosterone) DHEA, DHEAS or any growth promoters i.e. growth hormone itself or analogs of growth hormone
11. History of or current use of anti-androgen medications, i.e. Aldactone, Tagamet, estrogens
12. Alcohol intake > 30 grams (drink more than 2 beers per day OR more than 1 glass of wine or cocktail daily)
13. Having started a new medication during the past three months which may interfere with the outcome measures of the study
14. Polycythemia (HCT >52%)
15. History of PSA > 4.0 ng/dl
16. Hematocrit (HCT)< 36 %
17. Liver function tests greater than 2 times upper normal limits or history of abnormal electrolytes, calcium or Parathyroid hormone without workup, at the discretion of the investigator.
18. Previous hypogonadal treatment within last 3 months.

Methods

Schedule

Visit 1 Screening: Standard of care:

a. Obtain written informed consent
b. Obtain demographic information (age, gender, race, ethnicity)
c. Review concomitant medications
d. Review medical history
e. Vital Signs
f. Physical Exam
g. Questionnaires ADAM and SHIM
h. Morning blood draws for hormone lab testing. CBC and liver function tests if not previously documented in chart
i. Inclusion/Exclusion Criteria review
j. Schedule patient to return in at least one week to review any labs that were obtained in "h"
k. Men will be informed that they must attempt to have at least four sexual encounters over each of the eight week periods. The SEP 1-3 questionnaire will be given to the patient and the questions answered after each sexual encounter.
l. Men will be counseled that they are not allowed to take Viagra, Levitra or Cialis.

Visit 2 Day 0

a. Confirm eligibility criteria, review new labs results from visit 1
b. Vital signs
c. Questionnaires EHS, IIEF and collect SEP Q1-3 from previous visit

d. Review concomitant medications
e. Review any changes to medical history
f. Randomization of patient
g. Dispense study medication for first eight week period
h. Schedule patient to return in 8 weeks
i. Remind men that they must attempt to have at least 4 sexual encounters over the next 8 weeks
j. Dispense SEP Q1-3 to be completed after each sexual encounter
k. Remind men that they are not allowed to take Viagra, Levitra or Cialis.

**Visits 1 and 2 may be combined as long as all inclusion/exclusion criteria have been met and all lab results for inclusion have been obtained.

Visit 3 Week 8

a. Vital Signs
b. Questionnaires ADAM, EHS, IIEF and collect SEP Q1-3 from previous visit
c. Review concomitant medications
d. Review adverse events
e. Morning blood draw for hormone lab testing
f. Physical Exam
g. Drug accountability
h. Dispense study medication
i. Schedule patient to return in 8 weeks
j. Remind men that they must attempt to have at least 4 sexual encounters over the next 8 weeks
k. Dispense SEP Q1-3 to be completed after each sexual encounter
l. Remind men that they are not allowed to take Viagra, Levitra or Cialis

Visit 4 Week 16

a. Vital Signs
b. Questionnaires ADAM, EHS, IIEF and collect SEP Q1-3 from previous visit
c. Review concomitant medications
d. Review adverse events
e. Morning blood draw for hormone lab testing
f. Physical Exam
g. Drug accountability
h. Dispense study medication
i. Schedule patient to return in 8 weeks
j. Remind men that they must attempt to have at least 4 sexual encounters over the next 8 weeks
k. Dispense SEP Q1-3 to be completed after each sexual encounter
l. Remind men that they are not allowed to take Viagra, Levitra or Cialis

Visit 5 Week 24: End of Study

a. Vital Signs
b. Questionnaires ADAM, EHS, IIEF and collect SEP Q1-3 from previous visit
c. Review concomitant medications
d. Review adverse events
e. Morning blood draw for hormone lab testing
f. Physical Exam
g. Drug accountability

C. SUBJECT POPULATION (who, what, where)

- Male patients presenting to The Urological Institute of Northeastern New York for evaluation of symptomatic hypogonadism. All patients will be seen by one of our 3 andrologists (Dr. Andrew McCullough or Dr. Charles Welliver).
- 36 subjects will be enrolled.

- All patients will be seen at the South Clinical Campus at The Urological Institute of Northeastern NY

D. ASSESSMENTS

1. **Informed consent:** Subjects will be informed of the study plan and will provide written informed consent prior to the initiation of any study related procedures by the investigator or his designees.

2. **Vital Signs**: Blood pressure, pulse and weight will be evaluated at all Visits. Height will be done at visit 1 only.

3. **Physical Exam** (PE) will consist of the following: general appearance, Head and neck, Skin, Lungs, Heart, Lymph nodes, Back, Abdomen, Genitourinary, Extremities, Musculoskeletal, and Neurologic.

4. **Clinical Laboratory Tests**: Blood will be drawn for Serum Total Testosterone, Free Testosterone, Luteinizing Hormone, Follicular Stimulating Hormone, Estradiol, SHBG and Insulin Like Growth Factor 3. Prolactin will be drawn at Visit 1 only as standard of care. The blood for hormone labs will be drawn between 8-11am. Dr. McCullough or the Sub-Investigators Dr. Welliver or Dr. Ellen will review the lab results.

5. **Questionnaires:** ADAM, EHS, IIEF, SHIM and SEP Q1-3

A. SHIM- Over the Past 6 months:

1. How do you rate your confidence that you could get and keep an erection?
   - 0- None
   - 1- Very Low
   - 2- Low
   - 3- Low Moderate
   - 4- High
   - 5- Very High

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
   - 0- No sexual activity
   - 1- Almost never
   - 2- A few times (much less than 1/2 the time)
   - 3- Sometimes (about ½ the time)
   - 4- Most times (much more than ½ the time)
   - 5- Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   - 0- Did not attempt intercourse
   - 1- Almost never or never
   - 2- A few times (much less than 1/2 the time)
   - 3- Sometimes (about ½ the time)
   - 4- Most times (much more than ½ the time)
   - 5- Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   - 0- Did not attempt intercourse
   - 1- Almost never or never
   - 2- A few times (much less than 1/2 the time)
   - 3- Sometimes (about ½ the time)
   - 4- Most times (much more than ½ the time)
   - 5- Almost always or always

5. When you attempted sexual intercourse, how often was it satisfactory for you?

0- Did not attempt intercourse
1- Almost never or never
2- A few times (much less than 1/2 the time)
3- Sometimes (about ½ the time)
4- Most times (much more than ½ the time)
5- Almost always or always

B. ADAM Questionnaire
1. Do you have a decrease in libido (sex drive)? Yes/ No
2. Do you have a lack of energy? Yes/ No
3. Do you have a decrease in strength and/or endurance? Yes/ No
4. Have you lost height? Yes/ No
5. Have you noticed a decreased "enjoyment of life" Yes/ No
6. Are you sad and/or grumpy? Yes/ No
7. Are your erections less strong? Yes/ No
8. Have you noticed a recent deterioration in your ability to play sports? Yes/ No
9. Are you falling asleep after dinner? Yes/ No
10. Has there been a recent deterioration in your work performance? Yes/ No

C. EHS
How would you rate the hardness of your erection?
0 – Penis does not enlarge.
1 – Penis is larger, but not hard.
2 – Penis is hard, but not hard enough for penetration.
3 – Penis is hard enough for penetration, but not completely hard.
4 – Penis is completely hard and fully rigid.

D. IIEF- Over the past 4 weeks:
1. How often were you able to get an erection during sexual activity?
0 No sexual activity
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
0 No sexual activity
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always
3. When you attempted intercourse, how often were you able to penetrate (enter) your partner?
0 Did not attempt intercourse
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
0 Did not attempt intercourse

1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always

5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
0 Did not attempt intercourse
1 Extremely difficult
2 Very difficult
3 Difficult
4 Slightly difficult
5 Not difficult

6. How many times have you attempted sexual intercourse?
0 No attempts
1 One to two attempts
2 Three to four attempts
3 Five to six attempts
4 Seven to ten attempts
5 Eleven or more attempts

7. When you attempted sexual intercourse, how often was it satisfactory for you?
0 Did not attempt intercourse
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always

8. How much have you enjoyed sexual intercourse?
0 No intercourse
1 No enjoyment at all
2 Not very enjoyable
3 Fairly enjoyable
4 Highly enjoyable
5 Very highly enjoyable

9. When you had sexual stimulation or intercourse, how often did you ejaculate?
0 No sexual stimulation or intercourse
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always

10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?
1 Almost never or never
2 A few times (less than half the time)
3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always

11. How often have you felt sexual desire?
1 Almost never or never
2 A few times (less than half the time)

3 Sometimes (about half the time)
4 Most times (more than half the time)
5 Almost always or always

12. How would you rate your level of sexual desire?
    1 Very low or none at all
    2 Low
    3 Moderate
    4 High
    5 Very high
13. How satisfied have you been with your overall sex life?
    1 Very dissatisfied
    2 Moderately dissatisfied
    3 Equally satisfied & dissatisfied
    4 Moderately satisfied
    5 Very satisfied
14. How satisfied have you been with your sexual relationship with your partner?
    1 Very dissatisfied
    2 Moderately dissatisfied
    3 Equally satisfied & dissatisfied
    4 Moderately satisfied
    5 Very satisfied
15. How do you rate your confidence that you could get and keep an erection?
    1 Very low
    2 Low
    3 Moderate
    4 High
    5 Very high

E. SEP Q1-3
1. Were you able to achieve at least some erection (some enlargement of the penis)? Yes/ No
2. Were you able to insert your penis into your partner's vagina? Yes/ No
3. Did your erection last long enough for you to have successful intercourse? Yes/ No

7. **Concomitant medications** will be reviewed at each visit to ensure that the subject is not taking any prohibited medications.

8. **Adverse events** will be assessed after the first dose of study medication and visits 3, 4, and 5.

E. STUDY TREATMENT

In this double-blind clinical trial subjects will receive Anastrazole 1mg/day, clomiphene Citrate 25mg/day, and placebo in randomized schedule of eight week intervals.

Randomization: Eligible subjects will be randomized in order of the randomization schedule created by the statistician. The randomization code will be stored at the Albany Medical Center Hospital Research Pharmacy. Subjects will receive the next numbered bottle of medication at follow up visits 2, 3, and 4. Patients will take anastrozole, clompihene and placebo each for eight weeks but in a randomized order. The study will be for a total of 24 weeks (3 phases x 8 weeks=24 weeks). There are six possible schedules for the ordering of the medications/placebo: 1. anastrozole for eight weeks then clomiphene for eight weeks then placebo for eight weeks; 2. anastrozole for eight weeks then placebo for eight weeks then clomiphene for eight weeks; 3. clomiphene for eight weeks then anastrozole for eight weeks then placebo for eight weeks; 4. clomiphene for eight weeks then placebo for eight weeks then anastrozole for eight weeks; 5. placebo for eight

weeks then clomiphene for eight weeks then anastrozole for eight weeks; and 6. placebo for eight weeks then anastrozole for eight weeks then clomiphene for eight weeks.

Unblinding: Study medication must not be unblinded during the trial unless it is considered necessary by the investigator for the management of an adverse event or other medical emergency.

Anastrozole and Clomiphene will be purchased from commercial supply, blinded, packaged and labeled by Albany Medical Center Research Pharmacy according to the randomization schedule provided by the statistician. The anastrozole will be purchased as 1mg tablets and the clomiphene citrate will be purchased as 50 mg tablets that will be cut in half for the 25mg dose. The tablets will be placed in capsules to blind the medication. The capsules will be placed in bottles of 60 tablets to be dispensed at Visits 2, 3, and 4 in 8 week intervals.

Administration and accountability: Subjects will be instructed to take 1 capsule orally daily. Subjects will be instructed to return the study medication bottle and any remaining capsules. Drug accountability will be done at Visits 3, 4, and 5 by documenting the amount of remaining study medication.

F. Data Analysis

- **Data Collection Tables and Schedule**

	V1	V2 (day 0)	V3 (week 8)	V4 (week 16)	V5 (week 24)
Consent	X				
History	X				
Physical Exam	X		X	X	X
Vital Signs	X	X	X	X	X
Labs	X		X	X	X
Review labs		X			
Inclusion/Exclusio	X	X			
Dispense Drug		X	X	X	
Questionnaires	X	X	X	X	X
Randomization		X			
Drug			X	X	X
Adverse events			X	X	X

**Visits 1 and 2 may be combined as long as all inclusion/exclusion criteria have been met and all lab results for inclusion have been obtained.

- All data will be collected and stored in a locked room in the Urology Research Department at South Clinical Campus.

G. Risks

Clomiphene Citrate (FDA data reported form clinical trials involving females treated for infertility)

1. Abdominal discomfort or bloating (10.4%)
2. Breast discomfort (2.2%) (the incidence of this in men is not known but has been reported)
3. Visual Symptoms (1.5%): blurred vision, lights, floaters, waves, sensitivity to light, double vision, spots (most resolve with stopping treatment but there are reports of permanent symptoms)
4. Headache (1.3%)

Anastrozole (*FDA data reported from clinical trials involving females treated for breast cancer)

1. Common reactions (>10%): arthritis, pain, arthralgia, hypertension, depression, nausea and vomiting, rash, headache, bone pain, osteoporosis
2. In men, studies have report up to a 7% incidence of subclinical changes in LFTs. There were no changes in hematocrit, PSA, or urinary symptoms. At least one randomized clinical trial in men showed no clinically significant changes in bone density after a year of treatment with anastrozole.
3. Serious adverse events occurred in less than 1 in 10,000 these included: Skin reactions (lesions, blisters), allergic reactions, changes in liver functions test or hepatitis
4. NO serious adverse events have been reported in trials involving men treated for infertility or hypogonadism.

H. Benefits

- Improvements from medication include erectile function, energy, libido.

I. Confidentiality

- Data will identified by the patients name, date of birth, and medical record number while it is collected and stored in the secure research office in the urology clinic as well as the community care physicians electronic medical record.
- Data will be de-identified prior to running statistical analysis at the end of the study.
- Each subject will be assigned a numerical code that is stored in the urology research office for de-identification.
- The master key used will be destroyed after the conclusion of the study.

J. Options

Rather than participate in this study, patients may elect to choose a medical therapy (clomiphene citrate or anastrozole).

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