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A Multidisciplinary Team-Based Approach to Mitigate the Impact of Androgen Deprivation Therapy in Prostate Cancer: a Randomized Phase 2

The "STAND" (Supportive Therapy in Androgen Deprivation) Clinic

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
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UCSF Principal Investigator / Study Chair

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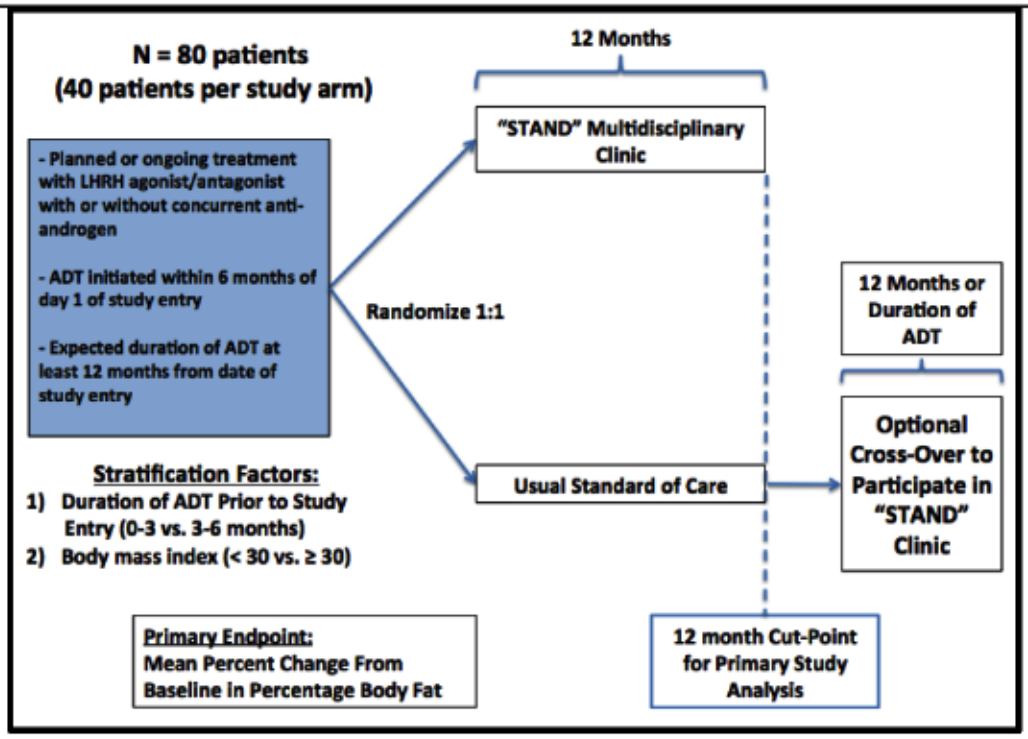
ABSTRACT

Title	**A Multidisciplinary Team-Based Approach to Mitigate the Impact of Androgen Deprivation Therapy in Prostate Cancer: a Randomized Phase 2 Study of the "STAND" Clinic**
Patient population	80 patients with prostate cancer who have recently started (within 6 months of study entry) or plan to pursue androgen deprivation therapy (ADT), with an expected duration of therapy of at least 12 months following study enrollment, will be eligible to participate in the randomized study. Twenty (20) patients currently receiving or planning to start combined chemohormonal therapy will be eligible to participate in the non-randomized pilot cohort. **Key Eligibility Criteria:** • Histologic confirmation of adenocarcinoma of the prostate • Receiving or planning to receive ADT with LHRH agonist or antagonist • Expected duration of ADT at least 12 months from study entry • Concurrent antiandrogen therapy allowed but not required • First dose of LHRH agonist or antagonist no more than 6 months prior to study entry • Prior/concurrent radiation therapy allowed • Physically able to participate in exercise program • Willing and able to travel to UCSF for monthly visits • **Randomized cohort only:** o No prior chemotherapy within 12 months of start date of study ▪ No planned chemotherapy during the initial 12 month period of study participation • **Non-randomized pilot cohort:** o Concurrent chemotherapy (initiated within 3 months of study entry) or planned chemotherapy within 3 months of study entry
Rationale for Study	Androgen deprivation therapy (ADT) is the most common systemic therapy applied in prostate cancer. It is associated with improvement in overall survival, regression of tumors, and symptom palliation in various disease states including concurrently with radiation therapy, following surgery, and for patients with metastatic disease. However, ADT is associated with numerous changes in body composition and metabolic perturbations leading to significant iatrogenic morbidity and mortality. ADT is associated with the development of the metabolic syndrome, increases in body fat, decrease in lean body mass, weight gain, hyperlipidemia, insulin resistance/diabetes, and, potentially, an increased risk of cardiovascular morbidity and mortality. It also impacts quality of life via muscle wasting, hot flashes, gynecomastia, sexual dysfunction, mood, and relationship changes. Given the broad spectrum of ADT-associated toxicities across numerous domains, there is a clear unmet medical need to develop systematic, multi-disciplinary approach to partially mitigate the toxicity of ADT. Many of ADT-associated toxicities are modifiable with careful management, although current practice data suggest that the vast majority of physicians who prescribe ADT do not manage these side effects in a consistent way, if at all. Multiple prior studies in the primary care setting demonstrate that integrated, multi-disciplinary efforts as compared to routine counseling during physician visits lead to more substantial changes in lifestyle habits, including improved diet, smoking cessation, and blood pressure management. Therefore, comprehensive management of the potential side effects of ADT with the use of a multi-disciplinary clinic may improve outcomes and partially reverse the side effects of ADT, as compared to usual standard of care. The "STAND (Supportive Therapy in ANdrogen Deprivation)" Clinic at UCSF was created for patients treated with ADT to address and mitigate the adverse effects of hormone therapy. The intent is to provide "one stop shopping" and provide patient navigation across a number of

	different disciplines, clinics and services. During the course of an integrated visit, the patient will have the following personalized assessment and counseling: • Patient care and counseling by a trained nurse practitioner and/or physician • Twelve monthly educational "modules" regarding ADT side effect management • Medication management including LHRH analogue injections during visit • Cardiovascular monitoring and risk reduction, including hypertension, hyperlipidemia, glucose monitoring, and cardiac risk stratification • Bone health monitoring and management • Nutrition counseling • Exercise training • Evaluation and counseling for relationship and mood changes by trained social worker • Assessment of quality of life and side effects of ADT with validated questionnaires (patients will also have opportunity to fill out questionnaires on-line ahead of clinic visit) The current randomized phase 2 cross-over study is designed to preliminary evaluate the longitudinal impact of participation in the "STAND" clinic (as compared to usual standard of care) on key metabolic parameters, quality of life, and patient satisfaction for men receiving hormone therapy for prostate cancer. Standard-of-care therapy will consist of every 3-month visits comprised of review of medical history, toxicity assessment, and lifestyle modification counseling provided by individual health care provider, LHRH analog injections by trained oncology nurse. Patients will have access to exercise, nutrition, and social work counseling if requested by patient or deemed necessary after consultation with health care provider. After 12 months on study, patients randomized to the usual standard-of-care arm will have the opportunity to cross-over and participate in the STAND clinic for the ensuing 12 months or for the remainder of ADT duration, whichever is shorter. Should the results indicate a beneficial impact of participation in a multi-disciplinary clinic in mitigating the short- and intermediate-term toxicities of ADT, this would form the justification for larger randomized clinical trials to assess the impact of clinic participation on longer-term co-morbidities including the incidence of diabetes, cardiovascular morbidity and mortality, and overall incidence of non-prostate cancer specific mortality.
Primary Objective	**Randomized cohort:** To compare the mean percent change from baseline to 12 months in percentage body fat mass among men with prostate cancer receiving androgen deprivation therapy randomized to participate in the "STAND" clinic vs. usual standard of care. **Non-randomized pilot cohort:** To determine the feasibility of completing multi-disciplinary STAND clinic visits while undergoing concurrent chemohormonal therapy for prostate cancer.
Secondary Objectives	**To compare the mean percent change from baseline to 12 months and patterns of change over time during participation in the STAND clinic vs. usual standard of care with respect to:** *Metabolic Impact on Diabetes and Cardiovascular Risk Factors:* - Fasting blood glucose - Fasting plasma insulin level - Insulin resistance as calculated by HOMA-IR - Hemoglobin A1c - Fasting lipids (total cholesterol, LDL, HDL, triglycercides) - Waist circumference - Body weight/body mass index - Exercise patterns as measured by validated questionnaire and home-based accelerometer assessment - Blood pressure

	Bone Health: - Bone density as assessed by DXA scan - 25-(OH) vitamin D serum levels *Quality of Life/Psychosocial Impact:* - Depression as measured by PHQ-9 - Cognitive function as measured by the Attentional Functional Index - Overall quality of life as measured by SF-12 - Fatigue as measured by Lee Fatigue Scale - Erectile and urinary function as measured by EPIC-26 - Hot flash severity as measured by Hot Flash Related Daily Interference Scale **Among men randomized to receive usual standard of care that cross-over to participate in the STAND clinic after month 12 of the study:** To measure the mean change from baseline at start of participation in the STAND clinic after 12 months of participation in: - Metabolic parameters including percentage body fat, fasting insulin/glucose, HOMA-IR, body weight/body mass index, waist circumference - Bone health - Quality of life **Among men in the non-randomized pilot cohort:** - To determine the mean change from baseline to 12 months during STAND clinic participation in the primary and secondary metabolic and quality of life parameters listed above.
Correlative Study Objectives	• To investigate for a relationship between inherited genetic polymorphisms of functional relevance near or within genes encoding proteins with roles in steroid hormone transport and androgen receptor signaling with changes in metabolic parameters among men treated with androgen deprivation therapy. • To investigate changes in trabecular bone micro-architecture as measured by High Resolution Peripheral QCT Imaging of radius and tibia during androgen deprivation therapy. • To investigate for relationship between 2nd digit to 4th digit length ration (2D:4D ratio) and percent change from baseline in quality of life metrics on androgen deprivation therapy. • To investigate for a relationship between 2nd digit to 4th digit length ratio and baseline empathy score as measured by validated questionnaire.
Study Design	Randomized, phase 2 study with cross-over design to assess the longitudinal impact of the multi-disciplinary STAND clinic on changes in key metabolic parameters, quality of life, and patient satisfaction among men receiving androgen deprivation therapy for prostate cancer. A non-randomized pilot cohort of patients receiving concurrent chemohormonal therapy will be enrolled in parallel to assess the feasibility of STAND clinic participation in this patient population. **Randomized study schema:**

	
Number of patients	80 patients with prostate cancer who are expected to receive at least 12 months of androgen deprivation therapy from the date of study enrollment will be enrolled. A separate non-randomized patient cohort of 20 patients who are receiving concurrent chemohormonal therapy will be enrolled in parallel.
Duration of study	Patients randomized to participate in the STAND clinic will be followed for 12 months. Men initially randomized to the usual standard-of-care will have the option to cross-over onto participation in the STAND clinic after month 12, and will be followed in the STAND clinic for an additional 12 months or until 6 months following last dose of ADT, whichever is shorter. Patients enrolled in the non-randomized chemohormonal cohort will participate in STAND clinic for 12 months.
Study Assessments	In the STAND clinic treatment arm, patients will have every 3 month visits with a health care provider, along with monthly educational modules, and multi-disciplinary assessment and counseling by exercise, nutrition, and symptom management service on a rotating schedule. In the usual care treatment arm, patients will have every 3 month visits with their usual health care provider, and will have unrestricted access to exercise, nutrition, and symptom management services upon patient request or as deemed necessary by health care provider. In the non-randomized chemohormonal cohort, patients will have schedule modified as necessary to fit with chemotherapy dosing schedule but will have on average every 3 month counseling with physical therapist, nutrition, and symptom management.

Study Endpoints	**Primary Endpoint** Randomized cohort: Mean percent change from baseline to 12 months in percentage body fat mass as measured by bioelectrical impedance analyzer. Non-randomized cohort: Percentage of completed STAND clinic visits during the course of the 12 month STAND clinic participation. **Secondary Endpoints** Mean percent change from baseline to 12 months and patterns of change from baseline with respect to the following: *Metabolic Impact on Diabetes and Cardiovascular Disease Risk Factors:* - Fasting blood glucose - Fasting plasma insulin level - Insulin resistance as calculated by HOMA-IR - Hemoglobin A1c - Fasting lipids (total cholesterol, LDL, HDL, triglycercides) - Waist circumference - Body weight/body mass index - Exercise patterns as measured by validated questionnaire and ambulatory accelerometer assessment - Blood pressure *Bone Health:* - Bone density at the lumbar spine, femoral neck, and total hip as assessed by DXA scan among patients without bone metastases at the time of study entry - Serum 25-(OH) vitamin D levels *Quality of Life/Psychosocial Impact:* - Depression as measured by PHQ-9 - Cognitive function as measured by Attentional Functional Index - Overall quality of life as measured by SF-12 - Fatigue as measured by Lee Fatigue Scale - Erectile and urinary function as measured by EPIC-26 - Hot flash severity as measured by Hot Flash Related Daily Interference Scale **Correlative Study Endpoints:** • Association between inherited genetic polymorphisms of functional relevance near or within genes encoding proteins with roles in steroid hormone transport and androgen receptor signaling with changes in metabolic parameters among men treated with androgen deprivation therapy. • Mean change from baseline in trabecular bone architecture as measured by trabecular bone number (TbN) and trabecular bone volume fraction (BV/TV) after 12 months of androgen deprivation therapy.

List of Abbreviations

AE	Adverse event
CHR	Committee on Human Research (UCSF IRB)
CRC	Clinical Research Coordinator
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IRB	Institutional Review Board
NCI	National Cancer Institute
PRC	Protocol Review Committee (UCSF)

Table of Contents

Protocol Signature Page 2

ABSTRACT 3

List of Abbreviations 8

1. Background and Rationale 12
1.1 Study Rationale and Clinical Significance 12
1.2 Rationale for the Clinical Study Endpoints 14

2. Hypothesis and Study Objectives 20
2.1 Hypothesis 20
2.2 Study Objectives 20

3. Study Design 23
3.1 Overall Study Characteristics 23
3.2 Study Endpoints 23
3.3 Study Schema 25

4. Study Population 26
4.1 Inclusion Criteria 26
4.2 Exclusion Criteria 27

5.1 Lupron Depot (Leuprolide acetate for depot suspension) Description, Formulation and Storage 28

5.1.1 Description 28

5.1.2 Formulation 28

5.1.3 Storage 28

5.2.2 Formulation 28

5.2.3 Storage 28

5.3.1 Description 29

5.3.2 Formulation 29

5.3.3 Storage 29

5.4 Telstar Description, Formulation, and Storage 29

5.4.1 Description 29

5.4.2 Formulation 29

5.4.3 Storage 29

6. Drug Treatment Plan 30

6.1 LHRH Route of Administration, Primary Side Effects, and Dose Modifications and Dosing Delays 30

6.1.1 Route of Administration 30

6.1.2 Primary Side Effects 30

7. Study Activities 31
7.1 Study Schedule 31
7.2 Screening Visit (within 6 weeks of Day 1 of Study) 33
7.3 Randomization 34
7.4 Day 1 Study Visit 34
7.5 Day 1 and Monthly Study Visits (+/- 2 weeks) 34
7.6 Every 3 Month Study Visits (+/- 2 weeks) 35
7.7 End of Month 12 Study Visit (+/- 2 weeks) 36
7.8 Concomitant Medications 37
7.9 Follow Up 37
7.10 Duration of Study 37

8. Assessment of Study Variables 38
8.1 Percent Body Fat Estimation 38
8.2 Patient-Reported Outcomes 38
8.3 Germline Polymorphisms 38
8.4 High Resolution Peripheral Quantitative CT Imaging 39

9. Planned Statistical Methods 41
9.1 Study Design 41
9.2 Determination of Sample Size and Study Power 41
9.3 Interim Analysis 42
9.4 Accrual 42
9.5 Analysis Populations 42
9.6 Demographics and Baseline Characteristics 43
9.7 Study Endpoints 43
9.8 Methods for Analysis 44

10. Study Management 47

10.1 Pre-study Documentation 47
10.2 Institutional Review Board Approval 47
10.3 Informed Consent 47
10.4 Changes in the Protocol 48
10.5 Case Report Forms (CRFs) 48
10.6 Retention of Records 49

11. References 50

Appendix 1. Selected Genetic Polymorphisms 52
Appendix 2. Quality of Life Questionnaires 53

Appendix 3. Charlson Co-Morbidity Index 66

Appendix 4: Bioelectrical Impedance Device for Assessment of Percentage Body Fat 67

Appendix 5: Accelerometer For Ambulatory Recording of Activity Levels 68

Appendix 6. Data and Safety Monitoring Plan for a Phase 2 Institutional Study..... 69

Appendix 7. Specimen Handling and Storage..... 70

1. Background and Rationale

1.1 Study Rationale and Clinical Significance

Androgen deprivation therapy (ADT), in which the circulating serum testosterone is reduced to a castrate-range (less than 50 ng/dL), is a standard treatment option for patients with prostate cancer across a variety of disease states, including adjuvant therapy for localized disease, a rising PSA after surgery and/or radiation therapy, and for radiographically detectable metastatic disease to the bones and other organs. ADT represents the most common systemic therapy applied in prostate cancer and nearly 40% of men will receive ADT within 6 months of receiving prostate cancer diagnosis. Though initially effective in the majority of patients in lowering the serum PSA and controlling or preventing disease progression, ADT is associated with a multitude of clinically significant yet potentially treatable toxicities. These include side effects that can adversely affect quality of life such as hot flashes, fatigue, decreased libido, erectile dysfunction, gynecomastia, and mood/cognitive changes, which can adversely impact patients' relationship with spouse, family members, and caregivers. ADT is associated with significant metabolic toxicities including increased risk of insulin resistance and diabetes, increase in body fat, lower body mass, and decreased bone mineral density, and increased risk for osteoporotic fractures [1-7]. The development of the metabolic and cardiac risk factors on ADT can paradoxically shorten, rather than extend, the life span of men with prostate cancer.

Many of these changes are modifiable with careful management, although current practice data suggest that the vast majority of physicians who prescribe ADT do not manage these side effects in a consistent way, if at all. A prior pilot study in which patients received a non-individualized educational "tool-kit" containing information and recommendations with respect to diet, exercise, and other lifestyle modifications among men starting ADT improved patients satisfaction and led to partial lifestyle changes; however patient retention on the program was incomplete in part due to lack of individualized counseling [8]. Individualized, comprehensive management of the potential side effects of ADT with the use of a multi-disciplinary clinic with "face-to-face" counseling provided by specialists across relevant disciplines may be more effective in promoting durable changes in lifestyle factors and potentially mitigating the side effects of ADT, as compared to usual standard of care or non-individualized educational hand-outs/materials. Multiple prior studies in the primary care setting demonstrate that higher intensity, individualized counseling, as compared to less intensive counseling including automated web- or telephone-based programs, lead to more substantial changes in lifestyle habits, including improved diet, weight reduction, and smoking cessation, and may in fact be more cost-effective when considering the improvement in rates of co-morbidity associated with higher intensity counseling [9-11]. In men initiating ADT, prospective participation in a structured clinic focused on mitigating the metabolic side effects of therapy has proven to be feasible and to potentially lessen weight gain, prevent decay in bone density/bone health, and mitigate adverse effects on fasting lipids in a recently reported Australian observational study

[12]. Thus, there is a strong rationale to directly compare participation in a multi-disciplinary clinic with standard-of-care physician visits in a randomized fashion among men receiving androgen deprivation therapy, to assess whether clinic participation leads to improvements in metabolic toxicities associated with this therapy.

The "STAND (Supportive Therapy in ANdrogen Deprivation)" Clinic at UCSF was created for patients treated with ADT to address and mitigate the adverse effects of hormone therapy. The intent is to provide "one stop shopping" and individualized counseling and therapy across a number of different disciplines, clinics and services. During the course of an integrated visit, the patient will have the following personalized assessment and counseling:

- Patient care and counseling by trained physician or nurse practitioner
- Nutrition counseling with trained dietitian
- Exercise training with certified exercise trainer with expertise in cancer patients
- Medication management including LHRH analogue injections
- Cardiovascular monitoring and risk reduction, including hypertension, hyperlipidemia, glucose monitoring, and cardiac risk stratification
- Bone health monitoring and management
- Evaluation and counseling for regarding symptoms and relationship and mood changes by symptom management service
- Assessment of quality of life and side effects of ADT with validated questionnaires

The current randomized phase 2 cross-over study is designed to preliminary evaluate the longitudinal impact of participation in the "STAND" clinic (as compared to usual standard of care) on key metabolic parameters, quality of life, and patient satisfaction for men receiving hormone therapy for prostate cancer. After 12 months on study, patients randomized to the usual standard-of-care treatment arm will have the opportunity to cross-over and participate in the STAND clinic for the ensuing 12 months or for the remainder of ADT duration, whichever is shorter. Should the results indicate a beneficial impact of participation in a multi-disciplinary clinic in mitigating the short- and intermediate-term toxicities of ADT, this would form the justification for larger randomized clinical trials to assess the impact of clinic participation on longer-term co-morbidities including the incidence of diabetes, cardiovascular morbidity and mortality, and overall incidence of non-prostate cancer specific mortality.

A separate non-randomized cohort of patients receiving concurrent chemohormonal therapy will be enrolled to assess the feasibility of STAND clinic participation among patients receiving chemotherapy for prostate cancer.

1.2 Rationale for the Clinical Study Endpoints

1.2.1 Rationale for the Primary Endpoint

The primary endpoint of the current study will be the mean percent change from baseline to 12 months in percentage body fat mass as calculated by bioelectrical impedence analyzer. Prior longitudinal studies have demonstrated a consistent mean percentage increase in percentage fat mass of 11-12% (+/- 1.5%) after 1 year of androgen deprivation therapy [13]. Cross-sectional imaging studies have shown a strong correlation with percentage body fat increases on ADT with increases in predominantly subcutaneous adipose tissue. Increases in body fat mass during ADT are strongly associated with other risk factors for diabetes and cardiovascular disease, including dyslipidemia, insulin resistance, and obesity. Results obtained via use of a bioelectrical impedence analyzer correlate with the use of other percent body fat assessments, including dual energy X-ray absorptiometry (DEXA) and underwater weighing methodologies, and intra-patient variability is low [14].

Measuring percentage body fat with handheld bioelectrical impedance device thus represents a readily obtainable, feasible, and clinically relevant marker of the metabolic impact of androgen deprivation therapy. It is hypothesized that comprehensive multi-disciplinary counseling may promote sustained lifestyle changes with respect to diet and exercise which may partially mitigate the adverse metabolic impact of ADT on percent body fat, and in turn, decrease the risk of longer term metabolic derangements including incidence of diabetes and cardiovascular morbidity and mortality.

1.2.2 Rationale for the Inclusion of Additional Metabolic Endpoints

Prior prospective longitudinal studies have characterized the potential impact of androgen deprivation therapy on metabolic risk factors for cardiovascular disease and diabetes. Among these include consistent increases in fasting plasma insulin and insulin resistance as measured by the Homeostatic Model (HOMA-IR), increases in hemoglobin A1c, dyslipidemia including increases in total cholesterol and serum triglycerides, as well as changes in body composition including increase in body weight, waist circumference [13,15]. Increases in hemoglobin A1c and other markers of insulin resistance during ADT are often clinically significant; androgen deprivation therapy was associated with an increased risk of the development of diabetes on multivariate analysis in prior large retrospective study [7]. Every 1% increase in hemoglobin A1C was associated with increased risk of microvascular complications including retinopathy, nephropathy, and neuropathy [16]. The HOMA-IR index is strongly associated with subsequent risk of developing diabetes and cardiovascular disease in prior prospective studies [17]. Whether or not the impact of ADT on these metabolic parameters translates into an increased risk of cardiovascular mortality is unclear with prior studies provided mixed evidence. Measuring these additional endpoints is likely to provide a more comprehensive assessment of the impact of participation in the STAND clinic on the metabolic toxicities of androgen deprivation, as compared to measurement of changes in percentage body fat alone.

1.2.3 Bone Health

For men without bone metastases at the time of study entry, the mean change from baseline to 12 months in bone mineral density as assessed by DXA scan will be a secondary study endpoint in the current observation study. Numerous prior studies have characterized the decline in bone mineral density observed with androgen deprivation therapy. In a prior randomized trial comparing standard ADT to high-dose bicalutamide (a non-castrating AR antagonist), the men randomized to the ADT treatment arm had a mean decline from baseline in lumbar spine bone mineral density of 2.5% after 12 months of therapy [18]. Reductions in bone mineral density with ADT are clinically relevant- prior observational studies have also demonstrated an increased risk of osteoporotic fractures with androgen deprivation therapy [19].

1.3.4 Quality of Life and Psychosocial Impact of Androgen Deprivation

Androgen deprivation therapy is associated with an adverse impact on overall quality of life as typical side effects including hot flashes, erectile dysfunction, fatigue, and depression.

1.3.4.1 Overall Quality of Life Assessment

A validated measure of general quality of life is the SF-12 QOL survey, an abbreviated form of the SF-36 with which it is tightly correlated [20]. In a prior prospective study of men undergoing ADT, there was a statistically and clinically significant mean decrease from baseline in the scores of several domains within the SF-36 profile, including general health, vitality, and composite physical health [21].

1.3.4.2 Hot Flashes

Hot flashes are a common and bothersome symptom associated with androgen deprivation therapy, though the exact mechanism remains unclear. Prior studies examining the impact of ADT on hot flashes have used a variety of scales to measure the incidence and severity of hot flashes, including the Hot Flash Score. The current study will use the Hot Flash Related Daily Related Interference Scale (HFRDIS), which has previously been validated in a study population of breast cancer survivors compared to age-matched controls [22]. In this study, the HFRDIS was internally consistent, demonstrated correlations with other hot flash variables, correlated with measures of affect and mood, and demonstrated sensitivity to change over time.

1.3.4.3 Erectile and Urinary Dysfunction

Erectile dysfunction is a well-characterized complication of androgen deprivation therapy, both in men with and those without prior radical prostatectomy or radiation therapy to the prostate gland. EPIC-26 is a well-validated measurement of erectile and urinary function which has been studied in various disease settings included prior prostate cancer studies and will be used to measure erectile function in the current study [23].

1.3.4.4 Fatigue

Fatigue is a common and bothersome side effect of androgen deprivation therapy which can have an adverse impact on quality of life for some men receiving androgen deprivation therapy. In a prior cross-sectional study comparing 57 men receiving ADT with 51 age-matched controls, more men in the ADT group had severe fatigue compared to the control cohort (14% vs. 4%, p = 0.03). The Lee Fatigue scale is a well-validated visual analog measure of fatigue, which has demonstrated high reliability and validity compared to the Stanford Sleepiness Scale [24]. The Lee Fatigue Scale will be used to measure the degree of fatigue and change in energy level experienced by patients receiving ADT in the current study.

1.3.4.5 Depression

Depression is common and frequently underdiagnosed among men receiving ADT for prostate cancer. Prior studies indicate a rate of depression in this patient population that far exceeds the expected prevalence among age-matched controls. In a prior cross-sectional study of 45 men receiving ADT (median duration of ADT was 3.3 years), the prevalence of depression as screened for by the structured clinical interview using the DSM-IV criteria was 12.8%, 8 times that of the national average in men [25]. In the current study, the PHQ-9, a well-validated screening metric for depression consisting of 9 items, will be used to measure the change in depressive symptoms among men being treated with androgen deprivation therapy for hormone sensitive prostate cancer. PHQ-9 results must be reviewed by treating health-care provider during the course of patient's study visit.

1.3.4.6 Cognitive Function

There is mixed evidence regarding the impact of androgen deprivation therapy on cognition. Several studies have demonstrated decrements in psychomotor speed/processing speed, reaction times, and working memory. Verbal memory and fluency have shown more mixed effects in prior studies. The Attentional Function Index is a well-validated metric of working memory and processing speed that was chosen for the current study to better capture the specific cognitive aspects potentially affected by ADT.

1.3.5 Rationale for the Correlative Study Endpoints

1.3.5.1: Germline Polymorphisms

In contrast to measuring the association between efficacy of ADT and germline polymorphisms, the association between ADT toxicity and germline variation in genes encoding proteins involved in steroid biosynthesis or drug metabolism is largely unexplored. In metastatic hormone-receptor positive breast cancer, certain polymorphisms within the estrogen receptor gene were associated with increased incidence of hot flashes in patients treated with tamoxifen [26].

With respect to primary androgen deprivation therapy with LHRH agonists, there have been several studies investigating the association of SNPs in genes belonging to the androgen

synthesis pathway and disease outcome. In a prior study investigating the association between genotypes from 127 SNPs in 20 different genes within the androgen synthetic pathway with disease outcomes in men treated with ADT for advanced prostate cancer, three polymorphisms in separate genes (CYP19A1, HSD3B1, and HSD17B4) were associated with time to progression on multivariate analysis [27]. Less is known, however, about the association between polymorphisms within candidate genes that might predict for some of the potential toxicities of ADT, including the metabolic toxicities discussed above. Predicting potential toxicity of ADT may be ultimately used to guide clinicians in a variety of clinical scenarios, including timing of initiation of ADT in men with biochemically relapsed disease.

The current study sample size will permit only an exploratory analysis of the associations between functional, non-synonymous germline polymorphisms and the metabolic toxicity of ADT. The hypothesis is that polymorphisms of functional relevance which deplete intra-cellular androgens may be associated with an increased likelihood of metabolic toxicities related to androgen deprivation therapy, including increasing risk of insulin resistance.

1.3.5.2 Trabecular Bone Micro-Architecture

Changes in BMD, especially those measured using DXA do not reflect the changes taking place in the cortical and trabecular bone compartments and do not entirely explain bone strength and fracture risk. We have recently shown, using high-resolution peripheral computed tomography (HRpQCT), that age and metabolism related changes in these compartments differ and regional changes in micro-architecture have profound impact on biomechanical characteristics of bone. Magnetic resonance imaging maybe used to quantifyfatty infiltrat**ion in muscle or sarcopenia** thus maybe a potential surrogate for assessing loss of strength. **In a prior study of** 26 men with metastatic prostate cancer on ADT the loss in the cortical bone compartment is greater than in trabecular bone, and that the loss in trabecular bone is responsible for **trabecular bone decreases**. These differential effects in cortical and trabecular bone, and loss of trabecular number has profound effects on bone strength. Furthermore, the differences between bone loss in men with metastatic disease may be different than those on primary prostate cancer and at the initiation of ADT therapy. Thus, we feel a group of men with primary prostate cancer starting on ADT would serve as a better model for male osteoporosis, and assist in describing the time-course of male hormone deficient onset of osteoporosis. High-resolution peripheral computed tomography is a low dose technique that provides images depicting cortical and trabecular bone structure.

Regional variation in trabecular structure across axial sections is often obscured by the conventional global analysis, which takes an average value for the entire compartment. We have characterized spatial variability in trabecular structure within a cross-section at the distal radius and tibia, and gender and age effects using in vivo high-resolution peripheral quantitative computed tomography (HR-pQCT) in 146 healthy individuals aged 20-78 years. Trabecular bone

volume fraction (BV/TV), number (Tb.N), thickness (Tb.Th), separation (Tb.Sp), and heterogeneity (Tb.1/N.SD) were obtained in a total of 11 regions-the entire trabecular compartment (the global means), inner, outer, and eight defined subregions. Regional variations were examined with respect to the global means, and compared between women and men, and between young (20-29 years old) and elderly (65-79 years old) adults. Substantial regional variations in trabecular bone structure at the distal radius and tibia were revealed (e.g. BV/TV varied -40% to +57% and -59% to +100% of the global means, respectively, for elderly women). The inner-lateral (IL) subregion had low BV/TV, Tb.N, and Tb.Th, and low Tb.Sp and Tb.1/N.SD at both sites; the opposite was true in the outer-anterior (OA) subregion at the distal radius and the outer-medial (OM) and -posterior (OP) subregions at the distal tibia. Gender differences were most pronounced in the inner-anterior (IA) subregion compared to the other regions or the global mean differences at both sites. Trabecular structure associated with age and differed between young and elderly adults predominantly in the inner-posterior (IP) subregion at the distal radius and in the IL and IA subregions at the distal tibia; on the other hand, it remained unchanged in the OA subregion at the distal radius and in the OM subregion at the distal tibia for both women and men. We demonstrated that not only the conventional global analysis can obscure regional differences, but also assuming bone status from that of smaller subregion may introduce a confounding sampling error. Therefore, a combined approach of investigating the entire region, each subregion, and the cortical compartment may offer more complete information.

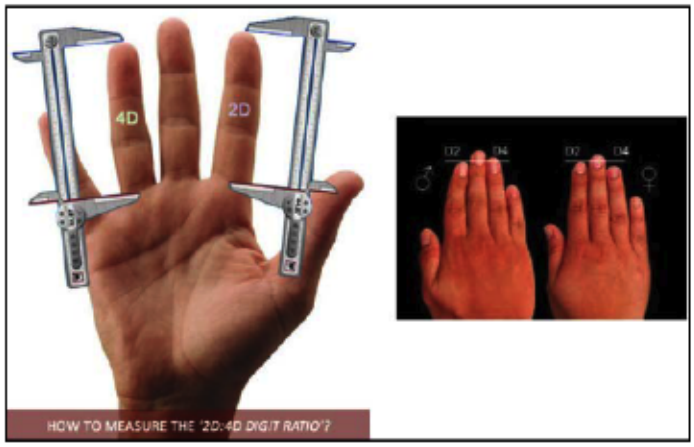
1.3.5.3 Second Digit: Fourth Digit Length Ratio and Fetal Testosterone Exposure

The ratio between the length of the 2nd and 4th digits, typically measured on the right hand, is a physical trait that correlates with fetal testosterone exposure. The finding can be measured throughout life and correlates with physical manifestations and disease processes that are associated with androgen excesses such as autism, myocardial infarction and prostate cancer. It has also been associated with behavioral traits that are commonly associated with androgen excess, such as risk taking.

Although the link between 2d:4d ratio and prostate cancer has been established in one study patient with a positive 2d:4d ratio (index finger longer than the ring finger on the right hand) had a 33% reduced risk of prostate cancer.

Given that it is a marker of brain 'priming' by testosterone, we hypothesize that patients with a higher 2d:4d ratio (greater testosterone exposure in utero) will be more sensitive to changes in serum testosterone at any point in life and therefore will experience a greater degree of typical androgen deprivation toxicities (hot flushes, decreased quality of life, mood swings etc.) than those with a lower ratio.

The ratio is measured on the right hand and can be performed at any point in study entry.


4D
2D
HOW TO MEASURE THE '2D:4D DIGIT RATIO'?

2. Hypothesis and Study Objectives

2.1 Hypothesis

The primary hypothesis of the study is that active participation in a multi-disciplinary clinic with individualized counseling regarding exercise and dietary habits, as compared to standard-of-care with physician counseling during the framework of follow-up visits, will lead to diminished impact of androgen deprivation therapy using objective measures and surrogate markers of insulin resistance and cardiovascular disease risk factors, including gains in body fat mass, fasting insulin/glucose levels, weight gain among men with prostate cancer. We further hypothesize that individualized educational sessions and counseling regarding psychosocial aspects of androgen deprivation will lead to improved patient understanding and satisfaction and overall less adverse impact on quality of life using validated patient-reported metrics addressing the specific issues raised with androgen deprivation therapy. Should the study results from this preliminary phase 2 study provide evidence supporting participation in the STAND clinic, this will provide the justification for a confirmatory randomized clinical trial across multiple investigational sites to assess the generalizability and reproducibility of the multi-disciplinary clinic, and to assess long-term impact of multi-disciplinary clinic participation on incidence of diabetes, cardiovascular disease, and non-prostate cancer related mortality. Ultimately, enrollment into a multi-disciplinary clinic for men receiving ADT may become a routine aspect of prostate cancer management as a means to mitigate the potentially significant toxicity of androgen deprivation therapy.

2.2 Study Objectives

2.2.1 Primary Objective

Randomized cohort: To compare the mean percent change from baseline to 12 months in percentage body fat mass among men with prostate cancer receiving androgen deprivation therapy randomized to participate in the "STAND" clinic vs. usual standard of care.

Non-randomized pilot cohort: To determine the feasibility of completing multi-disciplinary STAND clinic visits within context of concurrent chemohormonal therapy for prostate cancer.

2.2.2 Secondary Objectives

To compare the mean percent change from baseline to 12 months and patterns of change over time during participation in the STAND clinic vs. usual standard of care with respect to:

Metabolic Impact on Diabetes and Cardiovascular Risk Factors:

- Fasting blood glucose
- Fasting plasma insulin level
- Insulin resistance as calculated by HOMA-IR
- Hemoglobin A1c
- Fasting lipids (total cholesterol, LDL, HDL, triglycercides)
- Waist circumference
- Body weight/body mass index
- Exercise patterns as measured by validated questionnaire and ambulatory accelerometer assessment (see Appendices 2 and 5 respectively)
- Blood pressure

Bone Health:

- Bone density as assessed by DXA scan
- 25-(OH) vitamin D serum levels

Quality of Life/Psychosocial Impact:

- Depression as measured by PHQ-9
- Cognitive function as measured by the Attentional Functional Index
- Overall quality of life as measured by SF-12
- Fatigue as measured by the Lee Fatigue Scale
- Erectile and urinary function as measured by EPIC-26
- Hot flash severity as measured by Hot Flash Related Daily Interference Scale

Among men randomized to receive usual standard of care that cross-over to participate in the STAND clinic after month 12 of the study:

To measure the mean change from baseline at start of participation in the STAND clinic after 12 months of participation in:

- Metabolic parameters including percentage body fat, fasting insulin/glucose, HOMA-IR, body weight/body mass index, waist circumference
- Bone health
- Quality of life
- Patient satisfaction

Among men in the non-randomized pilot cohort:

- To determine the mean change from baseline to 12 months during STAND clinic participation in the primary and secondary metabolic and quality of life parameters listed above.

2.2.3 Correlative Study Objectives

- To investigate for a relationship between inherited genetic polymorphisms of functional relevance near or within genes encoding proteins with roles in steroid hormone transport and androgen receptor signaling with changes in metabolic parameters among men treated with androgen deprivation therapy.
- To investigate changes in trabecular bone micro-architecture as measured by High Resolution Peripheral QCT Imaging of radius and tibia during androgen deprivation therapy.
- To investigate for relationship between 2nd digit to 4th digit length ratio (2D:4D ratio) and quality of life on androgen deprivation therapy.
- To investigate for a relationship between 2nd digit to 4th digit length ratio and baseline empathy score as measured by validated questionnaire.

3. Study Design

3.1 Overall Study Characteristics

Randomized, phase 2 study with cross-over design to assess the longitudinal impact of participation in the multi-disciplinary STAND clinic vs. receipt of usual standard of care on changes in key metabolic parameters, quality of life, and patient satisfaction among men receiving androgen deprivation therapy for prostate cancer. Standard-of-care therapy will consist of every 3-month visits comprised of review of medical history, toxicity assessment, and lifestyle modification counseling provided by individual health care provider, LHRH analog injections by trained oncology nurse. Patients in the usual care treatment arm will have unrestricted access to exercise, nutrition, and symptom management service upon patient request or as deemed necessary by health care provider. Men randomized to participation in the STAND clinic will have every 3 month visits with health care providers and LHRH analog injections, monthly self-directed educational "modules" covering the various aspects of hormone therapy as well as every 3-month individualized counseling provided by registered dietitian, exercise trainer, and symptom management service. At the end of 12 months of study participation, patients initially randomized to receive standard-of-care, will have the option of crossing-over to participate in the STAND clinic for the ensuing 12 months.

A non-randomized pilot cohort of patients receiving concurrent chemohormonal therapy will be enrolled in parallel to assess the feasibility of STAND clinic participation in this patient population.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Randomized cohort: Mean percent change from baseline to 12 months in percentage body fat mass as measured by bioelectrical impedance analyzer (see Appendix 4).

Non-randomized chemohormonal cohort: Percentage of completed STAND clinic visits during the course of the 12 month STAND clinic participation.

3.2.2 Secondary Endpoints

Mean percent change from baseline to 12 months and patterns of change from baseline with respect to the following:

Metabolic Impact on Diabetes and Cardiovascular Disease Risk Factors:

- Fasting blood glucose
- Fasting plasma insulin level

- Insulin resistance as calculated by HOMA-IR
- Hemoglobin A1c
- Fasting lipids (total cholesterol, LDL, HDL, triglycercides)
- Waist circumference
- Body weight/body mass index
- Exercise patterns as measured by validated questionnaire and ambulatory accelerometer assessment (Appendices 2 and 5 respectively)
- Blood pressure

Bone Health:

- Bone density at the lumbar spine, femoral neck, and total hip as assessed by DXA scan among patients without bone metastases at the time of study entry
- Serum 25-(OH) vitamin D levels

Quality of Life/Psychosocial Impact:

- Depression as measured by PHQ-9
- Cognitive function as measured by Attentional Functional Index
- Overall quality of life as measured by SF-12
- Fatigue as measured by the Lee Fatigue Scale
- Erectile and urinary function as measured by EPIC-26
- Hot flash severity as measured by Hot Flash Related Daily Interference Scale

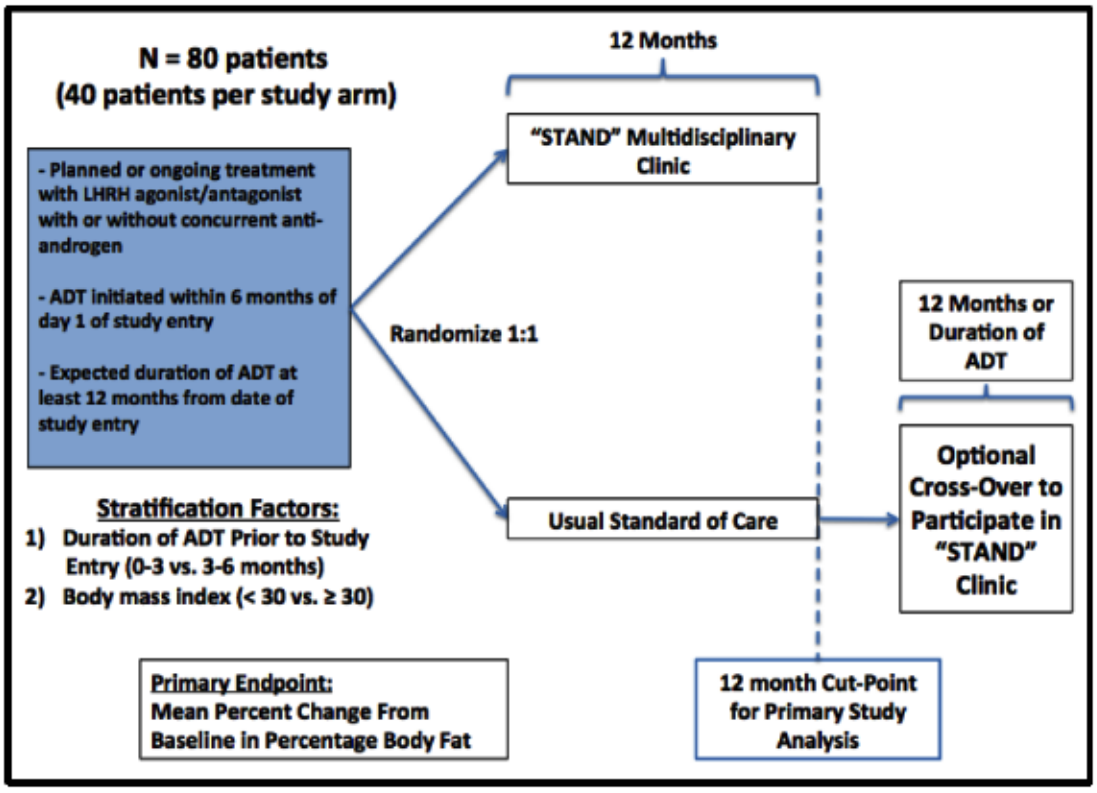
Patient Satisfaction:

- Patient satisfaction as measured by a validated questionnaire
- Patient insight and understanding of treatment and disease-related issues as measured by a self-administered assessment

3.2.3 Correlative Study Endpoints

- Association between inherited genetic polymorphisms of functional relevance near or within genes encoding proteins with roles in steroid hormone transport and androgen receptor signaling with changes in metabolic parameters among men treated with androgen deprivation therapy.
- Mean change from baseline in trabecular bone architecture as measured by trabecular bone number (TbN) and trabecular bone volume fraction (BV/TV) after 12 months of androgen deprivation therapy.
- Association between 2D:4D ratio with change in quality of life on androgen deprivation therapy.
- Association between 2D:4D ratio with baseline empathy score as measured by validated questionnaire.

3.3 Study Schema



3.3.1 Primary Completion:

Study accrual is anticipated to be approximately 2 patients per month, leading to an accrual duration of approximately 40 months. Anticipated time from last patient enrolled to primary study completion and analysis of primary and secondary endpoints equals approximately 12 months, leading to the primary completion of study in approximately 52 months from first patient enrolled.

Study accrual of the 20 patient non-randomized chemohormonal cohort will be completed in parallel and is estimated to be approximately 0.8 patients/month, leading to an approximate 24 patient accrual period.

3.3.2 Study Completion:

The total study duration including follow up is estimated to be 5 years.

4. Study Population

80 evaluable patients with prostate cancer with concurrent or planned treatment with androgen deprivation therapy will be eligible for study participation. Patients must have initiated ADT within 6 months prior to day 1 of study entry, and the expected duration of ADT must be at least 12 months from study entry.

20 patients who are receiving or planning to receive concurrent chemohormonal therapy will be enrolled in a parallel non-randomized cohort, to establish the feasibility of completing STAND clinic visits in this patient population.

4.1 Inclusion Criteria

- Histologic confirmation of adenocarcinoma of the prostate
- Receiving or planning to receive ADT with LHRH agonist or antagonist
- Expected duration of ADT at least 12 months from date of study consent
- Concurrent antiandrogen therapy allowed but not required
- First dose of LHRH agonist or antagonist no more than 6 months prior to date of study consent
- Prior/concurrent radiation allowed
- Other investigational agents in addition to LHRH agonist/antagonist are allowed (e.g. novel anti-androgens, androgen synthesis inhibitors)
- Prior androgen deprivation therapy allowed, provided there is documented evidence of testosterone recovery to > 150 ng/dL and greater than 12 months duration between last "effective" date of ADT and date of study consent
- **Randomized cohort only:**
    - No prior chemotherapy within 12 months of start date of study
    - No planned chemotherapy at least 12 months from study entry
- **Non-randomied pilot cohort:**
    - Concurrent chemotherapy (initiated within 3 months of study entry) or planned chemotherapy within 3 months of study entry
- ECOG performance status of 0 – 2
- Ability to sign written informed consent
- Willing to attend monthly clinic visits at UCSF

4.2 Exclusion Criteria

- Physically unable or unwilling to participate in recommended exercise programs or travel to UCSF on a monthly basis
- Presence of permanent pacemaker or implantable medical device.
    - Artificial joint prostheses and venous filters are allowed.

5. Study Drug

5.1 Lupron Depot (Leuprolide acetate for depot suspension) Description, Formulation and Storage

5.1.1 Description

Lupron Depot (Leuprolide acetate) is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH).

5.1.2 Formulation

Lupron Depot (Leuprolide acetate) for injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing leuprolide acetate (5 mg/mL), sodium chloride, USP (6.3 mg/mL) for tonicity adjustment, benzyl alcohol, NF as a preservative (9 mg/mL), and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF. The pH range is 4.0 to 6.0.

The vial is packaged as a 4 Day Patient Administration Kit with 14 disposable syringes and 28 alcohol swabs, NDC 0185-7400-85.

5.1.3 Storage

Store below 77°F (25°C). Do not freeze. Protect from light; store vial in carton until use.

Guidelines for Administration: See Treatment and Dose Modification section of protocol

5.2 Eligard Description, Formulation, and Storage

5.2.1 Description

Eligard is a sterile polymeric matrix formulation of leuprolide acetate, a GnRH agonist.

5.2.2 Formulation

Eligard is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous.

Eligard is administered subcutaneously, where it forms a solid drug delivery depot.

5.2.3 Storage

Store at 2 – 8 °C (35.6 – 46.4 °F)

Guidelines for Administration: See Treatment and Dose Modification section of protocol.

5.3 Zolodex Description, Formulation and Storage

5.3.1 Description

Zoladex (goserelin acetate) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH or LHRH).

5.3.2 Formulation

Zoladex (goserelin acetate) depot is supplied as a cylindrical rod of biodegradable and biocompatible D-L Lactide-glycolide copolymer. Each ZOLADEX depot contains goserelin acetate equivalent to 3.6 mg of goserelin. This depot is presented in a sterile ready-to-use syringe with a 16 gauge needle for a single subcutaneous injection. This single-dose syringe is assembled with a protective sleeve (SafeSystem™) in a sealed, sterile pouch that contains a desiccant.

5.3.3 Storage

Protect from light and moisture. Store in the intact package between 2°C and 25°C.

Guidelines for Administration: See Treatment and Dose Modification section of protocol

5.4 Telstar Description, Formulation, and Storage

5.4.1 Description

5.4.1 Trelstar is a synthetic decapeptide agonist analogue of gonadatropin release hormone (GnRH).

5.4.2 Formulation

Trelstar is administered as a single intramuscular injection in either buttock. The lyophilized microgranules are to be reconstituted in sterile water. No other diluent should be used. Due to different release characteristics, the dosage strengths are not additive and must be selected based on the desired dosing schedule: 3.75 mg every 4 weeks, 11.25 every 12 weeks or 22.5 mg every 24 weeks.

5.4.3 Storage

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Do not freeze Trelstar with MIXJECT.

Guidelines for Administration: See Treatment and Dose Modification section of protocol

6. Drug Treatment Plan

6.1 LHRH Route of Administration, Primary Side Effects, and Dose Modifications and Dosing Delays

6.1.1 Route of Administration

The LHRHa injections will be delivered either subcutaneously (Eligard®, Zoladex®) or intramuscularly (Lupron Depot® or Trelstar®) by a trained health care provider while on protocol therapy.

6.1.2 Primary Side Effects

Hot flashes, decreased libido, breast pain, gynecomastia, hyperglycemia, hypercholesterolemia, decreased bone mineral density, fatigue, anemia, mood changes.

6.1.3 Drug Supply

The drugs will be commercially supplied.

For a complete description of these drugs, please see the package inserts.

7. Study Activities

7.1 Study Schedule

	Pre-Study/ Screening (within 6 weeks of Day 1 of Study)	Day 1 Study Visit	End of Every Month (+/- 2 weeks)	End of Every 3 Months (+/- 2 weeks)	End of Month 12 Study Visit (+/- 2 weeks)	Follow Up Visit[l] (6 months after completion of STAND clinic)
Physical Exam with Health Care Provider (Both study arms)	X	X		X	X	X
LHRH Analogue[a]		X		X		
Exercise, Nutrition, Symptom Management counseling[b]		X	X			
Educational Modules (STAND clinic arm only)		X	X			
Counseling, review tests and questionnaires				X	X	X
Informed Consent	X					
Randomization	X					
Demographics	X					
Past Medical History	X					
Concomitant Medications[i]	X	X		X	X	
QOL/empathy Questionnaires[c]		X		X	X	X
Co-morbidity Assessment[d]	X					
Ratio of 2nd to 4th digit finger length[e]	X					
Weight/Body Mass Index/Percent Body Fat[f]	X	X		X	X	X
ECOG Performance		X		X	X	

DXA Scan[g]	X				X	
HRpQCT (optional)[h]	X				X	
Serum PSA[i]	X	X		X	X	X
Serum testosterone		X[j]			X	X
Serum 25-(OH) vitamin D level		X		X	X	
Fasting glucose/lipid panel, HgbA1c, insulin level		X		X	X	X
Hemoglobin A1c		X		X	X	X
Plasma/serum for banking[k]		X		X	X	X
PBMCs for germline polymorphisms (optional)[k]		X				

a. Patients who have started ADT prior to study enrollment will be kept on same schedule for next dose of LHRH analog and provider visit while on study. On study patients will receive LHRH agonist every 3 months (+/- 1 week), on same day as health care provider visits whenever possible.
b: Patients randomized to the STAND clinic will visit with one of three specialties (exercise, nutrition, symptom management) at each monthly visit. The total number of visits with each specialty will be four on an every 3-month basis. The rotation of the schedule of providers may be adjusted depending upon availability of provider and patient. Patients randomized to the usual care study arm will be referred to nutrition, exercise, and symptom management services upon patient request or as deemed necessary by health care provider.
c: Quality of life questionnaires to be completed include SF-12, EPIC-26, Hot Flash Related Daily Interference Scale, Lee Fatigue Scale, PHQ-9, Attentional Functional Index, Exercise questionnaires, and empathy quotient-8 (see Appendix 2). These questionnaires may be completed online ahead of scheduled visit or at the time of clinic visit, either electronically or on paper. The PHQ-9 scale must be completed on paper on the same day as study visit, and reviewed and signed by health care provider prior to patient discharge from clinic.
d: Assessed with Charlson Comorbidity Index (see Appendix 3)
e: Measured by caliper (see Section 1). For patients already enrolled on study who did not complete at baseline, this measurement will be performed at the next planned study visit.
f: Percent body fat to be measured using bioimpedance device on C1D1, every 3 months, and end of month 12 on study (see Appendix 4)
g: Bone mineral density measured at the lumbar spine, total hip, and femoral neck (performed within 12 weeks of day 1 of study)
h: High resolution quantitative peripheral CT of the radius and tibia (optional)
i: Baseline PSA determined during screening if not already taking ADT
j: Include screening assessment or serum testosterone of prior receipt of ADT
k: See Appendix 6 for collection and processing instructions
l: Following completion of STAND clinic participation, patients will be followed by telephone visit after 2 and 4 months to assess adherence to recommended diet/exercise plans. At 6 months, patients will return for clinic assessment.

7.2 Screening Visit (within 6 weeks of Day 1 of Study)

Screening procedures and informed consent as well as written health information authorization must be completed within 6 weeks of day 1 of study. All research-related procedures will be conducted after patient has signed written consent to participate in the study.

These procedures include:

- Physical exam and medical history
- Demographics and disease characteristics:
    - Date of prostate cancer diagnosis
    - Gleason grade and PSA at the time of diagnosis
    - Type and date of prior local therapy (if any)
    - Date of ADT initiation and indication (adjuvant, biochemical relapse, or metastatic disease)
    - Concurrent use of anti-androgen (yes/no)
    - Concurrent radiation therapy (yes/no)
    - Metastatic status at time of study entry (none, bone only, soft tissue, any visceral)

Clinical Assessment

- Co-morbidity assessment by Charlson Co-morbidity Scale (Appendix 3)
- Quality of life questionnaires (see Appendix 2):
    - SF-12, EPIC-26, HFRDIS, Lee Fatigue Scale, PHQ-9, Attentional Functional Index, exercise patterns, empathy scale
- Concomitant medication
- Weight andbody mass index
- Assessment of ratio of 2^{nd} digit to 4^{th} digit finger length using caliper assessment

Radiographic Assessment

- DXA Bone Density Scan (completed within 12 weeks of Day 1 of study)
- High resolution peripheral quantitative CT scan of the distal tibia and radius (optional)

Laboratory Assessment

- Baseline PSA measurement
- Serum testosterone (if prior receipt of androgen deprivation therapy)

7.3 Randomization

Once eligibility is confirmed and patient has signed informed consent, patients will be stratified according to duration of ADT prior to study entry (≤ 3 months vs. 3-6 months) and body mass index at study entry (≤ 30 vs. > 30). They will be randomized with equal probability to one of the two study arms from within each of the six strata. Balance in treatment assignment will be achieved using a randomized block design. Randomization will be carried out via computer generated random assignment. Randomization must be completed within 6 weeks of day 1 of study.

A non-randomized pilot cohort of patients receiving concurrent chemohormonal therapy will be enrolled in parallel to assess the feasibility of STAND clinic participation in this patient population.

7.4 Day 1 Study Visit

7.4.1 Clinical Assessment

- Physical examination
- Concomitant medications
- ECOG Performance Status
- Height, weight, body mass index, and percent body fat by bioimpedance measurement (see Appendix 6)
- LHRH Analogue

7.4.2 Laboratory Assessment

- Optional Peripheral blood collection for genotyping
- Extra serum and PBMCs collection for banking
- Fasting lipid panel (total cholesterol, triglycerides, LDL, HDL), glucose, insulin levels
- Hemoglobin A1c
- Serum 25-(OH) vitamin D level
- Serum PSA
- Serum testosterone

7.5 Day 1 and Monthly Study Visits (+/- 2 weeks)

Patients randomized to the STAND clinic will return to clinic on a monthly basis. During the course of these monthly visits, there will be a series of self-guided educational modules discussing various aspects of androgen deprivation therapy and management of side effects.

These modules will be comprised of PowerPoint slide presentations which the patients will view on a self-directed manner during their clinic visit, with the opportunity to ask questions before and after the presentation. In addition, on a rotating schedule, patients will meet one-to-one with a licensed exercise trainer, registered dietitian, and symptom management service to receive individualized counseling. The rotation of the schedule of providers may be adjusted depending upon availability of provider and patient. In total, patients will meet with each specialized service four times on a rotating every 3 month-schedule.

Patients enrolled in the non-randomized chemohormonal cohort will return to clinic on an approximately monthly basis for rotating visits with exercise, nutrition, and symptom management, with schedule of visits matching whenever possible the scheduled dates of infusion center appointments

Patients randomized to the standard-of-care arm will be referred to nutrition, exercise, and symptom management service upon patient request or if deemed necessary by health care provider, as per current standard-of-care and practice guidelines. Patients will have the opportunity to receive the educational modules for review outside the clinic setting

During the course of the visit with the exercise trainer, patients will review exercise patterns with the use of questionnaires filled out prior to visit and via the use of ambulatory accelerometer which quantifies activity level. Patients will receive individualized counseling regarding specific exercises, and reinforcement of establishing regular exercise routine. During the course of the visit, patients will have the opportunity to practice actual exercise routines under the supervision of the exercise trainer, and will receive in-person assessment of aerobic fitness level.

During the course of the visit with the registered dietitian, patients will review dietary habits with the use of diet logs filled out prior to each visit. Patients will receive individualized counseling on recommended foods/diet, and will receive feedback on progress on a longitudinal basis.

During the course of visit with symptom management service, patients physical and psychosocial issues will be addressed by trained health care provider. Counseling and medical management will be provided.

7.6 Every 3 Month Study Visits (+/- 2 weeks)

7.6.1 Clinical Assessment

- Physical exam
- Concomitant medications
- ECOG Performance Status
- Quality of life questionnaires
    - SF-12, EPIC-26, HFRDIS, Lee Fatigue Scale, PHQ-9, Attentional Functional Index, exercise pattern assessment, empathy scale

- Weight, body mass index, and percent body fat by bioimpedance measurement
- Patients will be referred to the Symptom Management Service, nutrition service, and/or exercise physiologist for further evaluation at the discretion of health care provider or per patient request (Standard-of-care treatment arm only)
- LHRH analogue administration
- Counseling regarding lifestyle modifications and review of the results of the above laboratory tests and quality of life questionnaires by a trained nurse practitioner or physician.
    - The PHQ-9 questionnaire screening for depression must be completed in person during the study visit and must be signed by treating health care provider prior to patient discharge from clinic

7.6.2 Laboratory Assessment

- Serum and plasma collection for banking
- Fasting lipid panel, glucose, and insulin level
- Hemoglobin A1c
- Serum 25-(OH) vitamin D level
- Serum PSA

7.7 End of Month 12 Study Visit (+/- 2 weeks)

7.7.1 Clinical Assessment

- Physical exam
- Concomitant medications
- ECOG Performance Status
- Quality of life questionnaires
    - SF-12, EPIC-26, HFRDIS, Lee Fatigue Scale, PHQ-9, Attentional Functional Index, empathy scale
- Weight, body mass index, and percent body fat by bioimpedance measurement

7.7.2 Laboratory Assessment

- Serum and plasma for banking
- Fasting lipid panel, glucose, and insulin levels
- Hemoglobin A1c
- Serum 25-(OH) vitamin D levels
- Serum PSA
- Serum testosterone

7.7.3 Radiographic Assessment

- DXA Scan
- High resolution peripheral quantitative CT scan of the distal tibia and radius (optional)

7.8 Concomitant Medications

Concomitant medications will be recorded at each study visit. The addition of medications to manage fasting blood glucose, lipids, bone density, or blood pressure will be allowed and at the discretion of the individual treating physician.

7.9 Follow Up

Patients randomized to the standard-of-care study arm will have the option of crossing-over to participation in the STAND clinic at the end of month 12 study visit. Patients who opt to participate in the STAND clinic will be followed for an additional 12 months. The STAND clinic schedule will be identical to that followed by patients initially randomized to the STAND clinic.

Following completion of STAND clinic participation, patients will be followed by telephone visit after 2 and 4 months to assess adherence to recommended diet/exercise plans. At 6 months following completion of the STAND clinic, patients will return for clinic assessment, which will include a physical exam, a measurement of weight, body mass index, percentage body fat, laboratory tests including evaluation of fasting glucose/lipid/insulin panels, hemoglobin A1c, plasma metabolites, serum PSA, serum testosterone and completion of quality of life questionnaires as outlined in the Appendix, and serum and plasma banking.

7.10 Duration of Study

The total duration of the study including follow up is expected to be approximately 5 years from the date the first patient is enrolled onto study.

8. Assessment of Study Variables

8.1 Percent Body Fat Estimation

Percent body fat will be estimated at baseline and every 3 months with the use of standard bioelectrical impedance monitor (see Appendix 4). Prior studies have demonstrated high reliability and strong correlation with other modalities including DXA scans.

8.2 Patient-Reported Outcomes

At baseline and every 3 months patients will complete quality of life and other questionnaires as outlined in Appendix 2. Patients will complete the questionnaires online within one week of study visit or at the time of study visit, either electronically or on paper. The PHQ-9 questionnaire must be completed on paper during the study visit. It is mandatory that the responsible health care provider for the study visit review and sign the results of the PHQ-9 prior to patient discharge from clinic.

8.3 Germline Polymorphisms

Collection of peripheral blood mononuclear cells for assessment of germline polymorphisms and their association with the relevant toxicities of ADT is an exploratory objective of the current study and patient participation in this aspect of the study is optional.

The genetic polymorphisms selected for this study were based on a literature review of prior studies which demonstrated significant associations between polymorphisms near or within select genes of interest encoding proteins involved in steroid hormone metabolism, intra-cellular transport, estrogen/androgen receptor signaling, and the IGF pathway with clinical outcomes on androgen deprivation therapy. Most prior studies included polymorphisms with a minor allele frequency > 5% in the CEU (Caucasian) population. The full set of polymorphisms to be analyzed is listed in Appendix 1.

Genomic DNA will be prepared from peripheral blood using a QIAamp DNA Blood Mini Kit (Quiagen Inc, Valencia, CA, USA). DNA will be stored at 4°C. Genotyping will be carried out using Sequenom iPLEX matrix-assisted laser desorption/ionization (MALDI)-time of flight mass spectrometry technology (Carlsbad, CA; http://www.sequenom.com/seq_genotyping.html/). Assays will be designed using Sequenom's MassARRAY AssignDesigner application, version 3.0. Polymerase chain reaction (PCR) and single base extension (SBE) oligonucleotides will be synthesized by Integrated DNA Technologies (Coralville, IA). PCR amplification will be performed using an input of 10 ng of DNA in a final volume of 6 L. The PCR products will be subsequently treated with shrimp alkaline phosphatase, and the SBE reactions will be initiated using iPLEX enzyme and mass-modified terminators (both Sequenom). After desalting, 7 nL of the SBE reaction will be spotted onto a SpectroCHIP (Sequenom) preloaded with 7 nL of 3-

hydroxypicolinic acid matrix. The SpectroCHIPs will be analyzed in automated mode by a MassArray Compact solid phase laser mass spectrometer system (Bruker Daltonics, Billerica, MA). The resulting spectra will be analyzed and genotypes called in real-time by the SpectroCaller algorithm, followed by additional user-initiated analysis with the SpectroTyper v.3.4A (Sequenom). The error rate on this platform is estimated to be less than 0.03%.

For the microsatellite analysis, DNA samples will be whole genome amplified using Illustra GenomiPhi V2 according to the manufacturer's recommended protocol (GE Healthcare, Chalfont St Gilles, UK). They will then be quantified using RNAseP Gene Expression Assay according to the manufacturer's recommended protocol (Applied Biosystems, Foster City, CA, USA). Polymerase chain reaction (PCR) will be performed using 2 μM final concentration for both forward and reverse primers, 1.5 mmol/L Mg, and 0.2 units of Platinum Taq DNA Polymerase (Invitrogen, Carlsbad, CA, USA) in a final volume of 10μL. After an initial denaturation of 5 min at 94°C, samples will be through 35 cycles after 94°C for 40 s, the proper annealing temperature for 30 s, and 72°C for 30 s, followed by a final extension step of 72°C for 10 min. One microlitre of PCR product will be added to a mixture of Hi-Di Formamide (Applied Biosystems) and ROX400HD Standard (Applied Biosystems). Samples will then be denatured for 5 min at 95°C and placed on ice for 3 min, followed by capillary electrophoresis on an ABI 3730XL(Applied Biosystems). Genotypes will be scored using GeneMapper 4.0 (Applied Biosystems).

8.4 High Resolution Peripheral Quantitative CT Imaging

The image collection will take place at the China Basin imaging facility at UCSF. 3D trabecular bone density and structure, cortical bone density, thickness and porosity at the distal radius and tibia will be measured using high-resolution peripheral quantitative computed tomography (HRpQCT).

Regional of Interest Definition

In the superior-inferior direction we will collect 18 mm of image data, we will analyze this stack in two stages, the distal 9 mm, then 9 mm-18 mm. In addition regional analysis for trabecular bone, in 8 regions will be performed. The trabecular compartment will be divided into two concentric regions (inner and outer sub-regions), where the area of the inner sub-region will be 60% of the entire trabecular region. The volume will be further divided into axial quadrants. In the leg, a line connecting the axial centroids of the tibia and fibula and it's orthogonal compliment will define approximately medial-lateral/anterior-posterior quadrants. In the forearm, the major and minor axes of the axial cross section of the radius will define the medial-lateral/anterior-posterior quadrants. Each sub-region denoted by a two letter acronym based on location: I or O for inner or outer sub-regions, respectively; and M, P, L, or A for medial, posterior, lateral and anterior, respectively. Mean trabecular densitometric and micro-

architectural indices will be computed for each individual sub-region. The cortical analysis will be done in the 4 axial quadrants.

9. Planned Statistical Methods

9.1 Study Design

Randomized, phase 2 study with cross-over design to assess the longitudinal impact of participation in the multi-disciplinary STAND clinic vs. receipt of usual standard of care on changes in key metabolic parameters, quality of life, and patient satisfaction among men receiving androgen deprivation therapy for prostate cancer. Standard-of-care therapy will consist of every 3-month visits comprised of review of medical history, toxicity assessment, and lifestyle modification counseling provided by individual health care provider, LHRH analog injections by trained oncology nurse. Patients will have access to exercise, nutrition, and symptom management counseling if so requested by the patient or deemed necessary by health care provider. Men randomized to participation in the STAND clinic will receive, in addition to standard every 3 month visits with health care providers and LHRH analog injections, monthly self-directed educational "modules" covering the various aspects of hormone therapy as well as every 3-month individualized counseling provided by registered dietitian, exercise trainer, and symptom management service. At the end of 12 months of study participation, patients initially randomized to receive standard-of-care, will have the option of crossing-over to participate in the STAND clinic for the ensuing 12 months.

A non-randomized pilot cohort of 20 patients receiving concurrent chemohormonal therapy will be enrolled in parallel to assess the feasibility of STAND clinic participation in this patient population.

9.2 Determination of Sample Size and Study Power

The sample size estimate is based upon the primary endpoint of the study, the mean percent change in percentage body fat from baseline to 12 months. Based on prior prospective longitudinal studies, it is estimated that men receiving ADT and standard-of-care physician counseling regarding expected toxicities will experience a mean 12% (sd = 17%) increase in percentage body fat after 12 months of ADT [13]. If men participating in the STAND clinic, with individualized exercise/nutrition counseling and longitudinal assessment, have, on average, no increase in percentage body fat mass after 12 months of hormone therapy, this would warrant further evaluation of a multi-disciplinary clinic in a larger randomized clinical trial with long-term endpoints of interest, including incidence of diabetes and potentially cardiovascular disease. An enrollment target of 32 evaluable patients per arm will provide power of 80% to detect an effect size of 0.71 in the difference in mean percent change from baseline to 12 months in percentage body fat mass between the two arms, using a two-sample t test and a two-tailed level of significance = 0.05. The total planned accrual is 40 patients per arm accounting for an inevaluable rate of 20%.

A sample size of 20 patients is chosen for the non-randomized chemohormonal cohort to establish the feasibility of a multi-disciplinary clinic in this patient population. The primary endpoint for this pilot cohort is the percentage of completed STAND clinic visits, with a target goal of 80%. A sample size of 20 patients (13 visits per patient; 260 visits in total) provides 17.5% precision to determine the percentage of completed visits at 95% confidence.

9.3 Interim Analysis

Interim analysis will be performed after 33% of the planned sample size of randomized patients complete 12-month care. To preserve the overall type I error rate at < 0.05, the Lan-DeMets spending function will be used to allocate nominal alpha-levels at the interim and final analyses. The efficacy stopping boundaries for the primary efficacy endpoint at the interim and final analyses are $p < 0.026$ and $p < 0.474$, respectively.

An interim analysis for the non-randomized cohort will be performed after 10 patients have been enrolled on the STAND clinic for a minimum of 6 months. If the percentage of completed STAND visits is less than 60%, the study schedule will be altered to ensure higher rates of patient adherence to the clinic schedule.

9.4 Accrual

A total of 80 patients will be enrolled in the randomized patient cohort at the University of California San Francisco. Study accrual is anticipated to be approximately 2 patients per month, leading to total study accrual duration of 40 months. Anticipated time from last patient enrolled to primary study completion and analysis of primary and secondary endpoints equals approximately 12 months, leading to an estimated primary study duration of 52 months. A total of 20 patients will be enrolled in the non-randomized chemohormonal cohort, at an estimated frequency of 0.8 patients/month, leading to an estimated accrual period of 24 months.

9.5 Analysis Populations

The primary analysis for the randomized cohort will include all patients who have a body fat % measurement at baseline and at month 12 on study (+/- 2 weeks). If a patient comes off study prior to obtaining the end of month 12 body fat % measurement, they will not be included in the primary study analysis.

All patients enrolled in the chemohormonal non-randomized cohort who complete C1D1 visit will be included in the analysis of the primary endpoint, the percentage of completed visits in the STAND clinic.

9.6 Demographics and Baseline Characteristics

Demographic variables will include age, race, and ethnicity. Baseline characteristics will include the following:

- Height, weight, body mass index, waist circumference, percentage body fat
- Assessment of co-morbidities including diabetes and heart disease (Appendix 3)
- Date of prostate cancer diagnosis
- Gleason grade and PSA at the time of diagnosis
- Type and date of prior local therapy (if any)
- Date of ADT initiation and indication (adjuvant, biochemical relapse, or metastatic disease)
- Baseline PSA at the start of ADT
- Concurrent use of anti-androgen
- Metastatic status at time of study entry (none, bone only, soft tissue, any visceral)

9.7 Study Endpoints

9.7.1 Primary Endpoint

Randomized cohort: Mean percent change from baseline to 12 months in percentage body fat mass as measured by bioelectrical impedance analyzer.

Non-randomized cohort: Percentage of completed STAND clinic visits.

9.7.2 Secondary Endpoints

Mean percent change from baseline to 12 months and patterns of change from baseline with respect to the following:

Metabolic Impact on Diabetes and Cardiovascular Disease Risk Factors:

- Fasting blood glucose
- Fasting plasma insulin level
- Insulin resistance as calculated by HOMA-IR
- Hemoglobin A1c
- Fasting lipids (total cholesterol, LDL, HDL, triglycercides)
- Waist circumference
- Body weight/body mass index
- Exercise patterns as measured by validated questionnaire and pedometer assessment
- Blood pressure

Bone Health:

- Bone density at the lumbar spine, femoral neck, and total hip as assessed by DXA scan among patients without bone metastases at the time of study entry
- Serum 25-(OH) vitamin D levels

Quality of Life/Psychosocial Impact:

- Depression as measured by PHQ-9
- Cognitive function as measured by Attentional Functional Index
- Overall quality of life as measured by SF-12
- Fatigue as measured by the Lee Fatigue Scale
- Erectile and urinary function as measured by EPIC-26
- Hot flash severity as measured by Hot Flash Related Daily Interference Scale

9.7.3 Correlative Study Endpoints

- Association between inherited genetic polymorphisms of functional relevance near or within genes encoding proteins with roles in steroid hormone transport and androgen receptor signaling with changes in metabolic parameters among men treated with androgen deprivation therapy.
- Mean change from baseline in trabecular bone architecture as measured by trabecular bone number (TbN) and trabecular bone volume fraction (BV/TV) after 12 months of androgen deprivation therapy.
- Association between 2D:4D ratio with change in quality of life on androgen deprivation therapy.
- Association between 2D:4D ratio and baseline and percent change from baseline in empathy score.

9.8 Methods for Analysis

Generally, frequency distributions, means, and standard deviations will be used to describe subject demographics and baseline characteristics. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, Chi-square test, as appropriate. Statistical significance will be declared based on alpha level of 0.05. For the endpoints with missing less than 25% of values, multivariate imputation using fully conditional specification (R MICE package) will be implemented. For endpoints missing more than 25% of values, the endpoint will be excluded from the final analysis.

9.8.1 Analytic Plan for the Primary Objective

Two-sample t-test will be used to compare the mean percent change from baseline in percentage body fat after 12 months of study participation. The changes in percentage body fat across the

different time points will be evaluated using repeated measures analysis of covariance. To further characterize the patterns over the time and investigate the effect of treatment arm assignment, a linear mixed model will be applied with adjusting for stratification factors and covariates including Charlson co-morbidity index score, age, and baseline depression score as measured by PHQ-9. Patients who do not have a baseline or end-of-month 12 percentage body fat measurement, or those that start medications known to affect body fat/body weight during the course of the 12-month study, including metformin, insulin, corticosteroids, mirtazapine, or megestrol, will be excluded from the primary endpoint analysis. In an exploratory analysis, these patients will be retained to assess the impact of STAND clinic participation on changes in percentage body fat over time both before and after initiation of medical management.

For the non-randomized chemohormonal cohort, the point estimate and 95% confidence interval of the percentage of completed STAND clinic visits will be reported.

9.8.2 Analytic Plan for the Secondary Objectives

Two-sample t test will be used to compare the mean change from baseline to 12 months for the secondary endpoints which hold the normality assumption. For endpoints that do not hold the normality assumption, as well as for ordinal level of measurements, Wilcoxon-rank-sum test will be used. To evaluate the changes in secondary endpoints across the different time points, repeated measures analysis of covariance will be used for continuous endpoints (appropriate transformation will be applied if normality assumption doesn't hold), while repeated measures generalized estimation equation with a cumulative logic categorical will be applied for the ordinal level of measurements. Generalized linear mixed models with adjustment for stratification factors and possible covariates will be applied to further characterize the patterns over the time and investigate the effect of the care type with appropriate link function. Results will be displayed in a graphical fashion. Patients who start medications known to affect endpoint being analyzed (e.g. statins for the lipid panel measurement) will be excluded from the main statistical analysis. In a sensitivity analysis these patients will be retained to assess impact of STAND clinic participation on study outcomes. No adjustment for multiple comparisons will be made for the analysis of the secondary, exploratory objectives.

For patients who cross-over from standard-of-care to participate in the STAND clinic, the mean change from month 12 to month 24 after twelve months of participation in the STAND clinic with respect to the study endpoints will be descriptively reported.

During the follow-up phase of the study, the mean change from completion of STAND clinic participation to 12 months after completion with respect to study endpoints will be descriptively reported.

9.8.3 Analytic Plan for the Correlative Objectives

The relationship between each pre-selected SNP genotype and the percent change from baseline to 12 months on-study in percentage body fat, fasting plasma glucose, body mass index, waist circumference, and fasting insulin among men undergoing ADT will each be tested using a two-sample t test or Wilcoxon-rank-sum test as appropriate when the SNPs are in dominant or recessive fashion. When SNPs are in the additive model, for each SNP, a generalized linear model with an appropriate link will be used considering each baseline-12 month change as the response variable and SNP genotype (coded as 0, 1, and 2 for zero, one and two copies of minor allele) as the predictor. Analysis will be extended to adjust for possible risk factors by fitting multivariate generalized linear models for each baseline-12 month change and each SNP. Multiple testing adjustments will be done for each baseline-12 month change across all SNPs by controlling for false discovery rate.

The mean percent change from baseline in trabecular bone microarchitecture parameters including trabecular bone number and trabecular bone volume assessed by high resolution quantitative peripheral CT will be descriptively reported for the entire study population. In an exploratory fashion, the mean percent change between those randomized to the STAND versus usual care treatment arms will be compared using Mann-Whitney test.

The distribution of the 2D:4D finger length ratio will be determined for the entire study population. As the optimal cut-off to define sensitivity to androgen deprivation therapy is not known, the study cohort will be dichotomized into those with 2D:4D ratios above and below the median respectively. The mean percent change from baseline in QOL scores from the collected questionnaires as well as the baseline and mean percent change from baseline in empathy score will be compared between dichotomized subgroups using the Mann-Whitney test.

No adjustment for multiple comparisons will be made for the analysis of the correlative study endpoints.

10. Study Management

10.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR) Parts §50, §54, and §312, GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR 56 and applicable regulatory requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Committee on Human Research (UCSF's IRB). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the UCSF Committee on Human Research (CHR), any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation. If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation.

10.5 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. study data will be entered into OnCore® and RedCAP, UCSF's Clinical Trial Management System (CTMS) via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. Each CRF must be reviewed for accuracy by the Investigator, corrected as necessary, and then approved. Alternatively, the Investigator may sign individual, printed CRFs. These signatures attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the Data and Safety Monitoring Committee (DSMC) and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement among the Principal Investigator, the Trial Statistician, and the Protocol Project Manager.

10.6 Retention of Records

The Investigator agrees to maintain a complete and current record of all documentation associated with the study. All of the documents shall be kept together. Each should be available for ready review. These study documents will include the:

- protocol
- protocol amendments, when applicable
- Investigator's current curriculum vitae
- documentation of CHR approvals for the protocol, amendments, informed consents and advertisements used to recruit patients
- site visit log
- correspondence (all "to" and "from" correspondence)
- case report forms and informed consent documents for individual patients
- final report for the study if available.

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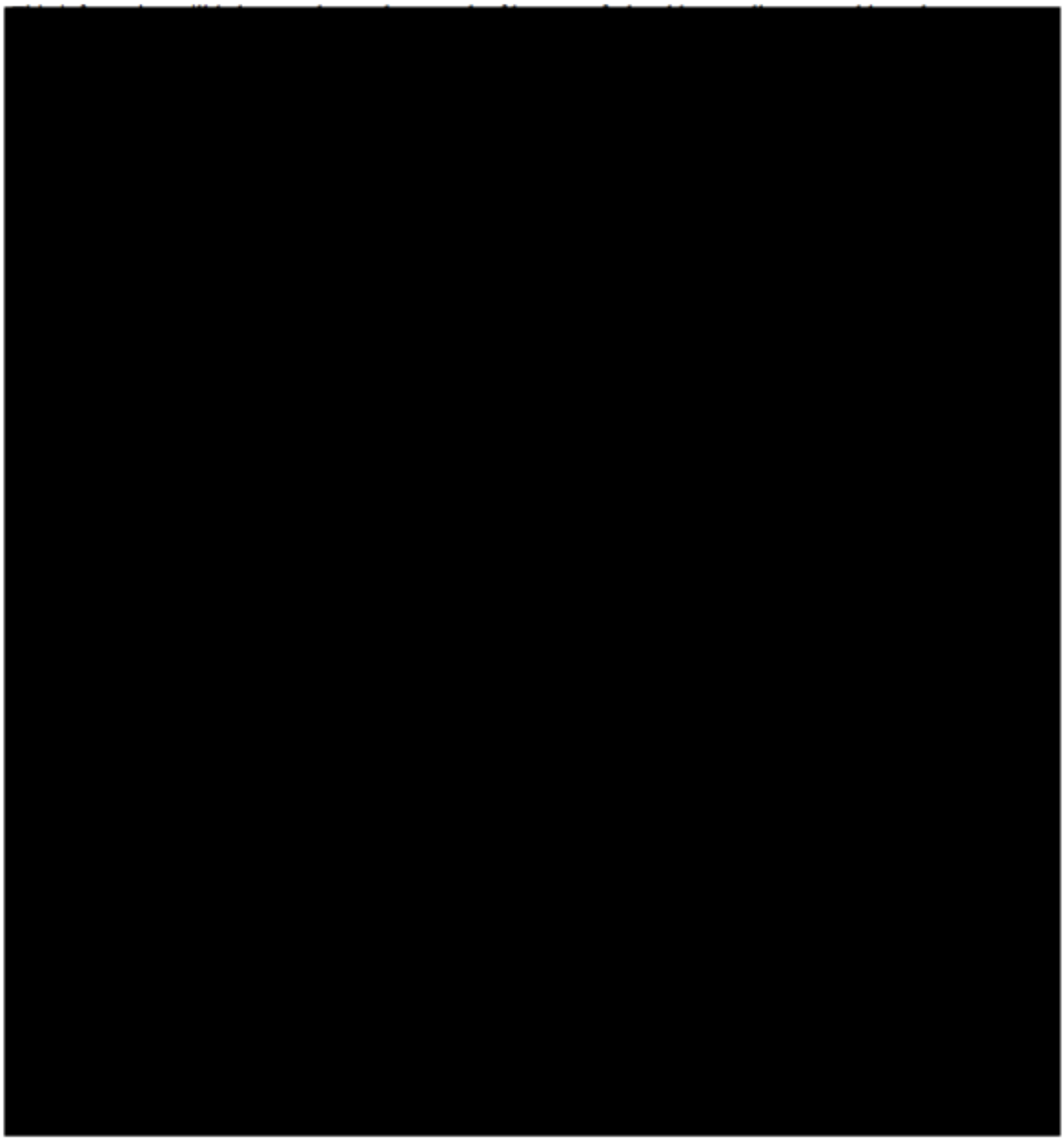
Appendix 1. Selected Genetic Polymorphisms

Gene	Polymorphism	Location	Protein	Reference
CYP19A1	$(TTTA)_n$	Intron 4	Aromatase	Tsuchiya N, et al J of Clin Oncol 2006
CYP19A1	rs1870050 A>C	5 kb upstream	Aromatase	Ross R, et al J of Clin Oncol 2008
HSD3B1	rs1856888 A>G	13 kb upstream	HSD	Ross R, et al J of Clin Oncol 2008
HSD17B4	rs7737181 C>G	Intron	HSD	Ross R, et al. J of Clin Oncol 2008
SLCO1B3	334 T>G	Exon 3	OATP	Hamada A, et al. Clin Cancer Res 2008
SLCO1B3	699 G>A	Exon 6	OATP	Hamada A, et al. Clin Cancer Res 2008
SLCO2B1	rs12422149 A>G	Exon 7	OATP	Yang M, et al. J of Clin Oncol 2011
SLCO2B1	rs1789693	Intron 7	OATP	Yang M, et al. J of Clin Oncol 2011
SLCO2B1	rs1077858	Intron 8	OATP	Yang M, et al. J of Clin Oncol 2011
AR	$(CAG)_n$	Exon 1 (NTD)	Androgen Receptor	Stanford J, et al. Cancer Res 1997
AR	$(GGC)_n$	Exon 1 (NTD)	Androgen Receptor	Stanford J, et al. Cancer Res 1997
AR	rs17302090	Promoter	Androgen Receptor	Lindstrom et al Clin Cancer Res 2007

Appendix 2. Quality of Life Questionnaires

SF-12®:

SF-12®:



SF-12® Cont'd:

[redacted]

EPIC-26:

1. Over the past 4 weeks, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number)
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control during the last 4 weeks?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number)
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number)
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you during the last 4 weeks?

   (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding with urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Need to urinate frequently during the day.....	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you during the last 4 weeks?

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number)
   Moderate problem..... 4
   Big problem..... 5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements	0	1	2	3	4
c. Losing control of your stools	0	1	2	3	4
d. Bloody stools	0	1	2	3	4
e. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number)
Moderate problem..... 4
Big problem..... 5

8. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your ability to have an erection?	1	2	3	4	5
b. Your ability to reach orgasm (climax)?	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections during the last 4 weeks?

None at all..... 1
Not firm enough for any sexual activity..... 2
Firm enough for masturbation and foreplay only..... 3 (Circle one number)
Firm enough for intercourse..... 4

10. How would you describe the FREQUENCY of your erections during the last 4 weeks?

I NEVER had an erection when I wanted one..... 1
I had an erection LESS THAN HALF the time I wanted one..... 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number)
I had an erection MORE THAN HALF the time I wanted one..... 4
I had an erection WHENEVER I wanted one..... 5

11. Overall, how would you rate your ability to function sexually during the last 4 weeks?

Very poor	1	
Poor	2	
Fair	3	(Circle one number)
Good	4	
Very good	5	

12. Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

13. How big a problem during the last 4 weeks, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes	0	1	2	3	4
b. Breast tenderness/enlargement	0	1	2	3	4
c. Feeling depressed	0	1	2	3	4
d. Lack of energy	0	1	2	3	4
e. Change in body weight	0	1	2	3	4

Lee Fatigue Scale:

DIRECTIONS: You are asked to place an "X" through these lines to indicate how you are feeling RIGHT NOW. For example, suppose you have not eaten since yesterday. Where would you put the "X" on the line below?

not at all hungry _____ extremely hungry

You would probably put the "X" closer to the "extremely hungry" end of the line. This is where I put it:

not at all hungry _____ extremely hungry

NOW PLEASE COMPLETE THE FOLLOWING ITEMS.

not at all tired _____ extremely tired

not at all sleepy _____ extremely sleepy

not at all drowsy _____ extremely drowsy

not at all fatigued _____ extremely fatigued

not at all worn out _____ extremely worn out

not at all energetic _____ extremely energetic

not at all active _____ extremely active

not at all vigorous _____ extremely vigorous

not at all efficient _____ extremely efficient

not at all lively _____ extremely lively

not at all bushed _____ totally bushed

not at all exhausted _____ totally exhausted

keeping my eyes open is no effort at all _____ keeping my eyes open is a tremendous chore

moving my body is no effort at all _____ moving my body is a tremendous chore

concentrating is no effort at all _____ concentrating is a tremendous chore

carrying on a conversation is no effort at all _____ carrying on a conversation is a tremendous chore

I have absolutely no desire to close my eyes _____ I have a tremendous desire to close my eyes

I have absolutely no desire to lie down _____ I have a tremendous desire to lie down

Hot Flash Related Daily Interference Scale (HFRDIS)

Please circle one number to the right of each phrase to describe how much DURING THE PAST WEEK hot flashes have INTERFERED with each aspect of your life. Higher numbers indicate more interference with your life. If you are not experiencing hot flashes or if hot flashes do not interfere with these aspects of your life, please mark zero to the right of each question.

	Do not interfere										Completely interfere
1. Work (work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
2. Social activities (time spent with family, friends, etc.)	0	1	2	3	4	5	6	7	8	9	10
3. Leisure activities (time spent relaxing, doing hobbies, etc.)	0	1	2	3	4	5	6	7	8	9	10
4. Sleep	0	1	2	3	4	5	6	7	8	9	10
5. Mood	0	1	2	3	4	5	6	7	8	9	10
6. Concentration	0	1	2	3	4	5	6	7	8	9	10
7. Relations with others	0	1	2	3	4	5	6	7	8	9	10
8. Sexuality	0	1	2	3	4	5	6	7	8	9	10
9. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
10. Overall quality of life	0	1	2	3	4	5	6	7	8	9	10

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ **DATE:**_____

Over the last 2 *weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

TOTAL:

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

Attentional Functional Index

I. At this time, how well do you feel you are functioning in each of the areas below?
Place a mark through the line at whatever point best describes how you are doing in each area at present.

1. Getting started on activities (tasks, jobs) you intend to do.
   Not at all _____ Extremely well
2. Following through on your plans.
   Not at all _____ Extremely well
3. Doing things that take time and effort.
   Not at all _____ Extremely well
4. Making your mind up about things.
   Not at all _____ Extremely well
5. Keeping your mind on what you are doing.
   Not at all _____ Extremely well
6. Remembering to do all the things you started out to do.
   Not at all _____ Extremely well
7. Keeping your mind on what others are saying.
   Not at all _____ Extremely well
8. Keeping yourself from saying or doing things you did not want to say or do.
   Not at all _____ Extremely well
9. Being patient with others.
   Not at all _____ Extremely well

II. At this time, how would you rate yourself on:

10. How hard you find it to concentrate on details.
    Not at all _____ A great deal
11. How often you make mistakes on what you are doing.
    Not at all _____ A great deal
12. Forgetting to do important things.
    Not at all _____ A great deal
13. Getting easily annoyed or irritated.
    Not at all _____ A great deal

Exercise Pattern Assessment (Baseline):

8. What is your usual walking pace outdoors? ○ Unable to walk eight blocks or climb a flight of stairs due to physical impairment.
○ Easy, casual (less than 2 mph) ○ Normal, average (2–2.9 mph) ○ Brisk pace (3–3.9 mph) ○ Very brisk/striding (4 mph or faster)

9. How many flights of stairs (not steps) do you climb daily? (Do not include time spent on stair or exercise machines.)
○ No flights ○ 1–2 flights ○ 3–4 flights ○ 5–9 flights ○ 10–14 flights ○ 15 or more flights

10. During the past year, what was your average total time per week at each activity?

	AVERAGE TOTAL TIME PER WEEK												
	NONE	1–4 Min.	5–19 Min.	20–39 Min.	40–80 Min.	1.5 Hrs.	2–3 Hrs.	4–6 Hrs.	7–10 Hrs.	11–20 Hrs.	21–30 Hrs.	31–40 Hrs.	40+ Hrs.
Walking to work or for exercise (including golf)	○	○	○	○	○	○	○	○	○	○	○	○	○
Jogging (slower than 10 minutes/mile)	○	○	○	○	○	○	○	○	○	○	○	○	○
Running (10 minutes/mile or faster)	○	○	○	○	○	○	○	○	○	○	○	○	○
Bicycling (including stationary machine)	○	○	○	○	○	○	○	○	○	○	○	○	○
Biking intensity: ○ Low ○ Medium ○ High													
Lap swimming	○	○	○	○	○	○	○	○	○	○	○	○	○
Swimming intensity: ○ Low ○ Medium ○ High													
Tennis	○	○	○	○	○	○	○	○	○	○	○	○	○
Tennis intensity: ○ Low ○ Medium ○ High													
Squash or racquetball	○	○	○	○	○	○	○	○	○	○	○	○	○
Other aerobic exercise (exercise classes, etc.)	○	○	○	○	○	○	○	○	○	○	○	○	○
Lower intensity exercise (yoga, stretching, toning)	○	○	○	○	○	○	○	○	○	○	○	○	○
Moderate outdoor work (e.g., yardwork, gardening)	○	○	○	○	○	○	○	○	○	○	○	○	○
Heavy outdoor work (e.g., digging, chopping)	○	○	○	○	○	○	○	○	○	○	○	○	○
Weight training/resistance exercises arms	○	○	○	○	○	○	○	○	○	○	○	○	○
(include machines such as LifeFitness) legs	○	○	○	○	○	○	○	○	○	○	○	○	○
Standing or walking around work	○	○	○	○	○	○	○	○	○	○	○	○	○
Standing or walking around home	○	○	○	○	○	○	○	○	○	○	○	○	○
Sitting at work or commuting	○	○	○	○	○	○	○	○	○	○	○	○	○
Sitting at home while watching TV/VCR/DVD	○	○	○	○	○	○	○	○	○	○	○	○	○
Other sitting at home (e.g., desk, eating, computer)	○	○	○	○	○	○	○	○	○	○	○	○	○

11. In an average week, on how many days do you usually exercise (include brisk walking or more strenuous activity)?
○ None ○ 1 day ○ 2 days ○ 3 days ○ 4 days ○ 5 days ○ 6 days ○ 7 days

Please record any exercise that you do for the seven consecutive days prior to your visit with exercise trainer.

Date	Day of Week	Time	Type of Activity	Duration (minutes)	Heart Rate	Perceived Intensity	Nausea/Fatigue (1-10 with 10 feeling great)	Comments
	MONDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	TUESDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	WEDNESDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	THURSDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	FRIDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	SATURDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	
	SUNDAY					☐Light ☐Moderate ☐Vigorous	___ Nausea ___ Fatigue	

FOOD AND BEVERAGE WORKSHEET

Name: _____

Birthdate: _____

Day of the Week: _____

→ Please record all foods & beverages consumed for the day - the more detailed the record, the more accurate the analysis will be. For example: turkey sandwich (2 slices whole wheat bread, 3 oz turkey, ½ cup lettuce, ¼ cup tomato, 1 tbsp mustard). Include two week days & one weekend day.

Time	Food or Beverage	Amount

Was this day typical? ☐ Yes ☐ No

If not, how so?

EQ-8 Quotient

Please answer on a scale of 1-5 (1 disagree strongly; 5 agree completely) how well each statement matches your personality:

1. I find it easy to put myself in somebody else's shoes.

2. I am good at predicting how someone will feel.

3. I am quick to spot when someone in a group is feeling awkward or uncomfortable.

4. Other people tell me I am good at understanding how they are feeling and what they are thinking.

5. I find it hard to know what to do in a social situation.

6. I often find it hard to judge if something is rude or polite.

7. It is hard for me to see why some things upset people so much.

8. Other people often say that I am insensitive, though I don't always see why.

Appendix 3. Charlson Co-Morbidity Index

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Appendix 4: Bioelectrical Impedance Device for Assessment of Percentage Body Fat

ImpediMed DF50

Instruction Manual Link:

http://www.impedimed.com/products/df50/df50-for-usa.htm

Appendix 5: Accelerometer For Ambulatory Recording of Activity Levels

Actigraph GT3X+ Accelerometer

Accelerometer Participant Instructions

- Please wear the belt with the accelerometer for seven days, starting the morning of _____ and ending the evening of_____.
- Wear the belt around your waist with the accelerometer placed on your right side. The device should be attached securely to your body so it does not have any extraneous movement.
- Please wear the belt with the accelerometer at all times when awake, from rising in the morning until going to sleep at night, for seven consecutive days.
- The device is **NOT** waterproof – remove the belt when bathing or swimming.
- Please return the belt with the accelerometer in person, or via USPS in the provided addressed stamped envelope, as soon as possible after completing your seven days.
- If any questions, please contact us via email or telephone: Evelyn Hang at HangE@cc.ucsf.edu or 415-885-3357.

Appendix 6. Data and Safety Monitoring Plan for a Phase 2 Institutional Study

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of Grade 2 and higher adverse events.
- Review of suspected adverse reactions considered "serious".

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. The discussion will include the number of subjects, significant toxicities in accordance with the protocol, and observed responses.

Adverse Event Review and Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study treatment, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study treatment.

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study treatment and it is determined to be related either to the study treatment or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair within **1 business day** of knowledge of this event. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

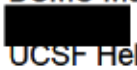
If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:
Phone:
Email:
Address:

DSMC Monitors



UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94115

* DSMP approved by NCI 09/February2012

Appendix 7. Specimen Handling and Storage

At baseline, for patients who agree to participate in this optional component of the study, a 12-mL blood sample in two plastic EDTA tubes will be collected from each participant. Samples will be stored in a 80 degrees below Celsius freezer in the UCSF Helen Diller Family Comprehensive Cancer Center. Genomic DNA will be extracted by using a QIAmp DNA Mini Kit ([redacted]) according to the UCSF DNA Bank standard operating procedures. Batched DNA samples will be taken to the Kroetz laboratory at UCSF Mission Bay campus for polymorphism assessment.

In addition, at baseline and after every 3 months on study, and at 6 months following completion of STAND clinic participation, 20 mL of whole blood will be collected in one tigertop (serum) and one lavender top tube (plasma) and centrifuged at 3000 rpm for 10 minutes. The serum and plasma will be decanted into two 2-mL polypropylene screw cap (leak-proof) vials (four total vials) that have been properly labeled with the unique specimen log number and stored at -80 degrees Celsius.

Samples will be catalogued individually in password protected tissue database. Patient identifiers will be removed from this database and substituted with study ID numbers. Annotations for individual tissue/blood samples will be made for processing.