A Feasibility Study Followed by a Randomized Phase II Study of Yoga for Radiation Therapy Side Effects in Prostate Cancer.

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List of Abbreviations

CAM – Complementary and Alternative Medicine

ED – Erectile Dysfunction

SD – Sexual Dysfunction

UI – Urinary Incontinence

IIEF - The International Index of Erectile Function Questionnaire.

IPSS - The International Prostate Symptom Score Sheet

BFI - Brief Fatigue Inventory

FACT-G - Functional Assessment of Cancer Therapy-General

Study Summary

Title	A Feasibility Study Followed by a Randomized Phase 2 Study of Yoga for Radiation Therapy Side Effects in Prostate Cancer
Short Title	Yoga for Prostate Cancer
Protocol Number	UPCC# 05813
Phase	Feasibility study followed by a randomized Phase II study
Methodology	A single arm pilot followed by a 2-arm study
Study Duration	12 months for Feasibility. 36 months for Phase II
Study Center(s)	Perelman Center for Advanced Medicine
Objectives	The purpose of this study is to ascertain the feasibility of yoga interventions as well as the effect of yoga on radiation-related fatigue, sexual dysfunction and urinary incontinence in patients with non-metastatic prostate cancer.
Number of Subjects	63
Diagnosis and Main Inclusion Criteria	Non-metastatic prostate cancer patients undergoing radiation therapy
Study Product, Dose, Route, Regimen	N/A
Duration of administration	Twice weekly yoga sessions for duration of radiation treatment.
Reference therapy	N/A
Statistical Methodology	The primary hypothesis will be tested using a two-group t-test to compare difference scores between Yoga and control groups.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

It is estimated that 241,740 men will be diagnosed with prostate cancer in 2012. From 2005-2009 the median age at diagnosis for cancer of the prostate was 67 years of age; approximately 9.5% between the ages of 45 and 54, 31.6% between 55 and 64, and 35.5% between 65 and 74 years old. (1).

For most cancer patients, the most common side effects of cancer as a disease, and cancer treatment are pain, depression and fatigue (2). Cancer –related Fatigue (CRF) is defined as "a common, persistent, and subjective sense of tiredness related to cancer or to treatment of cancer that interferes with usual functioning (3). CRF differs from everyday life fatigue, which is usually temporary and can be relieved by rest or sleep. The impact of CRF on a patient's ability to function in daily life is considerable and has been found to adversely affect patients' quality of life even more than pain (4-8). Fatigue is reported in 40 -75% of cancer patients. The prevalence of CRF increased to 60-93% in patients receiving radiotherapy (RT) (4-6), and when Visual Analogue Fatigue Scales were used, the percentage rose up to 99% (9).

However too many cancer patients suffering from fatigue receive inadequate treatment for their symptoms (2). The National Comprehensive Cancer Network guidelines recommend that integrative non-pharmacologic interventions be implemented for managing CRF. Various studies demonstrated positive effect from physical activity interventions during and after cancer treatment. These studies also showed that exercise is safe and well tolerated by patients during various cancer treatments including radiation therapy (10-13).

Specifically, prostate cancer patients report high levels of urinary and sexual adverse effects with more than half of the patients reporting poor sexual drive (14). Erectile

dysfunction (ED) is defined by the National Institute of Health as "the inability to achieve or maintain an erection sufficient for satisfactory sexual performance" (15). ED is reported in 21% to 85% of patients (16-19). The etiology of ED after RT is still debatable, with studies demonstrating occlusive vascular disease and hemodynamics interferences, nerve damage and or damage to the proximal penile structures, such as the penile bulb, the neurovascular bundle, and the local vascular structures (16, 18). Urinary incontinence (UI) is loss of bladder control. There are several forms of UI. The most common type is stress incontinence, which is caused by a loss of outlet resistance at the bladder neck. UI occurs when the bladder detrusor muscle contracts involuntarily during bladder filling, and is a more common side effect of RT. The prevalence of UI after RT is 24% and may take years to develop (14, 16).

The popularity of complementary and alternative medicine (CAM) has been growing rapidly in the general population with up to 69% of Americans now using some modality of CAM (20). Among cancer patients the prevalence of CAM use has increased two to threefold in the last two decades (21-23). Most cancer patients use CAM hoping to boost their immune system, relieve pain and control cancer and cancer treatment's side effects (24). The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as "a group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine" (http://nccam.nih.gov/health/whatiscam/). Research on the use of yoga as a modality for alleviating prostate cancer patients' side effects has been minimal (25).

"The primary aim of yoga is to restore the mind to simplicity and peace, and free it from confusion and distress. This sense of calm comes from the practice of yogic asanas and pranayama." B.S. K. Iyengar. Yoga rejuvenates the body, restores natural energy, decreases pain, reduces stress, as well as increases muscular strength and flexibility. Nevertheless, most research done in the past using yoga as a treatment modality used women and breast cancer patients as the treatment groups. Participation of men in yoga may be a challenge. The first goal of our study is to evaluate the feasibility of using yoga as a treatment modality in prostate cancer patients. If successful, we will continue seamlessly to a randomized study to determine the effects of yoga on fatigue as measured by the Brief Fatigue Inventory (BFI). We will also ascertain the effects of yoga on overall

QOL as measured by the Functional Assessment of Cancer Therapy-General (FACT-G) instrument, E.D. and U.I by using the IIEF and IPSS questionnaires respectively. The long-term goal of our study is to determine the approximate effect of yoga on fatigue and QOL to inform a subsequent larger randomized study of yoga compared to a control group of patients receiving standard supportive care. QOL instruments will be administered pretreatment, during treatment, and within a week of the last yoga class or by the end of radiation.

2 Study Objectives

1. To determine the feasibility of implementing yoga interventions for men with non-metastatic prostate cancer undergoing radiation therapy.

2. To examine the effect of yoga on cancer and radiation related fatigue, stress levels and patients' quality of life, in addition to standard of care, during active radiation therapy.

3. To examine the effect of yoga intervention on SD, ED and UI during active radiation therapy.
4. To examine the effect of yoga intervention on caregiver quality of life during patient's active radiation therapy as measured by the FACT-G

3 Study Design

3.1 General Design

1. This study will have 2 phases, and will consist of a preliminary study of feasibility, and a two-arm, phase 2 randomized study of efficacy, with a go/ no-go decision for phase 2 based on feasibility.

2. Those enrolled in the feasibility study will be part of the yoga treatment arm at analysis time.

3.2 Study Measures

1. Baseline information will be collected prior to start of yoga therapy. (age, race/ethnicity, marital/partner status, educational history, income, residence location, travel time to facility, method of travel, details regarding co-morbidities, disease stage, detail of their current radiotherapy).
2. The Brief Fatigue Inventory (BFI) questionnaire is a 9 –item scale that will be used to rapidly assess fatigue severity. The first three questions rate the severity of the patient's fatigue at its "worst", "usual" and "now" levels over the last 24 hours, with 0 meaning "no fatigue" and 10 being "fatigue as bad as you can imagine". Six questions assess the amount that fatigue has interfered with different aspects of the patient's life during the past 24 hours. The interference items include general activity, mode, walking ability, normal work (includes both work outside the home and housework), relations with others, and enjoyment of life. The interference questions are measured on a 0 -10 scale, with 0 being "does not interfere" and 10 being "completely interferes". Scores on this scale range from 0-10, with a mean score of 4.7 and S.D of 2.8. The BFI questionnaire will be completed by patients at the following time points:

    a. Prior to start of radiotherapy i.e. on the day of consultation or on the day of simulation or setup.
    b. Bi-weekly while receiving radiotherapy

i. A treatment week is defined as 5 consecutive days of radiotherapy. If a patient misses treatment for any reason his treatment week is shifted back one day.

c. Within a week of the last yoga class or by the end of radiation.

3. The FACT-G is a commonly used instrument measuring general QOL reflecting symptoms or problems associated with malignancies across 4 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); and functional well-being (7 items). Patients rate all items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, and disease-specific concerns. Six additional experimental items request information regarding how each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. FACT-G is a 27 item compilation of general questions divided into 4 primary QOL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. FACT-G takes about 5 minutes to complete and has been written at the 6th grade level. FACT-G questionnaire will be completed by patients and their caregivers who enroll on study at the following time points:

a. Prior to start of radiotherapy i.e. on the day of consultation or on the day of simulation or setup.

b. In the 4^{th} week of radiotherapy (when treatment-related symptoms are expected to peak)

i. A treatment week is defined as 5 consecutive days of radiotherapy. If a patient misses treatment for any reason his treatment week is shifted back one day.

c. Within a week of the last yoga class or by the end of radiation.

4. The International Index of Erectile Function Questionnaire (IIEF-5), also referred to as the Sexual Health inventory for Men (SHIM) will be used to assess ED and

SD. Scores range from 0 to 25. Scores (>20) indicate normal degree of erectile function. Scores 10> indicate moderate to severe erectile dysfunction. The IIEF will be completed by patients at the following time points:

a. Prior to start of radiotherapy i.e. on the day of consultation or on the day of simulation or setup.

b. In the 4th week of radiotherapy (when treatment-related symptoms are expected to peak)

    i. A treatment week is defined as 5 consecutive days of radiotherapy. If a patient misses treatment for any reason his treatment week is shifted back one day.

c. Within a week of the last yoga class or by the end of radiation.

5. The International Prostate Symptom Score Sheet (IPSS) will be used to determine the severity of enlarged prostate conditions and measures UI symptoms. Scores on this scale range from 0 to 35, where a score of 8-19 indicate moderately symptomatic, and 20-35 – severely symptomatic. The 8th question on this scale is on QOL and is assigned a score of 1 to 6, where 6 indicates terrible. The IPSS will be completed by patients at the following time points:

    a. Prior to start of radiotherapy i.e. on the day of consultation or on the day of simulation or setup.

    b. In the 4th week of radiotherapy (when treatment-related symptoms are expected to peak)

        i. A treatment week is defined as 5 consecutive days of radiotherapy. If a patient misses treatment for any reason his treatment week is shifted back one day.

    c. Within a week of the last yoga class or by the end of radiation.

6. Yoga interventions will consist of twice-weekly classes, 75 minutes each that will be offered by a yoga instructor. The simplified poses to be used in this study will

include seated (using a chair), standing, and reclining. Yoga poses can and will be modified based on each subjects specific needs and restrictions. Not all yoga poses will be performed each session. Each session will begin with breathing and centering techniques (taking inventory of the levels of energy, posture, stress, emotions, and breath). Yoga poses will consist of the following:

- Sitting on chair: neck and shoulder series (neck and shoulders side, front and back movements, shoulder rolls, and arms movement), table pose with opposite arm and leg movement, side bend (seated Parighasana), simple chair twist (Bharadvajasana).

- Standing poses: mountain pose (Tadasana Samasthithi), warrior II series (Virabhadrasana II), half moon (Ardha Chandrasana) variation at the wall, front warrior series, forward stretch/ bend variation (Uttanasana).

- Recline poses will include: inverted lake pose (Viparita Karani), bridge pose variation (Setubandha Sarvangasana), recline/ sited bound angle pose (Supta Baddhakonasana), camel pose (Ustrasana) at the wall, modified shoulder stand (salamba sarvangasana), reclining big toe posture with a belt (Supta Padangustasana), and corpse pose (Savasana).

3.3 Study Endpoints

3.3.1 Pilot Study

The primary goal of this pilot is to determine the feasibility of recruiting and retaining men into a clinical trial of yoga to improve fatigue and health related quality of life in prostate cancer patients undergoing radiation treatment. The endpoint is the number of evaluable patients accrued, with a minimum target goal of 15 of the first 75 eligible patients approached.

3.3.2 Randomized Phase II Study

3.3.2.1 Primary Study Endpoints

The primary goal is to determine the effect size of yoga on fatigue. The endpoint is the difference in BFI fatigue score between time points during radiation therapy and baseline prior to radiation.

3.3.2.2 Secondary Endpoints

The effect size of yoga on ED, UI and general QOL

4 Subject Selection and Withdrawal

4.1 Subject Recruitment and Screening

Patients will be recruited from the Perelman Radiation Oncology Center and will be assessed for eligibility before starting treatment. Patients will be pre-screened for barriers to participation in physical activity using the standard of care metric 'ECOG Performance Status'. All potentially eligible candidates will then be asked to take the Yoga in Prostate Cancer Study Questionnaire (**see appendix***) to assess baseline beliefs, goals and interest in study participation and approached with details of the clinical study to assess their eligibility and interest in enrollment. This survey would be offered to all prostate cancer patients seen in the department of radiation oncology during both the feasibility and randomized phases of the trial. The questionnaires from all patients who complete one will be analyzed as a separate, smaller part of the overall study to better understand barriers and promoters to enrollment. Patients and caregivers will be officially enrolled in the study only after eligibility is confirmed, the informed consent process is performed and relevant signatures are obtained.

4.2 Inclusion Criteria

Patients

1. Prostate cancer patients undergoing active radiation therapy (external beam radiation with photons and/ or protons). Prior or concurrent androgen deprivation therapy is permitted.

2. Patients of age ≥18 years, and all races will be included in the study.

3. Patients must have an ECOG Performance Score ≤ 1

4. All patients must sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of the University of Pennsylvania.

5. Patients must be English-speaking.

Caregivers

1. Subject is age ≥18 years
2. Subject is English-speaking
3. Subject must sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of the University of Pennsylvania.

4.3 Exclusion Criteria

Patients

1. Patients with medical restrictions that may interfere with or prevent them from taking part in the yoga interventions per their physician orders as evaluated by ECOG Performance Status score.

2. Active, regular cigarette smokers, such that smoking may interfere with relaxation and breathing modalities of the yoga interventions. (Smokers that have been smoke-free for 6 months may be included)

3. Patients who currently practice or have recently practiced yoga (taken a yoga class on a regular basis in the last 6 months).
4. Patients who are undergoing chemotherapy for any reason

5. Patients with evidence of metastatic disease

Caregivers

1. Subjects that are unwilling or unable to provide informed consent
2. Subjects with medical restrictions that may interfere with or prevent them from taking part in the yoga interventions
3. Active, regular cigarette smokers, such that smoking may interfere with relaxation and breathing modalities of the yoga interventions. (Smokers that have been smoke-free for 6 months may be included)
4. Patients who currently practice or have recently practiced yoga (taken a yoga class on a regular basis in the last 6 months).

4.4 Randomization

Both patients and caregivers will be randomized (without replacement) by lists created using small permuted blocks.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

The principal investigator may withdraw subjects if it is felt to be necessary for the health and safety of the subject. Additionally subjects may be withdrawn for not following study instructions. We expect up to 20% of subjects to drop out from the study due to time constraints, use of other CAM, and concurrent illness.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

All efforts will be made to connect with the subjects by mail and/or phone to better understand the reasons for the withdrawal and make an assessment for better future recruitment, as well as for a better implementation of the yoga interventions.

5 Study Drug

N/A

6 Study Procedures

Feasibility and Yoga Treatment Arm

Subjects will participate in two 75 minute sessions per week for the duration of radiation treatment with a yoga instructor offered for free by Patient Family Services in the Perelman Center of Advanced Medicine. Numerous sessions will be offered each week. Each session will begin with breathing and centering techniques (taking inventory of the levels of energy, posture, stress level, emotions, and breath). Yoga poses will consist of the following and can be modified based on patient needs: Sitting on chair: neck and shoulder series (neck and shoulders side, front and back movements, shoulder rolls, and arms movement), Table pose with opposite arm and leg movement. Side bent. Simple chair twist. Standing poses: Mountain pose, Warrior II series, Half Moon variation at the wall, Front warrior series, forward stretch/ bend variation with a chair. Recline poses will include: inverted lake pose (legs up the wall with a blanket for support), bridge pose variation, recline/ sited bound angle pose, modified Camel pose at the wall, modified Shoulder stand (legs up the wall with block support), reclining big toe posture with a belt, and corpse pose (Savasana – final rest). Modifications can and will be made based on

each subjects specific needs and physical restrictions. Poses will be added progressively. Not all poses will be done each session. Additionally subjects will fill out 4 types of QOL forms at various points during the study. The first is to be completed prior to start of radiation treatment, bi-weekly during treatment and within a week of the last yoga class or by the end of radiation

No Yoga Treatment Arm

Control patients who are randomized to standard of care will not undergo any yoga intervention or participate in any structured yoga program during the study duration. They will undergo cancer and side effect treatment per standard of care, and they will be asked to complete all study-related questionnaires at the same time points as the patients in the yoga treatment arm.

7 Statistical Plan

7.1 Design

This is a feasibility study followed by a seamless transition to a randomized phase II study.

7.1.1 Pilot study

Feasibility (aim 1) will be declared if we successfully accrue 15 evaluable patients of the first 75 approached. Patients participating in the feasibility portion of the study will move seamlessly into the phase II study. The data from these patients will be included in the phase II trial portion of this study. Given the number of prostate cancer patients historically treated in the Radiation Oncology department, we anticipate that this rate of enrollment would allow completion of the phase II trial within <3 years.

7.1.2 Randomized phase II trial

7.1.2.1 Sample size determination

Our goal is to estimate effect sizes for a larger study. We are setting our recruitment aim for phase 2 up to 48 subjects, a 20% increase from our target enrollment in order to account for potential subject drop out and arrive at N = 40. Inclusion of subject data from

the feasibility portion results in N = 55 up to N = 63 should subject attrition levels prove lower than expected. Two groups (35 v 20) give us power to estimate an effect size for yoga participation with a 95% confidence interval that is approximately 1.1 standard-deviations wide (compared to the SD of the raw measure). For the corresponding care-givers, two groups (20 v 20) give power to estimate a CI that is 1.3 SD wide. The effect will be measured as a time x treatment interaction (difference of difference scores). From our own preliminary data, and from Hwang et al. (2008), we know that the within subject correlation for fatigue measures is approximately 0.5, and that the SD for the difference score will be similar to that of the raw measure at individual time points. For the time x treatment interaction, we will be able to detect a standardized effect size of d=0.7 (0.8 for caregivers) at α=0.05 (one-sided) with 80% power.

7.1.2.2 Statistical Methods

This randomized study is a two-arm longitudinal controlled trial of yoga as a means of reducing fatigue over the course of radiation therapy for prostate cancer, with measures taken prior to treatment, during treatment, and in follow-up. The analysis will include the initial subjects from the feasibility study as an addition to the treatment arm, and we will control for any differences between the feasibility group and the randomized treatment arm using indicators. The primary measure, and most secondary measures, are Likert-style summary scores on a 0-10 scale and will be treated as Gaussian. The exception is retention, which is a binomial count of those remaining enrolled to the end.

Prior to performing analyses, standard data cleaning procedures will be applied (e.g., checking for outliers and data entry errors, creating summary scores for analysis, and checking that analysis assumptions are met). The assumptions underlying the statistical methods will be examined through the use of standard tests of normality, and graphical displays (27). All analyses will be conducted using Stata software (Stata Corporation, College Station, TX).

We will calculate descriptive statistics for all variables in the study. For outcome variables, we will summarize by treatment group (Yoga versus control) and by time point. We will also estimate correlations within subject for each of the study measures taken at different times.

The primary outcome for the randomized, phase II study will be the difference score of BFI fatigue while undergoing radiation therapy minus BFI fatigue prior to radiation. The primary hypothesis will be tested using a two-group t-test to compare difference scores between Yoga and control groups. This will be a one-sided test with type-1 error at a=0.05. Similar analysis will be conducted using BFI fatigue at follow-up versus pre-radiation, and for all of the FACT-G fatigue measures. We will test the difference using a one-sided z-test. The FACT-G analysis will be repeated for caregivers (Aim 4).

Effect sizes will be reported for all outcome measures as standardized differences. The effect size will reflect the time x treatment interaction, and the standard deviations will be adjusted for within-subject correlation to aid in designing a larger study.

7.1.2.3 Subject Population(s) for Analysis

Statistically evaluable subjects are those who have attended at least 50% of the available yoga sessions offered on the days they receive radiation treatment.

	Subject attends treatment	Subject misses treatment (inclement weather or machine downtime)
Yoga offered	Counts towards evaluability	Counts towards evaluability
Yoga session not offered	Doesn't count for or against evaluability	Doesn't count for or against evaluability

- All caregivers will follow the same evaluability guidelines as the radiation therapy population. If their associated subject undergoes treatment, the caregiver is also considered to have undergone "treatment".

3 Evaluable Sections

- 50 – 70% attendance rate
- 71 – 80% attendance rate
- > 80% attendance rate

8 Safety and Adverse Events

8.1 Assessing and Reporting of AE/ SAE's

Although we do not anticipate any adverse and serious adverse events occurring from participation in this trial, should any AE's or Serious Adverse Events (SAE) occur and are determined by the PI to be related they will be reported to the IRB and Data Safety and Monitoring Committee (DSMC) in accordance with the specific procedures of each entity. Should any SAE's or AE's occur they will be assessed using NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0)

8.2 Institutional Review Board (IRB) Notification by Investigator

All events meeting the Penn IRB Standard Operative Procedure for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:
(1) Unforeseen; and (2) indicate that participants are at increased risk of harm. The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**: an Adverse Event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the Principal Investigator is both unexpected and related to research procedures.

Note: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol,

any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; an event is "related to the research procedures" if the event is deemed probably or definitely related.

The **one exception** for prompt reporting within 10 days applies to death of a research participant. If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, a submitted report will be required within three working days.

All non-serious adverse events will be reported to the Principal Investigator via the toxicity care report forms. Further reporting details can be found in the accompanying manual of operating procedures.

8.3 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

Any expected, unrelated event that is a Grade 3 or higher should be reported to the DSMC within 10 days. All unexpected deaths or deaths related to the study agent or device need to be reported to the DSMC within 24 hours. All other AEs should be reported within 30 days of knowledge. Any SAEs, regardless of site, are to be reported to the Principal Investigator within 24 hours via telephone or email.

8.4 Abramson Cancer Center's Internal Data and Safety Monitoring

Data and Safety Monitoring Committee

The Abramson Cancer Center DSMC is charged with the responsibility of reviewing all SAEs, deviations, and Medical/Safety Monitoring reports for all cancer-based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data on a monthly basis and makes recommendation necessary to ensure subject safety and study integrity. The Department of Compliance and Monitoring (DOCM) will

monitor and audit the progress and conduct of all cancer-based studies in accordance with their National Cancer Institute-approved Institutional Data and Safety Monitoring Plan.

Protocol Exceptions/ Deviations

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

All exceptions/ deviations from the study protocol will be handled as follows:

An exception is a one time, **intentional** action or process that departs from the IRB and CTSRMC approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented IRB and DSMC approval is required

A deviation is a one time, **unintentional** action or process that departs from the IRB and DSMC approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

- **Non-Reportable -** During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. a subject not showing up for a study visit, laboratory errors, subject confusion, etc.). These types of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories), but they must be documented in a timely manner to show the impact of the deviation and corrective/follow-up **actions that are being** taken.

Documentation can be in clinic/progress notes or in notes/memos to file. Notes/memos should be signed and dated.

- **Reporting Deviations/Exceptions** - Reports to the IRB and DSMC will be done via the DSMC website at www.ctsrmc.org. Reportable deviations must also be sent to the study MM (if applicable). Please reference above section.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents

and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

Electronic case report forms will be developed and completed in Velos in lieu of paper case report forms with the exception of Eligibility and AE/SAE forms which will be printed out to be signed by the PI.

9.4 Records Retention

HIPAA Retention Period (45 CFR164.530(j):

Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 15 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 15 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 15 years after the research is fully terminated.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review.

This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is being funded by the Department of Radiation Oncology at the University of Pennsylvania.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

The University of Pennsylvania does not intend to provide payment for subject participation in this research study.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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Appendix A

Study ID: Date:

Yoga for Prostate Cancer
Study Questionnaire

You have been invited to participate in a research study because you are a prostate cancer patient here at the Perelman Center for Advanced Medicine, and your oncologist has recommended radiation therapy for your treatment. The purpose of this questionnaire is to better understand patients' interest in and barriers to participating in therapeutic yoga during their radiation therapy for prostate cancer. This is an anonymous questionnaire, so please do not put your name anywhere on this document. Participation is voluntary, meaning you may choose to participate or not. Choosing not to participate will not negatively affect the services and benefits to which you are otherwise entitled. There are no risks or benefits to completing this questionnaire. All information collected will be stored securely by the research team. You do not have to answer any question you do not want to answer, and you can stop the questionnaire at any time. If you choose to participate, completion and return of this questionnaire indicates your understanding and consent to the above conditions.

Yoga is a 5000 year-old spiritual tradition from India, and one of the most popular and commonly practiced mind-body therapies in the United States today. The following questions ask for your opinion about the use of yoga for cancer-related side effects.

Please do your best to answer each question. If a question is not clear, please let our study coordinator or Dr. Neha Vapiwala know. Thanks again for your time and interest!

1. Did you practice yoga before your cancer diagnosis?

- ☐ Yes
- ☐ No

2. Have you practiced yoga since your cancer diagnosis?

- ☐ Yes
- ☐ No

3. According to you, what does yoga involve? (Please check all that apply)

- ☐ Physical postures and stretching
- ☐ Breathing techniques
- ☐ Meditation and spiritual healing
- ☐ Exercise
- ☐ I have no knowledge of yoga

4. How interested are you in practicing yoga regularly?

Not at all interested ☐
A little interested ☐
Moderately interested ☐
Mostly interested ☐
Completely interested ☐

5. What prevents or would prevent you from practicing yoga regularly?

I find it difficult to practice yoga because…		Not at all agree	A little agree	Moderately agree	Mostly agree	Complete agree
I do not have interest in or knowledge of yoga	☐	☐	☐	☐	☐	
I cannot afford it	☐	☐	☐	☐	☐	
I am not flexible enough	☐	☐	☐	☐	☐	
I cannot bend or twist due to health reasons	☐	☐	☐	☐	☐	
My religious beliefs do not permit me	☐	☐	☐	☐	☐	
My job is very demanding	☐	☐	☐	☐	☐	
I have a lot of responsibilities at home	☐	☐	☐	☐	☐	

There are no yoga classes where I live	☐	☐	☐	☐	☐
Nobody in my family/friends practice yoga	☐	☐	☐	☐	☐
My oncologist never recommended it to me	☐	☐	☐	☐	☐
I had a bad experience in the past	☐	☐	☐	☐	☐

6. We are interested in performing a yoga study on improving cancer- and treatment-related side effects, specifically urinary and erectile dysfunction amongst prostate cancer patients. What is your level of interest in participating in this type of yoga study?

Not at all interested ☐

A little interested ☐

Moderately interested ☐

Mostly interested ☐

Completely interested ☐

7. Although most patients agree that clinical studies are important for improving medical knowledge and patient care, many do not participate in clinical studies. How much do you agree with the following statements related to participating in a yoga study?

I find it difficult to participate in a yoga study because….	Do not agree at all	Agree a little	Moderately agree	Mostly agree	Comple agree
I don't want to be part of an experiment	☐	☐	☐	☐	☐
I don't want to be in the 'placebo' (no yoga) group	☐	☐	☐	☐	☐
My job is very demanding	☐	☐	☐	☐	☐
I have a lot of responsibilities at home	☐	☐	☐	☐	☐

I don't trust medical researchers	☐	☐	☐	☐	☐
I don't want to share my private health information	☐	☐	☐	☐	☐
I cannot bend or twist due to health reasons	☐	☐	☐	☐	☐
I am not flexible enough	☐	☐	☐	☐	☐
My religious beliefs do not permit me	☐	☐	☐	☐	☐
I am not interested	☐	☐	☐	☐	☐
My physician or loved ones may not support my participation	☐	☐	☐	☐	☐

8. Each man with prostate cancer may have his own different hopes and expectations for how a yoga study could impact him. For each statement below, please pick the closest answer by checking the box:

If I participate in a yoga study, I hope and expect that…	Do not agree at all	Agree a little	Moderately agree	Mostly agree	Completely agree
My urinary and/or sexual side effects from my cancer and treatment would improve a lot	☐	☐	☐	☐	☐
I would be better able to cope with my side effects, even if they don't improve	☐	☐	☐	☐	☐
My energy level would increase	☐	☐	☐	☐	☐
My anxiety about my diagnosis and treatment would decrease	☐	☐	☐	☐	☐

Thank you very much for your time and thought in answering our questionnaire!

Sincerely,

The Yoga in Prostate Cancer Research Study Team