Status Page

PROTOCOL **13-056**

Closed To New Accrual

Closure Effective Date: 06/05/2017
No new subjects may be enrolled in the study as described above.
Any questions regarding this closure should be directed to the study's Principal Investigator

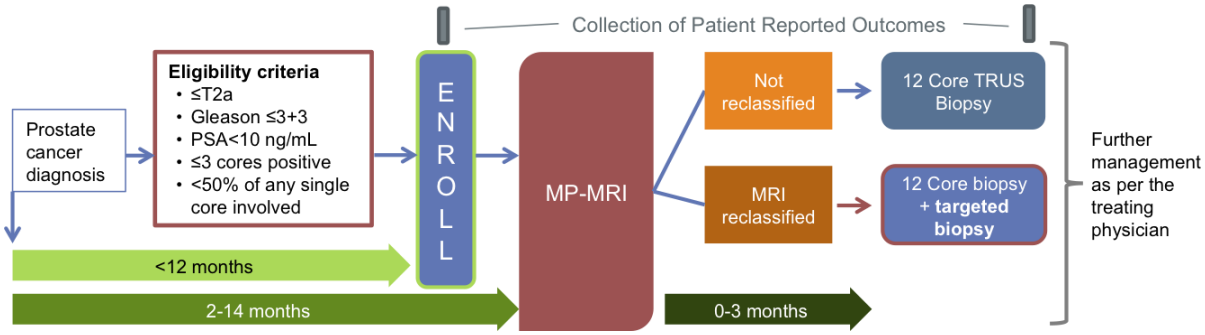
Protocol Version Date: November 25, 2014

Local Protocol #:13-056

Title: A phase II, prospective study of MRI in the reclassification of men considering active surveillance in prostate cancer

Principal Investigator:

SCHEMA


Collection of Patient Reported Outcomes
Prostate cancer diagnosis
Eligibility criteria
• ≤T2a
• Gleason ≤3+3
• PSA<10 ng/mL
• ≤3 cores positive
• <50% of any single core involved
ENROLL
MP-MRI
Not reclassified
MRI reclassified
12 Core TRUS Biopsy
12 Core biopsy + targeted biopsy
Further management as per the treating physician
<12 months
2-14 months
0-3 months

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1. OBJECTIVES

This study's primary objective is to determine the sensitivity and specificity of multiparametic, endorectal-magnetic resonance imaging (MP-erMRI) in classifying prostate cancer disease extent and grade relative to transrectal ultrasound-guided (TRUS) biopsy in men considering active surveillance (AS). We hypothesize MP-erMRI prior to AS for men with low risk disease can identify men who harbor more extensive or higher-risk prostate cancer. Identifying and treating these higher risk men early may result in better outcomes for both groups. Specifically, more men will remain on AS in follow up and those who are treated early will have better outcomes. We anticipate that correctly identifying individuals likely to remain on AS will make this initial treatment approach more appealing to men with newly diagnosed low-risk prostate cancer and to their physicians.

1.1 Study Design

A prospective, single arm study assessing the sensitivity and specificity of multi-parametric magnetic resonance imaging in identifying men whose disease will be upgraded on subsequent repeat biopsy in individuals with previously untreated prostate cancer considering AS.

1.2 Primary Objectives

Determine the sensitivity and specificity of MP-erMRI relative to repeat 12 core TRUS biopsy for classifying upgrading of disease extent or Gleason grade in men considering AS

1.3 Secondary Objectives

- Determine the frequency of MP-erMRIs which appear to reclassify men with low risk disease considering AS
- Determine effect of MP-erMRI and rebiopsy on patient-reported health states
- Correlate the pathology findings from a targeted biopsy with the MP-erMRI findings for those men who fall into the reclassified category.

2. BACKGROUND

2.1 Study Disease

Prostate cancer is a major cause of morbidity and mortality among men in the United States. Many men with prostate cancer have a slow growing tumor and experience an indolent course even without curative therapy [1]. The Scandinavian trial of radical prostatectomy versus watchful waiting [2, 3] demonstrated that definitive local therapy compared to observation alone decreases subsequent risk of metastases and prostate cancer death. However, 15 men had to have a surgical resection to prevent one cancer-specific death during a median 12 years of follow-up. Conversely, some men with apparently localized disease die of their cancer despite initial therapy because of the presence of undiagnosed micrometastases.
This biologic heterogeneity in prostate cancer has been brought into sharp focus as a result of widespread adoption of prostate specific antigen (PSA) screening in many countries, with a resulting marked migration towards the diagnosis of lower-risk prostate cancer [4]. There are now more than 240,000 men in the United

States diagnosed with prostate cancer each year [5], and 90 percent of prostate cancers are clinically localized at time of diagnosis [4]. Data from the randomized trials of PSA screening [6, 7] highlight the considerable overdiagnosis and overtreatment of men with screen-detected prostate cancer with very low prostate-cancer specific mortality rates in modern series [8-10].

In this setting, there is an increasing recognition that some men may defer or even avoid treatment. This strategy of AS focuses on closely monitoring patients and intervening only when their disease becomes clinically significant. This stands in contrast to the watchful waiting approach used in the Scandinavian study, where men are simply observed and palliative treatments are instigated when necessary [3]. For AS, the aim is to intervene with curative intent at the time of disease progression. Given the long natural history of low-risk disease [11], this strategy could both spare many men the morbidity associated with surgery or radiation and provide significant cost savings [12] without negatively affecting cancer-related death rates.

While many groups have prospectively explored AS [13-18] with generally excellent clinical outcomes, significant questions remain regarding which men are most suitable for AS and what thresholds for treatment should be utilized.

The success of AS is predicated on several assumptions. The ability to reliably: (*1*) identify men who are at a low-risk of having incurable disease at diagnosis, (*2*) identify men unlikely to progress to incurable disease in the interval between visits, and (*3*) identify clinical or pathologic features from biopsy suggesting the need for immediate definitive local treatment. All three of these remain challenging and likely reduce the number of clinicians and patients who feel comfortable with AS. In this protocol, we aim to better identify men most likely to continue on AS, and therefore those most likely to benefit from this approach.

As summarized in the tables, several groups have published their experience with AS. Typically, men with low-risk disease have been selected for AS (**Table 1**), followed with PSAs and rebiopsies every 1-2 years (**Table 2**), and with limited follow-up, have been shown to have excellent cause-specific survival rates (**Table 3**).

Table 1: Eligibility Criteria for Reported Prospective Studies (after[23])

	T stage	Gleason	PSA	cores positive	PSA density
Royal Marsden [16]	T1c-T2a	≤ 3+4	≤ 15	≤ 50%	NA
University of Miami [19]	T1-T2	≤ 6	≤ 10	≤ 2 cores; ≤ 20% of any core pos	NA
Johns Hopkins [18]	T1	≤ 3+3	NA	≤ 2 cores; ≤ 50% of any core	≤ 0.15 ng/mL/mL
UCSF [17]	≤ T2	≤ 3+3	≤ 10	≤ 33% of cores pos; ≤50% of any core	NA
University of Toronto [20]	NA	≤ 6 (age >70 ≤ 3+4)	≤ 10 (age>70, ≤ 15)	NA	NA
European Randomized Screening Study [21]	Tc-2	≤ 3+3	≤ 10	≤ 2 cores pos	≤ 0.2 ng/mL/mL
MSKCC [22]	≤ T2a	≤ 3+3	≤ 10	≤ 3 cores pos; ≤ 50% of any core	NA

Disease Extent

Broadly, two types of failure of AS as an initial management strategy can be considered: (*1*) development of incurable disease or (*2*) relatively rapid reclassification of the patient from low-risk to higher risk necessitating definitive treatment. Longer follow-up will be needed to better identify the first group as most series have reported low rates of metastatic disease or prostate cancer specific mortality. Lacking randomized studies comparing follow up approaches, the second group has been identified variously (**Table 2**) but typically with either a rise in the PSA or an increase in the tumor grade or volume. Both markers are associated with disease progression but decision making around small changes in PSA rely on untested assumptions [24] regarding the relationship between PSA and tumor volume, location or aggressiveness. Unlike PSA, where one would have to

predict future trends, the amount and grade of disease present at diagnosis is thought to be simply undersampled using current diagnostic approaches [25-27].

Table 2: Follow-up Protocol

	PSA/DRE	Rebiopsy	Indication for Radical Treatment
Royal Marsden[16]	q3mo x 2 yr; q6mo after 2 yr	at 1 yr and then q 3 yr	PSA velocity >1ng/mL/yr Gleason ≥4+3 >50% Cores positive
University of Miami[19]	q3-4 mo x 2 yr; q6mo after 2 yr	At 6-12 mo and as clinically indicated thereafter	Gleason >3 Increase in tumor volume (% of cores pos or amount of tumor within a core)
Johns Hopkins[18]	q6mo	q1yr	Gleason >6 > 2 cores; >50% of any core
UCSF[17]	q3mo	U/S: q6-12 mo bx: q12-24 mo	PSA velocity >0.75 ng/mL/yr Gleason grade increase
University of Toronto[20]	q3mo x 2 yr; q6mo after 2 yr	At 6-12 mo; q3-4 yrs until pt 80	PSADT <3yr Gleason upgrade Clinical progression (volume)
European Randomized Screening Study[21]	Per center	Per center	Per center
MSKCC[22]	q6mo	Immediate confirmatory At 12-18mo and then q2-3 yrs	PSA >10ng/mL Gleason >6 T>2a >3 cores positive or >50% of any core positive

Entry Criteria

Critical to avoiding reclassification based on disease grade or extent is the ability to accurately select men likely to harbor low-risk disease. Early work by Epstein et al at. at Johns Hopkins found clinical factors associated with very low volume, low grade disease [28] which are now incorporated into practice guidelines from the National Comprehensive Cancer Network. These factors include a T category of T1c, Gleason grade of 6 or lower, two or fewer prostate biopsy cores positive for cancer, none of which have >50 percent tumor involvement and a PSA density ([PSA]/prostate volume on transrectal ultrasound) of less than 0.15 ng/mL/mL. While Johns Hopkins has adopted similar criteria for entry into their AS protocol, other groups have been less restrictive (**Table 1**). Nomograms now exist which predict men likely to harbor low volume, low risk disease [29-31] though how these should be applied to selecting men for AS remains to be determined.

The challenge at the time of diagnosis remains that the standard 12 biopsy is inadequate to accurately predict the final Gleason score secondary to sampling errors [25-27]. Reported rates vary widely but it is estimated that approximately one-third of cases are upgraded on Gleason between the diagnostic biopsy and a radical prostatectomy [26]. Confidently identifying men at diagnosis likely to have organ-confined disease at the outset is thought to be important as extracapsular extension (ECE) or seminal vesicle invasion (SVI) at the time of local therapy are associated with a poor outcome [32]. A systematic review of surgical outcomes for men with very limited disease extent on diagnostic biopsy suggests that adverse pathologic findings such as ECE are present in up to 50% of cases though much of the data was from 10 or more years ago with fewer biopsy samples taken [33]. Exploring the rates of ECE or SVI among large surgical cohorts categorized by whether they met entrance criteria for the various AS protocols, groups have found rates of 7 percent ECE for the Johns Hopkins criteria which is the most restrictive to 18 percent for the Royal Marsden criteria which is

Table 3: Reasons for active treatment and outcomes across reported series (after[23])

most permissive [25]. Taking the same approach of retrospectively comparing a surgical cohort to the various published AS protocol entry criteria, Gleason upgrading was noted in 23-35 percent of men and seminal vesicle involvement was seen in between 2 and 9 percent depending on the study entrance criteria. Other recent studies

have found that using the Epstein criteria, more than 10% of men treated with prostatectomy have disease reclassification [25, 34] highlighting the need for additional markers of disease extent.

				Reason for treatment overall - %			Outcomes - %			
	n	Median F/U - mo	Treatment at 2 yrs - %	Gleason	PSA	No progression	OS	CSS	PFS	Failure after local therapy
Royal Marsden[16]	326	22	27	10	13	2	98	100	73	5
University of Miami[19]	230	32	~7	10	NA	NA	100	100	86	0
Johns Hopkins[18]	633	32	20	14	NA	9	98	100	54	9
UCSF[17]	376	47	15	9	7	8	97	100	54	1
University of Toronto[20]	450	82	16	9	14	3	68	97	70	50
European Randomized Screening Study[21]	616	52	~18	NA	12	18	91	99	68	NA
MSKCC[22]	238	22	16	13	14	11	NA	NA	NA	NA

Rebiopsy

In light of the significant sampling errors in the classification of men considered appropriate for active surveillance, repeat biopsy in follow up has been used as a component of surveillance protocols. Memorial Sloan Kettering Cancer Center adopted a strategy of recommending immediate rebiopsy for all men considering AS at their institution [35]. Between 2002 and 2007, 104 men who met eligibility criteria for AS at Memorial Sloan Kettering Cancer Center (**Table 1**) underwent immediate 14-core rebiopsy [35]. Among these rebiopsies, 26% had no cancer identified. For those with cancer on the rebiopsy, 77% had Gleason ≤6, 22% had Gleason 7 and one man had Gleason 9. From the standpoint of upstaging of disease extent, 13% were found to have >3 cores positive and 16% had >50% of any core involved. In total, 27% had either upstaging or up-grading on the biopsy. A subset of these men, 64%, had an erMRI prior to re-biopsy with 27% showing a finding concerning for ECE. None of the men without evidence of ECE were up-staged or upgraded compared to 39% among those with concerning MRI features. A subsequent analysis showed that those men without cancer identified on the confirmatory biopsy were less likely to progress to definitive treatment over the course of the study [22]. Other retrospective analyses show similar results [36, 37]. In line with these results, the first biopsy following diagnosis has tended to result in the greatest number of men being upgraded on AS protocols [38, 39].
Though biopsy remains the gold standard for reclassification, it carries what appear to be increasing risks [40, 41]. Highlighting the short-term effects, in one recent report of nearly one thousand men who had undergone biopsy, 44% noted pain, 66% had hematuria, 37% had hematochezia, 93% had hemoejaculate and 18% had fever in the days following the procedure [42]. Many of these symptoms were not considered moderate or serious problems by the participants though 15% had some pain and 3% had fever two weeks or more after the biopsy. Significantly, the rates of hospitalization for infections following prostate biopsies appear to be increasing [40, 43, 44]. Though the absolute rates of sepsis following biopsy remain low [42, 43], the increasing risk appears to be related to resistance to antibiotics used in pre-biopsy prophylaxis [41, 45]. These findings highlight that approaches other than frequent, repeated biopsies will be necessary to classify men as candidates for AS.

Prostate MRI

MRI has been investigated as a non-invasive method to determine disease extent and provide insights into disease progression in prostate cancer [46]. Endorectal MRI has been shown to have variable sensitivity and specificity for tumor localization, extracapsular extension and seminal vesicle invasion [47-51]. While MRI can provide excellent morphologic information regarding the prostate, it also has the capacity to evaluate physiologic properties. Using diffusion-weighted images (DWI) and dynamic contrast-enhanced (DCE) imaging, multi-parametric (MP)-MRI may be better at correlating with disease risk [52] and localization [52-54]. Several groups have published on the use of MP-MRI in active surveillance populations [55]. MP-MRI may be better at correlating with disease risk and localization [56].

The group at the Royal Marsden reported on 80 men in their cohort of 326 on AS who had a diffusion-weighted (DW) MRI and a repeat biopsy as part of the protocol [55]. They found that the apparent diffuse coefficients (ADCs) were significantly correlated with adverse findings on repeat biopsy and on univariate analysis, was associated with a hazard ratio of 3.38 (95% CI 1.65-6.94) for progression to radical treatment. Ploussard reported a series of 96 patients who had low, but not very low risk disease who had undergone 21 core biopsies and subsequent erMRI prior to prostatectomy [57]. This was a T2-weighted MRI without contrast. Of the 68 men (82%) with radiographic T1 or T2 disease, 18% had pathologic T3 or T4 disease and 39% had Gleason upgrading. These data suggest that in slightly higher risk men, a standard T2-weighted MRI may be insufficient to accurately reclassify men considering AS.

More specifically, the group from Princess Margaret Hospital reported on a prospective AS protocol in which all men received multi-parametric MRI at the time of enrollment to assess its role in reclassifying their disease [58]. In this study, 60 men with T1c, Gleason 6, PSA <10 ng/mL, ≤3 cores involved and <50% involvement of any one core were enrolled. The 1.5 Tesla MRI was interpreted to classify men into three groups: (1) those with no visible tumor, (2) those with tumor ≤1 cm in size, and (3) those with tumor >1 cm (used to correspond to Epstein criterion for clinically significant disease). Those with either no tumor visible or with a tumor ≤1 cm in size were asked to undergo a repeat biopsy at approximately one year after initial diagnosis. Those with lesions larger than 1 cm were asked to undergo an immediate repeat biopsy using a TRUS approach targeting the area of interest [59]. Reclassification was defined as Gleason 7, more than 3 positive cores or more than 50% of any one core involved. The overall reclassification rate was 32%, with 77%, 25% and 9% in groups 3, 2, and 1 respectively. Groups 3 and 2 had a higher mean number of biopsies than group 1 (16.2, 15.3 and 12.3 respectively). Half of the reclassifications were for Gleason 7 disease on rebiopsy and this finding was significantly more common among those with larger MRI lesions.

Given differences in how the groups were treated in this study, more biopsies in those with larger lesions and targeted biopsies for those with larger lesions, we aim to further clarify the role of MP-MRI in reclassifying men considering AS. We will specifically evaluate the accuracy of MP-MRI relative to standard TRUS biopsy as that has remained the gold standard for disease classification in men followed on surveillance in the published literature. If MP-MRI could replace repeat biopsy for men considering AS, it could have a dramatic impact on successfully selecting men likely to safely remain on surveillance.

Patient-reported outcomes in active surveillance

Up to one-third of men who initially opt for AS for management of their low risk prostate cancer may seek definitive treatment in the absence of clinical progression; instead citing patient preference, progression of urinary symptoms such as lower urinary tract symptoms (LUTS), or due to anxiety and distress [60-64]. Van den Bergh and colleagues hypothesized that men with prostate cancer on AS, who essentially live with untreated disease, may experience overwhelming feelings of anxiety and distress [65]. They found than in a population of 150 men with recently diagnosed prostate cancer who had selected AS, that patients reported lower anxiety and distress scores than anticipated. Of the 7% of men who opted to cease AS and move onto definitive therapy for personal reasons, cited causes included anxiety and fear of prostate cancer

progression[66]. Recently, AS protocols are increasingly incorporating validated assessments of health-related quality of life (HRQOL) including urinary and sexual function, as well as psychosocial measures including uncertainty, anxiety, distress, satisfaction with cancer care into their evaluations of patients as they present for their prostate cancer monitoring.

Dall'Era reported that 33 percent of men on AS protocols at large oncology centers in multiple countries will subsequently switch to active treatment within 3-5 years of diagnosis, but also found that patient-reported HRQOL outcomes in men on AS are similar or better than those reported by men having undergone immediate radical therapy [67]. Kakehi and colleagues found no differences in general HRQOL between men who remained on AS and those undergoing radical prostatectomy after one year [62]. However they did note that the men on AS reported worse urinary function, sexual function, and bowel bother scores in comparison to their baseline levels after one year. Arredondo and colleagues found that, over 5 years, decreases were noted in all domains of HRQOL in 224 men on AS or watchful waiting [68]. Even when controlling for age, men on conservative management regimens appeared to have worsening perception of overall health and sexual function. Most recently, Vasarinen and colleagues reported that AS dose not provoke short-term disturbances in HRQOL and found that no patients in their series changed treatments due to anxiety; nor did they find changes in urinary function by the IPSS or in erectile function using the IIEF-5 questionnaire [68]. In comparison to an age-stratified Finnish population, patients with prostate cancer on AS reported better general mental and physical HRQOL at diagnosis and after 1 year of follow-up. Although more recent studies suggest that the impact of AS on a patient's overall health and psychosocial wellness may not be as great as was previously hypothesized, evaluation of patient's baseline HRQOL may predict better adherence with AS in the absence of clinical progression as certain factors such as baseline poor perception of physical health, high neuroticisim scores on personality assessments, high depression, and baseline anxiety scores appear to correlate with increased likelihood of changing from AS to definitive treatment, even without objective evidence of clinical progression [66].

Indeed, understanding of the morbidity of the surveillance measures employed in prostate cancer AS protocols is increasing and the importance of tracking these measures is being increasingly appreciated. Objective measurement of bowel, bladder, and erectile function in patients undergoing serial examination and biopsy may be helpful in predicting which men may not tolerate AS well, thereby assisting patient counseling and facilitating decision-making. There are few studies which have tracked HRQOL metrics over time in men on AS to better understand the magnitude of the role that HRQOL and psychosocial factors play in decision making as well as selection of treatment choices. To our knowledge, no studies to date assessing the incorporation of MRI into the patients' selection calculus for AS have incorporated patient-reported HRQOL in their analysis.

2.2 Rationale

In this study, our aim is to determine the sensitivity and specificity of MP-erMRI as it relates to initial re-biopsy among men with low-risk disease considering AS. Of the criterion used to take men off of AS, disease extent and grade appear to be under-assessed using current approaches. Lacking the full surgical specimens available from prostatectomy, repeat biopsies are the existing gold standard for classifying disease extent and grade. Comparing MP-MRI to the current standard of care, TRUS biopsy, we will specifically address the role of MP-erMRI in assessing men with low-risk disease for AS. We anticipate that the MRI will identify lesions of concern in up to one quarter of men. To assess the MRI accuracy, men with non-concerning MRIs and MRIs suggesting more extensive or higher-grade disease will both undergo TRUS biopsy. Men whose MRI shows an abnormal lesion will also have an immediate for-cause, guided biopsy to assess the lesion at the time of the

standard TRUS biopsy. This approach both addresses the scientific question of the study and safely identifies men with more extensive or aggressive disease.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 The subject will have histologically confirmed prostate cancer with all of the following features:

3.1.1.1 Minimum 10 core prostate biopsy showing histologically-confirmed prostate cancer within 12 months of enrollment reviewed by a pathologist from one of the DF/HCC associated hospitals

3.1.1.2 Gleason ≤3+3

3.1.1.3 No tertiary Gleason grade ≥4

3.1.1.4 ≤3 total cores positive

3.1.1.5 ≤50% of any given core involved with cancer

3.1.1.6 No evidence on biopsy of extracapsular extension

3.1.2 PSA within 4 months prior to study consent or within 30 days after study consent: <10 ng/mL

3.1.3 Clinical stage: ≤T2a & N0 or NX & M0 or MX

3.1.4 The subject is able and willing to abide by the study protocol or cooperate fully with the investigator or designee

3.1.5 The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document

3.1.6 Age ≥18

3.1.7 Life expectancy of greater than 10 years

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 First diagnosis of prostate cancer > 12 months prior to enrollment
3.2.2 Prior prostate cancer-directed therapy including:

3.2.2.1 androgen deprivation therapy

3.2.2.2 radiation therapy to the prostate (external beam or brachytherapy)

3.2.2.3 cryotherapy

3.2.2.4 high-intensity focused ultrasound (HIFU)

3.2.2.5 chemotherapy for prostate cancer

3.2.3 Prior transurethral resection of prostate

3.2.4 Subject who is deemed by the treating physician to have a contraindication to definitive treatment

3.2.5 Subjects with a contraindication to an MRI including those with a pacemaker, ferromagnetic aneurysm clip, or cochlear implants

3.2.6 Subjects with a contraindication to receiving Gadolinium containing contrast for the MRI

3.2.7 Conditions which make repeat TRUS biopsies not feasible

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

The only patient population which is excluded from this study is women by virtue of the fact women do not get prostate cancer. All other populations are potentially eligible for enrolment

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	0	+	10	=	10
Not Hispanic or Latino	0	+	120	=	120
Ethnic Category: Total of all subjects	0	+	130	=	130
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	8	=	8
Black or African American	0	+	8	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	0	+	114	=	114
Racial Category: Total of all subjects	0	+	130	=	130

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

N/A

4.4 Registration Process for Other Participating Institutions

N/A

5. TREATMENT PLAN

This is a single arm, prospective protocol investigating the sensitivity and specificity of MP-erMRI in assessing disease extent and grade relative to initial re-biopsy in men with low-risk prostate cancer who select AS as their initial treatment strategy. Following enrollment and registration, subjects will complete baseline patient-reported health state questionnaires.
Between 2 and 14 months following initial diagnostic biopsy, they will undergo a MP-erMRI. This will be systematically reviewed and men will be characterized into three groups: (*1*) "not reclassified" characterized by findings consistent with small, low-Gleason grade organ-confined tumors, (*2*) "reclassified" characterized by large, higher-Gleason grade organ-confined tumors, and (*3*) radiographic T3 and/or N1 disease. Those in group 3 will come off of protocol and proceed to management as per their treating physician. Those in groups 1 and 2 will proceed within 3 months of the MRI to a standard 12-core TRUS biopsy. For those in group 2 at the time of TRUS biopsy, they will also have a for-cause targeted biopsy of the lesion seen on MP-MRI. All men in groups 1 and 2 who do not have their disease reclassified with the TRUS biopsy or for-cause biopsy will proceed with AS as per their treating physician. Those who are pathologically reclassified will be managed per their treating physician. All study participants will come off study after the end of study visit that occurs within 60 days following the final biopsy.

Information about participants will be gathered according to the study calendar.

5.1 Patient-reported health states

Participants will be asked to complete patient-reported health state questionnaires at enrollment and following the final on-protocol biopsy. The questionnaire that will be provided to participants for self-administration will include the following:

- *The Mishel Uncertainty in Illness Scale Community Form for Active Surveillance* (MUIS-AS, Appendix A). The MUIS-AS will evaluate uncertainty, anxiety, and distress associated with the patient's cancer diagnosis.
- *The Service Satisfaction Scale for Cancer Care* (SSS-Ca, Appendix B). The SSS-Ca will evaluate the patient's satisfaction with both the process and outcome of their cancer related care.
- *The Expanded Prostate Cancer Index Composite – Clinical Practice* (EPIC-CP, Appendix C). The EPIC-CP is used to evaluate urinary and sexual function following treatment for prostate cancer. This will specifically be useful in order to assess the progression of urinary symptoms

overtime in these participants who may be required to undergo serial prostate biopsies, endorectal MRI, etc.

- *The American Urological Association Symptom Index* (AUA SI, Appendix D), which will be used to evaluate overall urinary bother and function

Questionnaires will be given to participants at their enrollment visit and at the end of study visit following biopsy. Participants will be instructed to complete them independently and to return them by mail to the project coordinator.

5.2 Multiparametric MRI

Between 2-14 months following the initial diagnostic biopsy, participants will undergo an endorectal prostate MRI. A 2-month delay from the initial biopsy is preferred to minimize the effects of post-biopsy hemorrhage. All MR examinations will be performed on a 3T whole-body scanner possessing a whole-body gradient coil set with sufficient strength and speed to perform an optimized MP-MRI, a whole body transmit/receive coil, an external rigid phased-array torso coil, and an MR-compatible power injector for administering intravenous contrast. A compatible endorectal coil will be used for phased-array/ecoil measurements. All studies will be obtained with the image plane perpendicular to the rectal wall/prostate interface.

5.2.1 Protocol:

5.2.1.1 The standardized 3T pulse sequences we will use will include fast spin echo (FSE) for T2 weighted-images (FOV: 14-18cm; slice thickness: 3mm; spacing: 3mm; TR/TE: 3000/102 msec; Matrix: 384x256; NEX=3). Dynamic Contrast Enhanced (DCE) imaging will be performed with 3D-Fast spoiled gradient (FSPGR) images using FOV: 26 cm; slice thickness: 6mm; spacing: 6mm; Matrix: 256x160; contrast (Gadolinium gadopentetate (Gd)) injection rate of 3mL/sec; slab thickness 16-20 slices, 5 sec/volume, repeat 60 times, with a total scan time of 5 minutes. Pharmacokinetic analyses of each slice will be performed using a custom research tool (OncoQuant, GE Global Research) using a population averaged bi-exponential arterial input function augmented with a first pass peak[69]. Single shot echo planar diffusion weighted imaging (DWI) will be performed using b values of 0 and 500, and 0 and 1400 with trace ADC maps generated at all b values.

5.2.2 Image Interpretation:

5.2.2.1 Images will be reviewed within the radiology department where the scans were obtained as per current protocols and a standard clinical report will be produced. Images will subsequently be analyzed by study radiologists with extensive experience in GU imaging. The images will be evaluated according to the proposed PIRADS scoring system guidelines. This will specifically look at signal intensity on T2 weighted image (with a discrete, homogenous low signal focus being suspicious for tumor). For DCE, both semi-quantitative and quantitative parameters will be evaluated, with particular attention paid to the dynamic enhancement curve type [70]: (type 1, persistent increase; type 2, plateau; and type 3, decline after initial upslope; type 3 being considered the most suspicious for

prostate cancer, particularly in the presence of a focal asymmetric enhancing lesion). Pharmacokinetic modeling, which will produce quantitative indices [such as K^{trans} (forward volume transfer constant) and v_e (fractional extracellular space)], will be incorporated into the analysis. DWI will also be scored according to signal intensity on high b value image (≥b1000) and values obtained on ADC map. Index lesion size will be measured on T2WI to categorize those ≥ or< 1 cm in size. Extracapsular extension (ECE) and seminal vesicle invasion (SVI) will also be evaluated for.

The interpretation of the MRI will place participants into the following categories:

1. **Not-reclassified**: any identified abnormality of the MRI is confined to the gland without definitive evidence of ECE or SVI. Additionally, no lesion is greater than 1 cm in size nor do any identifiable lesions have characteristics of high Gleason grade.
2. **Reclassified**: Disease appears to be confined to the prostate (no ECE or SVI) but one or more lesions appear either >1 cm in size or have imaging characteristics concerning for higher Gleason grade disease.
3. **T3 or N1:** disease appears to be clearly extending outside the prostate and/or into the seminal vesicles or there is evidence of pathologic involvement of lymph nodes.

If the MRI places a subject into the T3/N1 category, they will meet criteria for coming off protocol and will then receive further treatment per their treating physician. If a participant is in either the **not-reclassified** or the **reclassified** categories, they will proceed with the planned biopsy.

5.3 Prostate biopsy

All subjects who remain on protocol following the MP-MRI will undergo an on-protocol TRUS biopsy within 3 months of the MRI. This biopsy will therefore take place between approximately 2-17 months following their initial diagnostic biopsy.

5.3.1 Prophylaxis

5.3.1.1 Participants will be recommended to receive oral or IV antibiotic prophylaxis according the American Urologic Association Guidelines (http://www.auanet.org/content/media/antimicroprop08.pdf) and as per the standard of the institution. Further, anticoagulant or antiplatelet directed therapy will be managed prior to biopsy as per the standard of the participating institution.

5.3.2 TRUS Biopsy Sampling

A 12-core biopsy will be performed without specific targeting of lesions noted at the time of MRI. This approach is intended to provide an unbiased assessment of the accuracy of MP-MRI in predicting men reclassified based on the current gold standard TRUS re-biopsy. Each core will be individually labeled with laterally and anatomic site within the prostate.

5.3.3 Targeted rebiopsy

Participants in the **reclassified** category will have both a 12-core TRUS biopsy unguided by the results of the MRI and a biopsy targeting the lesion(s) of concern from the scan. The rationale for doing both biopsies is that to compare the MRI findings to the current gold-standard, a non-targeted TRUS biopsy, we need to include this regardless of the MRI findings. Because this biopsy may not capture the lesion noted on the scan, a targeted biopsy will be performed at the same time. The targeted biopsy will be performed according to the practices of the treating institution but will generally consist of conscious sedation with either an MRI-guided biopsy or a TRUS-guided biopsy directed based on images fused to the MRI. The number of cores taken will be at the discretion of the physician performing the biopsy. Standard of care transrectal ultrasound imaging (TRUS) may be augmented with the setup needed for spatial tracking of the TRUS images. The purpose of this is to facilitate research in spatial mapping biopsy samples within the prostate gland, and to aid with correlation of pathology analysis of the samples with TRUS and MRI imaging data. The tracking setup would be enabled by a tracking system consisting of an electromagnetic field transmitter that establishes the coordinate frame for tracking volume, and several sensors. The transmitter would be mounted on an articulated arm to the patient bed. One sensor will be attached to the handle of the TRUS probe before the procedure. The sensor will remain on the handle outside the patient at all times. The second sensor will be attached with the medical tape to the back of the patient. Prior to TRUS imaging, a calibration procedure may be necessary. If needed, such procedure would involve placing the TRUS probe in a water bath and imaging of a phantom, prior to the patient procedure. This component of the biopsy is not anticipated to add any additional risk or toxicity to the protocol.

5.3.4 Pathologic assessment

5.3.4.1 All specimens will be formalin fixed and paraffin embedded as per usual clinical care. Pathology will be reviewed by a pathologist with GU expertise for Gleason grade, disease extent, and number of cores positive. Additional features such as perineural invasion and high-grade PIN will be noted though these will not be used to determine continued protocol eligibility. Each of the cores will be labeled for biopsy location at the time of procedure and will be individually reported. Pathology will be reviewed at the treating center. Specimens will also be labeled as to whether they came from the TRUS biopsy or the targeted biopsy

5.3.4.2 TRUS Biopsy: Participants will come off study if they no longer meet eligibility criteria following rebiopsy:

- >3 cores positive for cancer
- >50% of any single core containing cancer
- any Gleason >3+3

5.3.4.3 Targeted Biopsy: Participants will be considered pathologically reclassified if either of the following criteria are met on the targeted biopsy:

- Gleason >3+3
- >7mm of any core involved with cancer

In this situation, using the criteria of number of cores involved with cancer will no longer be comparable across participants as the number of cores sampled will be variable based on the situation.

5.4 PSA

During the time that participants are on study, a PSA will be drawn as per the treating physician (typically every 3-6 months). A change in PSA will not be a criterion for discontinuation of this protocol though may be used clinically to change management at the discretion of the treating physician.

5.5 Duration of Follow Up/End of Study Visit

Participants will also be followed until their final study visit which will occur up to 60 days after the final biopsy.

5.6 Criteria for Removal from Study

Participants will be removed from the study when any of the criteria in section 5.3.3 or 5.3.4 applies. Additional criteria for removal from the study:

- Participant withdraws from the study
- The patient proceeds to prostate-cancer directed therapy
- Death from any cause
- General or specific changes in the participant's condition which render them unacceptable for completion of the protocol in the opinion of the treating investigator.
- Intercurrent illness that prevents completion of the protocol
- Investigator discretion

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Toxicity assessments will be done using CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the enrollement, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

6.1.1 Biopsy

Prostate biopsies are generally well-tolerated outpatient procedures. In addition to anticipatory anxiety, participants are at risk of the following complications:
Common (occurring in 20 to 90 out of 100 participants)

- mild discomfort (44%)
- hematuria (66%)
- hematospermia (93%)
- hematochezia (37%)
- fever (20%)

Occasional (occurring in 1 or 2 our of 100 participants)

- persistent bleeding (1-2%)
- urinary retention (<1%)
- infection requiring hospitalization (1-2%)

6.1.2 MRI

Participants may experience frustration or anxiety related to the time spent obtaining the MRI. Participants will also be at risk of the typical reactions from MRI with gadolinium contrast administration:
Occasional (occurring 2 or 3 out of 100 participants)

- Mild nausea (with or without vomiting), tingling sensation, headache, dizziness, coldness at the injection site, headache, warmth or pain at the injection site, paresthesias, dizziness and itching.

Rare (occurring in 1 participant or less out of 100)

- Severe anaphylactic reaction
- Severe nephrogenic systemic fibrosis (NSF) in participants with chronic renal insufficiency

7. STUDY CALENDAR

	Pre- Study	MRI Visit (2-14 months post initial biopsy)	Final Bx visit (within 3 months of MRI visit)	End of Study Visit (within 60 days of final bx)
Informed consent	X			
History[a]	X			
Pathology review	X[b]		X[d]	
PSA	X[c]			X[e]
Concurrent meds	X			
Height and weight	X			
Performance Status	X			
Patient-reported health	X[f]			X
Adverse event evaluation		X ---------- X		X

a: biopsy date, clinical T-category, was the subject staged with a CT of the abdomen and pelvis; was the subject staged with a bone scan; ACE-27 Comorbidity index (Appendix E)

b: DF/HCC pathology review of original biopsy (no. cores taken, no. cores positive for cancer; % involvement for each positive core; Gleason grade for each positive core; presence and grade of tertiary Gleason grade; evidence of extracapsular extension; evidence of perineural invasion)

c: last PSA level prior to biopsy diagnosing the prostate cancer

d: DF/HCC pathology review of "random" and targeted biopsy (as needed) (no. cores taken, no. cores positive for cancer; % involvement for each positive core; Gleason grade for each positive core; presence and grade of tertiary Gleason grade; evidence of extracapsular extension; evidence of perineural invasion)

e: most recent PSA value

f: MUIS-AS, Appendix A; SSS-Ca, Appendix B; EPIC-CP, Appendix C; AUA SI, Appendix D

8. ADVERSE EVENT REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

8.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

- respite care

8.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

8.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

8.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

8.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

8.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

8.3 Reporting to the Study Sponsor

8.3.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial study procedure, or within 30 days of the last study procedure treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Within the following 24-48 business hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

8.3.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

8.4 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

8.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

8.6 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

9. DATA AND SAFETY MONITORING

9.1 Data Reporting

9.1.1 Method

The QACT will collect, manage, and monitor data for this study.

9.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

9.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

9.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the

protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

10. REGULATORY CONSIDERATIONS

10.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

10.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given 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.

10.3 Ethics and Good Research Practice

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

10.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

10.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Primary Objective

The primary objective is to determine the sensitivity and specificity of Mp-erMRI relative to repeated standard 12-core TRUS biopsy for classifying upgrading of disease extent or Gleason grade in men considering AS. We hypothesize MP-erMRI prior to AS for men with low risk disease can identify men who harbor more extensive or higher risk prostate cancer.

The study will plan to enroll 130 participants who had diagnostic biopsy less than one year prior to enrollment. After enrollment, participants will undergo a MP-erMRI. This will be reviewed and participants will be characterized into 3 groups: "not reclassified" characterized by findings consistent with small, low-Gleason grade organ-confined tumors, "reclassified" characterized by large, higher-Gleason grade organ-confined tumors, and radiographic T3 and or N1 disease. Less than 10% (roughly 10) of participants who belong to group 3 will be taken off study. Those in groups 1 and 2 will proceed within 3 months of the MP-erMRI to a standard 12-core TRUS biopsy.

11.2 Hypothesis assumptions:

Participants in groups 1 and 2 will receive 12 core TRUS re-biopsy within 3 months of undergoing MP-erMRI. TRUS re-biopsy will be assumed as the gold standard for determining tumor size and grade.

11.2.1 Null hypothesis:

	TRUS Re-biopsy Results		
MP-erMRI Results	No Disease Upgrade	Disease Upgrade	Total
Not Reclassified	72	9	81
Reclassified	18 (20%)	21 (70%)	39
Total	90	30	120

11.2.2 Alternative hypothesis:

	TRUS Re-biopsy Results		
MP-erMRI Results	No Disease Upgrade	Disease Upgrade	Total
Not Reclassified	85	3	88
Reclassified	5 (6%)	27 (90%)	32
Total	90	30	120

11.3 Power and sample size calculation:

A true positive fraction (TPF) is defined as the probability of MP-erMRI tests show disease re-classified results when participants truly have upgraded disease according to 12 core TRUS re-biopsies. A false positive fraction (FPF) is defined as the probably of MP-erMRI tests show re-classified disease results when no upgrade disease was observed on 12 core TRUS re-biopsies. A TPF (sensitivity) of 90% and FPF (1-specificity) of 6% would be considered promising, whereas a TPF of ≤70% and a FPF of ≥20% are unacceptable. Sample size is calculated using the formula with asymptotic variances as proposed by Pepe [71], followed by a set of 5000 simulation to assess that the power is adequate. Simulation was done using STATA scrsize package (http://labs.fhcrc.org/pepe/dabs/software.html). Results showed that with 120 participants (25% have upgrade

re-biopsy vs. biopsy prior to enrollment), 81% power can be achieved (1-sided alpha 0.1). This ensures that there is at least 80% chance of drawing a positive conclusion if the MP-MRI is 94% specific and 90% sensitive.

11.4 Primary Analysis:

The observed TPF and FPF will be summarized as percentages with 90% CI. Joint CIs for TPF and FPF will also be examined. A positive conclusion is drawn if the lower limit of TPF is above the minimally acceptable level of 70% and the upper limit of FPF is below the minimally acceptable level of 20%. Table below gives 80% confidence intervals for the true but unknown TPF and FPF, given possible observed participants with reclassified disease by MRI among 30 true reclassified and 90 non-reclassified cases (by re-biopsy). Table below is an example of 80% CI given different scenarios observed reclassified participants number.

Disease Upgrade by Re-biopsy (n=30)			No Upgrade by Re-biopsy (N=90)		
Observed reclassified N by MRI	Observed TPF	80% CI	Observed Reclassified N by MRI	Observed FPR	80% CI
27	90%	(79%, 96%)	5	6%	(3%, 10%)
25	83%	(71%, 92%)	10	11%	(7%, 17%)
23	77%	(64%, 87%)	15	17%	(12%, 23%)
21	70%	(57%, 81%)	18	20%	(15%, 26%)

11.5 Secondary Objectives

Determine the frequency of MP-erMRIs which appear to reclassify men with low risk disease considering AS.

Determine the effect of MP-erMRI and repeated 12 core TRUS biopsy on patient-reported health states.

Correlate the pathology findings from the targeted biopsy with the MP-erMRI findings for those men who fall into the reclassified category.

11.6 Secondary Analysis

Secondary analysis will be summarized descriptively. Number and percentage of participants with reclassified disease by MP-erMRI will be summarized as numbers and percentages with 90% CI. Participants will be asked to complete self-reported health state questionnaires at enrollment and following the final on-protocol biopsy. A score will be given for each questionnaire answered by participants. The scores for the questionnaires will be summarized as median and inter-quartile ranges. Descriptive statistics will be utilized to correlate the targeted biopsy findings (disease extent in mm and Gleason score) with the findings from the MP-erMRI.

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Appendix A:

Name:_____

MISHEL UNCERTAINTY INDEX – COMMUNITY FORM FOR ACTIVE SURVEILLANCE (MUIS-AS)

The following questions are about your feelings about your cancer diagnosis:

Please indicate the answer that best describes your feeling about each aspect of the services you have received. We are interested in your overall experience during the last year with care or therapy that you have received related to your cancer therapy or its side effects

Please respond to the following questions, indicating the extent to which you feel the following emotions about your prostate cancer:

Feeling	*Not at all*	*A little*	*A moderate amount*	*A lot*	*A great deal*
Worried	0	1	2	3	4
Fearful	0	1	2	3	4
Anxious	0	1	2	3	4
Confident	0	1	2	3	4
Hopeful	0	1	2	3	4
Eager	0	1	2	3	4
Angry	0	1	2	3	4
Sad	0	1	2	3	4
Disappointed	0	1	2	3	4
Guilty	0	1	2	3	4
Disgusted	0	1	2	3	4
Exhilarated	0	1	2	3	4
Pleased	0	1	2	3	4
Happy	0	1	2	3	4
Relieved	0	1	2	3	4

Signature:_____ Date:_____

Appendix B

SERVICES SATISFACTION SCALE – FOR CANCER CARE (SSS-Ca)

The following questions are about your satisfaction with the cancer care you received

Please indicate the answer that best describes your feeling about each aspect of the services you have received. We are interested in your *overall experience during the last year* with care or therapy that you have received related to your cancer therapy or its side effects. By "practitioner" we mean the one or more doctors, clinicians, etc., who have worked with you in your cancer- related care.

What is your overall feeling about the . . .

	Completely satisfied	Very satisfied	Somewhat satisfied	Mixed	Somewhat unsatisfied	Very unsatisfied	Completely unsatisfied
Effect of health care services in helping you deal with your cancer and maintain your well being?	1	2	3	4	5	6	7
Effect of cancer treatment in preventing cancer progression or recurrence?	1	2	3	4	5	6	7
How well your confidentiality and rights as an individual have been protected?	1	2	3	4	5	6	7
Quality of cancer care you have received?	1	2	3	4	5	6	7
In an overall general sense, how satisfied are you with the cancer treatment you have received?	1	2	3	4	5	6	7

Name:_____

Signature:_____ Date:_____

Appendix C:

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)
A clinical tool to measure urinary, bowel, sexual and vitality/hormonal health

Patients: Please answer the following questions by checking the appropriate checkbox. All questions are about your health and symptoms in the LAST FOUR WEEKS. Select one answer for each question

1. Overall, how much of a problem has your urinary function been for you?

1 ☐ No problem 2 ☐ Very small problem 3 ☐ Small problem 4 ☐ Moderate problem 5 ☐ Big problem

2. Which of the following best describes your urinary control?

0 ☐ Total Control 1 ☐ Occasional dribbling 2 ☐ Frequent dribbling 4 ☐ No urinary control ____

3. How many pads or adult diapers per day have you been using for urinary leakage?

0 ☐ None 1 ☐ One pad per day 2 ☐ Two pads per day 4 ☐ Three or more pads per day ____

4. How big a problem, if any, has urinary dripping or leakage been for you?

0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

Clinicians: ADD the answers from questions 2-4 to calculate the Urinary Incontinence Symptom Score (out of 12): _____

5. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Pain or burning with urination	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
b. Weak urine stream/incomplete bladder emptying	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
c. Need to urinate frequently	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___

Clinicians: ADD the answers from questions 5a-5c to calculate the Urinary Irritation/Obstruction Symptom Score (out of 12): _____

6. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Rectal pain or urgency of bowel movements	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
b. Increased frequency of your bowel movements	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
c. Overall problems with your bowel habits	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___

Clinicians: ADD the answers from questions 6a-6c to calculate the Bowel Symptom Score (out of 12): _____

7. How would you rate your ability to reach orgasm (climax)?

0 ☐ Very good 1 ☐ Good 2 ☐ Fair 3 ☐ Poor 4 ☐ Very poor to none ____

8. How would you describe the usual quality of your erections?

0 ☐ Firm enough for intercourse 1 ☐ Firm enough for masturbation and foreplay only 2 ☐ Not firm enough for any sexual activity 4 ☐ None at all ____

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?

0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

Clinicians: ADD the answers from questions 7-9 to calculate the Sexual Symptom Score (out of 12): _____

10. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Hot flashes or breast tenderness/enlargement	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
b. Feeling depressed	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___
c. Lack of energy	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	___

Clinicians: ADD the answers from questions 10a-10c to calculate the Vitality/Hormonal Symptom Score (out of 12): _____

Name:_____ ***Signature:***_____ ***Date:***_____

Appendix D:

AUA Symptom Index Name:_____

Please answer the following questions by checking the appropriate check box. All questions are about your health and symptoms in the **LAST FOUR WEEKS.** Select one answer for each question.

	not at all	less than 1 in 5	less than 1/2 the time	about 1/2 the time	more than 1/2 the time	almost always
Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
During the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
During the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
During the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Over the past month, how many times per night did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 or more times

	Delighted	Pleased	Mostly satisfied	mixed	mostly dissatisfied	Unhappy	Terrible
How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?	0	1	2	3	4	5	6

Signature:_____ Date:_____

Appendix E:

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index. Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

Rev November 2003 Washington University School of Medicine Clinical Outcomes Research Office

SERVICES SATISFACTION SCALE – FOR CANCER CARE (SSS-Ca)

The following questions are about your satisfaction with the cancer care you received

Please indicate the answer that best describes your feeling about each aspect of the services you have received. We are interested in your *overall experience during the last year* with care or therapy that you have received related to your cancer therapy or its side effects. By "practitioner" we mean the one or more doctors, clinicians, etc., who have worked with you in your cancer- related care.

What is your overall feeling about the . . .

	Completely satisfied	Very satisfied	Somewhat satisfied	Mixed	Somewhat unsatisfied	Very unsatisfied	Completely unsatisfied
Effect of health care services in helping you deal with your cancer and maintain your well being?	1	2	3	4	5	6	7
Effect of cancer treatment in preventing cancer progression or recurrence?	1	2	3	4	5	6	7
How well your confidentiality and rights as an individual have been protected?	1	2	3	4	5	6	7
Quality of cancer care you have received?	1	2	3	4	5	6	7
In an overall general sense, how satisfied are you with the cancer treatment you have received?	1	2	3	4	5	6	7

Name:_____

Signature:_____ Date:_____

AUA Symptom Index Name:_____

Please answer the following questions by checking the appropriate check box. All questions are about your health and symptoms in the **LAST FOUR WEEKS**. Select one answer for each question.

	not at all	less than 1 in 5	less than 1/2 the time	about 1/2 the time	more than 1/2 the time	almost always
Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
During the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
During the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
During the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Over the past month, how many times per night did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 or more times

	Delighted	Pleased	Mostly satisfied	mixed	mostly dissatisfied	Unhappy	Terrible
How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?	0	1	2	3	4	5	6

Signature:_____ Date:_____

Name:_____

MISHEL UNCERTAINTY INDEX – COMMUNITY FORM FOR ACTIVE SURVEILLANCE (MUIS-AS)

The following questions are about your feelings about your cancer diagnosis:

Please indicate the answer that best describes your feeling about each aspect of the services you have received. We are interested in your overall experience during the **last year** with care or therapy that you have received related to your cancer therapy or its side effects

Please respond to the following questions, indicating the extent to which you feel the following emotions about your prostate cancer:

Feeling	*Not at all*	*A little*	*A moderate amount*	*A lot*	*A great deal*
Worried	0	1	2	3	4
Fearful	0	1	2	3	4
Anxious	0	1	2	3	4
Confident	0	1	2	3	4
Hopeful	0	1	2	3	4
Eager	0	1	2	3	4
Angry	0	1	2	3	4
Sad	0	1	2	3	4
Disappointed	0	1	2	3	4
Guilty	0	1	2	3	4
Disgusted	0	1	2	3	4
Exhilarated	0	1	2	3	4
Pleased	0	1	2	3	4
Happy	0	1	2	3	4
Relieved	0	1	2	3	4

Signature:_____ Date:_____

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

A clinical tool to measure urinary, bowel, sexual and vitality/hormonal health

Patients: Please answer the following questions by checking the appropriate checkbox. All questions are about your health and symptoms in the LAST FOUR WEEKS. Select one answer for each question

1. Overall, how much of a problem has your urinary function been for you?

1 ☐ No problem 2 ☐ Very small problem 3 ☐ Small problem 4 ☐ Moderate problem 5 ☐ Big problem

2. Which of the following best describes your urinary control?

0 ☐ Total Control 1 ☐ Occasional dribbling 2 ☐ Frequent dribbling 4 ☐ No urinary control ____

3. How many pads or adult diapers per day have you been using for urinary leakage?

0 ☐ None 1 ☐ One pad per day 2 ☐ Two pads per day 4 ☐ Three or more pads per day ____

4. How big a problem, if any, has urinary dripping or leakage been for you?

0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

Clinicians: ADD the answers from questions 2-4 to calculate the Urinary Incontinence Symptom Score (out of 12): _____

5. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Pain or burning with urination……	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Weak urine stream/incomplete bladder emptying	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Need to urinate frequently……	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

Clinicians: ADD the answers from questions 5a-5c to calculate the Urinary Irritation/Obstruction Symptom Score (out of 12): _____

6. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Rectal pain or urgency of bowel movements……..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Increased frequency of your bowel movements ..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Overall problems with your bowel habits……..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

Clinicians: ADD the answers from questions 6a-6c to calculate the Bowel Symptom Score (out of 12): _____

7. How would you rate your ability to reach orgasm (climax)?

0 ☐ Very good 1 ☐ Good 2 ☐ Fair 3 ☐ Poor 4 ☐ Very poor to none ____

8. How would you describe the usual quality of your erections?

0 ☐ Firm enough for intercourse

1 ☐ Firm enough for masturbation and foreplay only

2 ☐ Not firm enough for any sexual activity

4 ☐ None at all ____

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?

0 ☐ No problem 1 ☐ Very small problem 2 ☐ Small problem 3 ☐ Moderate problem 4 ☐ Big problem ____

Clinicians: ADD the answers from questions 7-9 to calculate the Sexual Symptom Score (out of 12): _____

10. How big a problem, if any, has each of the following been for you?	**No Problem**	**Very small problem**	**Small problem**	**Moderate problem**	**Big problem**	
a. Hot flashes or breast tenderness/enlargement..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
b. Feeling depressed…… ..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____
c. Lack of energy……..	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	____

Clinicians: ADD the answers from questions 10a-10c to calculate the Vitality/Hormonal Symptom Score (out of 12): _____

Name: _____ ***Signature:*** _____ ***Date:*** _____