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Defining and Measuring Adherence in Observational Studies Assessing Outcomes of Real-world Active Surveillance for Prostate Cancer: A Systematic Review

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Title: Defining and measuring adherence in observational studies assessing outcomes of real-world active surveillance for prostate cancer: a systematic review

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24

25   **Abstract**

26   **Context:** Evidence-based guidelines for active surveillance (AS), a treatment option for men
27   with low-risk prostate cancer, recommend regular follow-up at periodic intervals to monitor
28   disease progression. However, gaps in monitoring can lead to delayed detection of cancer
29   progression, leading to missed window of curability.

30   **Objective:** We aimed to identify the extent to which real-world observational studies reported
31   adherence to monitoring protocols among prostate cancer patients on AS. When reported, we
32   sought to characterize definitions of adherence.

33   **Evidence Acquisition:** We systematically reviewed observational studies assessing outcomes of
34   prostate cancer patients on AS, published before March 22, 2019 in PubMed, Embase, and
35   CENTRAL. Adherence definitions were considered time-bound if they included a pre-specified
36   time, and binary if adherence was assessed but did not specify a time interval. We assessed
37   study quality using the Strengthening the Reporting of Observational Studies in Epidemiology
38   checklist.

39   **Evidence Synthesis:** Forty-five studies met our inclusion criteria. Eleven studies did not report
40   any data on adherence to AS protocols. Twenty-five studies did not explicitly measure
41   adherence, but provided relevant data (e.g. number of patients who received a repeat biopsy).
42   Six studies reported adherence using a time-bound definition, while three studies used a binary
43   definition. Twenty-three studies provided information on patients lost to follow-up.

44 **Conclusion:** Most studies reporting outcomes of patients on AS did not measure or report
45 adherence. When reported, adherence was often not time-specific. As some AS patients will
46 benefit from maintaining a window of curability, clinical practices and future studies should
47 track and report adherence and associated factors.

48 **Patient Summary:** We reviewed real-world observational studies examining outcomes of
49 prostate cancer patients on AS. Most studies did not clearly define or report adherence to
50 monitoring protocols, which is important to consider for appropriate disease management.

51

52   **Introduction**

53   Prostate cancer is the most common cancer in men in the United States, and second
54   most common internationally.^{1,2} Most prostate cancers are low-risk and slow growing;
55   however, a subset can progress to more lethal disease.³ Active surveillance (AS) is the
56   recommended standard of care for low- and some intermediate-risk prostate cancers that have
57   little risk of progression.⁴ AS defers active treatment (e.g., surgery or radiation) with close
58   monitoring and leads to active treatment if the cancer progresses (e.g., low grade disease
59   becomes higher grade disease), the cancer is reclassified (e.g., detected a previously
60   undetected cancer of higher grade on confirmatory or surveillance biopsy), or the patient
61   decides to pursue active treatment. AS also provides the opportunity to maintain men's quality
62   of life without the potential adverse effects of treatment.⁵

63   AS eligibility criteria and monitoring guidelines vary widely by institution, but generally
64   recommend regular monitoring for disease progression that includes prostate-specific antigen
65   (PSA) tests, digital rectal exams (DRE), and repeat prostate biopsies at periodic intervals.⁶
66   However, the extent of patient adherence to AS protocols is unclear. Little is known about
67   which populations or settings are more vulnerable to monitoring gaps, or multi-level factors
68   associated with non-adherence or loss to follow-up (LTFU).

69   In this systematic review, we sought to identify if and how real-world observational
70   studies tracked and reported adherence to AS protocols when evaluating outcomes of prostate
71   cancer patients on AS. Specifically, we aimed to assess whether or not such studies reported
72   patient adherence to AS protocols (e.g., PSA tests, DREs, repeat biopsies, and duration and

frequency of monitoring received). When studies reported adherence, we sought to understand how investigators define and measure adherence, as well as the range of adherence rates.

Evidence Acquisition

Our review was guided by the PRISMA statement.⁷ We conducted a systematic literature search (PROSPERO #CRD42016051128) on March 8, 2018 and updated on March 22, 2019 in PubMed, Embase, and CENTRAL. We created our search strategy in collaboration with a clinical librarian (JBW) using text words and controlled vocabulary, including MeSH and Emtree terms (e.g., “active surveillance” and “Prostatic Neoplasms”[Mesh]). Appendix A details the complete search strategy.

Study eligibility criteria included: 1) focus on AS for prostate cancer; 2) real-world observational study reporting actual patient care (e.g., a retrospective medical chart review); 3) followed a predetermined evidence-based AS clinical eligibility criteria (e.g., PSA level, Gleason score, stage, number of positive cores, etc.) and an AS monitoring protocol (e.g., National Comprehensive Cancer Network [NCCN] guidelines – PSA every 6 months, annual DRE and biopsy);⁴ and 4) reported outcome data (e.g., survival rates, movement to active treatment, or LTFU). We excluded non-English studies, studies that evaluated outdated AS protocols, as well as studies that solely reported on active treatment patients. Clinical trials, interventional studies, efficacy trials (e.g., study cohorts with a study protocol), or studies comparing different treatment modalities to test protocols or treatment effectiveness were also excluded.

Two reviewers (GK, SL) independently screened titles and abstracts to determine relevancy and eligibility, and completed full text reviews. A third reviewer (US, BB, or NP)

reconciled discrepancies. We collected several data elements on adherence and outcomes (Table 1). We categorized studies as reporting adherence if they explicitly included a measure with the term “adherence” or “compliance”. We considered the adherence/compliance definition time-bound if it included the timeliness of monitoring (e.g. patient adherent if repeat biopsy completed within six months of a designated date). We considered the definition binary if it assessed adherence, but was not time-bound (e.g. testing received versus not). We tabulated adherence definitions and results, when provided. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist to assess study quality.⁸

Evidence Synthesis

We screened 6,118 articles’ titles and abstracts and reviewed the full text of 267 articles. After applying our inclusion and exclusion criteria, we included 45 studies (Figure 1), and classified them into four mutually exclusive groups (Figure 2).

Study characteristics

After removing participant sub-groups who did not meet our eligibility criteria (e.g., enrolled in a randomized controlled trial or who did not undergo AS), we ultimately included a total of 29,143 participants (range: 34 – 5,302) from 45 studies. The earliest enrollment in an AS program began in 1990,^{9,10} culminating as late as 2017.¹¹

Eligibility criteria into AS programs varied across studies; however, most studies restricted inclusion by diagnostic criteria – e.g., Gleason score ≤ 6 , PSA ≤ 10 ng/ml, $\leq 33\%$ positive biopsy cores, and $\leq 50\%$ involvement in a single core. Some studies stated they included select men with higher risk features, such as those with a strong preference for AS.^{9,12–}

¹⁹ A few studies considered patients' cognitive capacity to understand AS programs as well as their ability to attend follow-up visits.^{20,21} Eligibility criteria also changed over time in certain long-term studies, reflecting a general trend in the evolution of AS protocols.^{9,22–26}

Most studies reported follow-up time on AS, however the measure varied based on when investigators determined follow-up began (e.g. upon diagnosis or agreement to enroll into an AS program) and ended (e.g. upon study completion, movement to active treatment, or other censorship).^{9,10,12–19,21–24,27–44} Median follow-up time ranged from 16.9 months³³ to 6.7 years.^{31,33}

Patient characteristics

All 45 studies reported patient age and clinical characteristics – such as Gleason score, PSA, number of positive biopsy cores, risk classification, and clinical stage. Fourteen studies reported patient race/ethnicity.^{9,11,15,18,19,22,23,35–40,45} Four of these publications specifically focused on studying racial/ethnic minorities.^{22,23,35,37} Two studies reported patients' marital status.^{9,19} Two studies also reported tobacco use history;^{9,23} however, only one also reported history of substance abuse, mental illness, homelessness, and primary language.²³

AS protocols

Follow-up protocols varied across studies, using strict or modified NCCN,^{15,18,32,35,36,40,45} Prostate Cancer Research International Active Surveillance (PRIAS),^{13,25,26,33,43,46,47} Johns Hopkins,^{40,42,45} University of California San Francisco,^{9,11,23,38,48} Epstein,^{18,20,40–42} and other institution-specific protocols.^{49,50} All studies described PSA testing and biopsy schedules. Nine studies followed a protocol to assess PSA every three months for the first two years on AS, followed by every six months thereafter.^{20,24–26,31,33,43,46,47} For all other studies, PSA testing

intervals ranged from one to 12 months. Repeat biopsy schedules varied widely across studies as seen in seven publications that biopsied patients annually,^{17,18,35,40–42,45} and five that biopsied patients at one, four, seven, and ten years, and every five years thereafter.^{25,26,43,46,47} Follow-up protocols also varied by risk level at diagnosis and during follow-up, patient preference, and patient age. As with eligibility criteria, protocols changed over time to accommodate evolving evidence about AS safety and effectiveness.

Reported Adherence

While 11 studies did not report any data on adherence to AS protocols,^{11–13,18–20,31,32,35,37,45} 34 studies reported some form of adherence (e.g. time-bound, binary, or undefined).

Time-bound Definitions of Adherence

Six studies reported adherence using a time-bound definition.^{23,25,40,46,47,49} We considered adherence definitions time-bound if investigators' definitions included the number of monitoring events within a specific time interval. Reported adherence rates are included in Table 2.

No studies had the same adherence definition, although some were similar with varying degrees of flexibility. For example, Osterberg et al considered patients adherent if they received a biopsy within 12 months of the scheduled date,²³ whereas Tosoian et al, Bul et al, Bokhorst et al, and Soeterik et al determined patients to be adherent if they received biopsies within six months of the scheduled date.^{25,40,46,47} Lee et al did not provide additional time beyond the recommended interval for a repeat biopsy.⁴⁹

Binary Definitions of Adherence

Three studies used binary definitions of adherence that categorized surveillance as complete or incomplete, but did not include a specific time interval in which monitoring events needed to take place.^{30,33,41} For example, Becker et al assessed the proportion of patients that received four scheduled repeat biopsies.⁴¹ Similarly, Sugimoto et al evaluated the proportion of patients that received their first scheduled repeat biopsy.³³ And Hefermehl et al examined the proportion of PSA tests and biopsies performed compared to the total that should have been completed.³⁰ We summarize these results in Table 3.

Undefined measures of adherence

We included 25 studies that did not explicitly define adherence, but either (1) reported descriptive statistics of follow-up testing rates, including a time frame (such as median time from diagnosis to first repeat biopsy), or (2) included an incomplete or nonspecific measure of adherence (such as the absolute number of men who received repeat biopsies, rather than a proportion).^{9,10,14–17,21,22,24,26–29,34,36,38,39,42–44,48,50–53}

Twelve studies described the number of follow-up events within a specified time interval.^{15,17,21,22,27–29,34,42,44,51,52} Common measures included the time between surveillance exams and proportion of men who received a follow-up test within a time frame. For example, Hashine et al reported 55.2% of their cohort received the first repeat biopsy after a median 1.1 years on AS.²⁹ Meunier et al reported a mean of 1.0 ± 0.49 years between repeat biopsies.²²

The remaining 13 studies did not define adherence but reported a measure that we considered representative of adherence.^{9,10,14,16,24,26,36,38,39,43,48,50,53} For example, some studies reported the median number of biopsies received^{10,14,38} and the number of men who received a follow-up test.^{9,14,16,24,26,36,38,48,50,53} However, these measures lacked a corresponding time

frame, such that it is unclear if the tracked biopsies occurred within one year, two, or throughout the entire study period. Other studies lacked key information, such as the total number of patients on AS to compare to the number that received follow-up testing.^{26,50,53}

Lost to Follow-Up (LTFU)

Twenty-three studies provided information on patients LTFU. Rates of LTFU vary from none⁵² to 19.5%³⁰, however this measure was not consistently defined across studies making comparison infeasible. We saw various approaches to defining whether or not a patient was LTFU. Hefermehl et al considered patients LTFU after no response or information about the patient more than 12 months after the last scheduled appointment.³⁰ Osterberg et al, alternatively, considered 31% of patients LTFU after failing to reach them after three attempted phone calls, until querying a cross-institutional database that indicated only 17.3% of patients were truly LTFU.²³ In addition, some studies excluded patients LTFU.^{10,39,40,42}

Ballas et al examined the association between the chance of being LTFU and socioeconomic status (SES).³⁵ They found that the cumulative incidence of being LTFU at a safety-net hospital was significantly higher (57% at 5 years) than at a comprehensive cancer center (37% at 5 years), and that lower SES was associated with likelihood of being LTFU.

Study Quality and Potential Bias

According to the STROBE checklist,⁸ the overall quality of studies included was high. Across most studies, we found limited reporting on confounders related to patient outcomes, including clearly defined measures of adherence and patient characteristics such as SES, race, ethnicity, primary language, marital status, and other characteristics shown to influence access to care. Additionally, not all studies provided details on efforts to address potential sources of

bias^{9,12–14,21,24–29,33,34,43,46,48,50,52} or addressed how investigators handled missing data.^{9,10,12,14,15,17,18,20–22,24,25,27,28,31,33,34,37,40,43,44,46,47,49–53}

Discussion

The majority of observational studies evaluating clinical outcomes of men on AS do not measure adherence. When adherence is reported, assessment across studies and settings is heterogeneous. Not all studies provided a definition of the measure that considers the timeliness of the routine testing. In addition, a few studies excluded patients LTFU. Since the premise of AS is routine scheduled monitoring to assess disease progression or reclassification, timely adherence is essential to retain a window of curability. Although some studies report no significant mortality difference between AS and active treatment among men with low-risk prostate cancer,^{54,55} adherence to monitoring remains paramount for long-term patient safety, particularly among a subgroup of patients. Up to 30% of men diagnosed with low- and intermediate-risk prostate cancer harbor more aggressive disease missed on biopsy,^{47,56–58} and some men with higher risk disease may still opt for AS that necessitates regular follow-up.⁴ African American men may have a higher risk of disease reclassification, as found in a recent systematic review.⁵⁹ Additionally, men with intermediate-risk disease who can be safely monitored on AS have more than a three times higher risk of metastasis at 15-year follow-up.^{57,60} AS – including the extent to which it is followed – should be reported and studied to further understand the quality of AS care, resources needed to ensure high-quality monitoring (e.g., registries), and how protocols can be more widely implemented across diverse settings and populations safely to prevent overtreatment without compromising quality of life and

survival. This involves understanding a range of constructs including adherence and various implementation outcomes, which is critical to understanding the wider implementation and dissemination of AS in clinical practice.

Most studies did not evaluate the potential impact of multi-level factors on adherence. For example, only one study examined whether or not patients on AS experienced homelessness or had a history of mental illness,²³ and only two studies detailed how clinics performed monitoring or responded to patients' concerns surrounding AS (e.g. a dedicated nurse conducted follow-up activities and supported patients experiencing anxiety).^{16,21} Prior research indicates patient-, provider-, and system-level factors such as these may influence adherence.⁶¹⁻⁶⁶ For example, Kinsella et al identified multi-level barriers and facilitators to AS adherence including cancer characteristics (e.g., lower PSA), patients' perceived benefits and harms, social support (e.g., peer support, partner anxiety), receipt of useful information communicated by providers, healthcare organization and practice (e.g., educational classes on AS), and health policy factors (e.g., national guidelines).⁶⁴ We also recognize that adherence to AS protocols may vary by patient preference (e.g., refuses repeat biopsy), physician practice (e.g., tailors based on clinical and follow-up characteristics), health care system and country (e.g., follow NCCN versus the American Urological Association [AUA] guidelines or others),⁶⁷ and the availability of multi-parametric magnetic resonance imaging.⁶⁸ Identifying barriers and facilitators to AS adherence is crucial for successful long-term disease management that delays or avoids unnecessary treatment until it is warranted, and can inform intervention development.

As a framework to examine the interrelated components affecting high quality care, including adherence, the Chronic Care Model is a promising model for improving management of chronic conditions.⁶⁹ AS constitutes ongoing care for a chronic condition; as such, this framework suggests looking to a health system situated within a community, in which productive interactions between a prepared, proactive practice team and engaged and active patients drive positive health outcomes. Patient-centered strategies such as primary care provider (PCP) and specialty provider coordination, between-visit self-management support, technology-enabled workflows, as well as organizational support of providers monitoring high-risk populations are promising avenues for safe and effective long-term care.⁷⁰ Such team-based care and technology interventions present specific opportunities to improve the safety of outpatient monitoring. For example, PCPs can help ensure appropriate monitoring for their patients by ordering follow-up tests in collaboration with urology, and electronic medical record-based alerts and registries can prompt monitoring activities when well-integrated into care team workflows.^{70,71} If AS protocols are meant to be effective for detecting prostate cancer progression, guidelines must incorporate clear and defined adherence measures while offering care providers and patients guidance on tracking and following monitoring schedules. As experts call for consensus on AS eligibility criteria, monitoring guidelines, and thresholds for intervention,^{6,72} adherence must be measured and considered in the evaluation and selection of an optimal AS protocol.

Future studies should track and report variables relevant to follow-up care for and adherence to AS protocols. First, studies should determine a definition of adherence to AS protocols based on guideline-recommended time (e.g., every 6 months) or a pre-defined grace

period (e.g. within three months of recommended testing). Second, an adherence rate to monitoring (e.g., completed PSA testing, annual biopsy and DRE, etc.) should be calculated, along with the average time between monitoring. Third, studies should also report AS outcomes, including number and rate patients moved to active treatment, whether due to disease progression, reclassification, or patient preference. Lastly, studies should define and assess LTFU, including associated factors (e.g., race, comorbidities),⁷³ to identify patients at increased risk.

Even with clear recommendations for monitoring, improving adherence in real-world clinical settings can be challenging. Fragmented health records and limited resources in safety-net settings can introduce unique barriers to implementing evidence-based recommendations in prostate cancer care, particularly for AS.^{74–76} Patient-centered and technology-enabled solutions to measure and improve adherence must also be designed for and tested in settings that disproportionately care for low-income and vulnerable populations, many of whom already face barriers to accessing care.

While we report on studies that include both measures of adherence and compliance, it is important to differentiate between the two terms, as recommended by the World Health Organization.⁷⁷ The former connotes an active agreement between patient and provider: does the patient adhere to an agreed-upon recommendation? The latter suggests a more passive role of the patient: does the patient comply with a physician's orders? When discussing AS, the success of which is dependent on the patient's agreement and understanding of follow-up care, we believe that "adherence" better reflects the inherent shared decision-making paradigm.

There are limitations to this systematic review. First, since AS protocols differ across

settings, we could not compare adherence across studies. As a result, we decided to focus on primary data analysis of real-world observational studies within single or multiple settings using the same follow-up protocol, rather than secondary data analysis of cancer registries or consortiums employing various protocols. We also limited our review to studies that had predetermined evidence-based AS clinical eligibility criteria and monitoring protocols, which excluded a few studies (e.g., those reporting on the MUSIC consortium).^{73,78} This was done to capture studies that intended to follow patients who were clinically appropriate and monitored based on a predetermined protocol (e.g., NCCN). We also included non-US studies and recognize that differences in health care systems across countries have implications for variations in access to and quality of care. However, we hope our review illustrates the need for consistent definitions and reporting of adherence in order to move towards a standardized AS protocol. Also, the causality between adherence to AS and patient outcomes is not well understood due to the focus on short-term outcomes in the literature; however, successful receipt of timely follow-up visits and testing should be treated as a necessary metric when reporting AS outcomes.⁶¹

To our knowledge, this is the first systematic review that assesses the extent adherence to follow-up protocols is measured in real-world observational studies reporting outcomes of men on AS. Due to the large number of men managed by AS, this work offers valuable implications that may improve the delivery of care for prostate cancer patients on AS. In addition, previous studies demonstrating differences in prognostic value and prostate cancer specific mortality for men on AS by race and ethnicity indicate that it is imperative to thoroughly understand factors associated with successful disease management, including

adherence, in order to move the needle towards recognizing and reducing disparities.^{79,80}

Conclusions

Adherence to evidence-based AS protocols is not uniformly reported or defined in the scientific literature. As AS becomes a more common management strategy among men with low-risk prostate cancer, our findings highlight the need for more research to: (1) establish adherence definitions and measures relevant to AS; (2) include adherence as a quality improvement measure for AS outcomes; and (3) track and identify multilevel factors associated with adherence and LTFU.

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Authors Contributions: GK and SL designed the study with support from US, BB, and NP, developed the search strategy with support from JBW, screened and extracted all records, and drafted the manuscript. US, BB, and NP resolved discrepancies during the review. JBW performed the database search, as well as advised on data collection and management practices. US conceived of the study topic in close partnership with NP. NP takes responsibility for the integrity of this work. GK and SL served as co-first authors, each with equal contribution to the manuscript. All authors critically reviewed the manuscript and approved the final version, and meet ICMJE criteria for authorship.

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348

349 **Data Access and Responsibility:** Dr. Palmer had full access to all the data in the study and takes
350 responsibility for the integrity of the data and the accuracy of the data analysis.

351

352 **Data Sharing:** Data are available upon request.

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354 **PROSPERO Registration:** PROSPERO 2016:CRD42016051128

355 **Registration Link:**

356 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051128

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611 **Figure legends:**

612 Figure 1: PRISMA Flow Diagram

613 Figure 2: Flow diagram categorizing included studies

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615 **Tables:**616 **Table 1:** Data Elements

Study Design	Setting (e.g. private hospital, safety-net, population-based) Number of participants Country Active surveillance (AS) eligibility requirements (e.g. age, tumor grade, prostate-specific antigen [PSA] level) AS monitoring protocol (including testing type and frequency of monitoring)
Study Group Demographics	Age Race/Ethnicity Comorbidities Social demographics (e.g. Social economic status, homelessness, insurance status)
Adherence	Definition of adherence as defined by the study Any measure of patients adhering to PSA testing schedule Any measure of patients adhering to biopsy schedule Any measure of patients adhering to digital rectal exam schedule
Outcome	Definition of lost to follow-up (LTFU) as defined by the study Any measure of patients LTFU Any measure of patients moved to watchful waiting Any measure of patients moved to active treatment Any measure of prostate cancer-specific death

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617 AS = active surveillance; PSA = prostate-specific antigen; LTFU = lost to follow-up

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Table 2: Characteristics of studies measuring adherence using a time-bound definition (n=6)

Study info	Cohort name	Study period	Number of patients who elected Active Surveillance (AS)	Adherence measure	Adherence definition	Adherence results
Tosoian et al. 2011 ⁴⁰	Johns Hopkins	1995-2010	796	Adherence to repeat biopsies	Patient undergoes biopsy within 0.5 years of designated date	Year 1: 92% adherent Year 2: 91% adherent Total (12 years): 89% (79-100%)
Bul et al. 2013 ⁴⁶	PRIAS	2006-2012	2494	Adherence to first repeat biopsy	Patient undergoes biopsy within 1.5 years of initial diagnosis	81% adherent
Bokhorst et al. 2015 ²⁵	PRIAS	2006-2014	4547	Adherence to scheduled prostate-specific antigen (PSA) tests	At least 3 PSA tests/year in first 2 years, at least 1 PSA test/year in following years.	Total: 91% adherent
				Adherence to repeat biopsies	Biopsy within 6 months of designated date, or within 12 months for patients with prostate-specific antigen doubling time (PSA-DT) (3-10 years)	Year 1: 81% Year 4: 60% Year 7: 53% Year 10: 33% Total: 70% For men with PSA-DT(3-10): Year 2: 24% Year 8: 9% For men with > 4 years of follow-up, compliance is 30%
Lee et al. 2010 ⁴⁹	Kansas City Veterans Affairs	2004-2009	45	Adherence to first PSA	Patient receives 1 of 4 recommended PSA within first year	Year 1: 100%
				Adherence to first repeat biopsy	Patient receives 1 biopsy within 1 year	Year 1: 53.3%
Osterberg et al. 2017 ²³	UCSF	2004-2014	104	Proportion of patients that received follow-up PSA	Patient undergoes PSA every 3-6 months	≥ 1 follow-up PSA: 92% Median number of PSA tests: 7 (range 1-21).
				Proportion of men that received	Patient undergoes biopsy every 12-24 months	Year 10: <10% Average number of biopsies: 2 (range 1-5)

				biopsy		Year 10: <10%
Soeterik et al. 2019 ⁴⁷	PRIAS	2008-2014	958	Proportion of patients that received recommended PSA tests	Patient receives $\geq$ 75% recommended PSA tests for their follow-up duration	Total: 74% adherent (ranged from 55%-83% by hospital)
				Proportion of patients that underwent repeat biopsy	Patient undergoes biopsy within 6 months	Year 1: Ranged from 48%-79% by hospital
				Proportion of patients who received all scheduled biopsies	Patient who should undergo $\geq$ 1 biopsy misses none within follow-up period	Total: 52% adherent (ranged from 40%-68% by hospital)

Abbreviations: AS = active surveillance; PRIAS = Prostate Cancer Research International: Active Surveillance study; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time

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Table 3: Characteristics of studies measuring adherence using a binary definition (n=3)

Study info	Cohort name	Study period	Number of patients who elected Active Surveillance (AS)	Adherence measure	Adherence results
Becker et al. 2014 ⁴¹	HAROW	2008-2012	387/748 [‡]	Proportion that receive repeat biopsies	Biopsy 1: 73.6% Biopsy 2: 45.2% Biopsy 3: 23.8% Biopsy 4: 11.4%
Sugimoto et al. 2015 ³³	PRIAS-JAPAN	2010-2013	386	Proportion that receive first repeat biopsy	Biopsy 1: 75.8%
Hefermehl et al. 2016 ³⁰	Kantonsspital Baden, Switzerland	1999-2013	157	Proportion of performed prostate-specific antigen (PSA) tests to total expected	39.7% of PSA values missing
				Proportion of performed biopsies to total expected	81% men received confirmation biopsy, 19% did not
					36.5% biopsies were missing

Abbreviations: AS = active surveillance; HAROW = Hormonal treatment, Active Surveillance, Radiation therapy, OP, Watchful waiting study; PRIAS = Prostate Cancer Research International: Active Surveillance study; PSA = prostate-specific antigen

[‡]Subset of AS patients monitored by an AS protocol that met our inclusion criteria

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Figure 1: PRISMA Flow diagram

Figure 2: Flow diagram categorizing included studies

Appendix A

Searches run on November 3, 2016, March 8, 2018, and again on March 22, 2019.

No date limits. No language limits.

PubMed

("Prostatic Neoplasms"[Mesh] OR "Prostate Neoplasms" OR "Prostate Neoplasm" OR prostate neoplasm OR prostate neoplasms OR "Prostatic Neoplasm" OR "Prostate Cancer" OR "Prostate Cancers" OR "Cancer of the Prostate" OR "Prostatic Cancer" OR "Prostatic Cancers" OR "Cancer of Prostate" OR pca)

AND ("Watchful Waiting"[Mesh] OR "watchful waiting" OR "active monitoring" OR "watchful observation" OR "Active Surveillance" OR "surveillance" OR "Expectant Management" OR "Conservative Management")

AND ("low risk" OR low risk OR "early stage" OR "favorable risk" OR favorable risk OR favourable risk OR "favourable risk" OR indolent OR "clinically localized" OR localized OR localised OR "clinically insignificant" OR "low grade" OR "lower grade")

Initial search on 11/3/16= 2082

Updated search on 3/8/18= 406

Updated search on 3/22/19 = 275

Embase

('prostate cancer'/exp OR 'prostate neoplasms' OR 'prostate neoplasm' OR 'prostatic neoplasm' OR 'prostate cancer' OR 'prostate cancers' OR 'cancer of the prostate' OR 'prostatic cancer' OR 'prostatic cancers' OR 'cancer of prostate' OR pca OR (prostate AND neoplasm) OR (prostate AND neoplasms)) AND ('watchful waiting' OR 'active monitoring' OR 'watchful observation' OR 'active surveillance' OR 'surveillance' OR 'expectant management' OR 'conservative management') AND ('low risk' OR 'early stage' OR 'favorable risk' OR indolent OR 'clinically localized' OR localized OR localised OR 'clinically insignificant' OR 'low grade' OR 'favourable risk' OR 'lower grade' OR (favorable AND risk) OR (favourable AND risk) OR (low AND risk))

Initial search on 11/3/16= 3550

Updated search on 3/8/18= 739

Updated search on 3/22/19 = 686

CENTRAL

("Prostatic Neoplasms" OR "Prostate Neoplasms" OR "Prostate Neoplasm" OR prostate neoplasm OR prostate neoplasms OR "Prostatic Neoplasm" OR "Prostate Cancer" OR "Prostate

675 Cancers" OR "Cancer of the Prostate" OR "Prostatic Cancer" OR "Prostatic Cancers" OR "Cancer
676 of Prostate" OR pca)
677
678 AND ("watchful waiting" OR "active monitoring" OR "watchful observation" OR "Active
679 Surveillance" OR "surveillance" OR "Expectant Management" OR "Conservative Management")
680
681 AND ("low risk" OR low risk OR "early stage" OR "favorable risk" OR favorable risk OR
682 favourable risk OR "favourable risk" OR indolent OR "clinically localized" OR localized OR
683 localised OR "clinically insignificant" OR "low grade" OR "lower grade")
684
685 Initial search on 11/3/16= 134
686 Updated search on 3/8/18= 94
687 Updated search on 3/22/19 = 57
688
689 **All**
690
691 Total = 8023
692 Duplicates= 1907
693 Final total = 6116