SAMS

The Study of Active Monitoring in Sweden

Protocol version 2.1.1

SAMS-FU

A randomised, multi-centre, controlled trial comparing two different follow-up schedules for patients with low-risk, localised prostate cancer on active surveillance with selective, delayed intervention with curative intent

SAMS-ObsQoL

An observational, multi-centre study with quality of life assessment for patients with low-risk, localised prostate cancer on active surveillance with selective, delayed intervention with curative intent

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For the steering committee of SAMS

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Purpose and Aims

Withholding radical therapy for a large proportion of low-risk prostate cancer until signs of progress is a comparatively new strategy, named active surveillance. Active surveillance is recommended by The Swedish National Board of Health and Welfare, in spite of the fact that results from randomised studies of active surveillance are lacking. The criteria for active surveillance and for recommending delayed radical therapy are not validated. The optimal parameters and the time intervals for follow-up are not evaluated scientifically. The risk of not treating patients with aggressive cancers early enough, the long-term effects and the impact on quality of life are unknown.

The principle aim of the randomised SAMS-FU is to investigate an alternative to the standard follow-up schedule for active surveillance for low-risk prostate cancer. The investigated schedule includes a more extensive, initial set of biopsies and a less intensive subsequent follow-up, provided that the tumour is still classified as low-risk. The scientific hypothesis is that this alternative schedule for follow-up will identify the aggressive cancers earlier with less health-care resources and better quality of life for the patients, without increasing the total proportion of patients receiving radical therapy within 5 years.

Additional aims: In the SAMS (SAMS-FU and SAMS-ObsQoL) the quality of life and pelvic symptoms of patients on active surveillance will be investigated and compared to those of patients receiving immediate treatment with curative intent. In addition, SAMS will evaluate prognostic factors, criteria for intervention and the effects of 5-alpha-reductase inhibitors, the outcome after treatment with curative intent, time to symptoms and metastases from prostate cancer, prostate cancer specific survival, and overall survival. Hopefully, SAMS will increase our knowledge on active surveillance for low-risk prostate cancer, so that more patients with aggressive cancer will receive curative treatment and fewer patients will receive un-necessary treatment for indolent tumours and thereby maintain their quality of life better. The SAMS will also lead to better understanding of the psychological aspects of active surveillance, so that adverse reactions may be prevented or managed better in the future.

Background

The problem of over-treatment of low-risk prostate cancer

Prostate cancer is the second most common cancer-related cause of death within the European Union and in the United States. Because symptomatic prostate cancer most often is incurable, efforts are made to diagnose the disease in a preclinical, asymptomatic stage. At present, screening with blood tests for prostate-specific antigen (PSA) is the best method available to identify men with curable prostate cancer. Following repeated screening, almost all diagnosed cases have clinically localised tumours, the vast majority of which are also pathologically organ confined and curable (1). However, most patients with prostate cancer detected by screening would not develop lethal, many not even symptomatic, disease during their entire lifetime, even if left untreated. It has been calculated that the lead time for PSA-detected prostate cancer is approximately 10 years and that more than half of these cancer would never have progressed to clinical disease (2).

As a consequence of the increasing PSA testing of men without clinical signs of prostate cancer, the incidence of prostate cancer has increased dramatically. In Sweden the age-standardised incidence doubled between 1990 and 2004 (3). In 2007, half of the 9,000 newly diagnosed prostate cancers were detected because of PSA-testing (3). At least one third of the Swedish men aged 50 to 70 years have had a PSA-test (3). Unfortunately, it is not possible at the time of diagnosis to identify with certainty which patients that do and which do not need curative treatment.

The European Randomised Study of Screening for Prostate Cancer (ERSPC) reported a relative prostate cancer mortality reduction of 20% after 9 years of follow-up in the group of men invited to screening (4). However, for every prostate cancer death prevented 1,000 men had to be screened and 48 additional cases of prostate cancer were diagnosed. The

conclusions of the ERSPC study group were that there is a benefit of screening in terms of mortality reduction, but also the adverse effects of over-diagnosis and over-treatment of indolent prostate cancer. The Gothenburg section of the ERSPC reported results with longer follow-up (5). At 14 years after randomisation the prostate cancer mortality was only half as high among PSA-tested men as among population controls. For every prostate cancer death prevented 250 men had to be screened and 12 additional cases of prostate cancer were diagnosed.

Subsequent to the publication of the results from the ERSPC, the European Association of Urology published a statement on screening, including: "Over-diagnosis of prostate cancer leads potentially to significant over-treatment. Health professionals, especially urologists, should avoid over-treatment by developing safe methods of cancer surveillance/monitoring without invasive therapy. Invasive therapies should be tailored to patients' needs and the prognosis of cancers diagnosed" and "The EAU wishes to support and foster research needed to develop reliable active surveillance protocols for low-risk prostate cancers, prognostic markers, and targeted therapies in order to deliver optimal patient care" (6).

Active surveillance as a method to reduce over-treatment

Fortunately, the decision to treat or not to treat the patient with localised prostate cancer does not always have to be made immediately following diagnosis. Since the turn of the century a new treatment strategy has emerged: active surveillance with delayed selective intervention.

In brief, patients are selected for active surveillance by prognostic factors indicating a high likelihood of indolent prostate cancer: low tumour volume (local stage T1c-T2a and few biopsy cores with cancer), high tumour differentiation (Gleason score ≤ 6) and low PSA (≤ 10 µg/mL) (7). Low (0.15-0.2 µg/l/cc) PSA density (the serum PSA divided with the prostate volume) and high ratio between free and total serum PSA are additional factors indicating indolent disease (8-10).

The patients are followed every 3-6 months with digital rectal examniation and PSA-tests. Curative therapy is initiated only if there are signs of tumour progression or if the patient actively requests therapy. Most protocols for active surveillance include repeat biopsies scheduled every few years (7)

Active surveillance was introduced in clinical practice on a broad basis without having been tested in randomised clinical trials. In spite of this, The Swedish National Board of Health and Welfare (Socialstyrelsen) recommends active surveillance rather than surgery or radiotherapy for patients with low risk tumours and an expected remaining life-time of 10 to 20 years (11). In Sweden 1,000 patients with newly diagnosed prostate cancer commenced active surveillance in 2008 (data from the National Prostate Cancer Registry of Sweden).

Published results of active surveillance

With 3 to 7 years of median follow-up almost complete absence of prostate cancer deaths is reported, whereas one fifth of the patients died from other causes (12-16). Less than 1% of patients were reported with skeletal metastases. Approximately two thirds of the patients were alive without being treated after 5 years. However, the majority of hitherto presented patient series, which form the basis for our knowledge on active surveillance, are rather unstructured and heterogeneous, both as regards the patient mix and the protocols for follow-up and intervention (7). Randomised studies of active surveillance are lacking. The criteria for active surveillance and for recommending radical therapy are not validated. What parameters should be followed at what intervals and the impact on QoL are not evaluated scientifically. The long-term effects are unknown.

Areas of uncertainty regarding active surveillance

Although most authors who have published reports on active surveillance conclude that deferred curative treatment is feasible following initial active surveillance, some critical

issues must be elucidated before this alternative to immediate radical therapy can be recommended to patients with a long life expectancy (17).

Firstly, how should low-risk, localised prostate cancer be defined? What is the risk that the patient's prostate cancer is already at the edge of ''the window of opportunity'' and should be treated without delay? Most urologists and oncologists agree that patients with a life expectancy of more than 10 years should be recommended immediate treatment if there is a significant proportion of Gleason grade 4 or 5 in the tumour. The problem in this respect is that sampling of the prostate with transrectal biopsies commonly underestimates the Gleason score of the tumour compared to the prostatectomy specimen. The optimal number of biopies and the location of these are still to be defined.

Secondly, what is the risk that the tumour dedifferentiates over time or that poorly differentiated areas of cancer are not sampled at the initial set of biopsies? Some protocols include scheduled biopsies in the follow-up of their patients, whereas others do not (7). The optimal schedule for and extent of repeat biopsies is not known.

Thirdly, what parameters can reliably predict the development of lethal prostate cancer? They must herald progression before the disease becomes incurable, which for prostate cancer is when the primary tumour invades adjacent organs or seeds metastases. Prostate cancer is most often a slowly progressing disease, but the primary tumour may metastasize at a small volume compared to many other cancers. Most likely, the chance for cure is decreased substantially when tumour progression is obvious with digital rectal examination or (12, 15). One problem with PSA as a marker of tumour progression is that poorly differentiated tumours produce less PSA than slowly growing, well-differentiated tumours. Another problem is that many patients with low-risk localised prostate cancer have benign prostatic hyperplasia, which in many cases contributes to most of the PSA measured in blood serum. A small, but comparatively rapidly progressing cancer in a large gland may not give rise to a short PSA doubling time until metastases are seeded.

Fourthly, at what intervals should the patients be reassessed? Most groups reporting on active surveillance have visits scheduled every third month for the first 1–2 yr and every sixth month thereafter. For the majority of patients tumour progression is slow and not much happens from one year to another, but will biannual visits detect progression for all patients with potentially lethal disease? Our knowledge on the biology of the progression from localised prostate cancer to metastatic disease is still scarce.

Fifthly, what is the appropriate information to be discussed with the patient before the treatment strategy for localised prostate cancer is decided? We need long-term results from well conducted studies assessing the risks and benefits of active surveillance to present to our patients.

Sixthly, how does active surveillance for localised prostate cancer affect quality of life? Most patients treated with surgery or radiotherapy for localised prostate cancer will suffer from permanent side-effects with impairment of sexual, urinary or bowel function, which affect quality of life (18-21). The concept of active surveillance aims at avoiding these side-effects of treatment for the majority of patients that do not necessarily need treatment. This aim is reached for the majority of patients (12, 14-15), but what is the psychological impact of the knowledge of having an untreated cancer and of the uncertainty of whether active treatment will be recommended or not at the next scheduled visit? What is the psychological impact of following a biomarker which fluctuates over time? This is of interest not only in prostate cancer, but also in *e.g.* testicular cancer, ovarian cancer, and colorectal cancer. To what extent does delayed treatment lead to more side-effects than immediate treatment would have done (*e.g.* non nerve-sparing surgery or addition of hormonal therapy because of more advanced tumour with delayed therapy)? How do patients cope if deferred treatment with curative intent turns out to be initiated too late, at a time when the disease has already spread? Preliminary results of assessment of quality of life during active surveillance are promising (22-23), but no systematic comparison has as yet been made with a large cohort of men

receiving immediate therapy. Furthermore, there are no reports on anxiety and stress related to the follow-up visits. A recent study showed that one fifth of patients with high PSA values but no cancer diagnosed had high levels of stress and anxiety following prostate biopsies showing benign results, and that for half of them levels remained high for at least 3 months (24). More severe psychological effects can be expected for patients during follow-up for a diagnosed but untreated cancer.

In summary, active surveillance is beyond doubt effective as a strategy to reduce over-treatment, but knowledge is scarce about the risk of missing the window of curability and about how active surveillance affects the quality of life.

Considerations on follow-up and prostate biopsies during active surveillance

There are no results available from studies comparing different schedules of follow-up for patients on active surveillance. The follow-up schedules reported from various centres are fairly similar to each other and to the "standard arm B" in the SAMS-FU trial. These schedules include standard sets of prostate biopsies with 6-12 cores for diagnosis and during follow-up. However, several centres report that 20% to 30% of patients who were candidates for active surveillance but opted for radical prostatectomy, turned out to have intermediate-risk or even high-risk tumours (25-29). Particularly the anterior aspects of the prostatic gland, which cannot be assessed by digital rectal examination and are not sampled at routine biopsies, are likely to harbour large tumours (28, 30).

One method to identify the patients with tumours belonging to a higher risk group is to perform an extensive repeat biopsy, a so called "saturation biopsy". Recent studies indicate that the risk of failing to detect aggressive tumours is decreased if more biopsy cores are taken (31-34).

As a consequence, patients ought not to need as frequent follow-up visits after saturation biopsies as after standard biopsies. This presumption has never been tested in clinical practice and forms the basis for the randomisation in the SAMS-FU trial.

The effects of 5-alpha-reductase inhibitors during active surveillance

Testosterone stimulates cell growth in benign and malignant prostatic tissue. The enzyme converting testosterone to the biologically more active dihydrotestosterone, 5-alpha-reductase, is inhibited by two drugs used for treating benign prostatic hyperplasia: finasteride and dutasteride. Both these substances reduced the incidence of prostate cancer in large, randomised, double-blind, placebo-controlled trials (35-36). The reduction of prostate cancer was only noticed for low-grade cancer. Finasteride was associated with a higher incidence of high-grade cancers, but this was probably an effect of that the detection of such cancers were enhanced by the decreased prostate volume and by improved sensitivity of PSA (37-38). No significant increase in high-grade cancers was observed among the dutasteride-treated men in the REDUCE trial (35), and the sensitivity to detect high-grade cancer was increased at least as much as for finasteride (39).

Although these studies were performed among men without a diagnosis of prostate cancer, the effects were most likely due to decreased progression of small, low-grade tumours. The results ought thus to be applicable for patients on active surveillance, particularly those from the REDUCE study (dutasteride) which included patients with PSA 3 to 10 µg/l (35). The PCPT study (finasteride) included patients with PSA less than 3 µg/l only, and the effect decreased with increasing PSA (36). Dutasteride inhibits both iso-forms of 5-alpha-reductase, whereas finasteride inhibits only the iso-form that is least expressed in prostate cancer tissue (40).

Even if the tumours inhibited by 5-alpha-reductase inhibitors are of low grade (Gleason score ≤ 6) and may never progress to metastatic disease, the effects of 5-alpha-reductase inhibitors may be beneficial for patients on active surveillance for several reasons. Firstly, decreased progression of low-grade tumours would lead to decreased risk of radical therapy

and its subsequent side-effects. Secondly, the increased sensitivity of PSA to detect progression of high-grade tumours may increase the chance of initiating curative therapy in time for those who need it. Thirdly, the decrease in PSA values caused by 5-alpha-reductase inhibitors may be perceived beneficial by the patients and thus reduce stress and anxiety. Fourthly, most of these patients have benign prostatic hyperplasia (BPH), a disease more likely to progress to cause disturbing symptoms in men with PSA values above 3 µg/l (41).

The registered indications for dutasteride (Avodart®) and finasteride (Finasterid, Proscar®) are reduction of symptoms of BPH and reduction of the risks of urinary retention and need for surgery for BPH. Use of these drugs in the SAMS trial will thus be limited to patients with symptoms of BPH. Considering that there is evidence only for dutasteride to reduce progression of prostate cancer and increase the utility of PSA in the range 3 to 10 µg/l, Avodart® may be preferred for patients on active surveillance.

The National Prostate Cancer Registry of Sweden (NPCR) and the INCA data-base

The NPCR includes detailed information on tumour characteristics at the time of diagnosis and primary treatment for patients with prostate cancer. (42). Since 1996 the NPCR covers all of Sweden with 98% completeness compared to the National Cancer Register, in which registration is mandatory and regulated by law. Since 2008 the NPCR uses the INCA data-base with direct on-line registration of data via the Internet. INCA, short for "Information Network for Cancer Care" (Informationsnätverk för cancervården), is owned by the six Swedish oncological centres. The initiation of the INCA project was funded by the Swedish Cancer Foundation. The aims of INCA are to facilitate data acquisition and analysis for the various quality registries for cancer care, including the NPCR, and to be a platform for clinical research. The infrastructure for registration of data for prostate cancer patients, which has been developed by the NPCR and the INCA project, is very well suited to utilize for a clinical study such as SAMS, in which follow-up is intended to be as close to normal clinical practice as possible. At every urological unit in Sweden specific staff-members, usually nurses, continuously enter patient data via INCA to the NPCR. Adding the extra data for patients in the SAMS study will not much increase their work-load.

Clinical significance of the project

The results of SAMS will hopefully contribute to that less patients with indolent low-risk prostate cancer will receive unnecessary treatment and that more patients on active surveillance who need treatment will receive such when the disease is still curable. If the investigational arm for follow-up in the randomised SAMS-FU trial will be equal or better than the standard schedule for follow-up, efficacy of active surveillance can be increased and the health care resources allocated to this large group of patients can be reduced substantially. It is likely that the patients' stress and anxiety will be reduced with less frequent follow-up, but this has to be proved and is therefore investigated in SAMS.

SAMS will yield important knowledge on the outcome, including psychological aspects and quality of life, and on prognostic factors for patients with low-risk prostate cancer on active surveillance. We expect to identify specific psychological issues which increase the patients' anxiety, but are not addressed in today's patient care. Better understanding of these issues would make it possible to inform and support the patients in ways that reduce the psychological side-effects of active surveillance.

As a secondary effect, knowledge will increase among Swedish urologists and urology nurses on this relatively new treatment strategy. SAMS will be the first clinical trial using INCA as a study platform, and the experience will facilitate future clinical cancer studies using the INCA platform.

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Organisation of the Trial

Trial design
SAMS-FU is a prospective, multicentre, randomised, controlled study.
SAMS-ObsQoL is a prospective, multicentre, observational study.

Setting
Swedish urology departments.

ISRCTN number
The International Standard Randomised Controlled Trial Number is ISRCTN64891728.

Ethical review board approval
SAMS-ObsQoL was approved on 25 February 2010 (EPN 2010/62) and SAMS-FU on 5 December 2010 (EPN 2010/598) by the Regional Ethical Review Board at Lund University.

Trial period

Start enrolment date:	February 2011
Stop enrolment date:	2016
End of trial:	2026
First analysis of primary endpoint:	2018 (1 year after completed inclusion)
Principal analysis of primary endpoint:	2022 (5 years after completed inclusion)
Final trial report:	2027

Primary scientific hypothesis of SAMS-FU
For patients with low-risk prostate cancer planned for active surveillance an extensive, initial re-biopsy coupled with less intensive follow-up, including no further scheduled sets of prostate biopsies, will identify aggressive tumours earlier than the standard schedule for re-biopsy and follow-up, without increasing the proportion receiving active therapy with curative intent within 5 years.

Randomisation in SAMS-FU
Patients will be randomised 1:1 to either the investigational arm A with an extensive re-biopsy and less intensive follow-up, or to arm B with standard follow-up. Restricted randomisation with stratified permuted-block design will be used. The stratification will be made for age (above or below 65 years) and for local tumour stage (T1c or T2a).

Planned number of study subjects, statistical considerations
We expect that 30% of the patients will receive treatment with curative intent within 5 years. To reach 80% power in SAMS-FU to detect (two-sided alpha 0.05) a difference in the proportion treated with curative intent within 5 years (the primary endpoint) between 30% (standard arm) and 20% (investigational arm) 440 patients are needed, 220 in each arm. To compensate for patients lost to follow-up and for protocol violations, we intend to include 500 patients in SAMS-FU. If this number is reached before 5 years after the start of inclusion, the study will still continue to include patients until 5 years have passed to increase the statistical power.

We aim at including further 500 patients in SAMS-ObsQoL. For the analyses of quality of life, pelvic symptoms and treatment side-effects another 500 patients receiving treatment with curative intent shortly after diagnosis will be evaluated with the same Internet based questionnaire at the same time intervals for comparison.

Primary endpoint of SAMS-FU
Active therapy for prostate cancer with curative intent within 5 years from diagnosis.

Secondary endpoints
- Detection of more extensive or less differentiated cancer in repeat biopsy
- Therapy for prostate cancer with curative intent after more than 5 years from diagnosis
- Recurrence following therapy with curative intent
- Tumour characteristics in specimens from radical prostatectomy
- Hormonal therapy, chemotherapy or other non-curative therapy, including transurethral operations on the prostate (regardless whether the indication is prostate cancer or benign prostatic hyperplasia)
- Change of strategy to expectancy without curative intent
- Quality of life, symptoms of prostate cancer and side-effects of treatment
- Development of distant metastases
- Death from prostate cancer and from other causes.

Additional analyses
- Prognostic factors correlating with the endpoints, such as tumour extent, PSA (levels, density, kinetics), age, co-morbidity, physical activity, etc.
- Whether 5-alpha-reductase inhibitors facilitate detection of potentially lethal cancers and simultaneously decrease over-treatment of indolent cancers, without increasing the total number of tumours with Gleason score 8-10.
- The stress caused by the visits and PSA tests during follow-up. We hypothesize that the total burden of stress and anxiety will be reduced in arm A since it includes less frequent tests and visits.

Planned stratification of data
Data will be stratified according to
- Age at diagnosis of prostate cancer: Older versus younger than 65 years
- Local tumour stage: T1c versus T2a
- Patients fullfilling all inclusion and exclusion criteria in SAMS-ObsQoL versus those that do not.
- Treatment with 5-alpha-reductase inhibitors: < 1 year, > 1 year, or none.

Planned time-points for analyses
The first analysis for the primary endpoint of SAMS-FU will be performed 1 year after inclusion of the last patient. The second and final analysis will be performed 5 year after inclusion of the last patient. Both "intention to follow-up" according to study arm and "follow-up received" will be analysed.

The first analyses for the secondary endpoints will be performed after inclusion of the last patient. Subsequent analyses will be performed 5 and 10 years after inclusion of the last patient.

Economical issues
The study will be financed by several non-profit research foundations, none of which will be allowed to influence the protocol. Participating centres will receive reasonable economical compensation for their work during the study. During the initial phase, grants were received from Örebro läns landstings särfond nr 5, Gorthons stiftelse, The Swedish Cancer Foundation, and Gunnar Nilssons Cancerstiftelse.

Organisation of the SAMS study group
The steering committee includes the principal investigator, one urologist from each of the six health care regions in Sweden, one representative for the regional oncological centres and the INCA database, one research nurse, and one external expert (Appendix 4). A urologist is investigator at each participating study centre.

Data monitoring and safety committee
An independent committee will monitor the study outcome annually. If an unacceptable proportion of patients experience an adverse outcome (e.g. poorly differentiated or advanced cancer at initial re-biopsy in arm A, or metastastic disease or relapse after treatment with curative intent) this committee will request the SAMS steering committee to close the study.

We expect that less than 5% of the patients develop distant metastases and less than 2.5 % to die from prostate cancer within 10 years. The mortality from other causes than prostate cancer is expected to exceed the mortality from prostate cancer with a factor of at least 10 within the first 10 years of follow-up.

Since patients randomised to the investigational arm A in SAMS-FU will be subjected to more extensive initial prostate biopsies, a greater proportion of their tumours will fulfil the criteria for intervention at that time. Up to 30 percentage points more patients receiving active treatment within the first year following randomisation in arm A will therefore be accepted.

Plan of the Trial

Registration and randomisation
Patients are registered the regional INCA website: www.vinkcancer.se/sv/INCA, where they receive an individual study number. After inclusion in SAMS-FU, the patients are randomised automatically to either the investigational arm A or to the standard arm B.

Investigations prior to inclusion
- Blood samples within 2 months: PSA, creatinine, hemoglobin
- A general physical examination performed within 6 months

Baseline data, registered at the time of inclusion
- Co-morbidity (ASA classification)
- Family history of death in CVD (in patient questionnaire only)
- Smoking habits and physical activity (in patient questionnaire only)
- Height and weight for calculation of BMI (in patient questionnaire only)
- Pelvic symptoms and quality of life (in patient questionnaire only)
- PSA, including previous values within the past 2 years
- Prostate volume
- TNM classification according to UICC 2002
- Biopsy and pathology data with Gleason score according to ISUP 2005
- Whether a prostate MRI was performed prior to inclusion or not

Treatment with 5-alpha-reductase inhibitors
Patients with symptomatic benign prostatic hyperplasia (prostate volume ≥ 30 cc) should be counselled about the possible benefits and side-effects of 5-alpha-reductase inhibitors. Treatment decisions are then made at the discretion of the investigating urologist and the individual patient. Dutasteride is recommended because of evidence for decreased progression of low-grade prostate cancer and enhanced sensitivity for detecting high-grade prostate cancer among men with PSA 3 to10 µg/ml, but treatment with finasteride is an alternative. The criteria for intervention differ for patients with and without medication with 5-alpha-reductase inhibitors (see below).

Inclusion criteria
- Age 40 to 75 years
- Expected remaining life-time of more than 10 years
- Diagnosis of prostate cancer within the previous 6 months
- Peripheral zone prostate cancer diagnosed with a set of biopsies including 6-12 cores*
- Local therapy with curative intent is planned if progression during follow-up
- The patient has understood the concept of active surveillance and signed informed consent
- PSA < 13 µg/l
- PSA doubling time > 3 years during the last 2 years (if PSA-history available)
- PSA increase of < 2 µg/l during the last 2 years (if PSA-history available)
- PSA density < 0.2 µg/l/cc*
- Tumour stage (UICC 2002) T1c or T2a*
- Prostate volume < 90 cc*
- Gleason score ≤ 6* with no grade 4* or 5
- ≤ 33% of cores with cancer*
- ≤ 6 mm cancer in any one biopsy*

* Patients with T1-2, Gleason score ≤ 7 tumours may be included in SAMS-ObsQoL even if these criteria are not fulfilled. See comments below.

Exclusion criteria
- Cancer in prostate biopsy cores sampling exclusively the anterior parts of the gland*
- Cancer diagnosed at TUR-P*
- Evidence of metastatic cancer
- Any previous therapy for prostate cancer
- Treatment with 5-alpha-reductase inhibitors during the previous 12 months*
- Additional sets of prostate biopsies within the previous 12 months*
- Recurrent urinary tract infection or bacterial prostatitis
- Ano-rectal disease interfering with digital rectal examination or ultrasound
- Any other disease or circumstance that may interfere will study-related procedures

* These exclusion criteria do not apply to SAMS-ObsQoL. See comments below.

Comments on the inclusion of patients not fulfilling all criteria above in SAMS-ObsQoL
Some patients with low or intermediate risk tumours may, for various individual reasons, opt for active surveillance even if their prostate cancer does not fulfil all the criteria above. These patients may be included in SAMS-ObsQoL. The reason for including also patients with somewhat larger or less differentiated tumours is that SAMS in this way better reflects the current clinical practice in Sweden.

Follow-up and investigations during the study
Patients will be followed for a maximum of 15 years according to Appendix 3. Follow-up data will be registered annually via the Internet to CRFs in the INCA data-base. Patients will be contacted by the regional monitor when it is time to fill in the questionnaire.

Biopsy protocol

The method of sampling (diagonal "standard", or parallel "end-fire" biopsy canal), number and location (periphery of peripheral zone, paramedian peripheral zone, anterior) of biopsy cores, the total length of tissue and cancer, and the Gleason score are registered.

It is essential that urologists performing prostate biopsies in SAMS-FU are familiar with the method for sampling the anterior aspects of the gland. Particular attention should always be taken to obtain adequate sampling from the apex of the prostate.

In SAMS-FU the patients must be subjected to a set of biopsies within 3 months from randomisation according to randomisation arm (see Appendix 4 for definitions of the anatomical zones of the prostatic gland).

In SAMS-ObsQoL, in addition to the initial, diagnostic, biopsy a second set of biopsies should be obtained within 6 months from diagnosis (before or after). If not performed earlier, this second set may be performed after inclusion of the patient in the study.

SAMS-FU investigational arm A:

- Prostate volume < 30 cc (15-19 cores):
    - 8 symmetrically distributed cores in the periphery of the peripheral zone
    - 2 symmetrically distributed paramedian cores in the peripheral zone
    - 4 symmetrically distributed paramedian cores in the anterior part of the gland
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies
- Prostate volume 30-59 cc: (19-23 cores):
    - 10 symmetrically distributed cores in the periphery of the peripheral zone
    - 4 symmetrically distributed paramedian cores in the peripheral zone
    - 4 symmetrically distributed paramedian cores in the anterior part of the gland
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies
- Prostate volume 60-89 cc: (23-27 cores):
    - 12 symmetrically distributed cores in the periphery of the peripheral zone
    - 4 symmetrically distributed paramedian cores in the peripheral zone
    - 6 symmetrically distributed paramedian cores in the anterior part of the gland
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies

SAMS-ObsQoL and SAMS-FU standard arm B:

- Prostate volume < 30 cc: (9-13 cores):
    - 8 symmetrically distributed cores in the periphery of the peripheral zone
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies
- Prostate volume 30-59 cc: (11-15 cores):
    - 10 symmetrically distributed cores in the periphery of the peripheral zone
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies
- Prostate volume 60-89 cc: (13-17 cores):
    - 12 symmetrically distributed cores in the periphery of the peripheral zone
    - 1-2 extra cores from each area with cancer in the diagnostic set of biopsies

If the PSA value reaches the criteria for intervention but the patient is not treated, the next set of biopsies should be performed as in arm A.

In SAMS-FU experimental arm A no further sets of biopsies are scheduled following the initial re-biopsy, but biopsies as above should be obtained if PSA increases above the level for the criteria for intervention and the patient is not treated.

In SAMS-ObsQoL and SAMS-FU standard arm B further sets of biopsies are scheduled every second year after the re-biopsy with the same pattern of sampling as above. Biopsies are not obligatory in SAMS-ObsQoL from month 48 if PSA has increased < 0.5 µg/l during the past 2 years.

Criteria for initiating therapy with curative intent

- DRE or TRUS indicates progression
- Pathological progression:
  - > 33 % positive cores (additional cores from previous cancer site excluded)
  - > 6 mm cancer in any biopsy core
  - Any Gleason grade 4 or grade 5
- PSA increase* (patients not taking dutasteride or finasteride):
  - To total PSA > 15 µg/l
  - PSA density > 0.3 µg/l/cc
  - PSA doubling time < 3 years during the last 2 years
  - PSA increase of > 2 µg/l during the last 2 years
- PSA increase* (patients taking dutasteride or finasteride):
  - PSA density > 0.2 µg/l/cc
  - PSA increase of > 1 µg/l above nadir
- Physician's recommendation for other reasons
- Patient's request

* Since PSA values may fluctuate considerably due to infection and other benign causes, treatment decisions should always be based on 3 or more measurements. Unexpected rises of PSA should prompt a new PSA test within 1-3 months. If the PSA value is then declining, benign causes for the previous rise should be considered. Values considered not representative for evaluating the PSA kinetics of the tumour are marked as such in the CRF.

Registration of active therapy

- Cause of termination of active surveillance
- Type of therapy, including neoadjuvant and adjuvant therapy
- Pathology report, if surgery

Refraining from therapy if therapy is indicated by the protocol

If any of the criteria for initiating therapy is met but no such therapy is initiated, the reasons should be registered: patient's choice, physician's recommendation because the expected remaining life-time of the patient is considered too short in relation to the characteristics of the cancer, because the PSA values were not considered to reflect tumour progression (e.g. because of infection), or other. For patients in SAMS-ObsQoL and in both study arms of SAMS-FU an extensive set of biopsies, similar to the initial re-biopsy in arm A, is strongly recommended.

Assessment of quality of life, side effects of treatment and pelvic symptoms

The questionnaire consists of three parts: the first part assesses attitudes to and experiences of active surveillance, the second part various aspects of quality of life including the Hospital Anxiety and Depression Scale (HADS), and the third part pelvic symptoms, including possible side-effects of local therapy. The first part is developed based on the experience from previous studies on patients with localised prostate cancer. The third part is identical to the NPCR questionnaire ("Sverige-enkäten"), a validated instrument generally recommended in Sweden for patients who receive treatment with curative intent.

Assessments will be made at baseline, after 1 year and then every second year. The questionnaires are filled in by the patients via the Internet. The patients receive a written instruction of how this is done, including their individual study number which is the password for the Internet site, at the time for inclusion. The comparison group receiving treatment with curative intent shortly after diagnosis is evaluated with the same questionnaire at the same time intervals. The first questionnaire should be answered before any treatment is initiated.

An additional study will be performed for a subgroup of 100 patients, in which quality of life assessment will be made at short intervals before, at and after visits to their urologist. The

aim is to investigate the stress caused by the visits. The patients will be asked to fill in questionnaires including validated forms for assessing anxiety and targeted stress, HADS and IES, as well as ad hoc questions.

Patients that receive therapy that fails to cure them may be mentally affected by being treated too late, having missed the "window of opportunity". This will be studied specifically, but the methods for this are not yet defined.

Termination of active surveillance

Active surveillance is terminated if any anticancer therapy is initiated (radiotherapy, surgery, medical therapy other than 5-alphareductase inhibitors) or if the intention of follow-up is changed from curative to not curative ("classical" expectancy, watchful waiting). The following data should be registered when active surveillance is terminated:

- *Type of therapy, if initiated*
  Curative intent: surgery, radiotherapy, other.
  Not curative intent: endocrine therapy, other.
- *Reasons for therapy, if initiated*
  One or more of the criteria for initiating therapy should be registered as the reason for initiating active therapy. If therapy without curative intent is initiated, the reason for not choosing therapy with curative intent should be registered (patient's request, expected remaining life-time too short, other).
- *Reasons for changing to expectancy without curative intent*
  If decided that therapy with curative intent will not be indicated in the future, the reasons for this change of strategy should be registered: (patient's request, additional co-morbidity, advanced age, other).

Follow-up after termination of active surveillance

Following termination of active surveillance (therapy for prostate cancer initiated or change to expectancy without curative intent), the only investigation performed according to the SAMS protocol is:

- Bone scan every 12 months for untreated patients with PSA > 50 µg/l and for patients on endocrine therapy with PSA > 25 µg/l, if no distant metastases has been detected previously

The absence or occurrence the following events should be registered:

- Recurrence after treatment with curative intent
  - After surgery: PSA > 0,2 µg/l and rising
  - After radiotherapy: PSA > 2 µg/l and rising
  - Confirmed recurrence (e.g. histopathology) with PSA less than above
- Symptoms from progression of prostate cancer
- Distant metastases verified by imaging, cytology or histopathology
- Lost to follow-up because of emigration, withdrawal of study consent, etc
- Date of death

The cause of death will be evaluated and defined by a specific committee. It will be categorised as prostate cancer as a direct cause, prostate cancer as a contributing cause, complication of treatment for prostate cancer, other cancer, cardiovascular disease, or other.

List of amendments

The following changes in the protocol from SAMS 2.0 to 2.1 were decided at the steering committee meeting at Arlanda, September 27th, 2012. Only the inclusion and intervention criteria were changed. Changes are underlined. SAMS 2.1.1 was decided by the steering committee January 28th 2014.

Inclusion criteria (2.0)
- Age 40 to 75 years
- Expected remaining life-time of more than 10 years
- Diagnosis of prostate cancer within the previous 6 months
- Peripheral zone prostate cancer diagnosed with a set of biopsies including 6-12 cores*
- Local therapy with curative intent is planned if progression during follow-up
- The patient has understood the concept of active surveillance and signed informed consent
- PSA < 10 µg/l
- PSA doubling time > 3 years during the last 2 years (if PSA-history available)
- PSA increase of < 2 µg/l during the last 2 years (if PSA-history available)
- PSA density < 0.2 µg/l/cc*
- PSA free to total ratio ≥ 0.1 (10%)*
- Tumour stage (UICC 2002) T1c or T2a*
- Prostate volume < 90 cc*
- Gleason score ≤ 6* with no grade 4* or 5
- ≤ 25% of cores with cancer*
- ≤ 4 mm cancer in any one biopsy*

* Patients with T1-2, Gleason score ≤ 7 tumours may be included in SAMS-ObsQoL even if these criteria are not fulfilled. See comments below.

Inclusion criteria (2.1)
- Age 40 to 75 years
- Expected remaining life-time of more than 10 years
- Diagnosis of prostate cancer within the previous 6 months
- Peripheral zone prostate cancer diagnosed with a set of biopsies including 6-12 cores*
- Local therapy with curative intent is planned if progression during follow-up
- The patient has understood the concept of active surveillance and signed informed consent
- PSA < 13 µg/l
- PSA doubling time > 3 years during the last 2 years (if PSA-history available)
- PSA increase of < 2 µg/l during the last 2 years (if PSA-history available)
- PSA density < 0.2 µg/l/cc*
- ~~PSA free to total ratio ≥ 0.1 (10%)*~~ [this inclusion criterion is omitted]
- Tumour stage (UICC 2002) T1c or T2a*
- Prostate volume < 90 cc*
- Gleason score ≤ 6* with no grade 4* or 5
- ≤ 33% of cores with cancer*
- ≤ 6 mm cancer in any one biopsy*

* Patients with T1-2, Gleason score ≤ 7 cancers and PSA < 20 µg/l may be included in SAMS-ObsQoL even if these criteria are not fulfilled. See comments below.

List of amendments (continued)

Criteria for initiating therapy with curative intent (2.0)

- DRE or TRUS indicates progression
- Pathological progression:
  - > 25 % positive cores (additional cores from previous cancer site excluded)
  - > 4 mm cancer in any biopsy core
  - Any Gleason grade 4 or grade 5
- PSA increase* (patients not taking dutasteride or finasteride):
  - To total PSA > 10 µg/l
  - PSA density > 0.3 µg/l/cc
  - PSA doubling time < 3 years during the last 2 years
  - PSA increase of > 2 µg/l during the last 2 years
- PSA increase* (patients taking dutasteride or finasteride):
  - PSA density > 0.2 µg/l/cc
  - PSA increase of > 1 µg/l above nadir
- Physician's recommendation for other reasons
- Patient's request

Criteria for initiating therapy with curative intent (2.1)

- DRE or TRUS indicates progression
- Pathological progression:
  - > 33 % positive cores (additional cores from previous cancer site excluded)
  - > 6 mm cancer in any biopsy core
  - Any Gleason grade 4 or grade 5
- PSA increase* (patients not taking dutasteride or finasteride):
  - To total PSA > 15 µg/l
  - PSA density > 0.3 µg/l/cc
  - PSA doubling time < 3 years during the last 2 years
  - PSA increase of > 2 µg/l during the last 2 years
- PSA increase* (patients taking dutasteride or finasteride):
  - PSA density > 0.2 µg/l/cc
  - PSA increase of > 1 µg/l above nadir
- Physician's recommendation for other reasons
- Patient's request

2.1.1

Flow-chart page 22: Addition of "*** Not obligatory in SAMS-ObsQoL if PSA has increased < 0.5 µg/l during the past 2 years." . The biopsy from month 48 was marked ***.

Page 14: The underlined sentence was added at the bottom of the page: "In SAMS-ObsQoL and SAMS-FU standard arm B further sets of biopsies are scheduled every second year after the re-biopsy with the same pattern of sampling as above. Biopsies are not obligatory in SAMS-ObsQoL from month 48 if PSA has increased < 0.5 µg/l during the past 2 years."

Page 12: The underlined sentences were added:

Baseline data, registered at the time of inclusion

- Co-morbidity (ASA classification)
- Family history of death in CVD (in patient questionnaire only)
- Smoking habits and physical activity (in patient questionnaire only)
- Height and weight for calculation of BMI (in patient questionnaire only)

Appendix 1: Calculation of the PSA doubling time (PSA-DT)

PSA-DT correlates with the rate of progression of prostate cancer, but there is disagreement on how it should be calculated (van den Berg et al., Eur Urol 2008, 54:505). For example, if one uses all available PSA values from a long period of time, the calculation will be less affected by variations due to other factors than cancer progression such as infection. However, if a cancer that has initially been progressing very slowly changes phenotype to a more rapidly progressing one, this will not affect the PSA-DT much if one uses all PSA values sampled during several years. On the other hand, if one uses only the last 2 or 3 values, the PSA-DT may be much affected by a single value that may not be relevant for assessing the progression of the cancer.

In the SAMS study, we recommend that only the PSA values from the last 2 years are included and that the regression method is used for the calculation of the PSA-DT (Zhang et al., J Urol 2006, 176:1392). At least 3 values more than 2 months apart should be used for calculating the PSA-DT. There will be no central calculation of PSA-DTs during the study. It will thus be the investigators' responsibility to calculate the PSA-DT. An advantage of this practice is that the investigators may choose to disregard some PSA values, *e.g.* values affected by a urinary tract infection.

PSA-DT can be calculated by using the Memorial Sloan-Kettering Cancer Center Internet prediction tool, accessible at:

www.mskcc.org/applications/nomograms/prostate/PsaDoublingTime.aspx

To increase the sensitivity of the protocol to detect rapidly progressing cancers, PSA velocity (PSA-V) is also assessed as a criterion for inclusion and intervention in the SAMS study.

Appendix 2: Considerations on the expected remaining life-time

One of the inclusion criteria in the SAMS study is an expected remaining life-time of more than 10 years. The investigator should try to include all factors mentioned below to estimate the patients expected remaining life-time. Co-morbidity is likely to increase during follow-up, and age is definitely going to do so. If a patient's expected remaining life-time is estimated to clearly less than 10 years during follow-up, the treatment strategy should be changed from active surveillance to expectancy without curative intent. If so, this should be registered in the CRF.

Age
The average remaining life-time of Swedish men of different ages can be found via www.scb.se (search for "Återstående livslängd"). For example, men aged 65 years live another 18 years, men aged 70 years another 14 years, and men aged 75 years another 11 years, on average. However, this information relates to all Swedish men at a specific age and only hints the remaining number of years for an individual man. Men with more than average co-morbidity at a specific age are likely to live shorter, and *vice versa*.

Co-morbidity
Although the ASA-classification is registered at inclusion of SAMS, it is a blunt instrument on an individual basis. For patients with significant cardiovascular, pulmonary, renal, endocrine or other serious chronic disease it is advisable to consult the physician responsible for the treatment of the patient's disease regarding the risk of his death within 10 years.

Physical activity
There is a strong inverse correlation between physical activity and mortality (e.g. Leitzman et al., Arch Intern Med. 2007, 167:2453). The weekly physical activity is assessed at baseline in SAMS with the same categorisation as in the study by Leitzman et al.

Heredity
The cause of and the age at death of first- and second-degree relatives also affect a patient's life-expectancy. If most relatives have reached very old age an individual is more likely to do so too, than if most relatives have died early in cardiovascular disease. The heredity for cardiovascular death before the age of 80 years is assessed at baseline in SAMS.

Other risk factors
Smoking, alcohol or drug abuse, obesitas, hypertension and hyperlipidemia are examples of factors that affect an individual's chance of longevity. Although it is difficult to define their exact impact, they should be considered together with the other factors that affect the patients' life-expectancy. Smoking and BMI are assessed at baseline in SAMS.

Appendix 3: Follow-up schedule for patients on active surveillance.

After termination of active surveillance the patients are followed according to clinical practice and events are registered annually. Bone scan should be performed every 12 months if PSA is > 50 µg/l for patients without and > 25 µg/l for patients with endocrine therapy, if no distant metastases are detected previously.

Investigational arm A of SAMS-FU

Follow-up should, if possible, be made within (+/-) 1 month from schedule.

Month	**-3 to 0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**
Year					**1**				**2**		**3**		**4**
Informed consent	x												
PSA	x		x		x		x		x		x		x
DRE	x				x				x				x
TRUS/biopsies*	x												
Physical examination	x												
Co-morbidity	x												
Family history CV death	x												
Smoking habits	x												
BMI	x												
Physical activity	x												
QoL & symptoms**	x				x						x		

Month	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**	**102**	**108**	**114**	**120**
Year		**5**		**6**		**7**		**8**		**9**		**10**
PSA	x	x	x	x	x	x	x	x	x	x	x	x
DRE		x		x		x		x		x		x
TRUS/biopsies												
QoL & symptoms**		x				x				x		

Month	**126**	**132**	**138**	**144**	**150**	**156**	**162**	**168**	**172**	**180**
Year		**11**		**12**		**13**		**14**		**15**
PSA	x	x	x	x	x	x	x	x	x	x
DRE		x		x		x		x		x
TRUS/biopsies*										
QoL & symptoms**		x				x				x

* If the PSA value reaches the criteria for intervention but the patient is not treated, a set of biopsies should be taken with the same number and location of cores as the re-bipopsy.

** At inclusion the investigator should inform the patient how to get access to the questionnaire via the Internet. During follow-up the patients will be notified mail when it is time to fill in the questionnaire.

SAMS ObsQoL
Standard arm B of SAMS FU

Follow-up should, if possible, be made within (+/-) 1 month from schedule.

Month	**-3 to 0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**
Year					**1**				**2**		**3**		**4**
Informed consent	x												
PSA	x	x	x	x	x	x	x	x	x	x	x	x	x
DRE	x		x		x		x		x		x		x
TRUS/biopsies*	x								x				x***
Physical examination	x												
Co-morbidity	x												
Family history CV death	x												
Smoking habits	x												
BMI	x												
Physical activity	x												
QoL & symptoms**	x				x						x		

Month	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**	**102**	**108**	**114**	**120**
Year		**5**		**6**		**7**		**8**		**9**		**10**
PSA	x	x	x	x	x	x	x	x	x	x	x	x
DRE		x		x		x		x		x		x
TRUS/biopsies*				x***				x***				x***
QoL & symptoms**		x				x				x		

Month	**126**	**132**	**138**	**144**	**150**	**156**	**162**	**168**	**172**	**180**
Year		**11**		**12**		**13**		**14**		**15**
PSA	x	x	x	x	x	x	x	x	x	x
DRE		x		x		x		x		x
TRUS/biopsies*				x***				x***		
QoL & pelvic symptoms**		x				x				x

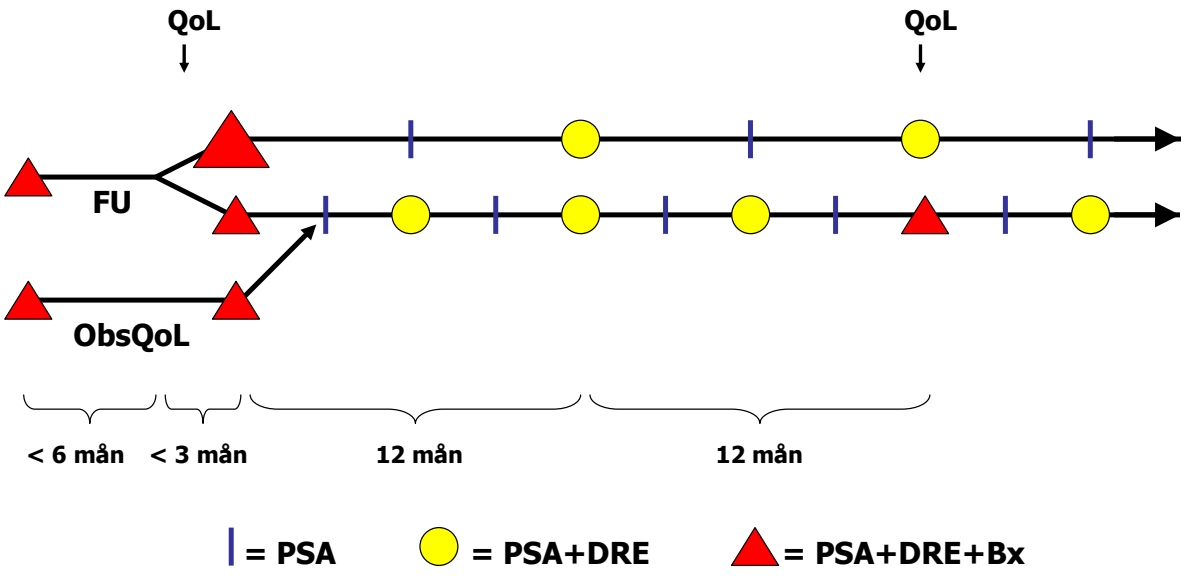
* If the PSA value reaches the criteria for intervention but the patient is not treated, the next set of biopsies should be taken with the same number and location of cores as in arm A.

** At inclusion the investigator should inform the patient how to get access to the questionnaire via the Internet. During follow-up the patients will be notified mail when it is time to fill in the questionnaire.

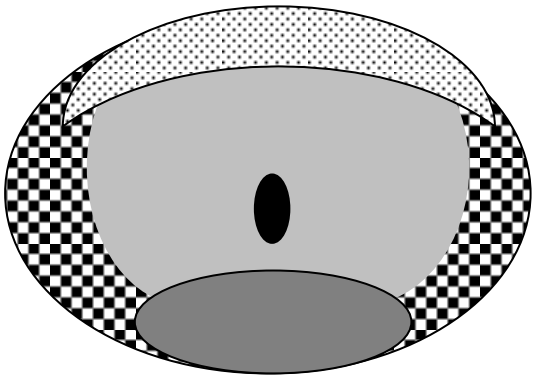
*** Not obligatory in SAMS-ObsQoL if PSA has increased < 0.5 µg/l during the past 2 years.

Flow chart for the first years of the SAMS.

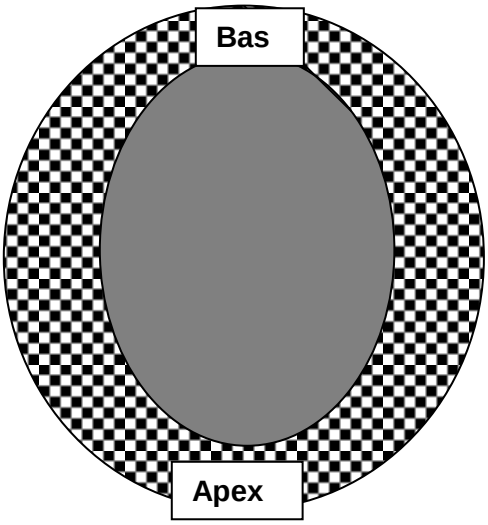
Patients in SAMS-ObsQoL are managed similarly as patients randomised to standard follow-up in SAMS-FU. The larger red triangle represents an extensive re-biopsy and the smaller standard biopsies..



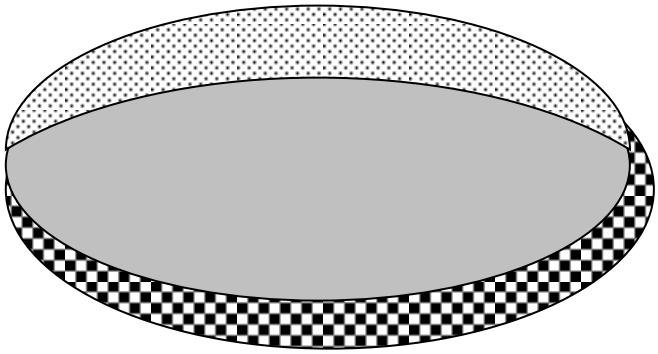
Appendix 4a: Definition of anatomical localisation of biopsies



A: Transverse section of the prostate
Squares represent the lateral part of the peripheral zone, dark grey the paramedian parts of the peripheral zone, light grey the adenomas in the transitional zone, dotted area where anterior cores should be sampled.

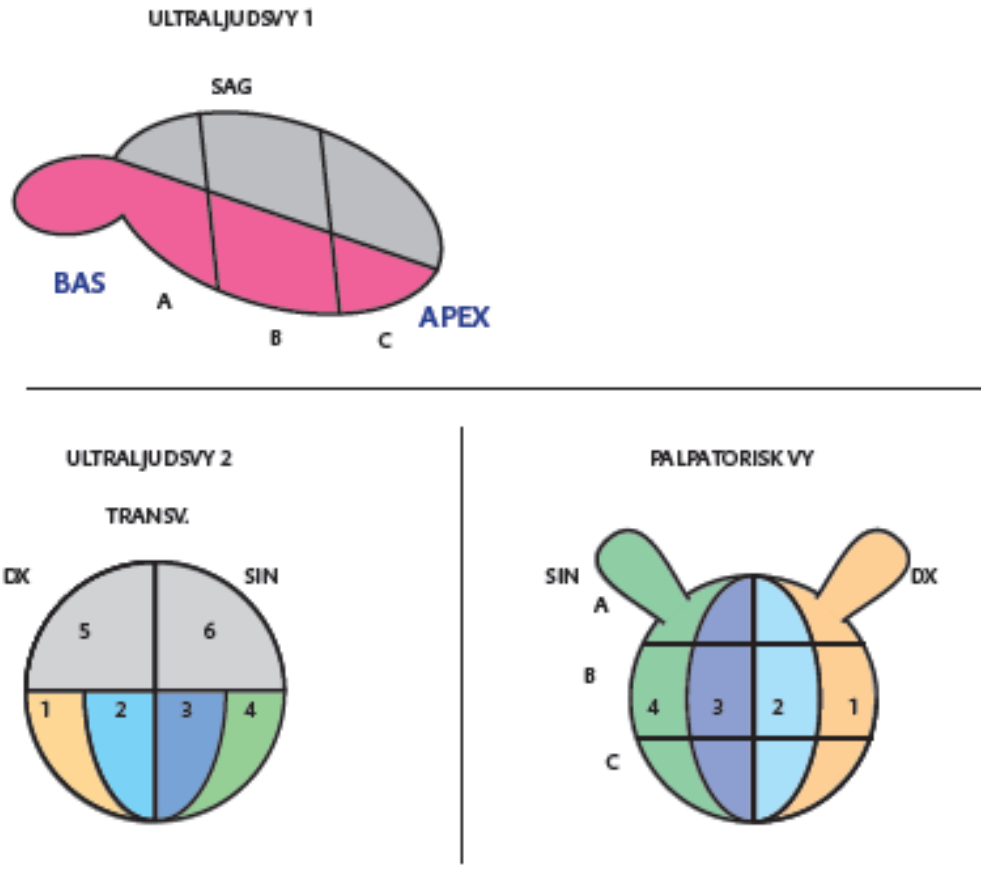


B: Dorsal aspect of the prostate
Squares represent the periphery of the peripheral zone, dark grey the paramedian parts of the peripheral zone.



C: Sagittal, paramedian section
Dotted area represents where anterior cores should be sampled, light grey the adenoma in the transitional zone, squares represent the peripheral zone.

Appendix 4b: Alternative figures for definition of the anatomical localisation of the biopsies



The periphery of the peripheral zone = A1, B1, C1, A2, C2, A3, C3, A4, B4, C4
Paramedian peripheral zone = B2 & B3
Paramedian anterior zone = A5, A6, B5, B6, C5, C6

Appendix 5: The steering committee of SAMS

Ola Bratt, MD, PhD, FEBU. *Principal investigator* for SAMS. Associate professor, Lund University. Consultant urological surgeon, Dept of Urology, Helsingborg Hospital

Eva Johansson, MD, PhD. *Responsible for quality-of-life ssessment.* Consultant urological surgeon, Dept of Urology, Academic Hospital, Uppsala

Annika Nilsson. Research nurse. Department of Urology, Helsingborg Hospital

Maria Nyberg. Research nurse. Department of Urology, Sahlgrenska University Hospital, Gothenburg

David Robinson, MD, PhD. Consultant urological surgeon, Dept of Urology, Ryhov Hospital, Jönköping

Andreas Josefsson, MD, PhD. Resident in urology, Department of Urology, Sahlgrenska University Hospital, Gothenburg

Erik Holmberg, PhD. Statistician, Oncological Centre, Gothenburg

Ove Andrén, MD, PhD. Consultant urological surgeon, Head of the Department of Urology, Örebro University Hospital

Stefan Carlsson, MD, PhD. Consultant urological surgeon, Head of the Prostate Cancer Team, Dept of Urology, Karolinska Hospital, Stockholm

Jonas Sandberg, MD. onsultant urological surgeon, Dept of Urology, Umeå University Hospital.

Pär Stattin, MD, PhD. Professor, consultant urological surgeon, Dept of Urology, Umeå University Hospital. Chairman of the National Prostate Cancer Registry

Lars Holmberg, PhD. Professor, Cancer Epidemiology Unit, King's College, London

The Following appendices are found in separate pdf-files

Appendix 6: Patient information for SAMS-ObsQoL, SAMS-FU and comparison group

Appendix 7: Questionnaire for quality of life assessment

Appendix 8: Questionnaire for assessment of pelvic symptoms (“Sverige-enkäten”)