SPCG-17
Prostate Cancer Active Surveillance Trigger Trial (PCASTT)

Scandinavian Prostate Cancer Group

Sponsor protocol number
SPCG-17, version 4.3 dated 2017-11-29

Clinical study phase
Phase III

Sponsor
Anna Bill-Axelson
Department of Surgical Sciences, Urology
Uppsala University

Coordinating Investigator
Anna Bill-Axelson
Uppsala University, Urology
Dag Hammarskjölds väg 26
SE-752 37 Uppsala
anna.bill.axelson@surgsci.uu.se
+46 (0) 701 679747
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APPENDIX I - QUALITY-OF-LIFE QUESTIONNAIRE
I. PROTOCOL SIGNATURE PAGE

Investigator’s Statement of Compliance

I have read and understood this protocol; version version 4.3 (dated 2017-11-29), and agree to conduct the study accordingly. I have also understood that this protocol contains information that is confidential. This information is provided to me as an investigator. The content of this protocol may not be disclosed to any other person without prior permission from sponsor. The foregoing shall not apply to disclosure required by governmental regulations or laws. However, I will prompt notice sponsor of any such disclosure. The study will be carried out in accordance with the Helsinki Declaration and Good Clinical Practice ICH-GCP. I have read and agree to comply with the investigator’s obligations stated in this protocol. I have understood that deviations from the protocol are to be made in the form of amendments, which must have prior written approval by the sponsor and the relevant Ethics Committee. I agree to ensure that all personnel that assist me in the conduct of the study are aware of their obligations. I agree to report any Serious Adverse Events to the sponsor and as required to the relevant Ethics Committee and Regulatory Authorities. This signature below constitutes the approval of this protocol and assurance that the study will be conducted accordingly.

Anna Bill-Axelson

Coordinating principle investigator name (print)

Coordinating principle investigator signature

Date (DD-MM-YYYY)
**Investigator’s Statement of Compliance**

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__________________________________
Investigator name (print)

______________________________
Investigator signature

______________________________
Date (DD-MM-YYYY)
# 2. TRIAL SYNOPSIS and FLOW CHART

<table>
<thead>
<tr>
<th>Study title</th>
<th>Prostate Cancer Active Surveillance Trigger Trial (PCASTT)</th>
</tr>
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<tbody>
<tr>
<td>Short title</td>
<td>SPCG-17</td>
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<tr>
<td>Clinical study phase</td>
<td>Phase III</td>
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<tr>
<td>Study objective</td>
<td>To test the safety of an AS protocol comparing current practice with standardized triggers for the initiation of curative treatment</td>
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<tr>
<td>Reference arm (1)</td>
<td>Current practise for AS</td>
</tr>
<tr>
<td>Intervention arm (2)</td>
<td>Standardized triggers for initiation of curative treatment</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized multicentre open-label clinical trial</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Newly diagnosed men (within 12 months) with untreated ≤T2a prostate adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>PSA &lt;15 ng/ml, PSA density ≤ 0.2 ng/ml/cc</td>
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<tr>
<td></td>
<td>All Gleason pattern 3+3=6 or Gleason pattern 3+4=7 (&lt;3 cores (or &lt;30% of cores if more than ten cores are taken), &lt;10 mm cancer in one core)</td>
</tr>
<tr>
<td></td>
<td>Life expectancy &gt;10 years with no upper age limit</td>
</tr>
<tr>
<td></td>
<td>Candidate for curative treatment if progression occurs</td>
</tr>
<tr>
<td></td>
<td>Signed written informed consent</td>
</tr>
<tr>
<td>Study start</td>
<td>Start of enrolment September 2016</td>
</tr>
<tr>
<td>Planned study stop</td>
<td>Planned end of enrolment 2020</td>
</tr>
<tr>
<td>Planned end of trial</td>
<td>Planned End of Study 2030</td>
</tr>
<tr>
<td>Planned data analysis</td>
<td>One year after enrolment stopped</td>
</tr>
<tr>
<td>Number of patients</td>
<td>2000</td>
</tr>
<tr>
<td>Primary variable</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>All analyses will follow the principle of intention to treat. The cumulative progression-free survival in the current practise group after five years from randomization is assumed to be 98%. We wish to be able to detect an absolute difference of 1.3% in the experimental arm. The risk of type 1 error is accepted as 5% with a two-sided test. The risk of type 2 errors shall be 15% corresponding to a power of 85%.</td>
</tr>
<tr>
<td>Participating countries</td>
<td>This is a multinational study involving the following countries: Sweden, Finland, Denmark, Norway, and England.</td>
</tr>
</tbody>
</table>
Patients who agree to randomization

- T1-T2a
- Gleason 3+3
- Gleason 3+4 (less than 3 cores (or less than 30% of cores if more than 10 cores are taken), and less than 10 mm in one core)
- PSA density less than or equal to 0.2 ng/ml/cc and total PSA less than 15 ng/ml
- More than 10 years of expected survival and deemed candidate for curative treatment at progression

TRIGGERS FOR RE-BIOPSIES

ARM 1
Current practice (urologist's judgement)

ARM 2
I. PSA density > 0.2 ng/ml/cc (systematic biopsies) and then at every 0.1 ng/ml/cc increase

II. MRI progression in men with previously only Gleason 3+3
   - ≥ 5 mm or more increase in size in any dimension of a measurable lesion (a measurable lesion is defined as ≥ 6 mm in longest diameter in any dimension in best depicted MR sequence)
   - Increase in PI-RADS score to 3, 4 or 5
   - High or very high suspicion of extra-capsular extension or seminal vesicle invasion
   - A new lesion with PI-RADS score 3, 4 or 5

III. MRI progression in men with Gleason grade 3+4
   - ≥ 5 mm or more increase in size in any dimension of a measurable lesion (a measurable lesion is defined as ≥ 6 mm in longest diameter in any dimension in best depicted MR sequence)
   - A new lesion with PI-RADS score 3, 4 or 5

TRIGGERS FOR CURATIVE TREATMENT

ARM 1
Current practice (urologist's judgement)

ARM 2
I. MRI progression in lesions with confirmed Gleason grade 4:
   - Increase in PI-RADS score to 4 or 5
   - High or very high suspicion of extra-capsular extension or seminal vesicle invasion

II. Pathological progression:
   - Gleason pattern 5
   - Primary Gleason pattern 4 in any core with ≥ 5 mm cancer
   - Gleason 3+4 in ≥ 3 cores (or ≥ 30% of cores if more than 10 cores are taken), or ≥ 10 mm cancer in one core
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>AS</td>
<td>Active Surveillance</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
</tr>
<tr>
<td>DMSC</td>
<td>Data Monitoring and Safety Committee</td>
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<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>ESUR</td>
<td>European Society of Urogenital Radiology</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MRSI</td>
<td>Magnetic Resonance Spectroscopy Imaging</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PI-RADS</td>
<td>Prostate Imaging Reporting and Data System</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PIVOT</td>
<td>Prostate cancer Intervention Versus Observation Trial</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria of Solid Tumours</td>
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<tr>
<td>SAMS</td>
<td>Study of Active Monitoring in Sweden</td>
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<tr>
<td>SPCG</td>
<td>Scandinavian Prostate Cancer Group</td>
</tr>
</tbody>
</table>
4. SUMMARY
Widespread prostate cancer-specific antigen (PSA) testing of asymptomatic men has dramatically increased the recorded incidence of prostate cancer in many western countries. It is now widely accepted that a large proportion of these men are overdiagnosed, because they have non-lethal disease, and overtreated with substantial side effects. To reduce overtreatment and adverse effects, active surveillance (AS) has emerged as a viable option that should be offered to patients with low-risk prostate cancer (1).

By monitoring disease progression, or lack thereof, and keeping the option to recommend radical local treatment open for a certain period of time, active surveillance might convey substantial benefits compared with routine initial prostatectomy or radiotherapy. There is, however, a lack of randomized evidence for when disease progression should trigger radical treatment with a curative intent in men who are on AS.

To fill this problematic knowledge gap, the Scandinavian Prostatic Cancer Group (SPCG) is promoting a large multicentre randomized trial. With the primary endpoint set to progression-free survival (based on the cumulative incidence of indicators of prostate cancer progression), the aim of this trial is to test the safety of an AS protocol comparing current practice with standardized triggers for initiation of curative treatment.

5. PARTICIPATING CENTRES
The trial is open to all centres meeting the following criteria:

- The local principal investigator shall accept the protocol.
- The local organization should permit the consideration of recruiting all consecutively diagnosed patients who are willing to be in AS, and who fulfil the inclusion criteria, to the trial.
- A 1.5 or 3Tesla (T) MRI
- The centre should possess prostate MRI expertise. If the competence is lower, the PI in each country will organize help with the MRI evaluation.
- The MRI should follow European Society of Urogenital Radiology (ESUR) guidelines and include:
  - T1 and T2 weighted images
  - Diffusion weighted imaging (DWI) including Apparent Diffusion Coefficient (ADC)
  - Dynamic contrast enhanced (DCE) imaging (optional)
  - Magnetic Resonance Spectroscopy Imaging (MRSI) (optional)
- Lesions should be reported according to PI-RADS version 2 (2).

The trial shall remain open to participation until the number of participant centres is likely to enrol a sufficient number of patients to the randomized trial of AS within four years from initiation of the trial.

To maintain high quality, each centre should try to screen at least 30 patients per year. An updated register of participating centres shall be kept at the trial secretariat.

6. BACKGROUND AND MOTIVATION
6.1 The Burden of Prostate Cancer
Prostate cancer is the most common non-cutaneous cancer in men in the Western world. The crude annual incidence of prostate cancer in the European Union is 78.9/100 000 person years and the mortality is 30.6/100 000. Though the incidence and survival rates differ between countries, mortality rates are similar (3, 4).
In Sweden, 10,452 men were diagnosed with prostate cancer in 2014. Approximately 2,400 men with prostate cancer die per year and this number has remained rather unchanged since 1970 (5). The difference in mortality-to-incidence ratio between countries is likely due to more vigorous PSA testing in the US. Most of the screen-detected tumours are indolent with a low risk of progression and death.

Before the PSA era most prostate cancers were detected due to symptoms or a palpable lesion at digital rectal examination. After the introduction of the widely used PSA test, the incidence more than doubled while the death rates remained rather constant. In Sweden, the proportion of prostate cancer detected due to PSA testing increased from 29% to 53% between 2004 and 2014. The proportion of low-risk tumours (PSA less than 10 ng/ml, Gleason score ≤ 6, and tumour stage T1 or T2) increased from 14% in 1998 to 27% in 2014, with approximately 1/3 of them deemed very low risk (defined as T1C, Gleason ≤ 6, not more than four positive biopsies and total cancer length not more than 4 mm in men less than 75 years old) (6).

The SPCG-4 trial, including men with low and intermediately graded clinically detected tumours before the PSA era showed a significant overall survival benefit of 12.7% after eighteen years of follow-up. However, the prostate cancer specific mortality difference in the low-risk group was only 3.8% and not significantly lower following radical prostatectomy compared with watchful waiting (7). The American randomized PIVOT trial that included PSA-detected tumours failed to show a survival benefit within twelve years of follow-up in men undergoing radical prostatectomy compared with watchful waiting, apart from a subgroup of men with high-risk tumours (8).

6.2 The Justification for Active Surveillance

Several reasons explain why PSA screening and management of early and especially screening-detected prostate cancer remains controversial, notwithstanding evidence that radical local treatment may convey survival benefit. Published screening trials show that if there is a mortality reduction following PSA screening for prostate cancer, it is modest. Also, in the light of overdiagnosis and overtreatment the cost-benefit balance is highly uncertain (9, 10). It is well documented that PSA testing entails a substantial overdiagnosis of indolent prostate cancer that would have remained asymptomatic during the remaining lifetime of patients.

Local treatment of prostate cancer with a curative intent – whether surgical or radio therapeutic – is burdened with substantial side effects, predominantly compromised sexual function and urinary incontinence following surgery, and bowel dysfunction and urgency after radiotherapy. Similar to the psychological stigmas of a cancer diagnosis (11,12), these somatic treatment complications affect men equally, regardless of any survival benefit from early diagnosis and treatment. Based on all these concerns, no official health authorities have hitherto recommended routine, population-based PSA screening for prostate cancer.

In clinical practice, however, both PSA testing of asymptomatic men as well as radical treatment of early stage disease continue on a large scale. But the growing awareness of overdiagnosis and overtreatment has stimulated alternative management strategies, often summarized as AS. Watchful waiting implies an active decision to not recommend active curative treatment and to treat only at emerging symptoms. AS on the other hand implies that this decision is postponed and the behaviour of the tumour is monitored with varying degrees of intensity and with different tools to detect disease progression, such as clinical assessment, repeated PSA testing and regular biopsies to detect Gleason upgrade.

Although AS is an attractive approach to reduce overtreatment and avoid side effects, the optimal design of surveillance programs has not yet been defined. Up to date, there is no randomized evidence to guide clinicians in
the decision when radical treatment is likely to be needed and beneficial. The decision to switch from AS to aggressive therapeutic intervention is therefore in the clinical practice of today triggered by evidence of progression chosen rather arbitrarily. For instance, increased PSA levels may reflect natural fluctuation, local tumour growth, transition to a more lethal phenotype, or indeed progression to a metastatic stage beyond cure by local treatment alone. Likewise, increase in Gleason score on repeat, biopsy might reflect the heterogenic nature of prostate cancer or scenarios similar to those described for a rising PSA level. Hence, any chosen threshold for active treatment could be premature, beneficial, or too late.

Reflecting the lack of valid evidence, the proportion of Swedish men with very low-risk prostate cancer and who is managed by AS in 2014 varied between 50% and 100% in different regions (6). Different AS protocols are used in Europe, the US, and in Canada. Most of them include low-risk disease (Gleason ≤6, T1c-T2a and PSA <10 ng/ml) although some also include intermediate-risk disease (Gleason = 7, T2 and PSA 10-20 ng/ml) (13). In a long term follow-up of Swedish men with untreated prostate cancer only a minority died within 15 years (low risk 8.9% and intermediate risk 19.6%) (14). This evidence indicates that the current proportion of 30-40% of men receiving active treatment after initial AS is too high. One reason for the high proportion of men changing from AS to treatment is that the threshold for treatment is low in the most commonly used AS protocols (15).

Recent research has established MRI as a valuable method for assessing men who enters AS. For example, the use of MRI and targeted biopsies increased detection of significant cancer with 30% and reduced detection of insignificant cancer with 17% (16). Moreover, MRI is very promising both for the selection of men who are eligible for AS and in conjunction with targeted biopsies to monitor specific lesions (16).

6.3 The Clinical Significance of SPCG-17

Although we know that the current thresholds for actively treating men who are on AS are probably too low and lead to a substantial overtreatment, the optimal triggers are not known. Only randomized trials can provide the solid data needed to transform AS from being arbitrary to being evidence-based. Evidence-based standardized triggers for curative treatment will render AS a safe alternative to immediate treatment for a large number of patients. Patients can safely be followed-up by nurses, which increase continuity. Furthermore, standardized triggers can decrease inequities of health care.

We propose a large multi-centre randomized trial. The study hypothesis is that standardized triggers will reduce overtreatment without increasing disease progression and prostate cancer mortality. With the primary endpoint set to progression-free survival (based on the cumulative incidence of indicators of prostate cancer progression), the aim of this trial is to test the safety of an AS protocol comparing:

I. Current practice
II. Standardized triggers for initiation of curative treatment

7. AIMS

7.1 Primary Endpoint

The primary endpoint, which is also used for safety and sample size calculation, is progression-free survival. This is defined as cumulative incidence of PSA relapse following curative treatment and cumulative incidence of androgen deprivation therapy in untreated men.
7.2 Secondary Endpoint

The secondary endpoints are:

- Cumulative incidence of pT3 at radical prostatectomy specimens
- Cumulative incidence of metastases
- Cumulative incidence of treatments with curative intent (mainly radical prostatectomies or local radiotherapy)
- Cumulative incidence of switch to watchful waiting
- Quality of life
- Costs

7.3 Final Endpoint

Cumulative prostate cancer mortality is the final effect measure at ten years.

8. PATIENT SELECTION

8.1 General Aspects

Centres who agree to collaborate in the proposed SPCG-17 trial shall aim to include all patients who fulfil the requirements for randomization. No randomization shall be made until all inclusion criteria are satisfied. This implies that definite reports should have been received from diagnostic work-up and from histological classification of biopsy specimen.

8.3 Sample Size

The total number of patients randomized in the AS component shall reach 2,000 before recruitment ceases. Each centre should randomize so many patients that it is reasonable to assume that all consecutive eligible cases were considered for inclusion in the trial.

8.4 Age Limits

The estimated remaining lifetime for the patient should be more than ten years. The investigator should evaluate the potential life expectancy of the participants based on age, co-morbidity and risk factors for death, such as frailty and smoking.

8.5 Enrolment

Before inclusion all patients should have undergone systematic biopsies and an MRI with targeted biopsies towards PI-RADS score 3, 4 and 5.

8.6 Inclusion Criteria

The inclusion criteria are:

- Recently (within 12 months) diagnosed adenocarcinoma of the prostate
- Tumour stage ≤ T2a, NX, M0 (former MX)
- PSA < 15 ng/ml, PSA density ≤ 0.2 ng/ml/cc
- Gleason pattern 3+3=6 (any number of cores, any cancer involvement)
- Gleason pattern 3+4=7 (<3 cores (or <30 % of cores if more than ten cores are taken) for systematic biopsies, and <10 mm cancer in one core (for any biopsy mode))
- Life expectancy >10 years with no upper age limit
- Candidate for curative treatment if progression occurs
- Signed written informed consent

8.7 Management of Biopsy and Serum Specimens
The biopsies should be handled according to local traditions and made available for a central review. In a separate sub-study we will invite patients to participate in a biomarker study with a separate protocol and ethical approval. Different biomarkers will be collected prospectively, but will not be utilised as triggers in the trial.

9. TRIAL PLAN – RANDOMIZATION and FOLLOW-UP
Randomization is not made until all eligibility criteria have been confirmed and a written informed consent has been obtained from the patient. A computerized off-centre trial service will provide an individual trial number and randomization allocation at inclusion and registration.

Patients are stratified by centre and Gleason score, randomized with equal distribution to two parallel groups; one is current practice (trial arm 1) and one applies standardized triggers for initiating curative treatment (trial arm 2). Randomization is done in blocks for each centre, with the number of patients in each block unknown to the investigators.

Both trial arms are followed-up every six months with PSA test and with an annual clinical check-up (including PSA test). Every second year, the patients will be examined with MRI with targeted biopsies at suspicious lesions (see figure below).

FOLLOW-UP SCHEDULE (both arms)

9.1 Repeat Biopsies
Re-biopsies in arm 1: according to current practice (the urologist’s judgement)
Re-biopsies in arm 2:
- A systematic re-biopsy should be performed if PSA density increases to > 0.2 ng/ml/cc and then repeated at every 0.1 ng/ml/cc increase.
- MRI progression in men with previously only Gleason grade 3+3:
  - ≥ 5 mm increase in size in any dimension of a measurable lesion (a measurable lesion is defined as ≥ 6 mm in longest diameter in any dimension in best depicted MR sequence)
• Increase in PI-RADS v.2 score to 3-5
• High or very high suspicion of extra-capsular extension or seminal vesicle invasion (4 or 5 on the Likert scale)
• A new lesion with PI-RADS v.2 score 3-5

• MRI progression in men with Gleason grade 3+4:
  o ≥ 5 mm increase in size in any dimension of a measurable lesion (a measurable lesion is defined as ≥ 6 mm in longest diameter in any dimension in best depicted MR sequence)
  o A new lesion with PI-RADS v.2 score 3-5

10. THRESHOLDS FOR INTERVENTIONS
The thresholds for intervention are as follows:
- Intervention in arm 1: according to current practice (the urologist’s judgement)
- Intervention in arm 2:
  MRI progression in lesions with confirmed Gleason grade 4:
  o Increase in PI-RADS v.2 score to 4 or 5
  o High or very high suspicion of extra-capsular extension or seminal vesicle invasion (4 or 5 on the Likert scale)

OR

Pathological progression:
  o Gleason pattern 5
  o Primary Gleason pattern 4 in any core with ≥ 5 mm cancer
  o Gleason 3+4 (≥ 3 cores (or ≥ 30% of cores if more than 10 cores are taken) from systematic biopsies, or ≥ 10 mm cancer in one core (from any biopsy mode))

11. FOLLOW-UP

11.1 Follow-Up Until Time of Event
Follow-up will occur continuously according to Section 9 until initiation of treatment, event of metastasis, or to a break point where AS is considered terminated and watchful waiting starts, or to death of any cause.

11.2 Follow-Up After an Event Occurred
After initiation of curative treatment, watchful waiting, or palliative treatment for cancer progression, the patient is followed according to the standard protocol of each participating centre. Trial CRFs are filled in annually. For patients lost to follow-up, endpoints will be assessed through in-patient, cancer, and causes of death registries.

12. DEFINITION OF OUTCOMES

12.1 Progression-Free Survival
Cumulative incidence of PSA relapse after curative treatment and cumulative incidence of androgen deprivation therapy in untreated men is the primary endpoint.
12.2 Prostate Cancer Mortality
For the final endpoint at ten years we will use prostate cancer mortality. For classification of causes of death, we will rely on blinded assessment of an external expert committee as defined under section 12.3.

12.3 Classification of Death
The external expert committee should attempt to classify death as follows:

- Death from prostate cancer
- Death with locally recurrent or metastatic prostatic cancer; but other main cause of death
- Death without evidence of tumour progression/recurrence
- Death from prostate cancer treatment complications and/or diagnostics complications

12.4 Distant Metastases
At the assessment after each follow-up examination, the patient is categorized as having either:

- No distant metastasis
- Suspected (PSA level and/or symptoms but without further verification) distant metastasis
- Confirmed (verified by imaging and/or cytology or biopsy) distant metastasis

12.5 Cumulative Incidence of Radical Prostatectomies or Radiotherapy with Curative Intent

12.6 Cumulative Incidence of pT3 in radical prostatectomy specimens

12.7 Quality of Life
Quality of Life will be assessed from questionnaires at baseline and every second year. Data will be presented as proportions with symptoms and relative risks. Outcome variables will be dichotomized using the same cut-off values that have been used previously.

12.8 Costs
Studied under separate protocol.

12.9 Biomarkers
Studied under separate protocol.

13. TIME PLAN
During 2016-2017, we have:

- Set up the trial secretariat.
- Developed the infrastructure for database management.
- Received ethical/IRB approval in Sweden.
- Had an all collaborator meeting (May 2016) as a trial start meeting.
- Received financial support from the Swedish Research Council and the Swedish Cancer Society.
- Begun enrolment into the SPCG-17 trial in Uppsala, October 2016, and started six other Swedish centres.
During 2018 we will:

- Start all other centres.

Our goal is to end the trial enrolment within four years. The first publication should be prepared one year after the trial enrolment has closed.

14. ETHICAL CONSIDERATIONS

This study will be conducted according to ICH-GCP, national law and guidelines, and the Helsinki declaration. Before the start of patient inclusion, an ethics review board in each country will approve this study protocol.

There are several reasons why a trial testing standardized triggers to reduce overtreatment are justified. Firstly, radical prostatectomy as well as local irradiation with a curative intent causes substantial side effects and compromise the quality of life. These complications affect all treated men equally, regardless of whether they benefit from the therapeutic intervention or not. Indeed, the substantial risk of overtreatment is one main reason why PSA testing has been discouraged and this argument applies to this trial as well. Secondly, the lack of evidence-based trigger points for curative treatment results in an uncertainty in patient information. This in turns possibly triggers anxiety, unequal treatment of patients, and lack of means to follow the quality of care for patients undergoing AS. Finally, radical local treatment is costly and resource demanding. As a corollary, the resources saved by a reduced number of therapeutic interventions might convey greater public health benefit if used for other purposes in the health care system.

The study aim is to reduce overtreatment without increasing disease progression and prostate cancer mortality. To ensure safety for the patients who are studied with the standardized triggers, we will have interim evaluation for early stopping.

15. STATISTICS

15.1 Sample Size for SPCG-17

The cumulative progression-free survival in the current practise group after five years from randomization is assumed to be 98%. We wish to be able to detect an absolute difference of 1.3% in the experimental arm. The risk of type 1 error is accepted as 5% with a two-sided test. The risk of type 2 errors shall be 15% corresponding to a power of 85%. In these circumstances, 1000 patients are required for each group and should be included within 4 years. This number is calculated on the assumption that 90% of the patients accept the management proposal to which they have been randomised.

15.2 Outcome Definition

All analyses will follow the principle of intention to treat and the primary outcome is progression-free survival due to the low prostate cancer mortality estimated in the study. Final endpoint at 10 years of follow-up is cumulative mortality from prostate cancer, with competing causes of death taken into account.
15.3 Interim Evaluation for Early Stopping

Because this trial typically enrols patients with screening-detected tumours or tumours detected in conjunction with diagnostic procedures for other diseases with very low risk of prostate cancer death after radical treatment, it is mandatory that AS as designed in the trial brings down the risk of a missed treatment opportunity to a level which is well balanced against the risk of overtreatment and ensuing side effects. A Data Monitoring and Safety Committee (DMSC; see Section 16.4) will follow serious adverse events in both trial arms every six months, and analyse data as they find appropriate for the purpose of patient safety. PSA relapse after curative treatment, androgen deprivation therapy in untreated men, progression to clinically locally advanced disease, distant metastatic disease, or death of prostate cancer, will be considered.

In order to also evaluate the follow-up with MRI there will be a comparison with the Swedish SAMS cohort of men monitored with repeated biopsies. The analyses will be strictly confidential unless the DMSC has concerns regarding patient safety or trial integrity and will then advice the Governing Board of the SPCG-17 trial. Following their advice, the Governing Board will make a final decision whether enrolment should be terminated or not.

15.4 Analysis During Follow-Up

The first full-scale analyses and publication of results will take place one year after the last patient has been enrolled into the trial. Subsequently, we plan to update analyses of all primary and secondary endpoints every three years. The decision whether or not results from these analyses should be submitted for publication in a scientific journal will depend on the originality of the findings and their relevance for clinical practice compared with the most recently published results.

16. STUDY ADMINISTRATION

16.1 Governing Board and Trial Group

The ultimate responsibility for all aspects of the SPCG-17 trial rests with a Governing Board. This Governing Board comprises:

- Dr Anna Bill-Axelson, the coordinating principal investigator of SPCG-17
- Drs Adami and Holmberg, co-initiators of the trial, and Dr Ola Bratt
- Two local principal investigators (one urologist and one radiologist with MRI expertise) as representatives for each participating country
- Dr Egevad, the reference pathologist

Besides the coordinating principal investigator, the trial group consists of all local principal investigators at participating centres (listed in section 21).

16.2 Secretariat

The central trial secretariat is found at Uppsala University, Urology, at Dag Hammarskjölds väg 26 (Majoren) in Uppsala. Trial coordination, the database managing and monitoring will be directed from this centre. All handling of individual patient information will be governed by the participating countries privacy information safety acts.

16.3 Pathology Panel
A group of three distinguished senior pathologists will be assigned as a review committee. They will have the following main tasks:

- If necessary, confirm the histopathology diagnosis that triggers curative treatment (Gleason grading and pT-stage)
- Classify causes of death, blinded to randomization group and based on abstraction of relevant data from hospital records, and whenever relevant, autopsy reports.

16.4 Data Monitoring and Safety Committee (DMSC)

Professor Laurence Klotz, Associate Professor Monique Roobol, and Professor Richard Martin, will be participants in the DMSC. The committee will erect a Data Monitoring and Safety Charter reviewed and authorized by the Governing Board. The purpose of the charter is to describe the roles and responsibilities of the DMSC, including the timing of meetings, methods of providing information to and from the DMSC, frequency and format of meetings, statistical issues, and relationships with the trial Governing Board.

The role of the DMSC is to safeguard the interests of trial participants, investigators and sponsor, to monitor the overall conduct of the trial, and to protect its validity and credibility. The committee will overview the trial, with special emphasis on outcomes that would indicate safety concerns or low probability of achieving the trial objectives making continued inclusion into the trial unethical. To ensure the follow-up (with MRI) safety, progression-free survival will be compared with a matched cohort from the Swedish SAMS study monitored with re-biopsies.

The DMSC will provide independent advice to the Governing Board. The analyses conducted by the DMSC are directed towards patient safety and trial overall scientific integrity not to be confused with analyses strictly directed towards evaluation of the trial hypotheses and fulfilling the scientific aims of the trial.

16.5 Database Management

The database management and monitoring will be directed from the trial secretariat. The coordinating principal investigator will authorize releases from the database. However, the principal investigator will not have access to results during the accrual. Access will be restricted to the data manager in charge and the trial statistician.

The DSMC will interact with the data manager and trial statistician for their analyses. All handling of individual patient information will be governed by the privacy information safety acts of the participating countries.

16.6 MRI

There will be a group of PI radiologists from each country led by Dr Cecilia Wassberg (Sweden). The radiology PI of each country will be responsible for the communication with participating Radiology Departments to ensure harmonization of the MRI protocol and information on how to fill out the imaging part in the CRF. One or more experienced radiologists reading prostate MRI will evaluate the MRI locally, and a clinical imaging report is mandatory at all sites. To evaluate the imaging parameters and triggers for SPCG-17, a comparison with baseline will be done. If the level of expertise at a participating site is lower required by the protocol, the site would receive help with evaluations from the country PI. Moreover, about 20% of the MRI cases will be collected randomly for centralised reading for inter-reader agreement. We also plan to build a database for MRI examinations, to be used for sub-analyses and inter- and intra-reader agreement.
MR triggers in this study are based on PI-RADS (v.2) and the increase in size of a measurable lesion. A measurable lesion is defined as ≥ 6 mm in the longest diameter in any dimension in best-depicted MR sequence. The rational for using a threshold of 6 mm is that a lesion should be visible in at least two sequential 3 mm slice thicknesses. Additionally, an increase in ≥ 5 mm in size in any dimension of a measurable lesion is in analogy with the RECIST criteria (17).

Some participating sites will include DCE in their standard MRI protocol. Clinical routine according to the local praxis should be followed as applied to renal function (GFR), contrast-allergy and MRI contra-indications. Hip replacement is not a contra-indication for MRI in SPCG-17.

Preparations at each participating site before including patients in SPCG-17:

- A responsible radiologist and contact person
- 1.5/3T MRI staff, informed about the SPCG-17 study
- Capacity and approximate numbers at site is estimated locally by the urologist and radiologist
- 1.5/3T MRI prostate protocol
- Baseline and follow-up MRI should if possible use the same magnet and technique.
- The prostate MR request should clearly state that the patient is participating in the SPCG-17 study
- Imaging parameters will be recorded on each patient’s CRF, either by the radiologist or the study nurse. The CRFs are designed according to the PRECISE recommendations (slightly modified versions) (18).

17. PUBLICATIONS

The ultimate responsibility for decisions to publish results from SPCG-17, as well as for authorship issues, rests with the Governing Board. All publications emanating from SPCG-17 shall be co-authored by all participating centres. In addition, clinicians who have contributed substantially may be added to the author list as appropriate. The ordering of authors should fairly reflect the number of patients enrolled as well as the intellectual contributions to each manuscript.

Each publication should end with an exhaustive list of all people who have been involved in the scholarly work of the trial such as local investigators, biostatisticians, pathologists, and others.

Whenever a new publication is planned, it is the responsibility of the Governing Board to assign first and senior authors. Shared first and/or last authorship is also strongly encouraged. There should be a time limit to assignments as first and last author and these assignments should be reconsidered should a manuscript not have been finished in a timely manner.

Because sample size calculations are based on the entire trial, fragmented reporting of centre specific results is strongly discouraged and should not take place without approval from the Governing Board.

18. FINANCE

Every effort will be made to obtain full funding for the entire SPCG-17 trial through one large grant. However, because this goal may not be achievable, at least not in a timely manner, combined funding from several sources, domestic and international, may be more realistic.
When a centre joins SPCG-17, the responsibility to cover local expenses rests with the local principal investigator.

19. INFORMATION TO PATIENTS
We will provide the Swedish patient information to all centres and an English version of this information. Each country will then add their country-specific obligatory patient information.

20. FORMS
20.1 Quality of life questionnaire
Quality of life will be assessed at baseline and every second year of follow-up, using a study-specific questionnaire that includes physical symptoms, symptom-induced stress (from the validated EPIC-26 form) and self-assessed quality of life questions with the previously used intensity scales 1-7 (see Appendix I).

20.2 Case Report Forms (CFRs)
The following electronic CRFs will be used in SPCG-17:
- Baseline data (to be recorded at inclusion)
- Inclusion visit and randomization
- Follow-up during AS (to be recorded annually)
- Biopsies during follow-up
- MRI during follow-up
- Ending active surveillance
- Follow-up after ending active surveillance (to be recorded annually)
- End of follow-up in SPCG-17
- Adverse events
21. **CONTACT INFORMATION**

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<thead>
<tr>
<th>Members, responsibilities, and function</th>
<th>Name &amp; contact details</th>
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<tbody>
<tr>
<td>Sponsor/coordinating PI</td>
<td>Anna Bill-Axelson</td>
</tr>
<tr>
<td></td>
<td>Department of Surgical Sciences, Uppsala University Akademiska Hospital, Uppsala</td>
</tr>
<tr>
<td></td>
<td>Dag Hammarskjölds väg 26</td>
</tr>
<tr>
<td></td>
<td>SE-752 37 Uppsala</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:anna.bill.axelson@surgsci.uu.se">anna.bill.axelson@surgsci.uu.se</a></td>
</tr>
<tr>
<td></td>
<td>+46-(0) 701 679747</td>
</tr>
<tr>
<td>Statistician</td>
<td>Hans Garmo</td>
</tr>
<tr>
<td></td>
<td>Regionalt cancercentrum (RCC), Uppsala</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:hans.garmo@kcl.ac.uk">hans.garmo@kcl.ac.uk</a></td>
</tr>
<tr>
<td>Database manager</td>
<td>Christoffer Lagerros</td>
</tr>
<tr>
<td></td>
<td>Lagerros IT AB</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:chrille@lagerros.se">chrille@lagerros.se</a></td>
</tr>
<tr>
<td></td>
<td>+46-(0) 733 249460</td>
</tr>
<tr>
<td>Study coordinator</td>
<td>Ulrika Åberg</td>
</tr>
<tr>
<td></td>
<td>Department of Surgical Sciences, Uppsala University</td>
</tr>
<tr>
<td></td>
<td>Dag Hammarskjölds väg 26</td>
</tr>
<tr>
<td></td>
<td>SE-752 37 Uppsala</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:ulrika.aberg@surgsci.uu.se">ulrika.aberg@surgsci.uu.se</a></td>
</tr>
<tr>
<td></td>
<td>+46-(0) 701 679744</td>
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</table>

**SWEDEN**

| PI Urology                             | Anna Bill-Axelson      |
|                                        | Contact information, see above |

| PI MRI                                 | Cecilia Wassberg       |
|                                        | Radiology and Nuclear Medicine |
|                                        | Karolinska University Hospital, Solna |
|                                        | cecilia.wassberg@gmail.com |

| Pathologist                            | Lars Egevad            |
|                                        | Lars.egevad@ki.se      |

| Co-investigators                       | Eva Johansson          |
|                                        | Department of Surgical Sciences, Urology, Uppsala University, Akademiska Hospital, Uppsala |
|                                        | evajson@icloud.com     |

|                                              | Pär Dahlman            |
|                                              | Department of Surgical Sciences, Radiology, Uppsala University, Akademiska Hospital, Uppsala |
|                                              | par.dahlman@akademiska.se |
Gothenburg  |  Johan Stranne  
| Department of Urology  
| Institute of Clinical Science  
| Sahlgrenska Academy  
| University of Gothenburg  
| Sahlgrenska University Hospital  
| Johan.stranne@vgregion.se  
| +46-(0) 31-3421000, +46-(0) 31-3421007  

Kjell Geterud  
Department of Radiology, Sahlgrenska University Hospital, Gothenburg  
kJell.geterud@vgregion.se

Stockholm KI  |  Olof Akre  
| Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet/Karolinska University Hospital, Solna  
| Olof.akre@ki.se  
| +46-(0) 709 640404  

Fredrik Jäderling  
Radiology and Nuclear Medicine  
Karolinska University Hospital  
Fredrik.jaderling@karolinska.se

Stockholm Danderyd  |  Tobias Nordström  
| Department of Medical Epidemiology and Biostatistics, Karolinska Institutet  
| Department of Surgery and Urology, Danderyd Hospital, Danderyd  
| Tobias_nordstrom@ki.se  
| +46-(0) 705 391791  

Jönköping  |  David Robinsson  
| Department of Urology  
| Ryhov Hospital, Jönköping  
| David.robinsson@rl.se  
| +46-(0) 36-326934, +46-(0) 38-135316  
| +46-(0) 703 443082  

Malmö  |  Anders Bjartell  
| Department of Urology  
| Skåne University Hospital, Malmö  
| anders.bjartell@skane.se  
| +46-(0) 40 332685  

Nils-Olof Wallengren  
Department of Radiology  
Skåne University Hospital  
nilsolof.wallengren@skane.se

Örebro  |  Ove Andrén  
| Department of Urology  
| Örebro University Hospital, Örebro  
| ove.andren@regionorebrolan.se  
| +46-(0) 19 6021010, +46-(0) 703 439913  

Wolfgang Krauss  
Department of Radiology  
Örebro University Hospital, Örebro  
wolfgang.krauss@regionorebrolan.se
<table>
<thead>
<tr>
<th>Location</th>
<th>Name</th>
<th>Department</th>
<th>Hospital</th>
<th>Email</th>
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<tbody>
<tr>
<td>Östersund</td>
<td>Karl-Johan Lundström</td>
<td>Department of Surgery</td>
<td>Östersund Hospital, Östersund</td>
<td><a href="mailto:karl-johan.lundstrom@regionjh.se">karl-johan.lundstrom@regionjh.se</a></td>
</tr>
<tr>
<td>Linköping/Norrköping</td>
<td>Jon Forsberg</td>
<td>Department of Urology</td>
<td>Linköping University Hospital, Linköping</td>
<td><a href="mailto:jon.forsberg@regionostergotland.se">jon.forsberg@regionostergotland.se</a></td>
</tr>
<tr>
<td>Umeå</td>
<td>Bengt Friedrich</td>
<td>Department of Urology</td>
<td>Norrland University Hospital</td>
<td><a href="mailto:bengt.friedrich@urologi.umu.se">bengt.friedrich@urologi.umu.se</a></td>
</tr>
<tr>
<td></td>
<td>Conny Ström</td>
<td>Department of Radiology</td>
<td>Norrland University Hospital</td>
<td>Conny.strö<a href="mailto:m@vl.se">m@vl.se</a></td>
</tr>
<tr>
<td>Sunderby</td>
<td>Periklis Koumoutsakos</td>
<td>Department of Urology</td>
<td>Sunderby Hospital</td>
<td><a href="mailto:Periklis.koumoutsakos@norrbotten.se">Periklis.koumoutsakos@norrbotten.se</a></td>
</tr>
<tr>
<td></td>
<td>Annika Larsson</td>
<td>Department of Radiology</td>
<td>Sunderby Hospital</td>
<td><a href="mailto:Annika.larsson@norrbotten.se">Annika.larsson@norrbotten.se</a></td>
</tr>
<tr>
<td></td>
<td>Martin Kopal</td>
<td>Department of Radiology</td>
<td>Sunderby Hospital</td>
<td><a href="mailto:Martin.kopal@norrbotten.se">Martin.kopal@norrbotten.se</a></td>
</tr>
<tr>
<td>Sundsvall</td>
<td>Mattias Tell</td>
<td>Department of Urology</td>
<td>Sundsvall Hospital</td>
<td><a href="mailto:mattias.tell@lvn.se">mattias.tell@lvn.se</a></td>
</tr>
<tr>
<td></td>
<td>Magnus Alm</td>
<td>Department of Radiology</td>
<td>Sundsvall Hospital</td>
<td><a href="mailto:magnus.alm@lvn.se">magnus.alm@lvn.se</a></td>
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<td>Research nurses</td>
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<tr>
<td>Uppsala</td>
<td>Monika Andersson</td>
<td>Department of Urology</td>
<td></td>
<td><a href="mailto:Monika.g.andersson@akademiska.se">Monika.g.andersson@akademiska.se</a></td>
</tr>
<tr>
<td></td>
<td>Pernilla Helgesson</td>
<td></td>
<td></td>
<td><a href="mailto:Pernilla.helgesson@akademiska.se">Pernilla.helgesson@akademiska.se</a></td>
</tr>
<tr>
<td>Orebro</td>
<td>Annica Nilsson</td>
<td></td>
<td></td>
<td><a href="mailto:Annica.nilsson@regionorebrolan.se">Annica.nilsson@regionorebrolan.se</a></td>
</tr>
<tr>
<td></td>
<td>Maria Forsström</td>
<td></td>
<td></td>
<td><a href="mailto:Maria.forsstrom@regionorebrolan.se">Maria.forsstrom@regionorebrolan.se</a></td>
</tr>
<tr>
<td>Location</td>
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</table>
| Göteborg      | Chatrine Hasselberg  
Chatrine.hasselberg@vgregion.se  
Ann Carlstrand  
anncarlstrand@vgregion.se |
| Östersund     | Margaretha Höög  
Eva-Britt Walther |
| Malmö         | Josefine Pethrus Riikonen  
josefine.pethrusrikonen@skane.se  
Gunilla Sundgren  
gunilla.sundgren@skane.se |
| Stockholm, KI | Kirsti Niemela  
kirsti.niemela@karolinska.se |
| Linköping/Norrköping | Malin Stahlgren (US, Linköping)  
malin.stahlgren@regionostergotland.se  
Helene Krook (Vrinnevi, Norrköping)  
Helene.krook@regionostergotland.se |
| Umeå           | Britt-Inger Dahlin  
BrittInger.Dahlin@vll.se  
Kerstin Almroth  
Kerstin.almroth@vll.se |
| Sunderby       | Hanna Nyberg  
Hanna.nyberg@norrbotten.se |
| Sundsvall     | Malin Lindell  
Malin.lindell@lvn.se |

**FINLAND**

**PI Urology**  
Antti Rannikko  
Department of Urology  
PL 340, 00029 HUS  
Helsinki University Hospital  
Antti.rannikko@urologipalvelu.fi  
Antti.rannikko@hus.fi

**PI MRI**  
Anu Kenttäemies  
anu.kenttamies@hus.fi

**Pathologist**  
Tuomas Mirtti  
Tuomas.mirtti@helsinki.fi  
Tuomas.mirtti@hus.fi

**Research nurses**  
Merja Rignell  
Merja.rignell@hus.fi

**DENMARK**
<table>
<thead>
<tr>
<th>PI Urology</th>
<th>Michael Borre</th>
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<tbody>
<tr>
<td></td>
<td>Department of Clinical Medicine, Urology</td>
</tr>
<tr>
<td></td>
<td>Aarhus University, Aarhus</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:borre@clin.au.dk">borre@clin.au.dk</a></td>
</tr>
<tr>
<td></td>
<td>+45-(0) 78 4526 16</td>
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<table>
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<tr>
<th>PI MRI</th>
<th>Bodil Ginnerup Pedersen</th>
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<td>Institut for Klinisk Medicin</td>
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<td></td>
<td>Aarhus University, Aarhus</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Boril@clin.au.dk">Boril@clin.au.dk</a></td>
</tr>
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<td>+45-(0) 78 456002</td>
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<tr>
<th>Pathologist</th>
<th>Søren Høyer</th>
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<tr>
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<td><a href="mailto:Soren.hoyer@aarhus.rm.dk">Soren.hoyer@aarhus.rm.dk</a></td>
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<th>Research nurses</th>
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<tr>
<td></td>
<td><a href="mailto:Susanne.Skou@skejby.rm.dk">Susanne.Skou@skejby.rm.dk</a></td>
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<tr>
<td></td>
<td>St Olavs Hospital, Trondheim</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:helena.bertilsson@stolav.no">helena.bertilsson@stolav.no</a></td>
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<th>Øystein Størkersen</th>
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<th>Inger Stokkan</th>
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<tr>
<td></td>
<td><a href="mailto:Inger.Johanne.Stokkan@stolav.no">Inger.Johanne.Stokkan@stolav.no</a></td>
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22. REFERENCES

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cancer
6. www.cancercentrum.se
17. http://www.eortc.org/recist/
Research Study SPCG-17

PART I. DEMOGRAPHICS AND QUESTIONS ABOUT QUALITY OF LIFE

General Questions

1. What year were you born?
   (E.g. 1945)

2. How tall are you?

3. What is your weight?

4. Are you currently:
   - Living with spouse or partner
   - In a significant relationship, but not living together
   - Not in a significant relationship
   - Widower

5. Do you have children?
   - No
   - Yes

6. Are you currently:
   - Working full time
   - Working part time
7. What level of education do you have? *(Specify the highest level of education that you have)*

- Elementary school
- High school
- College or university

8. During the last 4 weeks, how many hours per week did you spend on moderate physical exercise (i.e. walking, biking, swimming, and so on)?

- None
- Less than 1 hour per week
- 1-3 hours per week
- 3-7 hours per week
- More than 7 hours per week

9. What are your smoking habits? *(Only pick one answer)*

- Current smoker
- Occasional smoker (less than 1 cigarette per day)
- Past smoker
- Never smoked

10. How often do you drink alcohol?

- Never
- Once a month or less
- 2-4 times per month
- 2-3 times per week
- 4 times per week or more

11. How many standard drinks (see example below) do you typically drink at one occasion?

- 1-2
- 3-4
- 5-6
- 7-9
- 10 or more

In Sweden, one standard drink is for example:

- 5 cl of low alcohol beer (3.5% or less)
- 5 cl of high alcohol beer (< 3.5%)
- 1 dl of table wine (< 15% alcohol)
- A small glass of wine (> 15% alcohol)
- 4 cl of spirits or liqueurs
12. Have you been told by a doctor that you have any of the following? (Tick all that apply)

A. Heart disease (e.g. angina, heart attack, or heart failure)  
   - No  - Yes
B. High blood pressure  
   - No  - Yes
C. Leg pain while walking due to poor circulation  
   - No  - Yes
D. Lung disease (e.g. asthma, chronic bronchitis, emphysema)  
   - No  - Yes
E. Diabetes  
   - No  - Yes
F. Kidney disease  
   - No  - Yes
G. Liver disease  
   - No  - Yes
H. Problems caused by stroke  
   - No  - Yes
I. Neurological disease (e.g. Parkinson’s disease or Multiple Sclerosis)  
   - No  - Yes
J. Other cancer (than prostate cancer), within the last 5 years  
   - No  - Yes
K. Depression  
   - No  - Yes
L. Other psychiatric illness  
   - No  - Yes
M. Arthritis  
   - No  - Yes
N. Hemiplegia or paraplegia  
   - No  - Yes
O. HIV infection or AIDS  
   - No  - Yes

(modified from Charlson Comorbidity index Chaudhry et al 2005)

Questions About Quality of Life

Answer the following questions by circling the number that best fits your opinion.

13. During the last 4 weeks, how has your quality of life been?

1------------------2-------------3-----------------4----------5----------6--------7
No quality of life  Best possible quality of life

14. During the last 4 weeks, has your life felt meaningful?
During the last 4 weeks, how has your energy been?

Never | All the time

No energy | Best possible energy

During the last 4 weeks, how has your mental wellbeing been?

No wellbeing | Best possible wellbeing

During the last 4 weeks, how has your physical health been?

Worst possible health | Best possible health

During the last 4 weeks, how has your self-esteem been?

No self-esteem | Best possible self-esteem

Questions About Depression and Anxiety

During the last 4 weeks, have you felt depressed?

Never | All the time

During the last 4 weeks, have you been feeling worried or anxious?

Never | All the time

During the last 4 weeks, have you had trouble falling asleep at night?

- No, never
- Yes, at least once this month
- Yes, at least once a week
- Yes, at least 3 times per week
- Yes, every night
22. **During the last 4 weeks**, have you woken up during sleep due to worry or anxiety?

- [ ] No, never
- [ ] Yes, at least once this month
- [ ] Yes, at least once a week
- [ ] Yes, at least 3 times per week
- [ ] Yes, every night

23. **During the last 4 weeks**, have you taken any sleeping pills?

- [ ] No, never
- [ ] Yes, at least once this month
- [ ] Yes, at least once a week
- [ ] Yes, at least 3 times per week
- [ ] Yes, every evening

24. **During the last 4 weeks**, have you taken any tranquilizers (anti-anxiety medications)?

- [ ] No, never
- [ ] Yes, at least once this month
- [ ] Yes, at least once a week
- [ ] Yes, at least 3 times per week
- [ ] Yes, every day

25. **During the last 4 weeks**, have you taken any anti-depressants?

- [ ] No
- [ ] Yes

**Questions About Information**

26. I was given my prostate cancer diagnosis:

- [ ] In a doctor’s appointment
- [ ] By phone
- [ ] By mail
- [ ] If in another way, please specify: _________________________________

27. What do you think about the way that your prostate cancer diagnosis was given?

(Answer by circling the number that best fits your opinion)

1---------2---------3---------4---------5---------6---------7
Worst possible way  Best possible way
28. When you received your prostate cancer diagnosis, was someone with you?

☐ No  ☐ Yes

29. Have you told anyone about your prostate cancer diagnosis? *(Multiple answers are possible)*

☐ I have not told anyone about my prostate cancer
☐ Partner
☐ Children
☐ Grandchildren
☐ Close friend(s)
☐ Colleague(s)
☐ Other persons

30. How much information have you received from your doctor? *(Tick one box on each line)*

<table>
<thead>
<tr>
<th>No Information</th>
<th>Some Information</th>
<th>Quite a lot of Information</th>
<th>Plenty of Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. About prostate cancer – the disease and its natural progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. About different treatment options for prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. About possible side effects (unwanted effects) of prostate cancer treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. About how prostate cancer treatment may affect your quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

31. Where have you searched for information about prostate cancer? *(Multiple answers are possible)*

☐ I have not searched for information about prostate cancer
☐ Internet
☐ Radio
☐ TV
☐ Newspapers
☐ Patient brochures
☐ Patient association
☐ Friends or family
☐ If elsewhere, please specify: ________________________________
Questions About Active Surveillance and Treatment

32. Which alternative below describes your situation? (Tick the alternative that fits the best)

- I am currently in active surveillance (i.e. I am being followed-up closely with PSA tests and MRI, but have not received any curative treatment)
- I started on active surveillance but have since received curative treatment

33. If you have received curative treatment for prostate cancer, which treatment(s) have you received up to date?

(Multiple answers are possible. You may for example have received both surgery and radiotherapy, both radiotherapy and hormone therapy, or hormone therapy only.)

- I have not received any treatment, I am on active surveillance
- Surgical removal of all of the prostate gland (so called radical prostatectomy)
- Radiotherapy
- Radiotherapy combined with hormone therapy
- Only hormone therapy with shots (so called GnRH analogues)
- Only hormone therapy with pills (for example Bicalutamide, or Casodex)
- Surgical removal of the testicles
- If other treatment, please specify: ____________________________

34. Do you take the medicine finasteride (for example Proscar or Propecia) due to urination difficulties?

- No
- Yes

Questions about follow-up of your prostate cancer

35. Before the clinical check-up, do you feel:

(A number of questions (A to F) follow below. For each question, tick the box (No or Yes) that best fits your opinion.)

<table>
<thead>
<tr>
<th>Question</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Worried about meeting the doctor?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B) Worried that your prostate cancer has become more serious?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C) Worried that your prostate cancer has spread (metastasized) to a different part of your body?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Clinical Trial Protocol for SPCG-17

**APPENDIX I**

<table>
<thead>
<tr>
<th></th>
<th>Worried that the PSA test will show an elevated PSA level?</th>
</tr>
</thead>
<tbody>
<tr>
<td>D)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Worried that the prostate cancer causes your physical problems?</th>
</tr>
</thead>
<tbody>
<tr>
<td>E)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Worried about what the MRI scan will show?</th>
</tr>
</thead>
<tbody>
<tr>
<td>F)</td>
<td></td>
</tr>
</tbody>
</table>

36. At the time of the clinical check-up, do you feel worried about having an MRI scan?

- [ ] Not applicable, I have received treatment for my prostate cancer
- [ ] Not at all
- [ ] A little
- [ ] Moderately
- [ ] Very much

37. At the time of the clinical check-up, do you feel worried about having to go through a prostate biopsy test?

- [ ] Not applicable, I have received treatment for my prostate cancer
- [ ] Not at all
- [ ] A little
- [ ] Moderately
- [ ] Very much

38. At the time of the clinical check-up, do you experience discomfort when your doctor examines the prostate using his/her fingers?

- [ ] Not at all
- [ ] A little
- [ ] Moderately
- [ ] Very much

39. Does it make you feel reassured and safe that your doctor examines the prostate using his/her fingers?

- [ ] Not at all
- [ ] A little
- [ ] Moderately
- [ ] Very much

40. If you would choose;

- [ ] No, I do not want the doctor to examine my prostate with his/her fingers
- [ ] Yes, I want the doctor to examine my prostate with his/her fingers
PART 2  QUESTIONNAIRE FOR SYMPTOMS (EPIC-26)

The following questions are commonly used in prostate cancer research studies all over the world.

Below follows a few questions about symptoms that you may experience.

(Tick the alternative that best suits your opinion)

1. **Over the past 4 weeks**, how often have you leaked urine?
   - More than once a day
   - About once a day
   - More than once a week
   - About once a week
   - Rarely or never

2. Which of the following best describes your urinary control during the last 4 weeks?
   - No urinary control whatsoever
   - Frequent dribbling
   - Occasional dribbling
   - Total control

3. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?
   - None
   - 1 per day
   - 2 per day
   - 3 or more per day

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

<table>
<thead>
<tr>
<th></th>
<th>No Problem</th>
<th>Very Small Problem</th>
<th>Small Problem</th>
<th>Moderate Problem</th>
<th>Big Problem</th>
</tr>
</thead>
</table>
   A. Dripping or leaking urine | [ ] | [ ] | [ ] | [ ] | [ ] |
   B. Pain or burning on urination | [ ] | [ ] | [ ] | [ ] | [ ] |
   C. Bleeding with urination | [ ] | [ ] | [ ] | [ ] | [ ] |
   D. Weak urine stream or incomplete emptying | [ ] | [ ] | [ ] | [ ] | [ ] |
   E. Need to urinate frequently during the day | [ ] | [ ] | [ ] | [ ] | [ ] |
5. Overall, how big a problem has your urinary function been for you during the last 4 weeks? (Tick the alternative that best suits your opinion)

- No problem
- Very small problem
- Small problem
- Moderate problem
- Big problem

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

<table>
<thead>
<tr>
<th>No Problem</th>
<th>Very Small Problem</th>
<th>Small Problem</th>
<th>Moderate Problem</th>
<th>Big Problem</th>
</tr>
</thead>
</table>
   A. Urgency to have a bowel movement |
   B. Increased frequency of bowel movements |
   C. Losing control of your stools |
   D. Bloody stools |
   E. Abdominal/pelvic/rectal pain |

7. Overall, how big a problem has your bowel habits been for you during the last 4 weeks? (Tick the alternative that best suits your opinion)

- No problem
- Very small problem
- Small problem
- Moderate problem
- Big problem

Questions About Your Sexual Function

Sexuality is for many people an important part of life, and for others less important. Prostate illnesses may affect the sexual function. The sexual function comprises sexual satisfaction, erotic experiences, as well as sexual intercourse.

We would like to remind you that this study is confidential.

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

<table>
<thead>
<tr>
<th>Very Poor to None</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very Good</th>
</tr>
</thead>
</table>
A. Your ability to have an erection

B. Your ability to reach orgasm (climax)

9. How would you describe the usual quality of your erections during the last 4 weeks? (Tick the alternative that best suits your opinion)

- None at all
- Not firm enough for any sexual activity
- Firm enough for masturbation and foreplay only
- Firm enough for intercourse

10. How would you describe the frequency of your erections during the last 4 weeks? (Tick the alternative that best suits your opinion)

- I NEVER had an erection when I wanted one
- I had an erection less than half of the time I wanted one
- I had an erection about half the time I wanted one
- I had an erection more than half of the time I wanted one
- I had an erection whenever I wanted one

11. Overall, how would you rate your ability to function sexually during the last 4 weeks? (Tick the alternative that best suits your opinion)

- Very poor
- Poor
- Fair
- Good
- Very good

12. How big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks? (Tick the alternative that best suits your opinion)

- No problem
- Very small problem
- Small problem
- Moderate problem
- Big problem

13. How big a problem, if any, has each of the following been for you during the last 4 weeks? (Tick one box on each line)
14. Which of the following medications/aids have you tried and how did they work? (Tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>Not tried</th>
<th>Tried, but it didn't help</th>
<th>It helped, but I don't use it now</th>
<th>It helps, and I use it sometimes</th>
<th>It helps, and I always use it for sexual activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hot flashes</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>B. Breast tenderness/enlargement</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>C. Feeling depressed</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>D. Lack of energy</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>E. Change in body weight</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

15. How would you describe the usual quality of your erection with medication/aid during the last 4 weeks? (Tick the alternative that best suits your opinion)

- ☐ Not applicable, I do not use any medication or aid
- ☐ None at all
- ☐ Not firm enough for any sexual activity
- ☐ Firm enough for masturbation and foreplay only
- ☐ Firm enough for intercourse

16. Are you satisfied with your sexual life? (Answer by circling the number that best fits your opinion)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not satisfied at all</td>
<td>Not satisfied at all</td>
<td>Completely satisfied</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is there anything else that you feel is important when it comes to your disease that we have not asked you about? Please tell us!

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________