SPCG-17

Prostate Cancer Active Surveillance Trigger Trial (PCASTT)

Scandinavian Prostate Cancer Group

Sponsor protocol number	SPCG-17, version 6 dated June 17 2019
Clinical study phase	Phase III
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1. PROTOCOL SIGNATURE PAGE

Investigator's Statement of Compliance

I have read and understood this protocol; version 6 (dated June 17 2019), 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.

_____

Date (DD-MM-YYYY)

_____

Anna Bill-Axelson, coordinating principal investigator

Investigator's Statement of Compliance

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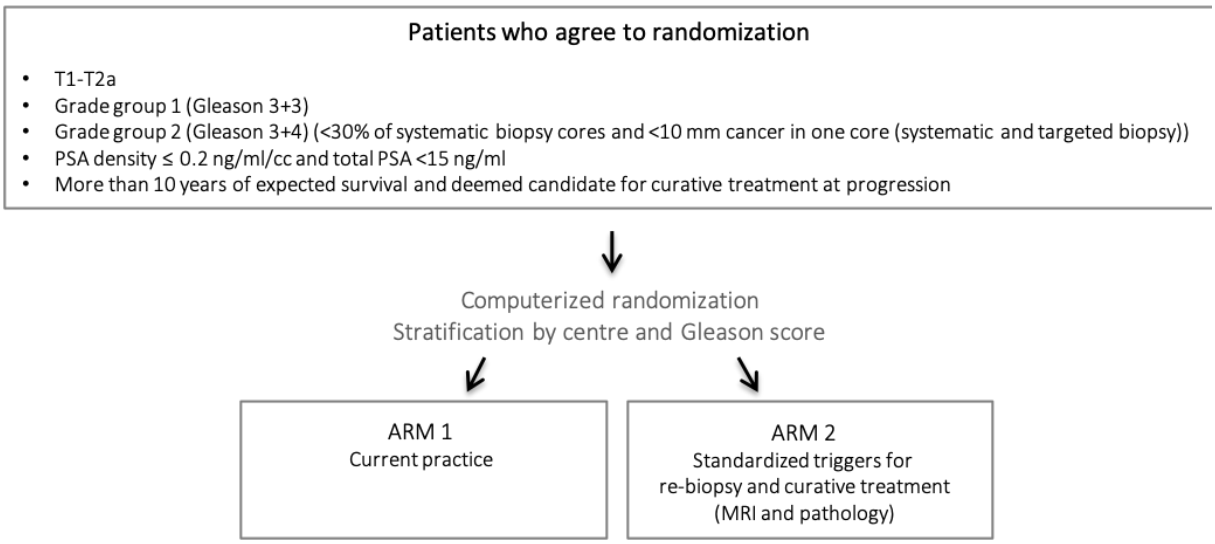
Investigator name (print)

_____ _____

Investigator signature Date (DD-MM-YYYY)

2. TRIAL SYNOPSIS and FLOW CHART

Study title	Prostate Cancer Active Surveillance Trigger Trial (PCASTT)
Short title	SPCG-17
Clinical study phase	Phase III
Study objective	To test the safety of an AS protocol comparing current practice with standardized triggers for the initiation of curative treatment
Reference arm (1)	Current practise for AS
Intervention arm (2)	Standardized triggers for initiation of curative treatment
Study design	Randomized multicentre open-label clinical trial
Inclusion criteria	Newly diagnosed men (within 12 months) with untreated ≤T2a prostate adenocarcinoma PSA <15 ng/ml, PSA density ≤0.2 ng/ml/cc All Grade group 1 (Gleason 3+3) Grade group 2 (Gleason 3+4) in <30% of systematic biopsy cores and <10 mm cancer in one core (systematic and targeted biopsy)) Life expectancy >10 years with no upper age limit Candidate for curative treatment if progression occurs Signed written informed consent
Study start	October 2016
Planned study stop	Planned end of enrolment 2021
Planned end of trial	Planned End of Study 2030
Planned data analysis	One year after enrolment stopped
Number of patients	2000
Primary variable	Progression-free survival
Statistical analysis	All analyses will follow the principle of intention to treat. The cumulative progression-free survival in the current practise group after 5 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%.
Participating countries	This is a multinational study involving the following countries: Sweden, Finland, Norway, and the UK.



TRIGGERS FOR RE-BIOPSY

ARM 1	ARM 2
Current practice (urologist's judgement)	I. **PSA density >0.2 ng/ml/cc, and then at every 0.1 ng/ml/cc increase (systematic biopsy)** II. **MRI progression in men with Grade Group 1 (3+3):** • ≥5 mm or more increase in size in any dimension of a measurable lesion (a measureable 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 Grade Group 2 (3+4):** • ≥5 mm or more increase in size in any dimension of a measurable lesion (a measureable 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	ARM 2
Current practice (urologist's judgement)	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 • Grade Group 2 (3+4) in ≥30% of cores (systematic biopsy), or ≥10 mm cancer in one core (systematic or targeted biopsy))

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADC	Apparent Diffusion Coefficient
AS	Active Surveillance
CRF	Case Report Form
DCE	Dynamic Contrast Enhanced
DMSC	Data Monitoring and Safety Committee
DWI	Diffusion Weighted Imaging
ESUR	European Society of Urogenital Radiology
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
GCP	Good Clinical Practice
MRI	Magnetic Resonance Imaging
MRSI	Magnetic Resonance Spectroscopy Imaging
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostate Specific Antigen
PIVOT	Prostate cancer Intervention Versus Observation Trial
RECIST	Response Evaluation Criteria of Solid Tumours
SAMS	Study of Active Monitoring in Sweden
SPCG	Scandinavian Prostate Cancer Group

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, 10452 men were diagnosed with prostate cancer in 2014. Approximately 2400 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 radiotherapeutic – 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).

Resent 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. For a definition of PSA relapse, see Section 10.1.

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 radio therapy)
- 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

Patients who fulfil the inclusion criteria outlined in Section 8.6 are eligible for enrolment in SPCG-17. The following also apply:

- Before inclusion, the patient must have been examined by MRI + MRI-targeted biopsy of lesions with PI-RADS 3-5.

- In patients diagnosed with MRI + MRI-targeted biopsy, systematic biopsy is optional.

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 systematic biopsy cores (or <30% of all systematic biopsy cores if more than 10), and <10 mm cancer in one core (systematic and targeted biopsy))
- 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

9.1 Randomization

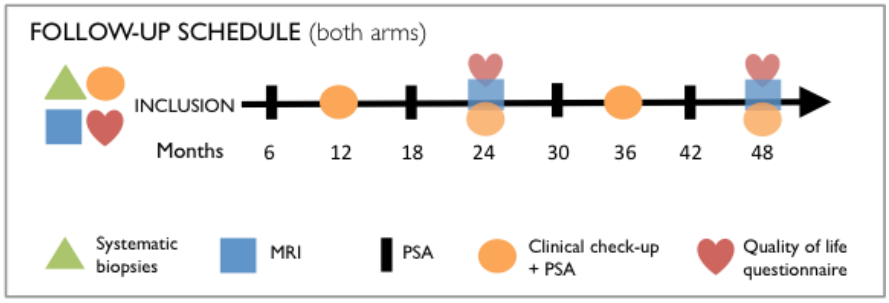
Randomization is not made until all eligibility criteria have been confirmed and a written informed consent has been obtained from the patient. A computerized off-centre trial service will provide an individual trial number and randomization allocation at inclusion and registration.

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.

9.2 Follow-Up

Both trial arms are followed-up in the same way (see figure below). The follow-up schedule consists of PSA test every sixth month, an annual clinical check-up including PSA test, and MRI every second year.

For patients with clinical stage T1c prostate cancer, the annual check-up may be done by phone interview.



The MRI examination every second year should be followed by MRI-targeted biopsy at suspicious lesions (PI-RADS score 3, 4 or 5). The first follow-up MRI should be performed two years after the MRI that was performed before inclusion in SPCG-17.

Every second year of follow-up the patients are also asked to fill in a trial-specific questionnaire about their health and their quality of life. The same questionnaire is given to the patients at inclusion, to be filled in before the patient is aware of which group he is randomized to (in order to receive baseline data).

9.2.1 Follow-Up Until Time of Event

Follow-up will occur continuously according to the schedule outlined in Section 9.2 until the initiation of treatment, the event of metastasis, or to a break point where AS is considered terminated and watchful waiting starts, or to death of any cause.

9.2.2 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.

9.3 Repeat Biopsies

In arm 1, re-biopsy is performed according to current practice (the urologist's judgement). In arm 2, re-biopsy should be triggered by the following:

- 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, defined as:
    - ≥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 MRI 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, defined as:
    - ≥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)
    - A new lesion with PI-RADS v.2 score 3-5

9.4 Triggers for curative treatment

In arm 1, curative treatment is initiated according to current practice (the urologist's judgement). In arm 2, curative treatment should be triggered by the following:

- MRI progression in lesions with confirmed Gleason pattern 4, defined as:
    - Increase in PI-RADS v.2 score to 4 or 5
    - High or very high suspicion of extra-capsular extension or seminal vesicle invasion (4 or 5 on the Likert scale)

- Pathological progression, defined as:
    - Gleason pattern 5
    - Primary Gleason pattern 4 in any core with ≥5 mm cancer
    - Gleason 3+4 (≥3 systematic biopsy cores or ≥ 30% of all systematic biopsy cores if more than 10), or ≥ 10 mm cancer in one core (systematic and targeted biopsy))

10. DEFINITION OF OUTCOMES

10.1 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.

Following radical prostatectomy, biochemical recurrence is defined by two consecutively rising PSA values >0.2 ng/ml. After radiotherapy (RT) with or without androgen deprivation therapy, the definition of PSA failure is any rise by 2 ng/ml or more above the nadir PSA value, regardless of the serum concentration of the nadir.

10.2 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 10.3.

10.3 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

10.4 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

10.5 Cumulative Incidence of Radical Prostatectomies or Radiotherapy with Curative Intent

10.6 Cumulative Incidence of pT3 in radical prostatectomy specimens

10.7 Quality of Life

Quality of Life will be assessed from questionnaires at baseline and every second year for as long as the patient is followed up in SPCG-17. 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.

10.8 Costs

Studied under separate protocol.

10.9 Biomarkers

Studied under separate protocol.

11. TIME PLAN

During 2016-2017, we:

- 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, the Swedish Cancer Society and the Nordic Cancer Union.
- Begun enrolment into the SPCG-17 trial in Uppsala, October 2016, and started six other Swedish centres.

During 2018 and 2019, we will:

- Start all other centres in the participating countries.

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

12. 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 healthcare 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.

13. STATISTICS

A detailed description of endpoints in the study and corresponding analyses is given in the Statistical Analysis Plan (SAP) for the study.

13.1 Sample Size for SPCG-17

The cumulative progression-free survival in the current practise group after 5 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.

13.2 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 accounted for.

13.3 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 14.4) 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.

13.4 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.

14. STUDY ADMINISTRATION AND QUALITY CONTROL

14.1 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:

- Associate professor Anna Bill-Axelson, the coordinating principal investigator of SPCG-17 and consultant in urology
- Professor Hans-Olov Adami and professor Lars Holmberg, co-initiators of the trial and senior advisors
- Professor Ola Bratt, consultant in urology
- Two local principal investigators (one urologist and one radiologist with MRI expertise) as representatives for each participating country
- Dr Egevad, reference pathologist

Besides the coordinating principal investigator, the trial group consists of all local principal investigators at participating centres (listed in section 19).

14.2 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.

14.3 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.

14.4 Data Monitoring and Safety Committee

Professor Laurence Klotz, Professor Monique Roobol, and Professor Richard Martin, constitute the DMSC. Professor Chris Metcalfe is the DMSC biostatistician. 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.

14.5 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.

14.6 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).

14.7 Monitoring

Monitoring of the SPCG-17 trial will be performed to verify the following:

- The rights and well-being of the trial participants
- Reported data is accurate, complete and verifiable from source documents
- Trial is conducted in compliance with currently approved protocol and other applicable regulatory requirements

The monitoring activities for the SPCG-17 trial are outlined in a Monitoring Plan. This plan identifies key central and on-site monitoring activities and specifies the parameters to be reviewed over the course of the trial. All monitoring activities will be coordinated from the trial secretariat and each activity will be documented by the monitor in a Monitoring Visit Report. Reports will be reviewed by the coordinating principal investigator and stored in the trial master file at the trial secretariat. The number of on-site visits may vary between sites. All sites are visited at least once before enrolment of their first patient.

15. 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.

16. 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 join SPCG-17, the responsibility to cover local expenses rests with the local principal investigator.

17. 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.

18. FORMS

18.1 Quality of life questionnaire

Quality of life will be assessed at baseline and every second year for as long as the patient is followed up in SPCG-17, 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).

18.2 Case Report Forms (CFRs)

The following electronic CRFs will be used in SPCG-17:

- Baseline data at inclusion
- Inclusion visit and randomization
- Annual follow-up in AS
- Biopsies during follow-up
- MRI during follow-up
- Ending AS
- Annual follow-up after ending AS
- End of follow-up in SPCG-17
- Adverse events

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20. REFERENCES

1. Klotz L. Cancer overdiagnosis and overtreatment. Curr Opin Urol 2012;22:203–09.
2. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS/PIRADS%20V2.pdf
3. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012;61:1079-92.
4. Meyer MS, Mucci LA, Andersson SO, et al. Homogeneous prostate cancer mortality in the Nordic countries over four decades. Eur Urol 2010;58:427-32.
5. www.socialstyrelsen.se/statistik/.../cancer
6. www.cancercentrum.se
7. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2014;370:928-38.
8. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
9. Schröder FH, Hugosson J, Roobol MJ, et al. ERSPC Investigators. Prostate cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981-90.
10. Heijnsdijk EA, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012;367:595-605.
11. Fang F, Fall K, Mittleman MA, et al. The trauma of a cancer diagnosis – immediate rise in risks of suicide and cardiovascular death. N Engl J Med 2012;366:1310-18.
12. Fang F, Keating NL, Mucci LA, et al. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: Cohort trial in the United States. J Natl Cancer Inst 2010;102:307-14.
13. DallEra MA, Albertsen PC, Bangma C et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976-83.
14. Rider JR, Sandin F, Andrén O, et al. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. Eur Urol 2013;63:88-96.
15. Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. Eur Urol 2015;67:993-1005.
16. Siddiqui MM, Rais-Bahrami S, Turkbey B et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-397. Review.

17. http://www.eortc.org/recist/

18. Moore CM, Giganti F, Albertsen P et al. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: The PRECISE recommendations – A report of a European school of Oncology Task Force. Eur Urol 2016 (in press).

Research Study SPCG-17

Health and Quality of Life in Men with Prostate Cancer

Thank you for taking part in this study.

A number of questions follow below (40 in part one and 17 in part two). Provide the answers that best describe you and your situation. If more than one alternative is possible, the question will indicate as much. Please try to answer all the questions.

PART 1. DEMOGRAPHICS AND QUESTIONS ABOUT QUALITY OF LIFE

General Questions

1. In which year were you born?
(Give four figures, e.g. 1945)

☐☐☐☐

2. How tall are you?

☐☐☐ cm

3. How much do you weigh?

☐☐☐ kg

4. Are you currently:

❑ Married or living with a partner
❑ Living alone with no partner
❑ Living alone but with a partner
❑ Widower

5. Do you have children?

❑ No ❑ Yes

6. Are you currently:

- ❑ Employed
- ❑ Looking for work
- ❑ Retired
- ❑ On long-term sick leave
- ❑ On disability pension

7. What is the highest level of your education?

- ❑ Basic education or equivalent
- ❑ Upper secondary, vocational school or equivalent
- ❑ University or college

8. During the last 4 weeks, how many hours per have you undertaken at least moderate physical exercise involving an elevated pulse rate (i.e. walking, cycling, swimming, etc.)?

- ❑ None
- ❑ Less than 1 hour per week
- ❑ 1-3 hours per week
- ❑ More than 3 and up to 7 hours per week
- ❑ More than 7 hours per week

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

- ❑ Smoke everyday
- ❑ Smoke occasionally (less than 1 cigarette per day)
- ❑ Former smoker
- ❑ Never smoked

10. How often do you drink alcohol?

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

11. How many standard drinks (see example below) do you typically drink on a day when you drink alcohol?

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

12. Do you have or have you ever had any of the following illnesses? If so, which? (Tick the appropriate box for each question)

Heart disease (e.g. angina, heart attack, or heart failure)	❑ No	❑ Yes
High blood pressure	❑ No	❑ Yes
Pains in the legs when walking owing to poor blood circulation	❑ No	❑ Yes
Lung disease (e.g. asthma, chronic bronchitis, or chronic obstructive pulmonary disease (COPD))	❑ No	❑ Yes
Diabetes	❑ No	❑ Yes
Kidney disease	❑ No	❑ Yes
Liver disease	❑ No	❑ Yes
Stroke	❑ No	❑ Yes
Neurological disease (e.g. Parkinson's disease or MS)	❑ No	❑ Yes
Other type of cancer than prostate cancer (in the last 5 years)	❑ No	❑ Yes
Depression	❑ No	❑ Yes
Other psychological illness	❑ No	❑ Yes
Rheumatism	❑ No	❑ Yes
Paralysis	❑ No	❑ Yes
HIV+ 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 which best describes you (1 is lowest and 7 highest).

13. <u>During the last 4 weeks,</u> what has your quality of life been like?

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

14. <u>During the last 4 weeks,</u> has your life felt meaningful?

1----------2----------3----------4----------5----------6----------7
Never All the time

15. During the last 4 weeks, what has your physical stamina been like?

1----------2----------3----------4----------5----------6----------7
No stamina Best possible stamina

16. During the last 4 weeks, what has your mental well-being been like?

1----------2----------3----------4----------5----------6----------7
No well-being Best possible well-being

17. During the last 4 weeks, what has your physical health been like?

1----------2----------3----------4----------5----------6----------7
Worst imaginable health Best imaginable health

18. During the last 4 weeks, what has your self-esteem been like?

1----------2----------3----------4----------5----------6----------7
No self-esteem Best imaginable self-esteem

Questions About Depression, Worry or Anxiety

19. During the last 4 weeks, have you felt miserable or depressed?

1----------2----------3----------4----------5----------6----------7
Never All the time

20. During the last 4 weeks, have you experienced worry or anxiety?

1----------2----------3----------4----------5----------6----------7
Never All the time

21. During the last 4 weeks, have you had difficulties sleeping at night?

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

22. During the last 4 weeks, have you woken during the night with feelings of worry, anxiety or unease?

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

23. During the last 4 weeks, have you taken any preparations to help you sleep?

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

24. During the last 4 weeks, have you taken any tranquilizers?

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

25. During the last 4 weeks, have you taken any anti-depressives, i.e. medication against feeling low or depressed?

❑ No ❑ Yes

Questions About Information

26. I was informed about my prostate cancer:

- ❑ At a meeting in person
- ❑ By telephone
- ❑ By mail
- ❑ In another way, which? _____

27. When you were informed about your prostate cancer, were you informed in a good way?
(Circle the number which best describes you or your situation)

1----------2----------3----------4----------5----------6----------7
Worst imaginable way Best imaginable way

28. Did you have a friend or relative with you when you were informed about your prostate cancer?

❑ No ❑ Yes

29. Who have you told about your prostate cancer? (NB! Several alternatives possible.)

- ❑ I have not told anyone about my prostate cancer
- ❑ Partner (married or otherwise)
- ❑ Child(ren)
- ❑ Grandchild(ren)
- ❑ Close friend(s)
- ❑ Work colleague(s)/other friends
- ❑ Other person

30. How much information have you received from your doctor? (For each row, tick the box that best describes your perception)

		No Information	Little Information	Quite a lot of Information	A great deal of Information
A.	About prostate cancer – the illness and its course	☐	☐	☐	☐
B.	About various treatment options for prostate cancer	☐	☐	☐	☐
C.	About side effects of the various treatment options	☐	☐	☐	☐
D.	About how the various treatments could affect your quality of life	☐	☐	☐	☐

31. Where have you looked for information about prostate cancer? (NB! Several alternatives possible.)

- ❑ I have not looked for information about prostate cancer
- ❑ Internet
- ❑ Radio
- ❑ TV
- ❑ Magazines
- ❑ Brochures intended for patients
- ❑ Patient association
- ❑ Friends or relatives
- ❑ Other, where? _____

Questions About Active Surveillance and Treatment

32. Which alternative below describes your situation? (Cross of one alternative)

I am currently on active surveillance (i.e. I go to checks with PSA tests and MRI examinations, treatment will become relevant if the cancer becomes more serious)
I started on active surveillance but have since received been treated

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

(NB! Several alternatives are possible. You may, for example, have undergone an operation and radiotherapy, radiotherapy and hormone treatment, or just hormone treatment.)

- ❑ I have not had any treatment, I am on active surveillance
- ❑ Removal of the whole prostate gland (so-called radical prostatectomy)
- ❑ Radiotherapy of the prostate gland
- ❑ Hormone treatment in connection with radiotherapy of the prostate gland
- ❑ Only hormone treatment by injection (so-called GnRH-analogue)
- ❑ Only hormone treatment with pills (e.g. Bicalutamide, or Casodex)

❑ Testicles have been removed by means of operation
❑ Other treatment, which? _____

34. Do you take the medication finasteride (e.g. Proscar or Propecia) to lessen problems with urinating?

❑ No ❑ Yes

Questions About Your Prostate Cancer Checks

35. Before these checks, do you feel:

(A number of sub-questions (A to F) follow below. For each sub-question, tick the box that best describes your perception.)

	NO	YES
A) Worried about meeting the doctor?		
B) Worried that your prostate cancer has become more serious?		
C) Worried that your prostate cancer has spread (metastasized) to a different part of your body?		
D) Worried that the PSA test will show an elevated PSA level?		
E) Worried that the prostate cancer causes your physical problems?		
F) Worried about what the MRI scan will show?		

36. In connection with your prostate cancer checks, do you feel worried about undergoing the MRI?

❑ Not relevant, I have been treated for my prostate cancer
❑ Not at all
❑ A little
❑ Moderately
❑ Very much

37. In connection with your prostate cancer checks, do you feel worried about needing to take new tissue samples (biopsies) from your prostate?

❑ Not relevant, I have been treated for my prostate cancer
❑ Not at all
❑ A little
❑ Moderately
❑ Very much

38. In connection with your prostate cancer checks, do you feel discomfort if the doctor examines your prostate with his/her finger?

❑ Not at all

- ❑ A little
- ❑ Moderately
- ❑ Very much

39. Do you feel a sense of safety in that the doctor examines your prostate with his/her finger?

- ❑ Not at all
- ❑ A little
- ❑ Moderately
- ❑ Very much

40. If you could choose;

- ❑ No, I do not want the doctor to feel my prostate
- ❑ Yes, I want the doctor to feel my prostate

PART 2 QUESTIONNAIRE FOR SYMPTOMS (EPIC-26)

These questions are used within prostate cancer research all over the world.

The next few questions concern problems you may be experiencing.
(Tick the box that best describes you or your situation)

1. During the last 4 weeks, how often has your urine leaked?

- ❑ More than once a day
- ❑ About once a day
- ❑ More than once a week
- ❑ About once a week
- ❑ Seldom or never

2. Which of the following alternatives best describes how well you have been able to control your urinating during the last 4 weeks?

- ❑ No control whatsoever
- ❑ Drip all the time
- ❑ Drip a little occasionally
- ❑ Full control

3. On average over the last 4 weeks, how many incontinence pads or adult diapers have you used per day owing to urine leakage?

- ❑ None
- ❑ 1 per day
- ❑ 2 per day
- ❑ 3 or more per day

4. How large a problem, if any, have the following symptoms been during the last 4 weeks?
(Cross of one alternative for each sub-question.)

		None	Very little	Little	Moderate	Large
A.	Urine leakage	❑	❑	❑	❑	❑
B.	Difficulty or pain in connection with urinating	❑	❑	❑	❑	❑
C.	Blood in urine	❑	❑	❑	❑	❑
D.	Weak stream or feeling of Incomplete emptying of bladder	❑	❑	❑	❑	❑
E.	Need to urinate often during the day	❑	❑	❑	❑	❑

5. Overall, how large a problem has urination been for you during the last 4 weeks? (Tick the box that best describes your perception.)

❑ No problem
❑ Very little problem
❑ Little problem
❑ Moderate problem
❑ Large problem

6. How large a problem, if any, have the following symptoms been for you during the last 4 weeks?
(Cross of one alternative for each sub-question.)

		None	Very little	Little	Moderate	Large
A.	Urgent need to empty the bowel immediately	❑	❑	❑	❑	❑
B.	Need to empty the bowel often	❑	❑	❑	❑	❑
C.	Inability to control the bowel function	❑	❑	❑	❑	❑
D.	Blood in faeces	❑	❑	❑	❑	❑
E.	Pain in abdomen/pelvis/rectum	❑	❑	❑	❑	❑

7. Overall, how large a problem has your bowel emptying been for you during the last 4 weeks? (Tick the box that best describes your perception.)

❑ No problem
❑ Very little problem
❑ Little problem
❑ Moderate problem
❑ Large problem

Questions About Your Sexual Functioning

For many people, sexuality is an important part of their life, for others, less so. Illness in the prostate can affect the sexual function. The sexual function includes self-satisfaction and erotic experiences as well as intercourse.

We would like to remind you that this study is carried out under the strictest confidentiality.

8. How would you rate the following during the last 4 weeks? (Cross of one alternative for each sub-question.)

		Very poor to non-existent	Poor	Moderate	Good	Very good
A.	Your ability to get an erection	❑	❑	❑	❑	❑
B.	Your ability to achieve orgasm?	❑	❑	❑	❑	❑

9. How long did your erection usually last during the last 4 weeks?
(Tick the box that best describes your perception)

❑ Non-existent
❑ Insufficient for any kind of sexual activity
❑ Sufficient for masturbation and foreplay
❑ Sufficient for intercourse

10. How would you describe your possibilities of obtaining an erection during the last 4 weeks?
(Tick the box that best describes your perception)

❑ I NEVER obtained an erection when desired
❑ Less than half of the times I wanted an erection
❑ Around half of the times I wanted an erection
❑ More than half of the times I wanted an erection
❑ Whenever I wanted an erection

11. Overall, how would you rate your sexual capability during the last 4 weeks?
(Tick the box that best describes your perception)

❑ Very poor
❑ Poor
❑ Moderate
❑ Good
❑ Very good

12. How large a problem have you had with your sexual capability during the last 4 weeks?
(Tick the box that best describes your perception)

❑ No problem
❑ Very little problem
❑ Little problem
❑ Moderate problem
❑ Large problem

13. How large a problem, if any, have the following symptoms been for you during the last 4 weeks?
(Cross of one alternative for each sub-question)

		None	Very little problem	Little problem	Moderate problem	Large problem
A.	Hot flushes	❑	❑	❑	❑	❑
B.	Tenderness/ swelling in chest	❑	❑	❑	❑	❑
C.	Feeling low	❑	❑	❑	❑	❑
D.	Lacking energy	❑	❑	❑	❑	❑
E.	Change in body weight	❑	❑	❑	❑	❑

14. Which of the following medications/sexual aids have you tried and how did they work?
(Cross of one alternative for each sub-question)

		Have not tried	Tried but it did not help	Helped but not using it now	Helps and I use it now and then	Helps and I always use it in connection with sexual activity
A.	Viagra, Sildenafil, Cialis, Levitra or other medications? If other pills, please give name: _____	❑	❑	❑	❑	❑
B.	Bondil (gel in urethra)?	❑	❑	❑	❑	❑
C.	Caverject (injection in the penis)?	❑	❑	❑	❑	❑
D.	Vacuum pump?	❑	❑	❑	❑	❑
E.	Other? If so, please state what: _____	❑	❑	❑	❑	❑

15. How long did your erection usually last with the aid of medication/sexual aid during the last 4 weeks? (Tick the box that best describes your perception)

❑ Not relevant, I do not use medications or sexual aids
❑ Non-existent
❑ Insufficient for any kind of sexual activity
❑ Sufficient for masturbation and foreplay
❑ Sufficient for intercourse

16. Are you satisfied with your sexual life?
(Circle the number which best describes you or your situation)

1----------2----------3----------4----------5----------6----------7
Not at all satisfied Completely satisfied

To conclude, we would like to ask

17. How satisfied are you with the care you have received as a prostate cancer patient? (Personalised service, information, etc.)

(Circle the number which best describes you or your situation)

1----------2----------3----------4----------5----------6----------7
Not at all satisfied Completely satisfied

Is there anything else that you think is important concerning your illness that we have failed to ask about? Please write and tell us!

_____

_____

_____

PROTOCOL VERSIONING

The table below details the version history for the SPCG-17 trial protocol. The list is cumulative and identifies changes from the preceding final version of the protocol.

Version	Date	Change(s)	Note(s)
2.1	2016-05-11		1st final version
3.0	2016-09-12	Section 2: Updated flow chart Section 5: Addition to the MRI protocol for SPCG17; it may also (optional) include Magnetic Resonance Spectroscopy Imaging (MRSI) Section 9: Revised criteria for re-biopsy; • Addition of size increase of a measureable lesion • The criteria is divided into: 1) progression in men with previously only Gleason grade 3+3 and 2) progression in men with Gleason grade 3+4) Section 9: Updated figure for follow-up in SPCG17 Section 13: Updated time plan Section 16.6: More information added Section 21: New contact information added	2nd final version
4.0	2016-11-24	Appendix added: Quality of Life Questionnaire Section 5 and 16.6: Revised criteria for MRI; • Both 1.5T and 3T MRI can be used • Dynamic contrast enhanced (DCE) imaging is optional (instead of recommended) Section 8.5: Updated enrolment criteria; all subjects should have undergone systematic biopsies but the criteria no longer state a minimum number of cores Section 8.6: Clarification added; the maximum number of cores with Gleason 3+4 that are allowed refers to systematic biopsies, not targeted biopsies. Section 9 and 10: Reference to the Likert scale	3rd final version

		added. “New suspicion of extracapsular extension or seminal vesicle invasion” is thereby changed to “High or very high suspicion of extracapsular extension or seminal vesicle invasion (4 or 5 on the Likert scale)” Section 13: Updated time plan Section 21: New contact information added. Section 22: References for RECIST and PRECISE added.	
5.0	2018-05-24	Entire document: “MRI” changed to “MRI” Section 8.5: Revised criteria; for patients who were diagnosed with prostate cancer after an MRI with targeted biopsies, systematic biopsies before inclusion in SPCG-17 are optional. Section 9: Clarification that the first follow-up MRI should be done two years after the inclusion MRI. Section 9: Clarification that the annual check-up of patients with clinical stage T1c prostate cancer may be done by phone interview. Section 9.1: Revised criteria for re-biopsy; if the PSA density increases to > 0,2 ng/ml/cc, a systematic re-biopsy should be performed and then repeated at every 0,1 ng/ml/cc increase. Section 13: Updated time plan Section 21: New contact information added New appendix added: Protocol Versioning	4th final version
6.0	May 7 2019	Section 10.1: The definition of PSA relapse after surgery and radiotherapy is changed to the definitions recommended by the EAU; o Progression after surgery is defined by two consecutively rising PSA values >0.2 ng/ml. o Progression after radiotherapy (with or without androgen-deprivation therapy) is defined by any rise by 2 ng/ml or more above the nadir PSA value, regardless of the serum concentration of the nadir.	5th final version

		Section 11: Time plan updated Section 14.7: Information on monitoring of the trial added Section 19: Contact information updated Editorial changes (e.g. layout)	