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PCASTt/SPCG-17 – A randomised trial of active surveillance in prostate cancer: rationale and design

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Abstract

Objective:

To evaluate the safety of a magnetic resonance imaging (MRI)-based active surveillance protocol with standardised triggers for repeated biopsies and radical treatment to reduce overtreatment of prostate cancer.

Design, Setting and Participants:

In all, 2000 men will be randomised between current practice and standardised triggers at centers in Sweden, Norway, Finland, Denmark and United Kingdom. Men with prostate cancer (diagnosed within 12 months), ≤T2a, prostate specific antigen (PSA) <15 ng/ml, PSA density ≤0.2 ng/ml/cc, any International Society of Urological Pathology (ISUP) Grade 1 or ISUP Grade 2 (<30 % of cores (systematic biopsies), < 10 mm cancer in one core (systematic or targeted biopsies)) are eligible. If diagnosed with systematic biopsies, MRI with biopsies targeted against Prostate Imaging and Reporting Data System version 2 (PI-RADS) 3-5 lesions are mandatory before inclusion. Identical basic follow-up in the two study arms: bi-annual PSA-testing, yearly clinical examination and MRI every second year.

Interventions:

In the experimental arm, only standardised triggers based on MRI and PSA density elicit repeated biopsies. MRI and histopathological progression trigger radical treatment.

Outcome measurements and statistical analysis:

Primary outcome: progression-free survival. Secondary endpoints: cumulative incidence of metastatic disease, treatments with curative intent, pT3-4 at radical prostatectomy, switch to watchful waiting, prostate cancer mortality and quality of life.

Results:

The study started inclusion in October 2016 and in October 2018, 275 patients were enrolled.

Conclusions:

PCASTt/SPCG-17 evaluates an MRI-based active surveillance protocol with standardised triggers for biopsy and treatment that intend to reduce overtreatment of prostate cancer without compromising patient outcome.

Trial registration:

The trial is registered to ClinicalTrials.gov, identification: NCT02914873. Study ID Numbers at ClinicalTrials.gov is SPCG-17.

Article summary

PCASTt/SPCG-17 is a randomised clinical trial of an MRI-based active surveillance protocol with defined triggers for repeated biopsies and radical treatment of prostate cancer. We will evaluate the safety of the surveillance protocol compared to current practice.

Strengths and limitations of the study

- The randomised design reduces chances of observed outcome being influenced by confounding factors.
- The trial size will allow quantifying clinically relevant endpoints with reasonable statistical precision.
- International multicentre study making results more generalisabe.
- Limitations include long follow-up that has to be undertaken to assess tumour progression.

Introduction

Following the introduction of PSA testing in the late 1980s, the incidence of prostate cancer increased dramatically in many countries [1]. Widespread PSA testing led to a downward stage migration, with a growing proportion of small and well differentiated cancers with low malignant potential even if left untreated [2].

Although overdiagnosis of prostate cancers has been documented on a group level [2], currently it is not possible to know if an individual man with prostate cancer will experience progression to lethal disease or not. As a consequence, many men unnecessarily undergo radical treatment. To reduce overtreatment and its side effects, without jeopardizing the potential benefit of radical treatment, active surveillance with selective, delayed therapy with curative intent was developed in the late 1990s [3].

In active surveillance, treatment with curative intent is initiated when and if investigations indicate progressive cancer. In watchful waiting only palliative treatment is initiated at symptoms. Several national guidelines recommend active surveillance for most low-risk cancers and selected favourable intermediate-risk cancers [4]. Different criteria are used to trigger radical treatment, but many patients are treated with curative intent without objective signs of disease progression [5]. Although multiple active surveillance cohorts show low rates of disease progression [6], no randomised trials help define which patients are suitable for active surveillance, how to monitor them or when to initiate treatment with curative intent. To fill some of these evidence gaps and reduce both over- and undertreatment, the Scandinavian Prostate Cancer Group (SPCG) is promoting a multinational randomised trial, Prostate Cancer Active Surveillance Trigger trial (PCASTt/SPCG-17), in which standardised triggers for repeat biopsies and initiation of treatment with curative intent, is compared with current

clinical practice for active surveillance of low-risk and favourable intermediate-risk prostate cancer.

Areas of uncertainty

Active Surveillance or immediate treatment with curative intent

None of three randomised trials has shown substantial survival benefit of radical treatment compared with watchful waiting or active monitoring in men with low-risk PCa [7-9]. The SPCG-4 trial began in 1989, i.e. before the PSA era, and included primarily men with palpable tumours. In this trial, radical prostatectomy resulted in a 3.8% (95% CI, -4,6 to 12,2) lower prostate cancer mortality in men with low-risk cancer, compared with watchful waiting, after 18 years of follow-up [7]. In the PIVOT trial, including predominantly men with PSA detected localised cancer, there was a 4% absolute reduction of prostate cancer specific mortality (95% CI, -0,2 to 8,3) after radical prostatectomy, compared with observation, after nearly 20 years of follow-up. Events were few in the subgroup analysis, ensuing low statistical precision [8]. In ProtecT, only men with PSA-detected tumours were included. After ten years of follow-up, prostate cancer specific survival was similar in the three treatment groups: 98.8% (95% CI, 98.4-99.5) after initial active monitoring, 99.0% (95% CI, 97.2-99.6) in men allocated to radical prostatectomy and 99.6% (95% CI, 98.4-99.9) in men allocated to radiotherapy, but progression to metastatic disease was less common after curative treatment [9].

Criteria for active surveillance

Most published active surveillance protocols include men with low-risk disease (ISUP grade 1 (Gleason score 3+3=6), T1c-T2a and PSA < 10 ng/ml), but some include intermediate-risk disease (ISUP grade 2 (Gleason score 3+4=7), T1c-T2 and PSA 10-20 ng/ml) [6]. ProtecT, the

only randomised trial addressing the question of active monitoring vs curative treatment, included all localised risk-groups but predominantly low risk. They found a higher risk of progression to metastases with active monitoring compared to radical treatment, after ten years [9]. However, active monitoring in their protocol consisted of repeated PSA-testing but apart from that was not specifically regulated.

Follow-up during active surveillance

Active surveillance protocols differ, but they typically include repeated digital rectal examinations, PSA testing and systematic, transrectal biopsies. Interpretation of digital rectal examination is subjective and cannot detect tumours in the anterior part of the prostate, which limit its usefulness [10]. PSA values fluctuate over time [11], and raising values may reflect inflammation or progression of benign hyperplasia, rather than tumour progression. Systematic biopsies can easily miss small multifocal cancers and large tumours in the anterior prostate. Histopathological evaluation of the specimen shows considerable inter-individual variation between pathologists [12].

Repeated biopsy and conversion to radical treatment

In Sweden, 30-40% of men managed by active surveillance receive treatment with curative intent within five years after diagnosis [13]. In a nationwide study, active surveillance was discontinued because of "patient preference" in 20%, by PSA progression in 52% and by biopsy progression in 24% of the men [13]. In the PRIAS study, about half of the men switched to curative treatment within 2.3 years [14]. Worry about whether the patient has an undetected high-risk cancer, without objective signs of progression or high-risk cancer, may entail unnecessary repeated biopsies and treatment to accommodate the clinicians´ and the patients´ concerns. Conversely, digital rectal examination, PSA and standard biopsies have low

sensitivity to detect high-grade cancer [10-12]. Hence, we don't know when repeated biopsies are required and when radical treatment is beneficial.

Magnetic resonance imaging

The use of MRI in the assessment of prostate cancer has increased. There is high level evidence that MRI has the ability to detect prostate cancer [15,16], but there is insufficient evidence on the benefit of repeated MRI during active surveillance [17]. According to the PROMIS study, MRI may reduce the proportion of men undergoing a prostate biopsy by one fourth, and the proportion of men diagnosed with clinically insignificant cancer by five percent, at the cost of delaying the diagnosis of a clinically significant cancer (defined as presence of any ISUP grade ≥3 (Gleason score 4+3=7) or a maximum cancer core length involvement of 6 mm or more in any location) in three percent of the men [18]. The negative predictive value of an unsuspicious MRI finding is high, and even higher when PSA density is low [19].

The randomised PRECISION trial indicates that MRI with targeted biopsies has higher detection rate than standard biopsies for ISUP grade ≥ 2 prostate cancer and reduces the detection of ISUP grade 1 cancer in biopsy naïve patients with clinical suspicion of prostate cancer [20]. In a retrospective review of repeated biopsies during active surveillance, MRI with targeted biopsies nearly doubled the detection of pathological progression compared to systematic biopsies [21]. This is however questioned by a recent prospective trial that showed no increase in up-grading with additional targeted biopsies vs systematic biopsies alone [22].

Active surveillance in intermediate-risk prostate cancer

The risk of cancer progression during active surveillance of patients with low-risk prostate cancer is low, but varies between studies, probably because of different inclusion criteria and indications for therapeutic intervention [6]. Active surveillance of intermediate-risk prostate cancer is debated, but it is supported by some data [23]. The Sunnybrook cohort - including men with low-risk and favourable intermediate-risk prostate cancer - showed a 2.8% progression to metastatic disease and 1.5% prostate cancer specific mortality within 15 years [24], with a more favourable outcome for men with low-risk cancer [25]. Eligibility was not influenced by PSA density or number of positive cores, and MRI was not used. Based on findings that MRI with targeted biopsies has a higher detection rate than standard biopsies for ISUP grade ≥2 prostate cancer [20] one must assume that many intermediate and high-risk tumours were undetected in this cohort. Despite this, the long-term cancer specific survival was high.

The PCASTt/ SPCG-17 trial

Study design

PCASTt/SPCG-17 is a multinational randomised trial comparing active surveillance using standardised triggers for repeated biopsy and radical treatment with current practice. The hypothesis is that standardised triggers will reduce overtreatment and adverse events and improve quality of life, without increasing disease progression or prostate cancer mortality. Approval for the trial was obtained from the Regional Ethical Review Board in Uppsala (2016/204).

Outcome measures

The primary endpoint is progression-free survival. Progression is defined as PSA relapse after treatment with curative intent (PSA level of >0.2 ng/ml following surgery, PSA level increase

of >2 ng/ml in consecutive PSA measurements following the first PSA measurement after radiotherapy and PSA level increase of >2ng/ml following radiotherapy and androgen deprivation therapy) or start of androgen deprivation therapy in previously untreated men. Secondary endpoints are the cumulative incidence of pT3 tumours, distant metastasis, treatment with curative intent and switch to watchful waiting. Prostate cancer death is the final endpoint at ten years. Quality-of-life endpoints will be analysed separately.

Participants & participating centres (Table 1, Table 2)

Eligible for inclusion are men with histopathological low-risk or favourable intermediate-risk adenocarcinoma of the prostate diagnosed within 12 months, who have not received any treatment and have at least ten years' expected lifetime. All men primarily diagnosed with prostate cancer from systematic biopsies should undergo MRI with biopsies targeted at PI-RADS 3-5 lesions before inclusion. For men primarily diagnosed with prostate cancer following MRI with targeted biopsies, subsequent systematic biopsies are optional. Centres in Sweden, Denmark, Finland, Norway and UK will participate.

Table 1 – inclusion criteria

- Adenocarcinoma of the prostate diagnosed within the past 12 months
- Tumour stage ≤T2a, NX, M0
- PSA <15 ng/ml and PSA density ≤0.2 ng/ml/cc
- Systematic biopsies with ≥10 cores (optional, if the diagnosis is based on MRI with targeted biopsies)
- MRI with targeted biopsies towards PI-RADS 3, 4 and 5 (according to PI-RADS v. 2)
- ISUP grade 1 (any number of cores, any involvement)
- ISUP grade 2 in <3 cores (or <30% of cores if >10 systematic cores were taken) and <10 mm cancer in one core (systematic or targeted)
- Life expectancy ≥10 years (no upper age limit)
- Candidate for curative treatment (surgery or radiotherapy) if progression occurs
- Signed written informed consent

PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System, ISUP = International Society of Urological Pathology

Table 2 – demands on participating centres

- The local organisation should commit to recruiting all consecutive patients who are willing to start on active surveillance and who fulfil the inclusion criteria
- A 1.5 or 3 Tesla MRI
- Access to prostate MRI expertise. If the local competence is uncertain, the national PI will organise external expertise for MRI evaluation
- The MRI should follow European Society of Urogenital Radiology (ESUR) guidelines and include:
  - T1- and T2-weighted images
  - Diffusion-weighted images (DWI) including Apparent Diffusion Coefficient (ADC)
  - Dynamic contrast enhanced (DCE) imaging and Magnetic Resonance Spectroscopy Imaging (MRSI) are optional

- The MR images should be reported according to PI-RADS v. 2

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

PCASTt/SPCG-17 aims to randomise 2,000 patients in 4 years, which will give an 85% power to detect a 1.3 percentage points progression-free survival difference between the study arms (2-sided alpha 0.05) under the assumption that 90% of the patients are managed per protocol according to randomisation. The progression-free survival in the current practise group five years after randomisation is assumed to be 98%, based on previous studies [24].

Patient reported outcome measures and follow-up

At inclusion and every second year during follow-up participants are requested to fill out a study-specific quality-of-life questionnaire including the Expanded Prostate cancer Index Composite (EPIC-26) [26], for separate quality-of-life analysis.

Basic follow-up is identical in both arms, with biannual PSA testing, annual clinical examination and MRI scan every second year (Figure 1). In the current practice arm, additional investigations are optional and it is up to the urologist to decide when it is time to repeat biopsies and initiate treatment with curative intent. In the experimental arm, follow-up is according to schedule, biopsies are only taken if the standardised triggers are reached (Table 3) and treatment with curative intent is only recommended if standardised triggers for radical treatment are reached (Table 4). At every follow-up, the patient is categorised as having no distant metastasis, suspected distant metastasis (according to PSA-level and/or symptoms) or verified distant metastasis (imaging or histopathology/cytology).

Table 3 – triggers for re-biopsies

ARM I	ARM 2	
According to current practice (the urologists´ judgement)	**I.**	**PSA density >0.2 ng/ml/cc (systematic biopsies)**
	II.	**MRI progression in men with ISUP grade 1 cancer (targeted biopsies)** - ≥5 mm or more increase in size in any dimension of a measurable lesion (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 suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on Likert scale) - A new lesion with PI-RADS score 3-5
	III.	**MRI progression in men with ISUP grade 2 cancer (targeted biopsies)** - ≥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 3-5

PSA=Prostate Specific Antigen, PI-RADS=Prostate Imaging Reporting and Data System, MRI=Magnetic Resonance Imaging, ISUP = International Society of Urological Pathology

Table 4 – triggers for radical treatment

ARM I	ARM 2	
According to current practice (the urologist´s judgement)	**I.**	**MRI progression in lesions with confirmed Gleason pattern 4** - Increase in PI-RADS score to 4 or 5 - High suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on the Likert scale)
	II.	**Pathological progression** - Gleason pattern 5 - Primary Gleason pattern 4 in any core with ≥5 mm cancer - ISUP grade 2 in ≥3 cores (or ≥30% of cores if >10 systematic cores), or ≥10 mm cancer in one core (systematic or targeted)

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

Follow-up continues according to the protocol until initiation of treatment with curative intent, detection of metastasis, switch from active surveillance to watchful waiting or death of any cause. For men who discontinue active surveillance, the follow-up and management continue according to standard clinical practice but with annual reporting in the study. In patients lost to follow-up, endpoints will be assessed through available registers in the participating countries.

Patient and Public Involvement

Patient experiences and priorities is important knowledge that may influence the definition of research questions. Patients were however not directly involved in designing this study,

defining outcome measures, the recruitment to and conduct of the study. A summary of results will be available for all participants and will also be presented to patient organisations and the public.

Experience from first two years of inclusion

The first patient was included in October 2016 at Uppsala University Hospital, Sweden. In 2017, six additional Swedish centres began enrolment and three Norwegian centres started enrolling patients in 2018. Centres in Finland, Denmark and the UK aim to start including patients later in 2018. Characteristics of the first 275 randomised patients are displayed in Table 5. Patients are stratified based on participating centre and Gleason score.

Table 5 - baseline characteristics for the first 275 included patients

	Current practice	Standardised triggers
n	139	136
Age (yr, mean (SD))	62 (6.2)	64 (6.2)
PSA (ng/ml, mean, (SD))	5.1 (2.3)	5.8 (2.3)
PSA-D (ng/ml/cc, mean (SD))	0.11 (0.04)	0.12 (0.04)
Clinical tumour stage (n (%))		
T1c	109 (78)	115 (85)
T2a	29 (21)	21 (15)
unknown	1 (1)	0
Comorbidity (n (%))		
ASA 1	94 (68)	84 (62)
ASA 2	40 (29)	52 (38)
ASA 3	4 (3)	0
unknown	1 (1)	0
Family history of PCa (n (%))		
Yes	33 (24)	38 (28)
No	102 (73)	95 (70)
Unknown	4 (3)	3 (2)
MRI technique (n (%))		
1.5 Tesla	20 (14)	16 (12)
3 Tesla	118 (85)	116 (85)
Unknown	1 (1)	4 (3)
MRI findings (n (%))		
PI-RADS 1-2	76 (55)	55 (40)
PI-RADS 3-5	63 (45)	81 (60)

yr = years, SD = standard deviation, PSA = prostate specific antigen, n = sample size, ASA = American Society of Anesthesiologists classification, PCa = prostate cancer, MRI = magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting and Data System

Discussion

The increasing use of active surveillance has reduced overtreatment of prostate cancer to some extent, but still a large number of men are overtreated [2]. Clearly, more patients should start on active surveillance, and fewer patients on active surveillance should convert to radical treatment.

Over the last decades there has been a Gleason score/ISUP grade inflation, partly due to the 2005 revision of the Gleason pattern definitions. The revision entailed that many patterns previously designated Gleason pattern 3 are now reported as pattern 4 and that the Gleason score/ISUP grade on needle biopsies always includes the highest Gleason grade, even if it is just a minimal component [27]. Because long-term outcomes of active surveillance and watchful waiting are chiefly based on studies undertaken before the 2005 revision, a substantial proportion of low-risk tumours in those studies would today be classified as intermediate-risk. Despite this, they had excellent survival without treatment. These results and the changes in Gleason grading suggests that also men with favourable intermediate-risk prostate cancer should be offered active surveillance. This is supported by the fact that MRI with targeted biopsies detects favourable intermediate-risk tumours that standard biopsies do not detect[18,20]. Hence, if all men with intermediate risk prostate cancer undergo immediate radical treatment, overtreatment would increase.

In PCASTt/SPCG-17, follow-up during active surveillance is based on PSA testing and repeated MRI, not on repeated systematic biopsies. Prostate biopsies are uncomfortable and distressful. They cause bleeding, sometimes urinary retention and about six percent experience febrile infection and one percent develop sepsis [28]. The incidence of serious infections is rising because of multidrug resistant bacteria [29]. It is therefore desirable to reduce

the number of biopsies during active surveillance. In the experimental arm of PCASTt/SPCG-17, biopsies are only performed when triggered which will likely reduce the number of biopsies. MRI with targeted biopsies detect at least as many histopathological intermediate-risk tumours as standard biopsies in biopsy naïve men[20,21], suggesting that MRI with targeted biopsies is viable in a surveillance program.

In PCASTt/SPCG-17 pre-specified changes in MRI trigger targeted biopsies to assess histopathological progression. Since histopathological progression may occur without MRI changes, the protocol also stipulates systematic biopsies if PSA density increases above pre-specified limits (Table 3). Radical treatment is triggered by MRI findings suggesting progression of a known ISUP grade 2 tumour and by biopsies showing more than a defined upper limit of Gleason pattern 4 or any Gleason pattern 5 (Table 4).

The strengths of PCASTt/SPCG-17 includes the randomised design and a trial size that will allow quantifying clinically relevant endpoints with reasonable statistical precision. A data monitoring and safety committee will oversee patient safety and the trial's scientific integrity. The safety of the MRI-based follow-up will be regularly evaluated by comparing the outcome with a matched group of men managed by active surveillance in the Swedish SAMS study, who are on active surveillance based on systematic transrectal biopsies [30]. During the long-term follow-up, new methods for monitoring and treatment might be introduced and applied in our patient cohort, obscuring the interpretation of the results. Furthermore, over time the triggers for repeated biopsies and treatment in the PCASTt/SPCG-17 trial's standard treatment arm might become more similar to the management of the men in the experimental group. Although this will affect the trial's ability to detect any difference between the two groups, the PCASTt/SPCG-17 experimental arm can still be used to assess the clinical safety

and acceptability of a standardised protocol and provide prospective data on the performance of MRI as a monitoring tool – both aspects key to patient safety under AS.

Conclusion

PCASTt/SPCG-17 is a randomised trial that evaluates the safety of an MRI-based active surveillance protocol, comparing standardised triggers for repeat biopsies and curative treatment. If the protocol proves to be as safe as current clinical practice, its implementation could lead to a reduction of the number of biopsies, reduce overtreatment of prostate cancer without compromising the outcome of the patients in terms of morbidity and mortality.

Contributors:

All authors (MSA, H-OA, LH, AB-A, KB, HB, MB, OB, DC, LE, HG, EJ, AR, MVH, FJ, CW and UWNÅ) have made the following contributions to the work: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest:

None of the contributing authors have any conflicts of interest.

Data sharing statement:

No individual participant data will be available. What data that will be shared, when it will be available, to whom and to what type of analyses is not applicable. Study protocol is available.

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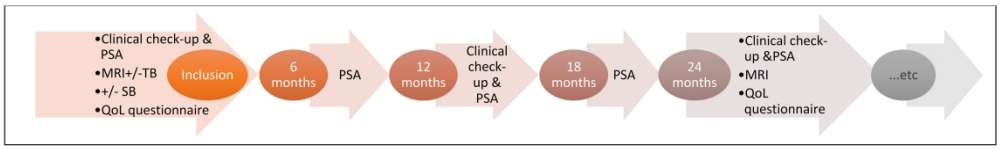
Figure 1 – Basic follow-up



PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, TB=Targeted Biopsies, SB=Systematic Biopsies, QoL=Quality of Life

286x59mm (600 x 600 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6,7,8,9,
	2b	Specific objectives or hypotheses	9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	10,11
	4b	Settings and locations where the data were collected	14
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	12,13,14
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	In protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	In protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	In protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	In protocol

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	12,13,14
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	n/a
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Uploaded in scholar one
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

PCASTt/SPCG-17 – A randomised trial of active surveillance in prostate cancer: rationale and design

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Keywords:	Active surveillance, MRI, Prostate cancer, Randomised trial

PCASTt/SPCG-17 – A randomised trial of active surveillance in prostate cancer: rationale and design

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Keywords Active surveillance; MRI; prostate cancer; randomised trial

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Abstract

Introduction:

Overtreatment of localised prostate cancer is substantial despite increased use of active surveillance.

Methods and analysis:

A randomised, multicentre, intervention trial designed to evaluate the safety of an MRI-based active surveillance protocol, with standardised triggers for repeated biopsies and radical treatment, with the aim to reduce overtreatment of prostate cancer. In all, 2000 men will be randomly allocated to either surveillance according to current practice or to standardised triggers at centers in Sweden, Norway, Finland, Denmark and the United Kingdom. Men diagnosed the past 12 months with prostate cancer, ≤T2a, prostate specific antigen (PSA) <15 ng/ml, PSA density ≤0.2 ng/ml/cc, any International Society of Urological Pathology (ISUP) Grade Group 1 are eligible. Men with ISUP Grade Group 2 in <30 % of cores on systematic biopsy and< 10 mm cancer in one core on systematic or targeted biopsy are also eligible. Men diagnosed on systematic biopsy should have an MRI and targeted biopsies against Prostate Imaging and Reporting Data System version 2 (PI-RADS) 3-5 lesions before inclusion. Identical follow-up in the two study arms: bi-annual PSA-testing, yearly clinical examination and MRI every second year. In the experimental arm, standardised triggers based on MRI and PSA density elicit repeated biopsies. MRI and histopathological progression trigger radical treatment. Primary outcome measure is progression-free survival. Secondary outcome measures are cumulative incidence of metastatic disease, treatments with curative intent, pT3-4 at radical prostatectomy, switch to watchful waiting, prostate cancer mortality and quality of life. Inclusion started in October 2016 and in October 2018; 275 patients have been enrolled.

Ethics and dissemination:

Ethical approval was obtained in each participating country before starting inclusion. One county awaits ethical approval. Results for the primary and secondary outcome measures will be submitted for publication in peer-reviewed journals.

Trial registration number:

Identification: NCT02914873. Study ID Numbers: SPCG-17.

Article summary

Strengths and limitations of this study

- The randomised design reduces chances of observed outcome being influenced by confounding factors.
- The trial size will allow quantifying clinically relevant endpoints with reasonable statistical precision.
- International multicentre study making results more generalisabe.
- Limitations include long follow-up that has to be undertaken to assess tumour progression.

Introduction

Following the introduction of PSA testing in the late 1980s, the incidence of prostate cancer increased dramatically in many countries [1]. Widespread PSA testing led to a downward stage migration, with a growing proportion of small and well differentiated cancers with low malignant potential even if left untreated [2].

Although overdiagnosis of prostate cancers has been documented on a group level [2], currently it is not possible to know if an individual man with prostate cancer will experience progression to lethal disease or not. As a consequence, many men unnecessarily undergo radical treatment. To reduce overtreatment and its side effects, without jeopardizing the potential benefit of radical treatment, active surveillance with selective, delayed therapy with curative intent was developed in the late 1990s [3].

In active surveillance, treatment with curative intent is initiated when and if investigations indicate progressive cancer. In watchful waiting only palliative treatment is initiated at symptoms. Several national guidelines recommend active surveillance for most low-risk cancers and selected favourable intermediate-risk cancers [4]. Different criteria are used to trigger radical treatment, but many patients are treated with curative intent without objective signs of disease progression [5]. Although multiple active surveillance cohorts show low rates of disease progression [6], no randomised trials help define which patients are suitable for active surveillance, how to monitor them or when to initiate treatment with curative intent. To fill some of these evidence gaps and reduce both over- and undertreatment, the Scandinavian Prostate Cancer Group (SPCG) is promoting a multinational randomised trial, Prostate Cancer Active Surveillance Trigger trial (PCASTt/SPCG-17), in which standardised triggers for repeat biopsies and initiation of treatment with curative intent, is compared with current

clinical practice for active surveillance of low-risk and favourable intermediate-risk prostate cancer.

Areas of uncertainty

Active Surveillance or immediate treatment with curative intent

None of three randomised trials has shown substantial survival benefit of radical treatment compared with watchful waiting or active monitoring in men with low-risk PCa [7-9]. The SPCG-4 trial began in 1989, i.e. before the PSA era, and included primarily men with palpable tumours. In this trial, radical prostatectomy resulted in a 3.8% (95% CI, -4,6 to 12,2) lower prostate cancer mortality in men with low-risk cancer, compared with watchful waiting, after 18 years of follow-up [7]. In the PIVOT trial, including predominantly men with PSA detected localised cancer, there was a 4% absolute reduction of prostate cancer specific mortality (95% CI, -0,2 to 8,3) after radical prostatectomy, compared with observation, after nearly 20 years of follow-up. Events were few in the subgroup analysis, ensuing low statistical precision [8]. In ProtecT, only men with PSA-detected tumours were included. After ten years of follow-up, prostate cancer specific survival was similar in the three treatment groups: 98.8% (95% CI, 98.4-99.5) after initial active monitoring, 99.0% (95% CI, 97.2-99.6) in men allocated to radical prostatectomy and 99.6% (95% CI, 98.4-99.9) in men allocated to radiotherapy, but progression to metastatic disease was less common after treatment with curative intent [9].

Criteria for active surveillance

Most published active surveillance protocols include men with low-risk disease (ISUP grade 1 (Gleason score 3+3=6), T1c-T2a and PSA < 10 ng/ml), but some include intermediate-risk disease (ISUP grade 2 (Gleason score 3+4=7), T1c-T2 and PSA 10-20 ng/ml) [6]. ProtecT, the

only randomised trial addressing the question of active monitoring vs curative treatment, included all localised risk-groups but predominantly low risk. They found a higher risk of progression to metastases with active monitoring compared to radical treatment, after ten years [9]. However, active monitoring in their protocol consisted of repeated PSA-testing but apart from that was not specifically regulated.

Follow-up during active surveillance

Active surveillance protocols differ, but they typically include repeated digital rectal examinations, PSA testing and systematic, transrectal biopsies. Interpretation of digital rectal examination is subjective and cannot detect tumours in the anterior part of the prostate, which limit its usefulness [10]. PSA values fluctuate over time [11], and raising values may reflect inflammation or progression of benign hyperplasia, rather than tumour progression. Systematic biopsies can easily miss small multifocal cancers and large tumours in the anterior prostate. Histopathological evaluation of the specimen shows considerable inter-individual variation between pathologists [12].

Repeated biopsy and conversion to radical treatment

In Sweden, 30-40% of men managed by active surveillance receive treatment with curative intent within five years after diagnosis [13]. In a nationwide study, active surveillance was discontinued because of "patient preference" in 20%, by PSA progression in 52% and by biopsy progression in 24% of the men [13]. In the PRIAS study, about half of the men switched to curative treatment within 2.3 years [14]. Worry about whether the patient has an undetected high-risk cancer, without objective signs of progression or high-risk cancer, may entail unnecessary repeated biopsies and treatment to accommodate the clinicians´ and the patients´ concerns. Conversely, digital rectal examination, PSA and systematic biopsies have low

sensitivity to detect high-grade cancer [10-12]. Hence, we don't know when repeated biopsies are required and when radical treatment is beneficial.

Magnetic resonance imaging

The use of MRI in the assessment of prostate cancer has increased. There is high level evidence that MRI has the ability to detect prostate cancer [15,16], but there is insufficient evidence on the benefit of repeated MRI during active surveillance [17]. According to the PROMIS study, MRI may reduce the proportion of men undergoing a prostate biopsy by one fourth, and the proportion of men diagnosed with clinically insignificant cancer by five percent, at the cost of delaying the diagnosis of a clinically significant cancer (defined as presence of any ISUP grade ≥3 (Gleason score 4+3=7) or a maximum cancer core length involvement of 6 mm or more in any location) in three percent of the men [18]. The negative predictive value of an unsuspicious MRI finding is high, and even higher when PSA density is low [19].

The randomised PRECISION trial indicates that MRI with targeted biopsies has higher detection rate than systematic biopsies for ISUP grade ≥ 2 prostate cancer and reduces the detection of ISUP grade 1 cancer in biopsy naïve patients with clinical suspicion of prostate cancer [20]. In a retrospective review of repeated biopsies during active surveillance, MRI with targeted biopsies nearly doubled the detection of pathological progression compared to systematic biopsies [21]. This is however questioned by a recent prospective trial that showed no increase in up-grading with additional targeted biopsies vs systematic biopsies alone [22].

Active surveillance in intermediate-risk prostate cancer

The risk of cancer progression during active surveillance of patients with low-risk prostate cancer is low, but varies between studies, probably because of different inclusion criteria and indications for therapeutic intervention [6]. Active surveillance of intermediate-risk prostate cancer is debated, but it is supported by some data [23]. The Sunnybrook cohort - including men with low-risk and favourable intermediate-risk prostate cancer - showed a 2.8% progression to metastatic disease and 1.5% prostate cancer specific mortality within 15 years [24], with a more favourable outcome for men with low-risk cancer [25]. Eligibility was not influenced by PSA density or number of positive cores, and MRI was not used. Based on findings that MRI with targeted biopsies has a higher detection rate than standard biopsies for ISUP grade ≥2 prostate cancer [20] one must assume that many intermediate and high-risk tumours were undetected in this cohort. Despite this, the long-term cancer specific survival was high.

The PCASTt/ SPCG-17 trial

Study design

PCASTt/SPCG-17 is a multinational randomised trial comparing active surveillance using standardised triggers for repeated biopsy and radical treatment with current practice. The hypothesis is that standardised triggers will reduce overtreatment and adverse events and improve quality of life, without increasing disease progression or prostate cancer mortality. Approval for the trial was obtained from the Regional Ethical Review Board in Uppsala (2016/204).

Outcome measures

The primary endpoint is progression-free survival. Progression is defined as biochemical recurrence after treatment with curative intent or start of androgen deprivation therapy in previously untreated men. Following radical prostatectomy, biochemical recurrence is defined as two consecutive rising PSA values >0.2 ng/ml. After primary radiation therapy and radiation therapy with androgen deprivation therapy, the definition of biochemical recurrence is any PSA increase 2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir[26]. Secondary endpoints are the cumulative incidence of pT3 tumours, distant metastasis, treatment with curative intent and switch to watchful waiting. Prostate cancer death is the final endpoint at ten years. Quality-of-life endpoints will be analysed separately.

Participants & participating centres

Eligible for inclusion are men with histopathological low-risk or favourable intermediate-risk adenocarcinoma of the prostate diagnosed within 12 months, who have not received any treatment and have at least ten years' expected lifetime. All men primarily diagnosed with prostate cancer from systematic biopsies should undergo MRI with biopsies targeted at PI-RADS 3-5 lesions before inclusion. For men primarily diagnosed with prostate cancer following MRI with targeted biopsies, subsequent systematic biopsies are optional. Inclusion criteria are listed in table 1. Centres in Sweden, Denmark, Finland, Norway and UK will participate. Demands on participating centres are listed in table 2.

Table 1 – inclusion criteria

- Adenocarcinoma of the prostate diagnosed within the past 12 months
- Tumour stage ≤T2a, NX, M0
- PSA <15 ng/ml and PSA density ≤0.2 ng/ml/cc
- Systematic biopsies with ≥10 cores (optional, if the diagnosis is based on MRI with targeted biopsies)
- MRI with targeted biopsies towards PI-RADS 3, 4 and 5 (according to PI-RADS v. 2)
- ISUP grade 1 (any number of cores, any involvement)
- ISUP grade 2 in <3 cores (or <30% of cores if >10 systematic cores were taken) and <10 mm cancer in one core (systematic or targeted)
- Life expectancy ≥10 years (no upper age limit)
- Candidate for curative treatment (surgery or radiotherapy) if progression occurs
- Signed written informed consent

PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System, ISUP = International Society of Urological Pathology

Table 2 – demands on participating centres

- The local organisation should commit to recruiting all consecutive patients who are willing to start on active surveillance and who fulfil the inclusion criteria
- A 1.5 or 3 Tesla MRI
- Access to prostate MRI expertise. If the local competence is uncertain, the national PI will organise external expertise for MRI evaluation
- The MRI should follow European Society of Urogenital Radiology (ESUR) guidelines and include:
  - T1- and T2-weighted images
  - Diffusion-weighted images (DWI) including Apparent Diffusion Coefficient (ADC)
  - Dynamic contrast enhanced (DCE) imaging and Magnetic Resonance Spectroscopy Imaging (MRSI) are optional

- The MR images should be reported according to PI-RADS v. 2

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

PCASTt/SPCG-17 aims to randomise 2,000 patients in 4 years, which will give an 85% power to detect a 1.3 percentage points progression-free survival difference between the study arms (2-sided alpha 0.05) under the assumption that 90% of the patients are managed per protocol according to randomisation. The progression-free survival in the current practise group five years after randomisation is assumed to be 98%, based on previous studies [24].

Patient reported outcome measures and follow-up

At inclusion and every second year during follow-up participants are requested to complete a study-specific quality-of-life questionnaire including the Expanded Prostate cancer Index Composite (EPIC-26) [27], for separate quality-of-life analysis.

Basic follow-up is identical in both arms, with biannual PSA testing, annual clinical examination and MRI scan every second year (Figure 1). In the current practice arm, additional investigations are optional and it is up to the urologist to decide when it is time to repeat biopsies and initiate treatment with curative intent. In the experimental arm, follow-up is according to schedule, biopsies are only taken if the standardised triggers are reached (Table 3) and treatment with curative intent is only recommended if standardised triggers for radical treatment are reached (Table 4). At every follow-up, the patient is categorised as having no distant metastasis, suspected distant metastasis (according to PSA-level and/or symptoms) or verified distant metastasis (imaging or histopathology/cytology).

Table 3 – triggers for re-biopsies

ARM I	ARM 2	
According to current practice (the urologists´ judgement)	**I.**	**PSA density >0.2 ng/ml/cc (systematic biopsies)**
	II.	**MRI progression in men with ISUP grade 1 cancer (targeted biopsies)** - ≥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 suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on Likert scale) - A new lesion with PI-RADS score 3-5
	III.	**MRI progression in men with ISUP grade 2 cancer (targeted biopsies)** - ≥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 3-5

PSA=Prostate Specific Antigen, PI-RADS=Prostate Imaging Reporting and Data System, MRI=Magnetic Resonance Imaging, ISUP = International Society of Urological Pathology

Table 4 – triggers for radical treatment

ARM I	ARM 2	
According to current practice (the urologist´s judgement)	**I.**	**MRI progression in lesions with confirmed Gleason pattern 4** - Increase in PI-RADS score to 4 or 5 - High suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on the Likert scale)
	II.	**Pathological progression** - Gleason pattern 5 - Primary Gleason pattern 4 in any core with ≥5 mm cancer - ISUP grade 2 in ≥3 cores (or ≥30% of cores if >10 systematic cores), or ≥10 mm cancer in one core (systematic or targeted)

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

Follow-up continues according to the protocol until initiation of treatment with curative intent, detection of metastasis, switch from active surveillance to watchful waiting or death of any cause. For men who discontinue active surveillance, the follow-up and management continue according to standard clinical practice but with annual reporting in the study. In patients lost to follow-up, endpoints will be assessed through available registers in the participating countries.

Patient and Public Involvement

Patient experiences and priorities is important knowledge that may influence the definition of research questions. Patients were however not directly involved in designing this study,

defining outcome measures, the recruitment to and conduct of the study. A summary of results will be available for all participants and will also be presented to patient organisations and the public.

Experience from first two years of inclusion

The first patient was included in October 2016 at Uppsala University Hospital, Sweden. In 2017, six additional Swedish centres began enrolment and three Norwegian centres started enrolling patients in 2018. Centres in Finland, Denmark and the UK aim to start including patients later in 2018. Characteristics of the first 275 randomised patients are displayed in Table 5. Patients are stratified based on participating centre and Gleason score.

Table 5 - baseline characteristics for the first 275 included patients

	Current practice	Standardised triggers
n	139	136
Age (yr, mean (SD))	62 (6.2)	64 (6.2)
PSA (ng/ml, mean, (SD))	5.1 (2.3)	5.8 (2.3)
PSA-D (ng/ml/cc, mean (SD))	0.11 (0.04)	0.12 (0.04)
Clinical tumour stage (n (%))		
T1c	109 (78)	115 (85)
T2a	29 (21)	21 (15)
unknown	1 (1)	0
Comorbidity (n (%))		
ASA 1	94 (68)	84 (62)
ASA 2	40 (29)	52 (38)
ASA 3	4 (3)	0
unknown	1 (1)	0
Family history of PCa (n (%))		
Yes	33 (24)	38 (28)
No	102 (73)	95 (70)
Unknown	4 (3)	3 (2)
MRI technique (n (%))		
1.5 Tesla	20 (14)	16 (12)
3 Tesla	118 (85)	116 (85)
Unknown	1 (1)	4 (3)
MRI findings (n (%))		
PI-RADS 1-2	76 (55)	55 (40)
PI-RADS 3-5	63 (45)	81 (60)

yr = years, SD = standard deviation, PSA = prostate specific antigen, n = sample size, ASA = American Society of Anesthesiologists classification, PCa = prostate cancer, MRI = magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting and Data System

Ethics and dissemination

The study has ethical approval from Sweden, Norway, Finland and UK. Denmark awaits ethical approval. The first analysis of primary and secondary end-points will take place one year after all men are included (and then every third year) and be published in peer-reviewed journal.

Discussion

The increasing use of active surveillance has reduced overtreatment of prostate cancer to some extent, but still a large number of men are overtreated [2]. Clearly, more patients should start on active surveillance, and fewer patients on active surveillance should convert to radical treatment.

Over the last decades there has been a Gleason score/ISUP grade inflation, partly due to the 2005 revision of the Gleason pattern definitions. The revision entailed that many patterns previously designated Gleason pattern 3 are now reported as pattern 4 and that the Gleason score/ISUP grade on needle biopsies always includes the highest Gleason grade, even if it is just a minimal component [28]. Because long-term outcomes of active surveillance and watchful waiting are chiefly based on studies undertaken before the 2005 revision, a substantial proportion of low-risk tumours in those studies would today be classified as intermediate-risk. Despite this, they had excellent survival without treatment. These results and the changes in Gleason grading suggests that also men with favourable intermediate-risk prostate cancer should be offered active surveillance. This is supported by the fact that MRI with targeted biopsies detects favourable intermediate-risk tumours that standard biopsies do not detect[18,20].

Hence, if all men with intermediate risk prostate cancer undergo immediate radical treatment, overtreatment would increase.

In PCASTt/SPCG-17, follow-up during active surveillance is based on PSA testing and repeated MRI, not on repeated systematic biopsies. Prostate biopsies are uncomfortable and distressful. They cause bleeding, sometimes urinary retention and about six percent experience febrile infection and one percent develop sepsis [29]. The incidence of serious infections is rising because of multidrug resistant bacteria [30]. It is therefore desirable to reduce the number of biopsies during active surveillance. In the experimental arm of PCASTt/SPCG-17, biopsies are only performed when triggered which will likely reduce the number of biopsies. MRI with targeted biopsies detect at least as many histopathological intermediate-risk tumours as standard biopsies in biopsy naïve men[20,21], suggesting that MRI with targeted biopsies is viable in a surveillance program.

In PCASTt/SPCG-17 pre-specified changes in MRI trigger targeted biopsies to assess histopathological progression. Since histopathological progression may occur without MRI changes, the protocol also stipulates systematic biopsies if PSA density increases above pre-specified limits (Table 3). Radical treatment is triggered by MRI findings suggesting progression of a known ISUP grade 2 tumour and by biopsies showing more than a defined upper limit of Gleason pattern 4 or any Gleason pattern 5 (Table 4).

The strengths of PCASTt/SPCG-17 includes the randomised design and a trial size that will allow quantifying clinically relevant endpoints with reasonable statistical precision. A data monitoring and safety committee will oversee patient safety and the trial's scientific integrity. The safety of the MRI-based follow-up will be regularly evaluated by comparing the outcome with a matched group of men managed by active surveillance in the Swedish SAMS study,

who are on active surveillance based on systematic transrectal biopsies [31]. During the long-term follow-up, new methods for monitoring and treatment might be introduced and applied in our patient cohort, obscuring the interpretation of the results. Furthermore, over time the triggers for repeated biopsies and treatment in the PCASTt/SPCG-17 trial's standard treatment arm might become more similar to the management of the men in the experimental group. Although this will affect the trial's ability to detect any difference between the two groups, the PCASTt/SPCG-17 experimental arm can still be used to assess the clinical safety and acceptability of a standardised protocol and provide prospective data on the performance of MRI as a monitoring tool – both aspects key to patient safety under AS.

Conclusion

PCASTt/SPCG-17 is a randomised trial that evaluates the safety of an MRI-based active surveillance protocol, comparing standardised triggers for repeat biopsies and curative treatment. If the protocol proves to be as safe as current clinical practice, its implementation could lead to a reduction of the number of biopsies, reduce overtreatment of prostate cancer without compromising the outcome of the patients in terms of morbidity and mortality.

Contributors:

All authors (MSA, H-OA, LH, AB-A, KB, HB, MB, OB, DC, LE, HG, EJ, AR, MVH, FJ, CW and UWNÅ) have made the following contributions to the work: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest:

None of the contributing authors have any conflicts of interest.

Data sharing statement:

No additional data.

Figure 1 – Basic follow-up. PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, TB=Targeted Biopsies, SB=Systematic Biopsies, QoL=Quality of Life

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Figure 1 – Basic follow-up. PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, TB=Targeted Biopsies, SB=Systematic Biopsies, QoL=Quality of Life

297x209mm (150 x 150 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6,7,8,9,
	2b	Specific objectives or hypotheses	9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	10,11
	4b	Settings and locations where the data were collected	14
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	12,13,14
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	In protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	In protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	In protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	In protocol

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	12,13,14
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	n/a
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Uploaded in scholar one
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on Page nuber
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes ClinicalTrials.gov
Protocol version	3	Date and version identifier	Available at ClinicalTrials.gov
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1 & 19, 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 19, 20 & ClinicalTrials.gov
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 9
	6b	Explanation for choice of comparators	9

Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10, 11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10, 11, Table 1 & 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 12, 13, 14, figure 1 table 3 & 4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	In protocol Available at ClinicalTrials.gov
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	In protocol Available at ClinicalTrials.gov
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	In protocol Available at ClinicalTrials.gov
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	In protocol Available at ClinicalTrials.gov
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In protocol Available at ClinicalTrials.gov
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	In protocol Available at ClinicalTrials.gov
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	In protocol Available at ClinicalTrials.gov
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	In protocol Available at ClinicalTrials.gov
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	In protocol Available at ClinicalTrials.gov
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	In protocol Available at ClinicalTrials.gov
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	In protocol Available at ClinicalTrials.gov
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 9

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	In protocol Available at ClinicalTrials.gov
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	In protocol Available at ClinicalTrials.gov
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	In protocol Available at ClinicalTrials.gov
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	In protocol Available at ClinicalTrials.gov
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 15, 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	In protocol Available at ClinicalTrials.gov
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	In protocol Available at ClinicalTrials.gov
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In protocol Available at ClinicalTrials.gov

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In protocol Available at ClinicalTrials.gov

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

PCASTt/SPCG-17 – A randomised trial of active surveillance in prostate cancer: rationale and design

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Urology
Keywords:	Active surveillance, MRI, Prostate cancer, Randomised trial

PCASTt/SPCG-17 – A randomised trial of active surveillance in prostate cancer: rationale and design

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Abstract

Introduction:

Overtreatment of localised prostate cancer is substantial despite increased use of active surveillance. No randomised trials help define how to monitor patients or when to initiate treatment with curative intent.

Methods and analysis:

A randomised, multicentre, intervention trial designed to evaluate the safety of an MRI-based active surveillance protocol, with standardised triggers for repeated biopsies and radical treatment, with the aim to reduce overtreatment of prostate cancer. 2000 men will be randomly allocated to either surveillance according to current practice or to standardised triggers at centers in Sweden, Norway, Finland and the United Kingdom. Men diagnosed the past 12 months with prostate cancer, ≤T2a, prostate specific antigen (PSA) <15 ng/ml, PSA density ≤0.2 ng/ml/cc, any International Society of Urological Pathology (ISUP) Grade Group 1 are eligible. Men with ISUP Grade Group 2 in <30 % of cores on systematic biopsy and <10 mm cancer in one core on systematic or targeted biopsy are also eligible. Men diagnosed on systematic biopsy should have an MRI and targeted biopsies against Prostate Imaging and Reporting Data System version 2 (PI-RADS) 3-5 lesions before inclusion. Identical follow-up in the two study arms: bi-annual PSA-testing, yearly clinical examination and MRI every second year. In the experimental arm, standardised triggers based on MRI and PSA density elicit repeated biopsies. MRI and histopathological progression trigger radical treatment. Primary outcome measure is progression-free survival. Secondary outcome measures are cumulative incidence of metastatic disease, treatments with curative intent, pT3-4 at radical prostatectomy, switch to watchful waiting, prostate cancer mortality and quality of life. Inclusion started in October 2016 and in October 2018; 275 patients have been enrolled.

Ethics and dissemination:

Ethical approval was obtained in each participating country. Results for the primary and secondary outcome measures will be submitted for publication in peer-reviewed journals.

Trial ID:

SPCG-17; NCT02914873.

Article summary

Strengths and limitations of this study

- The randomised design reduces chances of observed outcome being influenced by confounding factors.
- The trial size will allow quantifying clinically relevant endpoints with reasonable statistical precision.
- International multicentre study making results more generalisabe.
- Limitations include long follow-up that has to be undertaken to assess tumour progression.

Introduction

Following the introduction of PSA testing in the late 1980s, the incidence of prostate cancer increased dramatically in many countries [1]. Widespread PSA testing led to a downward stage migration, with a growing proportion of small and well differentiated cancers with low malignant potential even if left untreated [2].

Although overdiagnosis of prostate cancers has been documented on a group level [2], currently it is not possible to know if an individual man with prostate cancer will experience progression to lethal disease or not. As a consequence, many men unnecessarily undergo radical treatment. To reduce overtreatment and its side effects, without jeopardizing the potential benefit of radical treatment, active surveillance with selective, delayed therapy with curative intent was developed in the late 1990s [3].

In active surveillance, treatment with curative intent is initiated when and if investigations indicate progressive cancer. In watchful waiting only palliative treatment is initiated at symptoms. Several national guidelines recommend active surveillance for most low-risk cancers and selected favourable intermediate-risk cancers [4]. Different criteria are used to trigger radical treatment, but many patients are treated with curative intent without objective signs of disease progression [5]. Although multiple active surveillance cohorts show low rates of disease progression [6], no randomised trials help define which patients are suitable for active surveillance, how to monitor them or when to initiate treatment with curative intent. To fill some of these evidence gaps and reduce both over- and undertreatment, the Scandinavian Prostate Cancer Group (SPCG) is promoting a multinational randomised trial, Prostate Cancer Active Surveillance Trigger trial (PCASTt/SPCG-17), in which standardised triggers for repeat biopsies and initiation of treatment with curative intent, is compared with current

clinical practice for active surveillance of low-risk and favourable intermediate-risk prostate cancer.

Areas of uncertainty

Active Surveillance or immediate treatment with curative intent

None of three randomised trials has shown substantial survival benefit of radical treatment compared with watchful waiting or active monitoring in men with low-risk PCa [7-9]. The SPCG-4 trial began in 1989, i.e. before the PSA era, and included primarily men with palpable tumours. In this trial, radical prostatectomy resulted in a 3.8% (95% CI, -4,6 to 12,2) lower prostate cancer mortality in men with low-risk cancer, compared with watchful waiting, after 18 years of follow-up [7]. In the PIVOT trial, including predominantly men with PSA detected localised cancer, there was a 4% absolute reduction of prostate cancer specific mortality (95% CI, -0,2 to 8,3) after radical prostatectomy, compared with observation, after nearly 20 years of follow-up. Events were few in the subgroup analysis, ensuing low statistical precision [8]. In ProtecT, only men with PSA-detected tumours were included. After ten years of follow-up, prostate cancer specific survival was similar in the three treatment groups: 98.8% (95% CI, 98.4-99.5) after initial active monitoring, 99.0% (95% CI, 97.2-99.6) in men allocated to radical prostatectomy and 99.6% (95% CI, 98.4-99.9) in men allocated to radiotherapy, but progression to metastatic disease was less common after treatment with curative intent [9].

Criteria for active surveillance

Most published active surveillance protocols include men with low-risk disease (ISUP grade 1 (Gleason score 3+3=6), T1c-T2a and PSA < 10 ng/ml), but some include intermediate-risk disease (ISUP grade 2 (Gleason score 3+4=7), T1c-T2 and PSA 10-20 ng/ml) [6]. ProtecT, the

only randomised trial addressing the question of active monitoring vs curative treatment, included all localised risk-groups but predominantly low risk. They found a higher risk of progression to metastases with active monitoring compared to radical treatment, after ten years [9]. However, active monitoring in their protocol consisted of repeated PSA-testing but apart from that was not specifically regulated.

Follow-up during active surveillance

Active surveillance protocols differ, but they typically include repeated digital rectal examinations, PSA testing and systematic, transrectal biopsies. Interpretation of digital rectal examination is subjective and cannot detect tumours in the anterior part of the prostate, which limit its usefulness [10]. PSA values fluctuate over time [11], and raising values may reflect inflammation or progression of benign hyperplasia, rather than tumour progression. Systematic biopsies can easily miss small multifocal cancers and large tumours in the anterior prostate. Histopathological evaluation of the specimen shows considerable inter-individual variation between pathologists [12].

Repeated biopsy and conversion to radical treatment

In Sweden, 30-40% of men managed by active surveillance receive treatment with curative intent within five years after diagnosis [13]. In a nationwide study, active surveillance was discontinued because of "patient preference" in 20%, by PSA progression in 52% and by biopsy progression in 24% of the men [13]. In the PRIAS study, about half of the men switched to curative treatment within 2.3 years [14]. Worry about whether the patient has an undetected high-risk cancer, without objective signs of progression or high-risk cancer, may entail unnecessary repeated biopsies and treatment to accommodate the clinicians´ and the patients´ concerns. Conversely, digital rectal examination, PSA and systematic biopsies have low

sensitivity to detect high-grade cancer [10-12]. Hence, we don't know when repeated biopsies are required and when radical treatment is beneficial.

Magnetic resonance imaging

The use of MRI in the assessment of prostate cancer has increased. There is high level evidence that MRI has the ability to detect prostate cancer [15,16], but there is insufficient evidence on the benefit of repeated MRI during active surveillance [17]. According to the PROMIS study, MRI may reduce the proportion of men undergoing a prostate biopsy by one fourth, and the proportion of men diagnosed with clinically insignificant cancer by five percent, at the cost of delaying the diagnosis of a clinically significant cancer (defined as presence of any ISUP grade ≥3 (Gleason score 4+3=7) or a maximum cancer core length involvement of 6 mm or more in any location) in three percent of the men [18]. The negative predictive value of an unsuspicious MRI finding is high, and even higher when PSA density is low [19].

The randomised PRECISION trial indicates that MRI with targeted biopsies has higher detection rate than systematic biopsies for ISUP grade ≥ 2 prostate cancer and reduces the detection of ISUP grade 1 cancer in biopsy naïve patients with clinical suspicion of prostate cancer [20]. In a retrospective review of repeated biopsies during active surveillance, MRI with targeted biopsies nearly doubled the detection of pathological progression compared to systematic biopsies [21]. This is however questioned by a recent prospective trial that showed no increase in up-grading with additional targeted biopsies vs systematic biopsies alone [22].

Active surveillance in intermediate-risk prostate cancer

The risk of cancer progression during active surveillance of patients with low-risk prostate cancer is low, but varies between studies, probably because of different inclusion criteria and indications for therapeutic intervention [6]. Active surveillance of intermediate-risk prostate cancer is debated, but it is supported by some data [23]. The Sunnybrook cohort - including men with low-risk and favourable intermediate-risk prostate cancer - showed a 2.8% progression to metastatic disease and 1.5% prostate cancer specific mortality within 15 years [24], with a more favourable outcome for men with low-risk cancer [25]. Eligibility was not influenced by PSA density or number of positive cores, and MRI was not used. Based on findings that MRI with targeted biopsies has a higher detection rate than standard biopsies for ISUP grade ≥2 prostate cancer [20] one must assume that many intermediate and high-risk tumours were undetected in this cohort. Despite this, the long-term cancer specific survival was high.

The PCASTt/ SPCG-17 trial

Study design

PCASTt/SPCG-17 is a multinational randomised trial comparing active surveillance using standardised triggers for repeated biopsy and radical treatment with current practice. The hypothesis is that standardised triggers will reduce overtreatment and adverse events and improve quality of life, without increasing disease progression or prostate cancer mortality.

Outcome measures

The primary endpoint is progression-free survival. Progression is defined as biochemical recurrence after treatment with curative intent or start of androgen deprivation therapy in previously untreated men. Following radical prostatectomy, biochemical recurrence is defined as two consecutive rising PSA values >0.2 ng/ml. After primary radiation therapy and

radiation therapy with androgen deprivation therapy, the definition of biochemical recurrence is any PSA increase 2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir[26]. Secondary endpoints are the cumulative incidence of pT3 tumours, distant metastasis, treatment with curative intent and switch to watchful waiting. Prostate cancer death is the final endpoint at ten years. Quality-of-life endpoints will be analysed separately.

Participants & participating centres

Eligible for inclusion are men with histopathological low-risk or favourable intermediate-risk adenocarcinoma of the prostate diagnosed within 12 months, who have not received any treatment and have at least ten years' expected lifetime. All men primarily diagnosed with prostate cancer from systematic biopsies should undergo MRI with biopsies targeted at PI-RADS 3-5 lesions before inclusion. For men primarily diagnosed with prostate cancer following MRI with targeted biopsies, subsequent systematic biopsies are optional. Inclusion criteria are listed in table 1. Centres in Sweden, Finland, Norway and UK will participate. Demands on participating centres are listed in table 2.

Table 1 – inclusion criteria

- Adenocarcinoma of the prostate diagnosed within the past 12 months
- Tumour stage ≤T2a, NX, M0
- PSA <15 ng/ml and PSA density ≤0.2 ng/ml/cc
- Systematic biopsies with ≥10 cores (optional, if the diagnosis is based on MRI with targeted biopsies)
- MRI with targeted biopsies towards PI-RADS 3, 4 and 5 (according to PI-RADS v. 2)
- ISUP grade 1 (any number of cores, any involvement)
- ISUP grade 2 in <3 cores (or <30% of cores if >10 systematic cores were taken) and <10 mm cancer in one core (systematic or targeted)
- Life expectancy ≥10 years (no upper age limit)
- Candidate for curative treatment (surgery or radiotherapy) if progression occurs
- Signed written informed consent

PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System, ISUP = International Society of Urological Pathology

Table 2 – demands on participating centres

- The local organisation should commit to recruiting all consecutive patients who are willing to start on active surveillance and who fulfil the inclusion criteria
- A 1.5 or 3 Tesla MRI
- Access to prostate MRI expertise. If the local competence is uncertain, the national PI will organise external expertise for MRI evaluation
- The MRI should follow European Society of Urogenital Radiology (ESUR) guidelines and include:
  - T1- and T2-weighted images
  - Diffusion-weighted images (DWI) including Apparent Diffusion Coefficient (ADC)
  - Dynamic contrast enhanced (DCE) imaging and Magnetic Resonance Spectroscopy Imaging (MRSI) are optional

- The MR images should be reported according to PI-RADS v. 2

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

PCASTt/SPCG-17 aims to randomise 2,000 patients in 4 years, which will give an 85% power to detect a 1.3 percentage points progression-free survival difference between the study arms (2-sided alpha 0.05) under the assumption that 90% of the patients are managed per protocol according to randomisation. The progression-free survival in the current practise group five years after randomisation is assumed to be 98%, based on previous studies [24].

Patient reported outcome measures and follow-up

At inclusion and every second year during follow-up participants are requested to complete a study-specific quality-of-life questionnaire including the Expanded Prostate cancer Index Composite (EPIC-26) [27], for separate quality-of-life analysis.

Basic follow-up is identical in both arms, with biannual PSA testing, annual clinical examination and MRI scan every second year (Figure 1). In the current practice arm, additional investigations are optional and it is up to the urologist to decide when it is time to repeat biopsies and initiate treatment with curative intent. In the experimental arm, follow-up is according to schedule, biopsies are only taken if the standardised triggers are reached (Table 3) and treatment with curative intent is only recommended if standardised triggers for radical treatment are reached (Table 4). At every follow-up, the patient is categorised as having no distant metastasis, suspected distant metastasis (according to PSA-level and/or symptoms) or verified distant metastasis (imaging or histopathology/cytology).

Table 3 – triggers for re-biopsies

ARM I	ARM 2	
According to current practice (the urologists´ judgement)	**I.**	**PSA density >0.2 ng/ml/cc (systematic biopsies)**
	II.	**MRI progression in men with ISUP grade 1 cancer (targeted biopsies)** - ≥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 suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on Likert scale) - A new lesion with PI-RADS score 3-5
	III.	**MRI progression in men with ISUP grade 2 cancer (targeted biopsies)** - ≥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 3-5

PSA=Prostate Specific Antigen, PI-RADS=Prostate Imaging Reporting and Data System, MRI=Magnetic Resonance Imaging, ISUP = International Society of Urological Pathology

Table 4 – triggers for radical treatment

ARM I	ARM 2	
According to current practice (the urologist´s judgement)	**I.**	**MRI progression in lesions with confirmed Gleason pattern 4** - Increase in PI-RADS score to 4 or 5 - High suspicion of extra-capsular extension or seminal vesicle invasion (level of suspicion to be 4 or 5 on the Likert scale)
	II.	**Pathological progression** - Gleason pattern 5 - Primary Gleason pattern 4 in any core with ≥5 mm cancer - ISUP grade 2 in ≥3 cores (or ≥30% of cores if >10 systematic cores), or ≥10 mm cancer in one core (systematic or targeted)

MRI=Magnetic Resonance Imaging, PI-RADS=Prostate Imaging Reporting and Data System

Follow-up continues according to the protocol until initiation of treatment with curative intent, detection of metastasis, switch from active surveillance to watchful waiting or death of any cause. For men who discontinue active surveillance, the follow-up and management continue according to standard clinical practice but with annual reporting in the study. In patients lost to follow-up, endpoints will be assessed through available registers in the participating countries.

Patient and Public Involvement

Patient experiences and priorities is important knowledge that may influence the definition of research questions. Patients were however not directly involved in designing this study,

defining outcome measures, the recruitment to and conduct of the study. A summary of results will be available for all participants and will also be presented to patient organisations and the public.

Experience from first two years of inclusion

The first patient was included in October 2016 at Uppsala University Hospital, Sweden. In 2017, six additional Swedish centres began enrolment and three Norwegian centres started enrolling patients in 2018. Centres in Finland and the UK aim to start including patients later in 2018. Characteristics of the first 275 randomised patients are displayed in Table 5. Patients are stratified based on participating centre and Gleason score.

Table 5 - baseline characteristics for the first 275 included patients

	Current practice	Standardised triggers
n	139	136
Age (yr, mean (SD))	62 (6.2)	64 (6.2)
PSA (ng/ml, mean, (SD))	5.1 (2.3)	5.8 (2.3)
PSA-D (ng/ml/cc, mean (SD))	0.11 (0.04)	0.12 (0.04)
Clinical tumour stage (n (%))		
T1c	109 (78)	115 (85)
T2a	29 (21)	21 (15)
unknown	1 (1)	0
Comorbidity (n (%))		
ASA 1	94 (68)	84 (62)
ASA 2	40 (29)	52 (38)
ASA 3	4 (3)	0
unknown	1 (1)	0
Family history of PCa (n (%))		
Yes	33 (24)	38 (28)
No	102 (73)	95 (70)
Unknown	4 (3)	3 (2)
MRI technique (n (%))		
1.5 Tesla	20 (14)	16 (12)
3 Tesla	118 (85)	116 (85)
Unknown	1 (1)	4 (3)
MRI findings (n (%))		
PI-RADS 1-2	76 (55)	55 (40)
PI-RADS 3-5	63 (45)	81 (60)

yr = years, SD = standard deviation, PSA = prostate specific antigen, n = sample size, ASA = American Society of Anesthesiologists classification, PCa = prostate cancer, MRI = magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting and Data System

Ethics and dissemination

The study has ethical approval from Sweden (the Regional Ethical Review Board in Uppsala), Norway (REK Midt - Regional Ethics Committee Central), Finland (Ethics Committee of Surgery, Helsinki University Hospital) and UK (East of England - Essex Research Ethics Committee). The first analysis of primary and secondary end-points will take place one year after all men are included (and then every third year) and be published in peer-reviewed journal.

Discussion

The increasing use of active surveillance has reduced overtreatment of prostate cancer to some extent, but still a large number of men are overtreated [2]. Clearly, more patients should start on active surveillance, and fewer patients on active surveillance should convert to radical treatment.

Over the last decades there has been a Gleason score/ISUP grade inflation, partly due to the 2005 revision of the Gleason pattern definitions. The revision entailed that many patterns previously designated Gleason pattern 3 are now reported as pattern 4 and that the Gleason score/ISUP grade on needle biopsies always includes the highest Gleason grade, even if it is just a minimal component [28]. Because long-term outcomes of active surveillance and watchful waiting are chiefly based on studies undertaken before the 2005 revision, a substantial proportion of low-risk tumours in those studies would today be classified as intermediate-risk. Despite this, they had excellent survival without treatment. These results and the changes in Gleason grading suggests that also men with favourable intermediate-risk prostate cancer

should be offered active surveillance. This is supported by the fact that MRI with targeted biopsies detects favourable intermediate-risk tumours that standard biopsies do not detect[18,20]. Hence, if all men with intermediate risk prostate cancer undergo immediate radical treatment, overtreatment would increase.

In PCASTt/SPCG-17, follow-up during active surveillance is based on PSA testing and repeated MRI, not on repeated systematic biopsies. Prostate biopsies are uncomfortable and distressful. They cause bleeding, sometimes urinary retention and about six percent experience febrile infection and one percent develop sepsis [29]. The incidence of serious infections is rising because of multidrug resistant bacteria [30]. It is therefore desirable to reduce the number of biopsies during active surveillance. In the experimental arm of PCASTt/SPCG-17, biopsies are only performed when triggered which will likely reduce the number of biopsies. MRI with targeted biopsies detect at least as many histopathological intermediate-risk tumours as standard biopsies in biopsy naïve men[20,21], suggesting that MRI with targeted biopsies is viable in a surveillance program.

In PCASTt/SPCG-17 pre-specified changes in MRI trigger targeted biopsies to assess histopathological progression. Since histopathological progression may occur without MRI changes, the protocol also stipulates systematic biopsies if PSA density increases above pre-specified limits (Table 3). Radical treatment is triggered by MRI findings suggesting progression of a known ISUP grade 2 tumour and by biopsies showing more than a defined upper limit of Gleason pattern 4 or any Gleason pattern 5 (Table 4).

The strengths of PCASTt/SPCG-17 includes the randomised design and a trial size that will allow quantifying clinically relevant endpoints with reasonable statistical precision. A data monitoring and safety committee will oversee patient safety and the trial's scientific integrity.

The safety of the MRI-based follow-up will be regularly evaluated by comparing the outcome with a matched group of men managed by active surveillance in the Swedish SAMS study, who are on active surveillance based on systematic transrectal biopsies [31]. During the long-term follow-up, new methods for monitoring and treatment might be introduced and applied in our patient cohort, obscuring the interpretation of the results. Furthermore, over time the triggers for repeated biopsies and treatment in the PCASTt/SPCG-17 trial's standard treatment arm might become more similar to the management of the men in the experimental group. Although this will affect the trial's ability to detect any difference between the two groups, the PCASTt/SPCG-17 experimental arm can still be used to assess the clinical safety and acceptability of a standardised protocol and provide prospective data on the performance of MRI as a monitoring tool – both aspects key to patient safety under AS.

Conclusion

PCASTt/SPCG-17 is a randomised trial that evaluates the safety of an MRI-based active surveillance protocol, comparing standardised triggers for repeat biopsies and curative treatment. If the protocol proves to be as safe as current clinical practice, its implementation could lead to a reduction of the number of biopsies, reduce overtreatment of prostate cancer without compromising the outcome of the patients in terms of morbidity and mortality.

Contributors:

All authors (MSA, H-OA, LH, AB-A, KB, HB, OB, DC, LE, HG, EJ, AR, MVH, FJ, CW and UWNÅ) have made the following contributions to the work: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Drafting the work or revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interest:

None of the contributing authors have any conflicts of interest.

Data sharing statement:

No additional data.

Figure 1 – Basic follow-up. PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, TB=Targeted Biopsies, SB=Systematic Biopsies, QoL=Quality of Life

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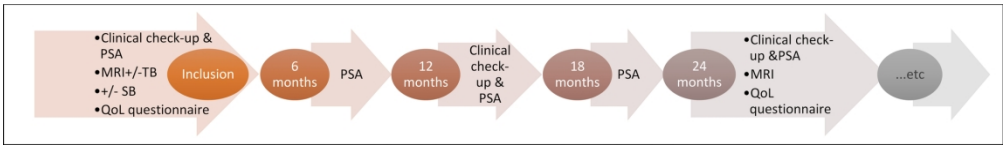

Figure 1 – Basic follow-up. PSA=Prostate Specific Antigen, MRI=Magnetic Resonance Imaging, TB=Targeted Biopsies, SB=Systematic Biopsies, QoL=Quality of Life

89x12mm (600 x 600 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on Page nuber
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes ClinicalTrials.gov
Protocol version	3	Date and version identifier	Available at ClinicalTrials.gov
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 19
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1 & 19, 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 19, 20 & ClinicalTrials.gov
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 9
	6b	Explanation for choice of comparators	9

Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10, 11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10, 11, Table 1 & 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 12, 13, 14, figure 1 table 3 & 4
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	In protocol Available at ClinicalTrials.gov
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	In protocol Available at ClinicalTrials.gov
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	In protocol Available at ClinicalTrials.gov
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	In protocol Available at ClinicalTrials.gov
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	In protocol Available at ClinicalTrials.gov
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	In protocol Available at ClinicalTrials.gov
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	In protocol Available at ClinicalTrials.gov
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	In protocol Available at ClinicalTrials.gov
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	In protocol Available at ClinicalTrials.gov
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	In protocol Available at ClinicalTrials.gov
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	In protocol Available at ClinicalTrials.gov
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 9

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	In protocol Available at ClinicalTrials.gov
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	In protocol Available at ClinicalTrials.gov
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	In protocol Available at ClinicalTrials.gov
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	In protocol Available at ClinicalTrials.gov
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3, 15, 16
	31b	Authorship eligibility guidelines and any intended use of professional writers	In protocol Available at ClinicalTrials.gov
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	In protocol Available at ClinicalTrials.gov
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	In protocol Available at ClinicalTrials.gov

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	In protocol Available at ClinicalTrials.gov

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.