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Fatigue, quality of life and metabolic changes in men treated with first-line enzalutamide versus abiraterone plus prednisolone for metastatic castration-resistant prostate cancer (HEAT): a randomised trial protocol

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Fatigue, quality of life and metabolic changes in men treated with first-line enzalutamide versus abiraterone plus prednisolone for metastatic castration-resistant prostate cancer (HEAT): a randomised trial protocol

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Abstract

Introduction

Enzalutamide and abiraterone acetate plus prednisolone (AAP) are used in combination with androgen deprivation therapy (ADT) to further suppress the androgen stimulation of metastatic castration-resistant prostate cancer (mCRPC). First-line mCRPC treatment with enzalutamide and AAP yields similar overall survival and radiographic progression-free survival in phase III trials. Thus, treatment selection relies on patient choice, cost and side effects. The aim of this randomised trial is to investigate differences in fatigue, health-related quality of life (HRQoL) and metabolic side effects in men treated with enzalutamide versus AAP.

Methods and analysis

In this ongoing open-label randomised (1:1) clinical trial, enzalutamide is compared with AAP as first-line treatment for men with mCRPC. The primary endpoint is fatigue assessed with the questionnaire Functional Assessment of Chronic Illness Therapy-Fatigue version 4 (FACIT-Fatigue). Secondary endpoints are changes in body composition (i.e. fat mass, visceral adipose tissue, subcutaneous adipose tissue and lean body mass assessed with dual x-ray absorptiometry), glucose metabolism assessed with a two-hour oral glucose tolerance test, serum lipids, blood pressure and HRQoL assessed with the questionnaire Functional Assessment of Cancer Therapy-Prostate (FACT-P). All study endpoints are assessed at baseline and 12-week post-intervention. Blood and urine samples are collected at baseline and at time of progression on allocated treatment for future investigation of predictive and prognostic biomarkers in prostate cancer treatment.

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5 The planned sample size is 170 participants. All participants are recruited from Herlev and Gentofte
6 Hospital, Denmark. Estimated last patient's last visit is February 2020.
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9 **Ethics and dissemination**

10 The study received project approval from the National Committee on Health Research Ethics and
11 Danish Data Protection Agency and Danish Medicines Agency (EudraCT no.: 2017-000027-
12 99). The results of the study will be published in peer-reviewed international journals and will be
13 presented at national and international conferences and symposiums.
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15

16 **Trial registration:** clinicaltrialsregister.eu, EudraCT no.: 2017-000099-27. Registered on 2017-04-26.

17 **Keywords:** castration resistant, prostate cancer, prostate neoplasm, Enzalutamide, Abiraterone, Abiraterone acetate, Hormone therapy, Adverse
18 events, side effects, Fatigue, Quality of life, Metabolic changes, Randomised controlled trial
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23 **Strength and limitations**

- 24 • This randomised clinical trial will report patient-reported and metabolic side
25 effects in a relatively large sample size.
- 26 • This is the first randomised head-to-head trial primarily comparing fatigue,
27 health-related quality of life and metabolic side effects in men with
28 metastatic castration-resistant prostate cancer treated with first-line
29 enzalutamide versus abiraterone plus prednisolone.
- 30 • The trial lacks assessment of long-term side effects.
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Introduction

During the past decade, several new treatment options have emerged for metastatic castration-resistant prostate cancer (mCRPC). These new treatment options include the androgen pathway inhibitors enzalutamide and abiraterone acetate. Enzalutamide blocks several steps in the androgen receptor signalling. Abiraterone inhibits enzymes (17 α -hydroxylase and 17, 20-lyase) in the androgen biosynthesis, and is combined with prednisolone to compensate for abiraterone-induced reductions in serum cortisol (1,2)

Enzalutamide and abiraterone acetate plus prednisolone (AAP) yield similar radiographic progression-free and overall survival results in the phase III trials (PREVAIL and COU-AA-302 respectively) which has led to approval as first-line mCRPC treatments (3–6). Thus, the choice between these two agents depends on the patient's preference, costs and agent-specific side effects.

Men with mCRPC that have been treated with ADT, have an increased risk of metabolic side effects and fatigue affecting health-related quality of life (HRQoL) (7,8). Androgen pathway inhibitors are generally safe, with low rates of grade 3 and 4 adverse events. Most of the reported adverse events of these treatments are similar in the mentioned phase III-trials, but the following adverse events were different: enzalutamide was associated with memory impairment and seizures; whereas AAP was associated with liver function abnormalities, peripheral oedema and cardiac events (3,5,9). Fatigue was the most common reported adverse event of both enzalutamide and AAP, although commonly emphasized as a side effect to enzalutamide (3,5). Comparing the results of the two trials is difficult, as the men in the control-group of the enzalutamide trial (PREVAIL) received placebo, whereas the men in the control-group of the AAP trial (COU-AA-302) received placebo plus prednisone (3,5). To date, no head-to-head comparison primarily exploring differences in the side effect profiles have, to our knowledge, been published.

In addition, AAP has been approved for hormone-naïve metastatic prostate cancer and enzalutamide is expected to gain similar approval (12,13, NCT02677896, NCT02319837). This change in treatment sequencing will result in longer exposure to side effects, making comparative studies with specific side effect endpoints even more essential.

This protocol describes an ongoing randomised clinical trial comparing self-reported fatigue and HRQoL and metabolic changes in men treated with enzalutamide or AAP as first-line treatment for mCRPC. The aim is that the results from this trial may help patients and physicians to choose the best tolerated treatment based on the difference in the side effects of enzalutamide and AAP.

Methods and analysis

Trial design

This is a single-centre open-labelled randomised (1:1) phase IV trial comparing first-line enzalutamide versus AAP in men with mCRPC. The trial is conducted at the Department of Urology, Herlev and Gentofte Hospital, Denmark. The primary objective is to compare fatigue assessed with the questionnaire Functional Assessment of Chronic Illness Therapy-Fatigue version 4 (FACIT-Fatigue).

Participants

Eligible participants are men with metastatic prostate cancer progressing on ADT, based on the prostate cancer working group 3 criteria (PCWG3) that include Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (12),13). Metastatic status is measured with computed

tomography (CT) scan of the thorax and abdomen and bone imaging (^{18}F -sodium fluoride (NaF) positron emission tomography-computed tomography (PET/CT) or prostate specific membrane antigen (PSMA) PET/CT). Inclusion criteria are age ≤ 90 years, an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and adequate organ function (creatinine < 1.5 x the upper limit of normal (ULN), total bilirubin < 1.5 x ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 2.5 x ULN). Exclusion criteria are visceral metastases, a prior history of seizures, known heart failure (New York Heart Association (NYHA) functional class > 2), diabetes mellitus, hypersensitivity to or previous treatment with enzalutamide or AAP or previous treatment with docetaxel. An exception to the latter is docetaxel in the metastatic hormone-naïve prostate cancer setting, if the treatment was completed more than six months prior to enrolment. Inclusion and exclusion criteria are depicted in **Table 1**. Eligibility is primarily assessed at the department's multidisciplinary team conference, where all patients are evaluated prior to starting first-line mCRPC treatment. Subsequently eligibility is confirmed by the primary investigator at a screening consultation before randomization. This ensures that all eligible men at Herlev and Gentofte Hospital are offered study participation. The timeline from screening to intervention is depicted in **Figure 1**.

Randomisation

Patients who meet the inclusion and exclusion criteria and have given a written informed consent are randomised at the screening consultation using the Randomization Module of Research electronic data capture (REDCap version 7.1.1. © 2018 Vanderbilt University, Nashville, USA). The allocation sequence is a computer-generated list of random numbers transferred to REDCap by a collaborator with no clinical involvement in the trial. Participants are randomly assigned to either enzalutamide or AAP in a 1:1 ratio without stratification. Randomization follows a block randomization with 60 men in the first block and 110 men in the last block. Participants and physicians are aware of the allocation arm after randomization. Data and outcome assessors are not blinded.

Interventions

Recruitment began in June 2017 and planned completion is December 2019. Herlev and Gentofte Hospital provides urological cancer care for a population of approximately 1.3 million. We estimate that around 150 men are offered either enzalutamide or AAP as first-line mCRPC treatment yearly at the Department of Urology, Herlev and Gentofte Hospital. Participants are randomised to receive one of the following treatments:

Enzalutamide

Participants are allocated to take 160 mg enzalutamide orally in the evening.

AAP

Participants are allocated to take 1000 mg abiraterone acetate orally at least 1 hour before a meal or two hours after a meal in the evening.

Participants are instructed to take 10 mg prednisolone orally in the morning.

Participants receive allocated treatment from baseline visit until biochemical and/or radiographic progression or at the treating physician's discretion. Compliance is ensured by registering the number of returned tablets at the follow-up visit. During the trial, all participants continue ADT. In addition, all participants follow normal standard of care according to local and national guidelines,

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4 such as being offered bone protecting agents (i.e. denosumab and calcium and vitamin D
5 supplements).
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8 **Outcomes**

9 ***Measurements***

10 Primary and secondary outcomes are assessed for all participants at baseline and 12-week post-
11 intervention by the primary investigator. A schedule of enrolment, interventions and assessments is
12 depicted in **Table 2**.
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15 ***Primary outcome***

16 The primary endpoint is the between-group differences in changed level of fatigue assessed with the
17 13-question questionnaire FACIT-Fatigue available and validated in Danish. The participants report
18 the past week's experienced fatigue by grading each question from one to four: "not at all", "a little
19 bit", "some-what", "quite a bite" and "very much". A minimal clinical important difference
20 (MCID) in fatigue is defined as a 3.0 points change on an individual level (14). Fatigue is assessed
21 at baseline, 12-week post-intervention and at time of disease progression on allocated treatment.
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25 ***Secondary outcomes***

26 The secondary outcomes are the between-group differences in changed HRQoL, body composition,
27 blood pressure, insulin sensitivity and resistance measured with a 4-point oral glucose tolerance test
28 (OGTT), serum lipids and androgen treatment response.
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31 ***HRQoL***

32 The between-group change in HRQoL is assessed with the 39-question questionnaire Functional
33 Assessment of Cancer Therapy - for patients with Prostate cancer version 4 (FACT-P) available and
34 validated in Danish. FACT-P is assessed with the same grading as the FACIT-fatigue questionnaire.
35 An MCID in HRQoL is defined as a 6 points change on an individual level (15). HRQoL is
36 assessed at baseline, 12-week post-intervention and at time of disease progression on allocated
37 treatment.
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40 ***Body composition***

41 Fat mass, body fat %, visceral adipose tissue volume (VAT), subcutaneous adipose tissue volume
42 (SAT) and lean body mass (LBM) are obtained using dual energy X-ray absorptiometry (DXA)
43 whole body fan-beam scans (Hologic Discovery, Bedford, Massachusetts, USA) with the software
44 APEX 4.0. VAT and SAT are measured in a 5 cm wide horizontal slice across the abdomen from
45 the iliac crest to the L4-L5 segment (16,17). Weight (BWB-800A, TANITA, Tokoyo, Japan) and
46 body mass index (height in meters²/weight in kilograms) is assessed as well. Systolic and diastolic
47 blood pressure is measured on the right arm after at least 20 minutes of rest (BP A3 Plus, Microlife
48 AG, Widnau, Switzerland).
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52 ***OGTT***

53 The first 60 participants undergo a two-hour oral glucose (75 g) tolerance test (OGTT) after at least
54 9 hours of fasting. Plasma glucose and insulin are measured after 0, 30, 60 and 120 minutes. The
55 whole body insulin sensitivity index (Matsuda index) are calculated from plasma glucose and
56 insulin concentrations attained from the two-hour OGTT in the subgroup of 60 participants (18).
57 The equation for calculating the Matsuda index is: $10.000/\sqrt{(FPG \times FPI \times \text{mean PG} \times \text{mean PI})}$.
58 FPG is the fasting plasma glucose and FPI is the fasting plasma insulin concentration. Fasting
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4 plasma glucose and insulin are measured in all 170 participants. Fasting insulin resistance is
5 calculated from the basal glucose and insulin concentrations using the homeostatic model
6 assessment (HOMA-IR) with following equation: $(FPG \times FPI)/22.5$ (19).
7

8 *Biochemical assays*

9 All blood samples are drawn before 10 am after a minimum of 9 hours of fasting.
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12 *Metabolic analyses*

13 Plasma glucose is analysed with an enzymatic assay (Vitros 5.1, Ortho-Clinical Diagnostics, USA).
14 Plasma insulin is analysed with a sandwich chemiluminescence immunoassay (ADVIA Centaur
15 XP, Siemens, Germany). Glycated haemoglobin (HbA1c) is measured by high-performance liquid
16 chromatography (Variant II TURBO, Bio-RAD, USA). Triglycerides, total cholesterol, HDL
17 cholesterol, LDL cholesterol and VLDL cholesterol are assayed by an enzymatic technique (Vitros
18 5.1 FS, Ortho-Clinical Diagnostics, USA).
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21 *Androgen treatment response*

22 Serum total testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS) and 17-
23 hydroxyprogesterone are measured by Liquid chromatography – tandem mass spectrometry
24 (Acquity UPLC Xevo™ TQ MS, Waters, USA). Sex hormone binding globulin (SHBG) is
25 analysed by a competitive chemiluminescence based immunoassay (Cobas, Roche Diagnostics,
26 Mannheim, Germany). Plasma Luteinizing hormone (LH) and follicle stimulating hormone (FSH)
27 are measured using sandwich chemiluminescence immunoassay (ADVIA Centaur®, Siemens,
28 Germany).
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31 *Additional measurements*

32 *Common terminology criteria for adverse events*

33 Adverse events will be registered at the 12-week post-intervention visit, using the common
34 terminology criteria for adverse events version 4 (20).
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39 *Metabolic biomarkers*

40 Samples of full blood and serum are prospectively collected at baseline and 12-week post-
41 intervention for future assessment of cardiac, adipose and inflammatory biomarkers.
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44 *Genetic biomarkers*

45 A biobank is generated during the trial and will be used for a future prospective, observational study
46 assessing the predictive and prognostic value of genetic biomarkers in circulating cell-free DNA
47 (ccfDNA). Samples from blood and urine are prospectively collected at baseline and at time of
48 disease progression on allocated treatment. Somatic alterations will be analysed from ccfDNA in
49 plasma, urine pellets and supernatant.
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52 **Patient and public involvement**

53 The patients treated with enzalutamide and AAP inspired us to the design of the trial's research
54 question and outcomes, by sharing their experience of the treatment and associated side-effects in
55 the out-patient clinic of Herlev and Gentofte Hospital. Fatigue is the primary outcome of the trial,
56 since fatigue is the most common and distressing symptom experienced by patients with mCRPC
57 (21). The burden of the intervention is partly assessed by patient-reported questionnaires assessing
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4 fatigue and HRQoL. Patients were not involved in the recruitment to or conduct of the trial. The
5 results of the trial will be made publically available through the homepage of Herlev and Gentofte
6 Hospital.
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8 9 **Sample size and statistical analysis**

10 The sample size calculation is based on the detection of a between-group MCID of 3.0 points on the
11 FACIT-Fatigue scale, with an anticipated drop-out of 10% (14). The standard deviation is assumed
12 to be 6.55, based on confidence limits from previous studies assessing fatigue in men with
13 metastatic prostate cancer (22–24). The sample size calculation is based on a two-tailed significance
14 level of 5% and a power of 80%. This required a sample size of 85 participants in each group, a
15 total of 170 men.
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18 The within-subject and between-group differences of the primary and secondary endpoints will be
19 analysed with linear mixed effect models using constrained longitudinal analysis (cLDA). The
20 between-group MCID in fatigue and HRQoL will be analysed with risk difference. An MCID in
21 fatigue is defined as an individual 3-point change in the FACIT-Fatigue total score. An MCID in
22 HRQoL is defined as an individual 6-point change in FACT-P total score. Interactions between
23 patient reported outcomes (fatigue and quality of life), and age (< 75 versus ≥ 75 years) and extent
24 of metastases (high versus low volume disease) will be tested in sub-group analyses using forest
25 plots. High volume disease is defined as ≥ 4 bone metastases with ≥ 1 bone metastases outside
26 pelvis and column. Interactions between metabolic changes, and BMI (<30 versus ≥ 30) and age
27 (<75 years versus ≥ 75) will be analysed in sub-group analyses using forest plots. The linear mixed
28 effect model using cLDA handles random missing data.
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32 **Ethics and dissemination**

33 Participants will receive standard first-line treatment for mCRPC. The primary investigator obtains
34 the written informed consent from all participants. The trial follows the ICH-GCP guidelines for
35 good clinical practice, the latest revision of the Declaration of Helsinki and the Danish rules on
36 Clinical Trials of Medicines in Humans. This trial is approved by the National Committee on
37 Health Research Ethics (H-17001347), Danish Data Protection Agency (2012-58-0004) and Danish
38 Medicines Agency (EudraCT no.: 2017-000027-99, www.clinicaltrialsregister.eu). The trial is
39 externally monitored by Good Clinical Practice Unit, Copenhagen University. The trial's results
40 will be published in peer-reviewed international journals or otherwise made publicly available and
41 will be presented at national and international conferences and symposiums irrespective of the
42 outcomes. Patient reported outcome and metabolic changes will be reported in the same publication,
43 while hormone analyses and genetic biomarkers will be reported in separate publications. Study
44 completion is expected by spring 2020, and dissemination of the results will begin as soon as
45 possible thereafter.
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50 **Discussion**

51 This article describes the protocol of an ongoing randomised clinical trial comparing fatigue,
52 HRQoL and metabolic changes in men with mCRPC treated with first-line enzalutamide versus
53 AAP.
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56 We chose fatigue as the primary endpoint since it is the most common and distressing symptom
57 affecting HRQoL in men with mCRPC (21). We assess changes in patient reported fatigue with the
58 validated 13-question questionnaire FACIT-Fatigue. Previous randomised clinical trials on
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4 enzalutamide and AAP measured the level of fatigue with Common Terminology Criteria for
5 Adverse Event with a coarse three-level grading, from fatigue “relieved by rest” to fatigue “limiting
6 self-care” (3,5). We expect that changes in fatigue will be reported more accurately from patients
7 using the 13-question questionnaires in contrast to the physician reported three-level grading used
8 in previously trials. We did not choose to assess fatigue by interviews since that would preclude a
9 statistical comparison of changes in fatigue, even though interviews might yield a more individual
10 assessment of fatigue.
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13 We chose to assess changes in patient reported HRQoL with the 39-question questionnaire
14 FACT-P, because FACT-P is developed and validated for assessing HRQoL in men with prostate
15 cancer. Changed HRQoL for men with metastatic prostate cancer has previously been measured
16 with FACT-P in randomized clinical trials, and the results can therefore be compared with existing
17 literature (25–27).
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20 We chose to comprehensively assess metabolic changes, including glucose metabolism measured
21 with oral glucose tolerance test and HbA1c, and body composition measured with DXA scans.
22 Previous randomised clinical trials on enzalutamide and abiraterone have measured following
23 metabolic adverse events: plasma glucose, weight, and blood pressure (3–6). We did not choose to
24 measure plasma glucose, because the within-subject plasma glucose varies widely, and fasting
25 plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed
26 diabetes (28,29). We chose to assess glucose metabolism with OGTT and HbA1c because the
27 hyperglycaemic disease process is a risk factor for microvascular complications, diabetes and
28 cardiovascular disease and may be present without fulfilling the criteria for diabetes (28). We chose
29 to measure BMI and body composition with DXA scans because both methods can identify obesity
30 and associated metabolic and cardiovascular risks (30–32), while DXA scans can identify body fat
31 which may be a better predictor of metabolic syndrome than BMI alone (33,34). We measure lean
32 body mass with DXA scans, because a loss of lean mass can over time contribute to a decrease in
33 muscle strength which are important predictors of balance, the occurrence of falls and mortality
34 (35,36).
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38 We chose 3-month follow-up to evaluate the treatments side effects and at the same time to avoid a
39 pronounced influence of disease progression on HRQoL and fatigue. In a cohort study of 21
40 participants metabolic changes appeared already after 7 to 10 days of treatment with low-dose
41 prednisolone (6 mg/day) (37). Changes in fatigue and HRQoL can be experienced within the first
42 three months of treatment with new androgen pathway inhibitors (25). The median time until
43 biochemical progression was 11.1 and 11.2 months for men with mCRPC treated with AAP and
44 enzalutamide, respectively (3,5). However, 14% (74/546) had biochemical progression after only 3
45 months' treatment with AAP; and 8% (70/854) had biochemical progression after 3 months'
46 treatment with enzalutamide (3,5).
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49 The lack of blinding can be perceived as a weakness, but we find that it is of minor importance and
50 unlikely to affect the objectively measured outcomes. Blood samples are analysed in an
51 independent laboratory, DXA scans are analysed with the same software and outcomes on fatigue
52 and HRQoL are reported by participants.
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Conclusion

The aim of this trial is to assess differences in the patient reported and metabolic side effects of enzalutamide and AAP. The results may in the future help patients and physicians to choose the best tolerated treatment and thereby reduce treatment induced morbidity and improve quality of life.

For peer review only

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Contributions

KKT, PBØ, JS, CK, HL, MF, GP and RB participated in the design of the study. KKT conceived the study and participated in its design and coordination. KKT and PBØ drafted the study protocol. KKT drafted the manuscript and all authors read and approved the final manuscript.

We want to thank the patients, treated with enzalutamide and AAP at Herlev and Gentofte Hospital, for inspiring us to design this trial by openly sharing their experience of their treatment and associated side-effects.

Funding statement

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Competing interests statement

The authors have following conflicts of interest:

PBØ is speaker for Astellas, Ipsen and Ferring.

MF is speaker for Ferring and Astellas and advisory board representative for Astellas.

HL is advisory board representative for Roche, Janssen, Astellas, Bayer and Sanofi-Aventis.

Tables

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Eligible for first line treatment with either enzalutamide or abiraterone acetate plus prednisolone as per standard of care guidelines • Age 18-90 years • Willing, capable and legally competent individuals • ECOG performance status 0-1 • Histologically confirmed adenocarcinoma of the prostate • Prior surgical orchiectomy or if on LHRH agonist/antagonist, then testosterone < 1.7 nmol/L at screening visit (participants must maintain LHRH agonist/antagonist therapy for duration of study treatment if not surgically castrated) • Evidence of metastatic disease on bone scan or CT scan • Evidence of biochemical or imaging progression in the setting of surgical or medical castration. Progressive disease for study entry is defined by one of the following criteria based on criteria of PCWG3: <ul style="list-style-type: none"> ○ Biochemical progression: Obtain sequence of rising PSA values at a minimum of 1-week intervals, resulting in increases over the nadir, with PSA > 1 ng/mL ○ Radiological progression: <ul style="list-style-type: none"> ▪ The appearance of two or more new bone lesions on bone scan ▪ Enlargement of a soft tissue lesion using the modified RECIST 1.1. • Adequate organ function defined as: <ul style="list-style-type: none"> ○ Creatinine < 1,5 x ULN ○ Total bilirubin < 1,5 x ULN ○ ALT or AST ≤ 2,5 x ULN 	<ul style="list-style-type: none"> • Inability to understand and/or stick to the written information • Previous treatment with docetaxel, with the exception of previous treatment with early docetaxel (≤ 6 series) ≥ 6 months before inclusion. • Diagnosed with diabetes mellitus and/or HbA1C > 48 mmol/mol. • Hypersensitivity towards components in abiraterone acetate plus prednisolone or enzalutamide • Ongoing treatment with high doses of glucocorticoids • Severe concurrent illness or co-morbid disease that would make the subject unsuitable for enrolment • Prior therapy with CYP17 inhibitors, enzalutamide or other experimental anti-androgens • Life expectancy < 6 months • Active concurrent malignancy • Treatment with Radium-223 • Known brain metastases • Liver or lung metastases on CT-scanning. • History of seizure or seizure disorder, or history of cerebrovascular stroke within 6 months of study entry. • Known cardiac failure (> NYHA class II)

ECOG, Eastern Cooperative Oncology Group. LHRH, luteinizing hormone-releasing hormone. CT, computed tomography. PCWG3, prostate cancer working group 3. RECIST, Response Evaluation Criteria in Solid Tumors. ULN, upper limit of normal. ALT, Alanine aminotransferase. AST, aspartate aminotransferase. HbA1C, Glycated haemoglobin. NYHA, New York Heart Association.

Table 2. Schedule of enrolment, interventions, and assessments.

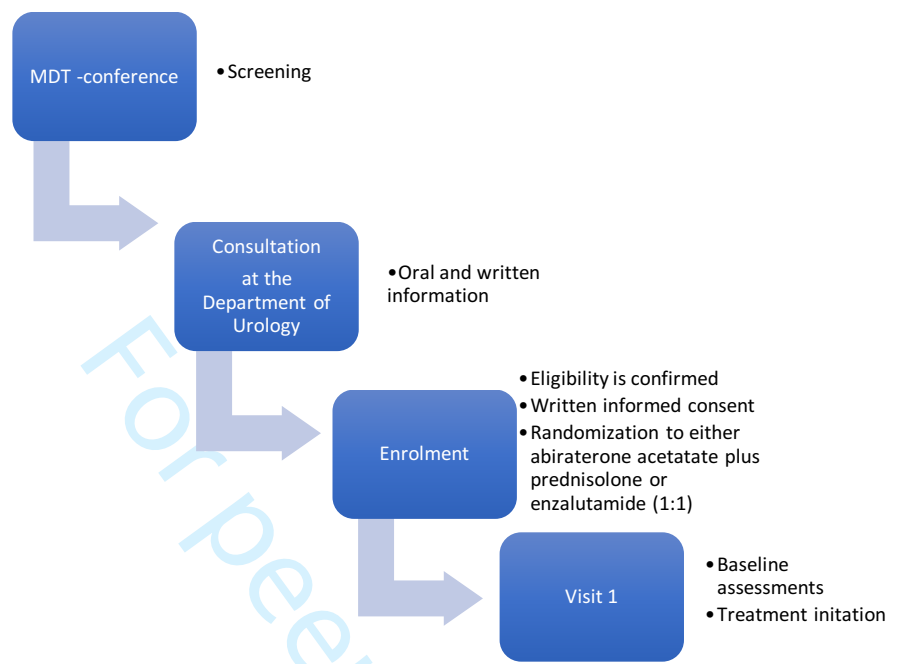
Visit	Randomization and enrollment	Baseline visit	12-week follow-up	Follow-up at time of disease progression
Time (weeks from treatment initiation)	-4± 2	0	+12 ± 2	+ 10 until the year 2023
Written informed consent	X			
Medical history	X			
Medication list	X	X	X	
ECOG Performance status	X	X	X	
Physical				
Height		X		
Blood pressure, weight, BMI		X	X	
Questionnaires				
FACIT-Fatigue		X	X	X
FACT-P		X	X	X
Samples				
Blood samples		X	X	X
Urine sample		X		X
Other paraclinical examinations				
DXA scan		X	X	
OGTT (only the first 60 participants)		X	X	
Safety				
Adverse Events			X	

ECOG, Eastern Cooperative Oncology Group. BMI, Body Mass Index, FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue. FACT-P, Functional Assessment of Cancer Therapy-Prostate. DXA, dual energy X-ray absorptiometry. OGTT, Oral Glucose Tolerance Test.

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Figures

Figure 1. Timeline from screening to intervention





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

Section/item	Item No	Description	Page
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1+10
	5b	Name and contact information for the trial sponsor	10
	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	10
	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)	NR
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	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3

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	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)	3
	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	3
	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)	3-4+13
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	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)	4
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
	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	5-6
	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+14
	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	6-7
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)			
Allocation:			4
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	
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	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NR
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	5-6
	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	4
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	7
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	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7

			7
	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)	
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	7
	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	NR
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	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NR
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
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)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
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	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11

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	4+8
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	NR
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	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NR
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Fatigue, quality of life and metabolic changes in men treated with first-line enzalutamide versus abiraterone plus prednisolone for metastatic castration-resistant prostate cancer (HEAT): a randomised trial protocol

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	prostatic neoplasms, castration resistant, enzalutamide, abiraterone, Adverse events < THERAPEUTICS, Urological tumours < UROLOGY

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Fatigue, quality of life and metabolic changes in men treated with first-line enzalutamide versus abiraterone plus prednisolone for metastatic castration-resistant prostate cancer (HEAT): a randomised trial protocol

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Abstract

Introduction

Enzalutamide and abiraterone acetate plus prednisolone (AAP) are used in combination with androgen deprivation therapy (ADT) to further suppress the androgen stimulation of metastatic castration-resistant prostate cancer (mCRPC). First-line mCRPC treatment with enzalutamide and AAP yields similar overall survival and radiographic progression-free survival in phase III trials. Thus, treatment selection relies on patient choice, cost and side effects. The aim of this randomised trial is to investigate differences in fatigue, health-related quality of life (HRQoL) and metabolic side effects in men with mCRPC treated with first-line enzalutamide versus AAP.

Methods and analysis

In this ongoing open-label randomised (1:1) clinical trial, enzalutamide is compared with AAP as first-line treatment for men with mCRPC. The primary endpoint is fatigue assessed with the questionnaire Functional Assessment of Chronic Illness Therapy-Fatigue version 4 (FACIT-Fatigue). Secondary endpoints are changes in body composition (i.e. fat mass, visceral adipose tissue, subcutaneous adipose tissue and lean body mass assessed with dual x-ray absorptiometry), glucose metabolism assessed with a two-hour oral glucose tolerance test, serum lipids, blood pressure and HRQoL assessed with the questionnaire Functional Assessment of Cancer Therapy-Prostate (FACT-P). All study endpoints are assessed at baseline and 12-week post-intervention. Blood and urine samples are collected at baseline and at time of progression on allocated treatment for future investigation of predictive and prognostic biomarkers in prostate cancer treatment.

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5 The planned sample size is 170 participants. All participants are recruited from Herlev and Gentofte
6 Hospital, Denmark. Estimated last patient's last visit is February 2020.
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9 **Ethics and dissemination**

10 The study received project approval from the National Committee on Health Research Ethics and
11 Danish Data Protection Agency and Danish Medicines Agency (EudraCT no.: 2017-000027-
12 99). The results of the study will be published in peer-reviewed international journals and will be
13 presented at national and international conferences and symposiums.
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16 **Trial registration:** clinicaltrialsregister.eu, EudraCT no.: 2017-000099-27. Registered on 2017-04-26.

17 **Keywords:** castration resistant, prostate cancer, prostate neoplasm, Enzalutamide, Abiraterone, Abiraterone acetate, Hormone therapy, Adverse
18 events, side effects, Fatigue, Quality of life, Metabolic changes, Randomised controlled trial
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23 **Strength and limitations**

- 24 • This randomised clinical trial will report patient-reported and metabolic side
25 effects in a relatively large sample size.
- 26 • This is the first randomised head-to-head trial primarily comparing fatigue,
27 health-related quality of life and metabolic side effects in men with
28 metastatic castration-resistant prostate cancer treated with first-line
29 enzalutamide versus abiraterone plus prednisolone.
- 30 • The trial lacks assessment of long-term side effects.
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Introduction

During the past decade, several new treatment options have emerged for metastatic castration-resistant prostate cancer (mCRPC). These new treatment options include the androgen pathway inhibitors enzalutamide and abiraterone acetate. Enzalutamide blocks several steps in the androgen receptor signalling. Abiraterone inhibits enzymes (17 α -hydroxylase and 17, 20-lyase) in the androgen biosynthesis, and is combined with prednisolone to compensate for abiraterone-induced reductions in serum cortisol (1,2).

Enzalutamide and abiraterone acetate plus prednisolone (AAP) yield similar radiographic progression-free and overall survival results in the phase III trials (PREVAIL and COU-AA-302 respectively) which has led to approval as first-line mCRPC treatments (3–6). Thus, the choice between these two agents depends on the patient's preference, costs and agent-specific side effects.

Men with mCRPC that have been treated with androgen deprivation therapy (ADT), have an increased risk of metabolic side effects and fatigue affecting health-related quality of life (HRQoL) (7,8). Androgen pathway inhibitors are generally safe, with low rates of grade 3 and 4 adverse events. Most of the reported adverse events of these treatments are similar in the mentioned phase III-trials, but the following adverse events were different: enzalutamide was associated with memory impairment and seizures; whereas AAP was associated with liver function abnormalities, peripheral oedema and cardiac events (3,5,9). Fatigue was the most common reported adverse event of both enzalutamide and AAP, although commonly emphasized as a side effect to enzalutamide (3,5). Comparing the results of the two trials is difficult, as the men in the control-group of the enzalutamide trial (PREVAIL) received placebo, whereas the men in the control-group of the AAP trial (COU-AA-302) received placebo plus prednisone (3,5). To date, no randomised head-to-head comparison primarily exploring differences in the side effect profiles have, to our knowledge, been published.

In addition, AAP has been approved for hormone-naïve metastatic prostate cancer and enzalutamide is expected to gain similar approval (10–12, NCT02677896, NCT02319837). This change in treatment sequencing will result in longer exposure to side effects, making comparative studies with specific side effect endpoints even more essential.

This protocol describes an ongoing randomised clinical trial comparing self-reported fatigue and HRQoL and metabolic changes in men treated with enzalutamide or AAP as first-line treatment for mCRPC. The aim is that the results from this trial may help patients and physicians to choose the best tolerated treatment based on the difference in the side effects of enzalutamide and AAP.

Methods and analysis

Trial design

This is a single-centre open-labelled randomised (1:1) phase IV trial comparing first-line enzalutamide versus AAP in men with mCRPC. The trial is conducted at the Department of Urology, Herlev and Gentofte Hospital, Denmark. The primary objective is to compare fatigue assessed with the questionnaire Functional Assessment of Chronic Illness Therapy-Fatigue version 4 (FACIT-Fatigue).

Participants

Eligible participants are men with newly diagnosed mCRPC, defined as metastatic prostate cancer progressing on ADT, based on the prostate cancer working group 3 criteria (PCWG3) (13)..

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4 Metastatic status is measured with computed tomography (CT) scan of the thorax and abdomen and
5 bone imaging (^{18}F -sodium fluoride (NaF) positron emission tomography-computed
6 tomography (PET/CT) or prostate specific membrane antigen (PSMA) PET/CT). Inclusion criteria
7 are age ≤ 90 years, an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and
8 adequate organ function (creatinine $< 1.5 \times$ the upper limit of normal (ULN), total bilirubin $< 1.5 \times$
9 ULN and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN).
10 Exclusion criteria are visceral metastases, a prior history of seizures, known heart failure (New
11 York Heart Association (NYHA) functional class > 2), diabetes mellitus, hypersensitivity to or
12 previous treatment with enzalutamide or AAP or previous treatment with docetaxel. An exception
13 to the latter is docetaxel in the metastatic hormone-naïve prostate cancer setting, if the treatment
14 was completed more than six months prior to enrolment. Inclusion and exclusion criteria are
15 depicted in **Table 1**. Eligibility is primarily assessed at the department's multidisciplinary team
16 conference, where all patients are evaluated prior to starting first-line mCRPC treatment.
17 Subsequently eligibility is confirmed by the primary investigator at a screening consultation before
18 randomization. This ensures that all eligible men at Herlev and Gentofte Hospital are offered study
19 participation. The timeline from screening to intervention is depicted in **Figure 1**.
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24 **Randomisation**

25 Patients who meet the inclusion and exclusion criteria and have given a written informed consent
26 are randomised at the screening consultation using the Randomization Module of Research
27 electronical data capture (REDCap version 7.1.1. © 2018 Vanderbilt University, Nashville, USA).
28 The allocation sequence is a computer-generated list of random numbers transferred to REDCap by
29 a collaborator with no clinical involvement in the trial. Participants are randomly assigned to either
30 enzalutamide or AAP in a 1:1 ratio without stratification. Randomization follows a block
31 randomization with 60 men in the first block and 110 men in the last block. Participants and
32 physicians are aware of the allocation arm after randomization. Data and outcome assessors are not
33 blinded.
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37 **Interventions**

38 Recruitment began in June 2017 and planned completion is December 2019. Herlev and Gentofte
39 Hospital provides urological cancer care for a population of approximately 1.3 million. We estimate
40 that around 150 men are offered either enzalutamide or AAP as first-line mCRPC treatment yearly
41 at the Department of Urology, Herlev and Gentofte Hospital. Participants are randomised to receive
42 one of the following treatments:
43

44 **Enzalutamide**

45 Participants are allocated to take 160 mg enzalutamide orally in the evening.
46
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48 **AAP**

49 Participants are allocated to take 1000 mg abiraterone acetate orally at least 1 hour before a meal or
50 two hours after a meal in the evening.
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52 Participants are instructed to take 10 mg prednisolone orally in the morning.
53

54 Compliance is ensured by registering the number of returned tablets at the follow-up visit. During
55 the trial, all participants continue ADT. In addition, all participants follow normal standard of care
56 and monitoring according to local and national guidelines at the Department of Urology, Herlev and
57 Gentofte Hospital, such as being offered bone protecting agents (i.e. denosumab and calcium and
58 vitamin D supplements). Participants receive allocated treatment from baseline visit until
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4 biochemical and/or radiographic progression or at the treating physician's discretion after which
5 appropriate choice of second-line mCRPC treatment will be decided at multidisciplinary team
6 conferences as per standard of care.
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10 **Outcomes**

11 *Measurements*

12 Primary and secondary outcomes are assessed for all participants at baseline and 12-week post-
13 intervention by the primary investigator. A schedule of enrolment, interventions and assessments is
14 depicted in **Table 2**.
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16

17 *Primary outcome*

18 The primary endpoint is the between-group differences in changed level of fatigue assessed with the
19 13-question questionnaire FACIT-Fatigue available and validated in Danish. The participants report
20 the past week's experienced fatigue by grading each question from one to four: "not at all", "a little
21 bit", "some-what", "quite a bite" and "very much". A minimal clinically important difference
22 (MCID) in fatigue is defined as a 3.0 points change on an individual level (14). Fatigue is assessed
23 at baseline, 12-week post-intervention and at time of disease progression on allocated treatment.
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26 *Secondary outcomes*

27 The secondary outcomes are the between-group differences in changed HRQoL, body composition,
28 blood pressure, insulin sensitivity and resistance measured with a 4-point oral glucose tolerance test
29 (OGTT), serum lipids and androgen treatment response.
30
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32 *HRQoL*

33 The between-group change in HRQoL is assessed with the 39-question questionnaire Functional
34 Assessment of Cancer Therapy - for patients with Prostate cancer version 4 (FACT-P) available and
35 validated in Danish. FACT-P is assessed with the same grading as the FACIT-fatigue questionnaire.
36 An MCID in HRQoL is defined as a 6 points change on an individual level (15). HRQoL is
37 assessed at baseline, 12-week post-intervention and at time of disease progression on allocated
38 treatment.
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41 *Body composition*

42 Fat mass, body fat %, visceral adipose tissue volume (VAT), subcutaneous adipose tissue volume
43 (SAT) and lean body mass (LBM) are obtained using dual energy X-ray absorptiometry (DXA)
44 whole body fan-beam scans (Hologic Discovery, Bedford, Massachusetts, USA) with the software
45 APEX 4.0. VAT and SAT are measured in a 5 cm wide horizontal slice across the abdomen from
46 the iliac crest to the L4-L5 segment (16,17). Weight (BWB-800A, TANITA, Tokyo, Japan) and
47 body mass index (height in meters²/weight in kilograms) is assessed as well. Systolic and diastolic
48 blood pressure is measured on the right arm after at least 20 minutes of rest (BP A3 Plus, Microlife
49 AG, Widnau, Switzerland).
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52 *OGTT*

53 The first 60 participants undergo a two-hour oral glucose (75 g) tolerance test (OGTT) after at least
54 9 hours of fasting. Plasma glucose and insulin are measured after 0, 30, 60 and 120 minutes. The
55 whole body insulin sensitivity index (Matsuda index) are calculated from plasma glucose and
56 insulin concentrations attained from the two-hour OGTT in the subgroup of 60 participants (18).
57 The equation for calculating the Matsuda index is: $10.000/\sqrt{(FPG \times FPI \times \text{mean PG} \times \text{mean PI})}$.
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4 FPG is the fasting plasma glucose and FPI is the fasting plasma insulin concentration. Fasting
5 plasma glucose and insulin are measured in all 170 participants. Fasting insulin resistance is
6 calculated from the basal glucose and insulin concentrations using the homeostatic model
7 assessment (HOMA-IR) with following equation: $(FPG \times FPI)/22.5$ (19).
8
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10 *Biochemical assays*

11 All blood samples are drawn before 10 am after a minimum of 9 hours of fasting.
12

13 *Metabolic analyses*

14 Plasma glucose is analysed with an enzymatic assay (Vitros 5.1, Ortho-Clinical Diagnostics, USA).
15 Plasma insulin is analysed with a sandwich chemiluminescence immunoassay (ADVIA Centaur
16 XP, Siemens, Germany). Glycated haemoglobin (HbA1c) is measured by high-performance liquid
17 chromatography (Variant II TURBO, Bio-RAD, USA). Triglycerides, total cholesterol, HDL
18 cholesterol, LDL cholesterol and VLDL cholesterol are assayed by an enzymatic technique (Vitros
19 5.1 FS, Ortho-Clinical Diagnostics, USA). C reactive protein is analysed with a latex-enhanced
20 immuno-turbidimetric test (Atellica CH 930, Siemens, Germany).
21
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23 *Androgen treatment response*

24 Serum total testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS) and 17-
25 hydroxyprogesterone are measured by Liquid chromatography – tandem mass spectrometry
26 (Acquity UPLC Xevo™ TQ MS, Waters, USA). Sex hormone binding globulin (SHBG) is
27 analysed by a competitive chemiluminescence based immunoassay (Cobas, Roche Diagnostics,
28 Mannheim, Germany). Plasma Luteinizing hormone (LH) and follicle stimulating hormone (FSH)
29 are measured using sandwich chemiluminescence immunoassay (ADVIA Centaur®, Siemens,
30 Germany).
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33 *Additional measurements*

34 *Common terminology criteria for adverse events*

35 Adverse events will be registered at the 12-week post-intervention visit, using the common
36 terminology criteria for adverse events version 4 (20).
37

38 *Metabolic biomarkers*

39 Samples of full blood and serum are prospectively collected at baseline and 12-week post-
40 intervention for future assessment of cardiac, adipose and inflammatory biomarkers.
41

42 *Genetic biomarkers*

43 A biobank is generated during the trial and will be used for a future prospective, observational study
44 assessing the predictive and prognostic value of genetic biomarkers in circulating cell-free DNA
45 (ccfDNA). Samples from blood and urine are prospectively collected at baseline and at time of
46 disease progression on allocated treatment. Somatic alterations will be analysed from ccfDNA in
47 plasma, urine pellets and supernatant.
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54 **Patient and public involvement**

55 The patients treated with enzalutamide and AAP inspired us to the design of the trial's research
56 question and outcomes, by sharing their experience of the treatment and associated side-effects in
57 the out-patient clinic of Herlev and Gentofte Hospital. Fatigue is the primary outcome of the trial,
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4 since fatigue is the most common and distressing symptom experienced by patients with mCRPC
5 (21). The burden of the intervention is partly assessed by patient-reported questionnaires assessing
6 fatigue and HRQoL. Patients were not involved in the recruitment to or conduct of the trial. The
7 results of the trial will be made publicly available through the homepage of Herlev and Gentofte
8 Hospital.
9

10 11 **Sample size and statistical analysis**

12 The sample size calculation is based on the detection of a between-group MCID of 3.0 points on the
13 FACIT-Fatigue scale, with an anticipated drop-out of 10% (14). The standard deviation is assumed
14 to be 6.55, based on confidence limits from previous studies assessing fatigue in men with
15 metastatic prostate cancer (22–24). The sample size calculation is based on a two-tailed significance
16 level of 5% and a power of 80%. This required a sample size of 85 participants in each group, a
17 total of 170 men.
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20 The within-subject and between-group differences of the primary and secondary endpoints will be
21 analysed with linear mixed effect models using constrained longitudinal analysis (cLDA). The
22 between-group MCID in fatigue and HRQoL will be analysed with risk difference. An MCID in
23 fatigue is defined as an individual 3-point change in the FACIT-Fatigue total score. An MCID in
24 HRQoL is defined as an individual 6-point change in FACT-P total score. Interactions between
25 patient reported outcomes (fatigue and quality of life), and age (< 75 versus ≥75 years) and extent
26 of metastases (high versus low volume disease) will be tested in sub-group analyses using forest
27 plots. High volume disease is defined as ≥ 4 bone metastases with ≥ 1 bone metastases outside
28 pelvis and column. Interactions between metabolic changes, and BMI (<30 versus ≥ 30) and age
29 (<75 years versus ≥ 75) will be analysed in sub-group analyses using forest plots. The linear mixed
30 effect model using cLDA handles random missing data.
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34 35 **Ethics and dissemination**

36 Participants will receive standard first-line treatment for mCRPC. The primary investigator obtains
37 the written informed consent from all participants. The trial follows the ICH-GCP guidelines for
38 good clinical practice, the latest revision of the Declaration of Helsinki and the Danish rules on
39 Clinical Trials of Medicines in Humans. This trial is approved by the National Committee on
40 Health Research Ethics (H-17001347), Danish Data Protection Agency (2012-58-0004) and Danish
41 Medicines Agency (EudraCT no.: 2017-000027-99, www.clinicaltrialsregister.eu). The trial is
42 externally monitored by Good Clinical Practice Unit, Copenhagen University. The trial's results
43 will be published in peer-reviewed international journals or otherwise made publicly available and
44 will be presented at national and international conferences and symposiums irrespective of the
45 outcomes. Patient reported outcome, metabolic changes, hormone analyses and genetic biomarkers
46 will be reported in separate publications. Study completion is expected by spring 2020, and
47 dissemination of the results will begin as soon as possible thereafter.
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51 52 **Discussion**

53 This article describes the protocol of an ongoing randomised clinical trial comparing fatigue,
54 HRQoL and metabolic changes in men with mCRPC treated with first-line enzalutamide versus
55 AAP.
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57 We chose fatigue as the primary endpoint since it is the most common and distressing symptom
58 affecting HRQoL in men with mCRPC (3,5,25,26). We assess changes in patient reported fatigue
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4 with the validated 13-question questionnaire FACIT-Fatigue. Previous randomised clinical trials on
5 enzalutamide and AAP measured the level of fatigue with Common Terminology Criteria for
6 Adverse Event with a coarse three-level grading, from fatigue “relieved by rest” to fatigue “limiting
7 self-care” (3,5). We expect that changes in fatigue will be reported more accurately from patients
8 using the 13-question questionnaires in contrast to the physician reported three-level grading used
9 in previously trials. We did not choose to assess fatigue by interviews since that would preclude a
10 statistical comparison of changes in fatigue, even though interviews might yield a more individual
11 assessment of fatigue.
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15 We chose to assess changes in patient reported HRQoL with the 39-question questionnaire
16 FACT-P, because FACT-P is developed and validated for assessing HRQoL in men with prostate
17 cancer. Changed HRQoL for men with metastatic prostate cancer has previously been measured
18 with FACT-P in randomized clinical trials, and the results can therefore be compared with existing
19 literature (27–29).
20

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22 We chose to comprehensively assess metabolic changes, including glucose metabolism measured
23 with oral glucose tolerance test and HbA1c, and body composition measured with DXA scans.
24 Previous randomised clinical trials on enzalutamide and abiraterone have measured following
25 metabolic adverse events: plasma glucose, weight, and blood pressure (3–6). We did not choose to
26 measure plasma glucose, because the within-subject plasma glucose varies widely, and fasting
27 plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed
28 diabetes (30,31). We chose to assess glucose metabolism with OGTT and HbA1c because the
29 hyperglycaemic disease process is a risk factor for microvascular complications, diabetes and
30 cardiovascular disease and may be present without fulfilling the criteria for diabetes (30). We chose
31 to measure BMI and body composition with DXA scans because both methods can identify obesity
32 and associated metabolic and cardiovascular risks,(32–34) while DXA scans can identify body fat
33 which may be a better predictor of metabolic syndrome than BMI alone (35,36). We measure lean
34 body mass with DXA scans, because a loss of lean mass can over time contribute to a decrease in
35 muscle strength which are important predictors of balance, the occurrence of falls and mortality
36 (37,38).
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40 We chose 3-month follow-up to evaluate the treatments side effects and at the same time to avoid a
41 pronounced influence of disease progression on HRQoL and fatigue. In a cohort study of 21
42 participants metabolic changes appeared already after 7 to 10 days of treatment with low-dose
43 prednisolone (6 mg/day) (39). Changes in fatigue and HRQoL can be experienced within the first
44 three months of treatment with new androgen pathway inhibitors (27). The median time until
45 biochemical progression was 11.1 and 11.2 months for men with mCRPC treated with AAP and
46 enzalutamide, respectively (3,5). However, 14% (74/546) had biochemical progression after only 3
47 months' treatment with AAP; and 8% (70/854) had biochemical progression after 3 months'
48 treatment with enzalutamide (3,5).
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51 The lack of blinding can be perceived as a weakness, but we find that it is of minor importance and
52 unlikely to affect the objectively measured outcomes. Blood samples are analysed in an
53 independent laboratory, DXA scans are analysed with the same software and outcomes on fatigue
54 and HRQoL are reported by participants.
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Conclusion

The aim of this trial is to assess differences in the patient reported and metabolic side effects of enzalutamide and AAP. The results may in the future help patients and physicians to choose the best tolerated treatment and thereby reduce treatment induced morbidity and improve quality of life.

For peer review only

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Contributions

KKT, PBØ, JS, CK, HL, MF, GP and RB participated in the design of the study. KKT conceived the study and participated in its design and coordination. KKT and PBØ drafted the study protocol. KKT drafted the manuscript and all authors read and approved the final manuscript.

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Funding statement

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Competing interests statement

The authors have following conflicts of interest:

PBØ is speaker for Astellas, Ipsen and Ferring.

MF is speaker for Ferring and Astellas and advisory board representative for Astellas.

HL is advisory board representative for Roche, Janssen, Astellas, Bayer and Sanofi-Aventis.

Tables

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Eligible for first line treatment with either enzalutamide or abiraterone acetate plus prednisolone as per standard of care guidelines • Age 18-90 years • Willing, capable and legally competent individuals • ECOG performance status 0-1 • Histologically confirmed adenocarcinoma of the prostate • Prior surgical orchiectomy or if on LHRH agonist/antagonist, then testosterone < 1.7 nmol/L at screening visit (participants must maintain LHRH agonist/antagonist therapy for duration of study treatment if not surgically castrated) • Evidence of metastatic disease on bone scan or CT scan • Evidence of biochemical or imaging progression in the setting of surgical or medical castration. Progressive disease for study entry is defined by one of the following criteria based on criteria of PCWG3: <ul style="list-style-type: none"> ○ Biochemical progression: Obtain sequence of rising PSA values at a minimum of 1-week intervals, resulting in increases over the nadir, with PSA > 1 ng/mL ○ Radiological progression: <ul style="list-style-type: none"> ▪ The appearance of two or more new bone lesions on bone imaging ▪ Enlargement of a soft tissue lesion using the modified RECIST 1.1. • Adequate organ function defined as: <ul style="list-style-type: none"> ○ Creatinine < 1,5 x ULN ○ Total bilirubin < 1,5 x ULN ○ ALT or AST ≤ 2,5 x ULN 	<ul style="list-style-type: none"> • Inability to understand and/or stick to the written information • Previous treatment with docetaxel, with the exception of previous treatment with early docetaxel (≤ 6 series) ≥ 6 months before inclusion. • Diagnosed with diabetes mellitus and/or HbA1C > 48 mmol/mol. • Hypersensitivity towards components in abiraterone acetate plus prednisolone or enzalutamide • Ongoing treatment with high doses of glucocorticoids • Severe concurrent illness or co-morbid disease that would make the subject unsuitable for enrolment • Prior therapy with CYP17 inhibitors. enzalutamide or other experimental anti-androgens • Life expectancy < 6 months • Active concurrent malignancy • Treatment with Radium-223 • Known brain metastases • Liver or lung metastases on CT-scanning. • History of seizure or seizure disorder, or history of cerebrovascular stroke within 6 months of study entry. • Known cardiac failure (> NYHA class II)

ECOG, Eastern Cooperative Oncology Group. LHRH, luteinizing hormone-releasing hormone. CT, computed tomography. PCWG3, prostate cancer working group 3. RECIST, Response Evaluation Criteria in Solid Tumors. ULN, upper limit of normal. ALT, Alanine aminotransferase. AST, aspartate aminotransferase. HbA1C, Glycated haemoglobin. NYHA, New York Heart Association.

Table 2. Schedule of enrolment, interventions, and assessments.

Visit	Randomization and enrollment	Baseline visit	12-week follow-up	Follow-up at time of disease progression
Time (weeks from treatment initiation)	-4± 2	0	+12 ± 2	+ 10 until the year 2023
Written informed consent	X			
Medical history	X			
Medication list	X	X	X	
ECOG Performance status	X	X	X	
Physical				
Height		X		
Blood pressure, weight, BMI		X	X	
Questionnaires				
FACIT-Fatigue		X	X	X
FACT-P		X	X	X
Samples				
Blood samples		X	X	X
Urine sample		X		X
Other paraclinical examinations				
DXA scan		X	X	
OGTT (only the first 60 participants)		X	X	
Safety				
Adverse Events			X	

ECOG, Eastern Cooperative Oncology Group. BMI, Body Mass Index, FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue. FACT-P, Functional Assessment of Cancer Therapy-Prostate. DXA, dual energy X-ray absorptiometry. OGTT, Oral Glucose Tolerance Test.

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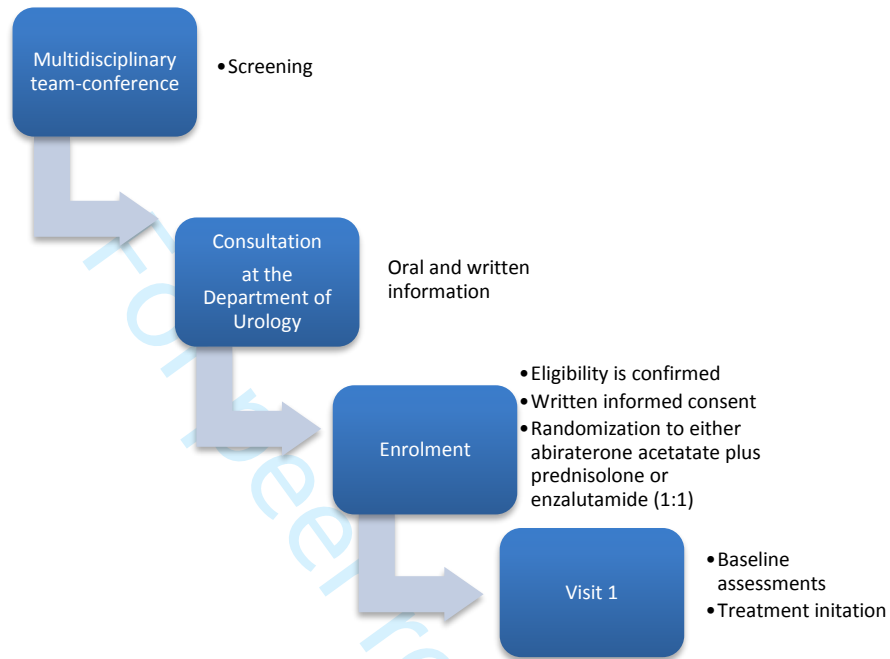
Figure legends

Figure 1. Timeline from screening to intervention

For peer review only

Figure

Figure 1. Timeline from screening to intervention





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

Section/item	Item No	Description	Page
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1+10
	5b	Name and contact information for the trial sponsor	10
	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	10
	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)	NR
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	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3

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	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)	3
	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	3
	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)	3-4+13
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	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)	4
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
	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	5-6
	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+14
	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	6-7
	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)			
Allocation:			4
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	
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	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NR
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	5-6
	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	4
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	7
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	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7

			7
	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)	
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	7
	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	NR
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	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NR
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
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)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
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	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11

1 2 3 4 5	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	4+8
6 7 8	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	NR
9 10 11 12 13 14	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	7
15 16 17		31b	Authorship eligibility guidelines and any intended use of professional writers	10
18 19 20 21		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NR
22 23	Appendices			
24 25 26	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
27 28 29 30 31 32	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	

33 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 34 Explanation & Elaboration for important clarification on the items. Amendments to the
 35 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
 36 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
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