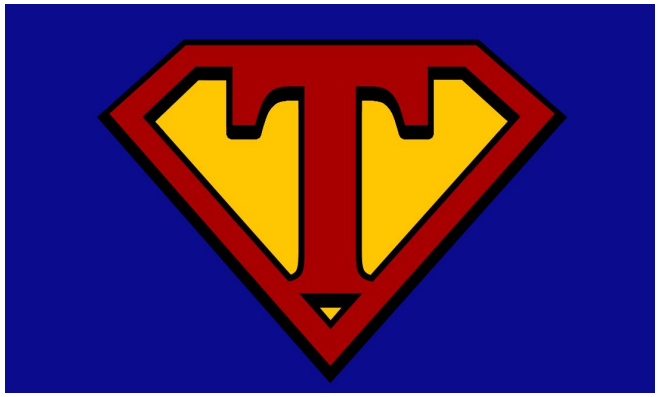
Clinical trial protocol:

Impact of peri-operative tEstosterone levels oN Functional and oncological Outcomes following RadiCal prostatEctomy (ENFORCE)



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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
AR	Adverse Reaction
AMI	Acute Myocardial Infarction
BCR	Biochemical Recurrence
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
CT	Computed Tomography
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EBRT	External Beam Radiation Therapy
ED	Erectile dysfunction
EPIC-26	Expanded Prostate Cancer Index Composite – short form
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FSH	Follicle-stimulating hormone
FT	Free Testosterone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
Hb	Hemoglobin
HT	Hematocrit
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier

ISUP	International Society of Urological Pathology
LH	Luteinising hormone
LRP	Laparoscopic Radical Prostatectomy
MACE	Major Adverse Cardiovascular Events
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
ORP	Open Radical Prostatectomy
PCa	Prostate Cancer
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PRL	Prolactine
PROM	Patient Reported Outcome Measure
PSA	Prostate Specific Antigen
PSM	Positive Surgical Margin
PLND	Pelvic Lymph Node Dissection
QoL	Quality of Life
RARP	Robot Assisted Radical Prostatectomy
RP	Radical Prostatectomy
(S)AE	(Serious) Adverse Event
SHBG	Sex Hormone Binding Globuline
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TT	Total Testosterone
TRT	Testosterone Replacement Therapy
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UI	Urinary incontinence

WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Radical prostatectomy (RP) is currently the most common treatment for non-metastatic prostate cancer (PCa). Two frequent side effects of this procedure are urinary incontinence and erectile dysfunction, both having a significant negative impact on quality of life.
Additionally, it is known that with age the testosterone level in men declines. This does not lead to symptoms in all men (asymptomatic testosterone deficiency). Both testosterone deficiency (TD) and radical prostatectomy are well-established to have a significant negative impact on sexual performance and are likely to add up in patients with a low testosterone following RP.
Objective: The aim of this study is to assess the effect of testosterone replacement therapy (TRT) on functional and oncological outcomes in testosterone deficient men following RP for PCa.
Study design: This study is a phase 3 prospective, randomized, placebo-controlled, single-blind clinical trial.
Study population: All men over 18 years old diagnosed with non-metastatic prostate cancer who are scheduled for RP within three months as primary treatment, can be prescreened for inclusion. Prior to the RP, serum testosterone will be determined. Subsequently, within six weeks after the RP, serum testosterone will be determined again and patients will be screened for inclusion. If necessary, a third measurement of testosterone will be done. Eligible patients meet the criteria for TD and other inclusion criteria.
Intervention: Patients will be randomized for testosterone replacement therapy (TRT) or placebo as a daily administered topical gel starting within 8 weeks after RP. Patients will receive TRT or placebo for one year following RP and will be monitored for another year for functional outcomes and for four more years to establish 5-year biochemical recurrence (BCR) free survival.
Main study parameters/endpoints:
The primary study endpoint is a clinically relevant (12 points or more) difference in the EPIC-26 domain for sexual functioning 12 months after RP in favor of testosterone deficient men receiving TRT compared with testosterone deficient men receiving placebo. Secondary endpoints include: urinary incontinence score, hormonal functioning score and BCR-free survival.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The number of visits and blood drawings are equal to standard of care follow-up after RP, with the exception of two or three extra blood samples at the first prescreening visit and within six weeks following RP. We ask patients to remain with their hospital for 24 months after RP for follow-up and to complete online questionnaires for the given visits. The five-year biochemical recurrence (BCR) free survival will be obtained through patient's medical records and if insufficient, through the Dutch Cancer Registry (NKR).
Patients who receive TRT or placebo can experience local side-effects such as itching, rash and/or irritation at the site of application. In addition, patients who receive TRT can experience systemic side-effects are gain of weight, hot flashes, acne and an increase in red blood count level.
Furthermore, TRT might improve sexual functioning, urinary continence, hormonal functioning and BCR-free survival, but this is not certain and is subject of research in this study.

1. INTRODUCTION AND RATIONALE

Prostate cancer

Prostate cancer (PCa) is the most prevalent solid malignancy in men in the Western world. In the Netherlands, over 13.000 men were diagnosed with prostate cancer in 2019[1]. If the disease is limited to the prostate or locally advanced, several treatment options are available such as active surveillance, surgery, external beam radiotherapy (EBRT) or brachytherapy. The most common treatment for non-metastatic PCa is surgical removal of the prostate; a radical prostatectomy (RP). In the Netherlands an estimated 2.500 procedures are performed on a yearly basis. Two common side-effects of this procedure are urinary incontinence (5-27%) and erectile dysfunction (ED) (57-89%) which have a significant negative impact on the quality of life[2 3 4 5]. These functional results can improve up until 12 months after surgery, but remain mostly stable after 12-24 months. Patient Reported Outcome Measures (PROMs) are used to objectively document these functional outcomes. The Expanded Prostate cancer Index Composite-26 (EPIC-26) is a commonly used and validated PROM to assess the five domains; urinary incontinence, urinary obstructive, bowel, sexual and hormonal functioning in men who underwent treatment for prostate cancer [6 7]. Following RP most patients have an undetectable PSA, which is an indicator of successful treatment of PCa. However, up to one-third of patients experience a rising PSA during follow-up, an event known as biochemical recurrence (BCR)[8]. A BCR is therefore a common event and associated with worse overall survival, especially in high-risk cases[9].

Testosterone deficiency in aging men

It is known that serum testosterone levels decline with age. At the age of 70, around 30% of men are testosterone deficient (TD)[10]. This does not necessarily lead to symptoms. Late-onset hypogonadism is defined as the combination of TD and the presence of at least three symptoms[11]. The Massachusetts Male Aging Study (MMAS) collected data of aging men in the late 1980s and 1990s, they found a prevalence of symptomatic testosterone deficiency between 6% and 12%[12]. A few years later the same research group verified these findings with the data from the Boston Area Community Health (BACH) survey and found that 28.1% of men above 50 years had a low total testosterone and 6.6 % of men above 50 years symptomatic testosterone deficiency[13]. The number of symptomatic men increases with age; in men 70-79 years they found a prevalence of 18.4%.

Testosterone replacement therapy

The current EAU guideline on late-onset hypogonadism states that testosterone replacement therapy (TRT) is indicated in adult men with low testosterone and concomitant signs and symptoms of TD following unsuccessful treatment of obesity and comorbidities [14]. TRT has been shown to improve sexual functioning in hypogonadal men[15 16]. The aim of TRT is to restore testosterone to physiological levels. Several agents are available; oral preparations, intramuscular injections and transdermal gels. Testosterone gel is a commonly used agent and widely available.

Testosterone and prostate cancer

In 1941, Charles B. Huggins described the association between testosterone and PCa, a discovery for which he received the Nobel Prize in 1966[17]. He discovered the positive effect of castration (i.e. testosterone depletion) on metastatic prostate cancer, which is as of today the cornerstone of the treatment of patients with metastatic PCa. More recently there has been a challenge to this paradigm of lowering testosterone levels in PCa patients, as two studies demonstrated the potential beneficial, but counterintuitive, effect of supraphysiological levels of testosterone in men with advanced prostate cancer[18 19]. In addition, another study showed that men with preoperative low serum testosterone levels had worse pathological outcomes and a higher rate of BCR following radical prostatectomy[20]. The interaction between testosterone and PCa therefore remains complex, not fully understood and requires more research.

Testosterone and RP

Several studies evaluated the safety of TRT in TD men after initial local treatment of PCa. Recently, an extensive systematic review and meta-analysis was published analyzing 21 studies in which patients received TRT following definitive local therapy for non-metastatic PCa[21]. Overall, they did not find an increased rate of BCR in all groups. Nor did subgroup analysis of patients who underwent RP show an increased BCR rate. More specifically, subgroup analyses showed that patients who had undergone a RP experienced lower (though not significant) BCR rates than those who underwent a non-surgical treatment. This is possibly explained by the differences in patient population and disease characteristics such as tumor stage and grade, time of TRT and the definition of BCR, which was not standardized among included studies. Several comments are made by the authors. The studies included in the review varied widely in terms of design, methods, interventions and follow-up duration. Secondly, their analysis included patients who were eligible for testosterone replacement therapy and thus at lower risk for BCR. A more recent study retrospectively analyzed 850 patients who underwent RP[22]. Preoperative testosterone levels were determined, 152 patients (18%) with low preoperative calculated free testosterone and delayed post-operative sexual function recovery, were placed on TRT and matched to control cases. A significant lower BCR rate in the TRT group was established. Furthermore, they found that the time to BCR was delayed by approximately 1.5 years. Due to the non-randomized nature of this study, the authors recommend a multi-center, prospective randomized trials, as we now propose in this protocol.

Conclusion of rationale

Testosterone replacement therapy in (a)symptomatic testosterone deficient men after RP is safe and may improve functional and oncological outcomes but is not common practice. Further research is warranted to evaluate its potential benefits.

2. OBJECTIVES

Primary Objective:

To evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP, leads to better outcomes in the domain of sexual functioning 12 months after RP compared to testosterone deficient men who receive placebo therapy.

Secondary Objectives:

1. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of sexual functioning 3 months after RP.
2. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of sexual functioning 24 months after RP.
3. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of hormonal functioning 12 months after RP.
4. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of hormonal functioning 24 months after RP.
5. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP, leads to both a reduction of and longer interval to BCR following RP, at 1, 2 and 5 years after RP.

Exploratory objective:

6. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of urinary continence 12 months after RP.
7. Evaluate if TRT in (a)symptomatic testosterone deficient men with prostate cancer undergoing RP leads to better outcomes in the domain of urinary continence 24 months after RP.

3. STUDY DESIGN

This study is a phase 3 prospective, randomized, placebo-controlled, single-blind clinical trial to evaluate the effect of TRT on sexual functioning in testosterone deficient men following RP.
The study will consist of four phases; a prescreening phase before RP, a screening phase after RP, a treatment phase and a follow-up phase. During the prescreening phase testosterone levels will be determined pre-operatively and within six weeks post-operatively for all patients. If both values are not in concordance with each other, another measurement will be done. At six weeks after RP patients will be screened for inclusion. Only TD men will be included and asked for written informed consent. Men who have normal testosterone levels cannot proceed in the study, but will be asked to give permission to use their oncological and functional outcomes as a reference cohort. Randomization will take place (TRT vs. placebo) on a 1:1 ratio. Patients will enter a 1-year treatment phase, followed by a 1-year follow-up phase for functional outcomes.

Prescreening phase

In participating centers all patients who are scheduled for RP will be asked to participate in this study. If a patient is eligible for prescreening according to inclusion and exclusion criteria, they will be informed about the study. After written informed consent, a blood sample (drawn in het morning between 07:00-11:00, in a fasting state) will be collected to determine serum testosterone (free and total) and SHBG. Clinical data (age, weight, height, BMI, medical history, ECOG-performance status, ASA classification, non-age adjusted Charlson Comorbidity Score, marital status) will be collected from the electronical patient record. Disease specific data (clinical T and MRI stage, initial PSA, maximum Gleason score/ISUP grade at biopsy, prostate volume on imaging) will be collected as well. Patients must have a minimum baseline score of 40 points for the sexual functioning domain, as this reflects a minimally satisfactory sexual functioning.

RP

The RP will take place as scheduled, but within three months following written informed consent for prescreening. Operative parameters such as technique (robot-assisted (RARP), laparoscopic (LRP) or open (ORP)), nerve sparing (no/unilateral/bilateral), use of NeuroSafe (intra-operative frozen section), pelvic lymph node dissection (PLND), blood loss, total time of surgery, and intra-operative complications will be recorded in the database. The prostate and if applicable lymph nodes will be examined by the pathologist conform normal practice. The pathology report must include: pT-stage, Gleason score/ISUP grade, presence of positive surgical margins (PSM) as well as location and length, and in case of PLND: number of nodes removed, presence of nodal involvement and number of positive nodes. These items will be recorded in the database as well.

After RP

Within six weeks after RP an additional blood test for PSA, free and total testosterone, SHBG, hemoglobin (Hb), hematocrit (HT), liver function, and lipid profile will be done. When preoperative total testosterone was <8 nmol/l, or between 8-12 nmol/l with a free testosterone <225 pmol/l, LH will be

determined subsequently to confirm the diagnosis of late-onset hypogonadism. If LH is below its normal limit, the patient is not eligible for the study and referred to the endocrinologist for further investigation. Again, this test has to be taken between 07:00 and 11:00 in the morning in a fasting state.

Third testosterone measurement

Patients who had a normal testosterone before RP, but a testosterone deficiency after RP need to have a confirmation measurement of testosterone and LH. Patients who were testosterone deficient on two previous occasions and with a normal or elevated LH do not need additional testing at this moment.

Screening phase

At six weeks after RP the prescreening phase will end and patients will be screened for inclusion at the screening visit. If patients meet the eligibility criteria for TRT following RP (see the criteria bellow), patients will be asked to participate in the study. Patients will be asked to sign a second informed consent form for the study. Patients with testosterone deficiency defined as a total testosterone <8.0 nmol/l or total testosterone 8-12 nmol/l and free testosterone < 225 pmol/l will be included.

Patients with normal testosterone levels

Patients who were eligible for prescreening but have a normal testosterone level are not eligible for further participation in the trial. We do ask them to give consent to use their functional and oncological outcomes as a reference for testosterone deficient patients. Functional outcomes are measured with the EPIC-26 up to two years after surgery and oncological outcomes are defined as the occurrence of a biochemical recurrence up to five years after surgery.

Eligible for testosterone replacement therapy:

1. Testosterone deficiency: total testosterone < 8nmol/l OR total testosterone 8-12 nmol/l and free testosterone < 225 pmol/l, measured at two separate occasions and normal or elevated LH.
2. Unmeasurable PSA level (<0.1) within six weeks of follow up
3. pT2-T3a after RP
4. ISUP 1-3 independent of surgical margin status or ISUP 4-5 with negative surgical margins
5. No metastatic lymph nodes if a PLND has been done
6. No general contra-indications for testosterone therapy
7. At least one-sided nerve-sparing procedure
8. A minimum baseline score of 40 points for the sexual functioning domain as measured by the EPIC-26 questionnaire.

Randomization and treatment phase

Patients will be randomized for TRT or placebo and start with daily application of TRT/placebo after

randomization, within eight weeks after RP at latest.

Evaluation of testosterone level and dosage adjustment

Patients will visit their physician at 3, 6 and 9 months after RP. Serum testosterone level will be measured before the visit. The measurement must take place in the morning before application of the gel. For patients who receive testosterone gel, their serum testosterone level should be within 17-20 nmol/l. If the current testosterone level is below that value, the daily dosage should be increased with one pump actuation. If the testosterone level is above 20 nmol/l the daily dosage should be decreased with one pump actuation. The daily dosage should not exceed 4 pump actuations.
If patients exceed the upper limit of 20nmol/l with one dosage actuation, they should stop with the treatment.
Patients who receive placebo gel will also have their testosterone level measured as a reference, but there will be no dosage adjustment in the placebo group.

Penile rehabilitation

All participants are allowed to use additional medication for penile rehabilitation if they request. The following protocol can be used:

1. PDE-5 inhibitor (sildenafil or tadalafil) on demand or daily use
2. Intracavernous (phenatolamine/papaverine) or intra-urethral (alprostadil) injections

The use of additional medication for penile rehabilitation will be registered in the eCRF.

Continuation of testosterone therapy after treatment phase

If patients who were treated with TRT, experience worsening of their symptoms after TRT stops, it is allowed for those men to continue treatment after evaluation of their testosterone levels. This will be registered in the eCRF.

Safety of treatment

The safety of treatment of patients in will be evaluated at 3-, 6- and 9-months following RP.
Withdrawing a patient from treatment is indicated if any of the following events occur:

1. Detectable serum PSA
2. Hematocrit $\geq$ 54%
3. Any adverse event (AE) that leads to substantial changes in risk-benefit consideration according to the local investigator
4. Delay of drug administration of more than 28 days for any reason
5. Elevation of ALAT 1.5x above its normal value
6. Exceeding the upper limit of 20 nmol/l testosterone with one dosage actuation

See paragraph 8.4.1 for a full list of withdrawal criteria.

Testosterone half-life time and antihormonal treatment after TRT

The half-life time of testosterone gel is around 10-100 minutes. Therefore, in case a biochemical recurrence is found and there is an indication for antihormonal treatment, patients should stop immediately with the application of testosterone gel. After 72-96 hours the serum testosterone level is back to its baseline level.

Evaluation of major adverse cardiovascular events

During treatment and follow-up, patients will be evaluated if any of the following Major Adverse Cardiovascular Events (MACE) as defined for this study did occur:

1. Myocardial infarction (MI)
2. Cerebrovascular Accident (CVA)
3. Hospitalization because of heart failure
4. Cardiac interventions including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).
5. Pulmonary embolism (PE)
6. Deep-venous thrombosis (DVT)
7. Death; if no cause is known, cardiac death will be assumed.

Checks and visits:

3-month FU

- Laboratory tests: PSA, TT, FT, SHBG, Hb, HT, lipid profile and ALAT
- Evaluate safety criteria to continue TRT or placebo
- In patients who receive TRT: serum testosterone level will be evaluated and if required adjustments to the application dosage will be made.
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF

6-month FU

- Laboratory tests: PSA, TT, FT, SHBG, Hb, HT, lipid profile and ALAT
- Evaluate safety criteria to continue TRT or placebo
- In patients who receive TRT: serum testosterone level will be evaluated and if required adjustments to the application dosage will be made.
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF

9-month FU

- Laboratory tests: PSA, TT, FT, SHBG, Hb, HT, lipid profile and ALAT
- Evaluate safety criteria to continue TRT or placebo
- In patients who receive TRT: serum testosterone level will be evaluated and if required

adjustments to the application dosage will be made.
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF

12-month FU
- Laboratory tests: PSA, TT, FT, SHBG, Hb, HT, lipid profile and ALAT
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF
- Stop application of testosterone/placebo gel.

18-month FU
- Laboratory tests: PSA, TT, FT, SHBG, LH
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF

24-month FU
- Laboratory tests: PSA, TT, FT, SHBG, LH
- Completion of EPIC-26
- Registration of cardiovascular events.
- Completion of eCRF

24-60 months

Resume oncological follow-up conform local protocol.

60-month FU

5-year BCR free survival rate: The 5-year BCR-free survival will be established through revision of the medical records.

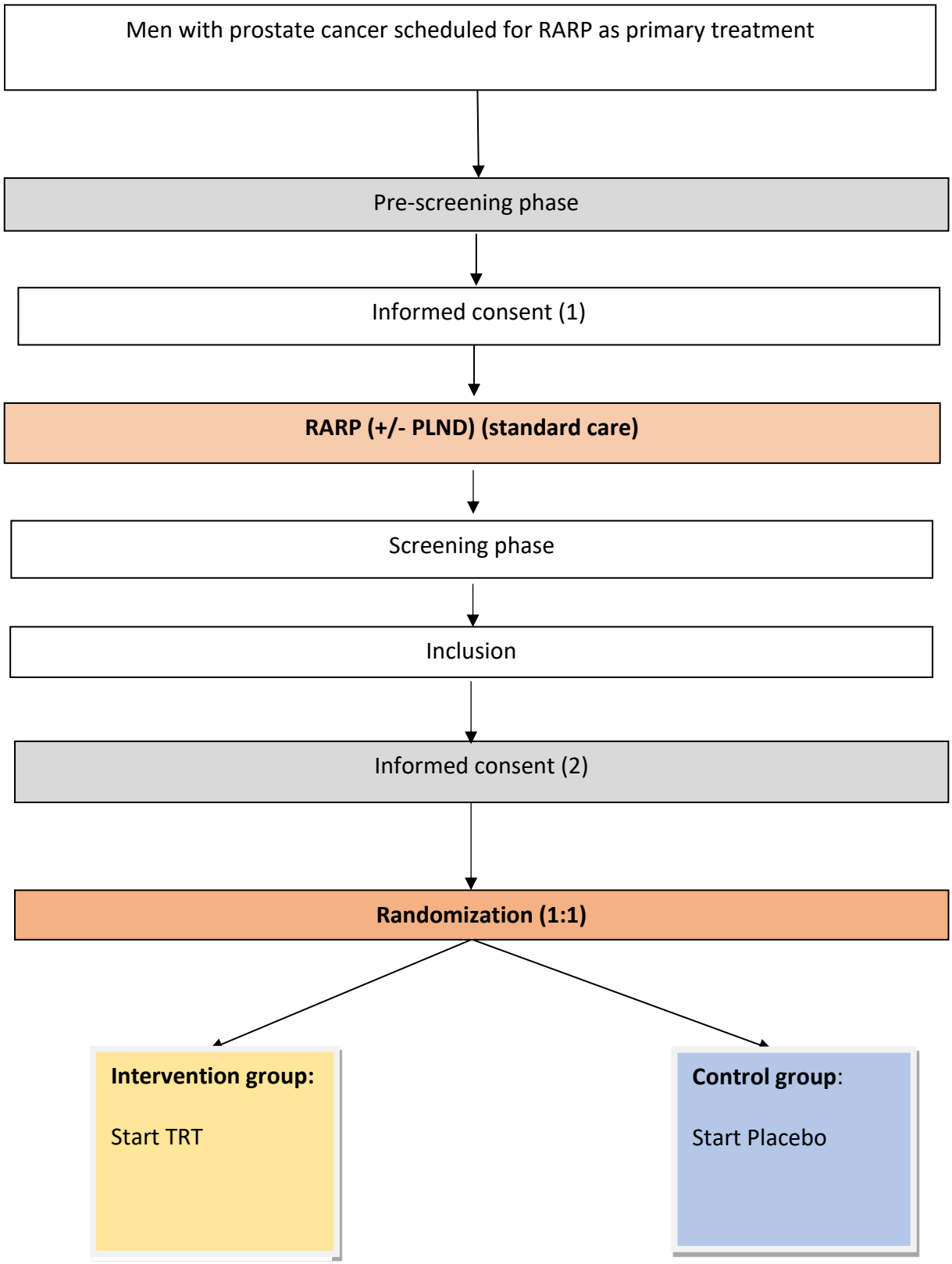

Diagram 1: flow-chart of phases

Time and event schedule 1: Prescreening, screening, procedures and assessments

Phase:	**Prescreening**			**Screening**
Assessment	Prior to RP	<6 weeks after RP	<6 weeks after RP	6-weeks after RP
Informed consent	X			X
PSA	X	X		
TT, FT, SHBG[1]	X	X	X[3]	
LH		X[2]	X[3]	
Lipid spectrum		X		
ALAT		X		
Hb, HT		X		
Prescreening comedication check	X			
Prescreening criteria	X			
Inclusion/exclusion criteria check	X			X
Demographics	X			
Medical history	X			
EPIC-26	X			
RP data				X
Pathology data				X
Doctor visit	X			X
Inclusion				X

[1]laboratory tests must be taken between 07:00-11:00 in the morning in a fasting state.
[2]In case a low testosterone is found prior to RP; LH will be measured after RP.
[3]If a low testosterone is found after RP; a confirmation test will be done.

Time and event schedule 2: treatment and follow-up phase

Phase:	**Treatment**					**Follow-up**		
Assessment	6-8-weeks after RP	3-months after RP	6-months after RP	9-months after RP	12-months after RP	18-months after RP	24-months after RP	5-years after RP
Randomization	X							
Doctor visit	X	X	X	X	X	X	X	
PSA		X	X	X	X	X	X	X
TT, FT, SHBG[1]		X	X	X	X	X	X	
ALAT		X	X	X	X			
Hb, HT		X	X	X	X			
Lipid profile		X	X	X	X			
Adjustment of application dosage based on serum TT level		X	X	X				
Assessment of safety of TRT/placebo		X	X	X				
EPIC-26		X	X	X	X	X	X	
Cardiovascular Events Questionnaire		X	X	X	X	X	X	
Assessment of BCR		X	X	X	X	X	X	X

[1]Blood collection during treatment should be taken before application of the gel in the morning.

4. STUDY POPULATION

4.1 Population (base)

All men who are diagnosed with non-metastatic prostate cancer who are scheduled for RP as primary treatment are eligible for prescreening for this study. The diagnosis of prostate cancer must be confirmed by either biopsy (transperineally or transrectal) or found in prostate tissue after transurethral resection of the prostate (TURP) for assumed benign prostate hyperplasia (BPH). Patients must have completed the current standard of care diagnostic path to exclude visceral or bone metastasis if suspected. This may include additional imaging (CT-thorax/abdomen, bone scintigraphy, and/or PSMA-scan) at the physician's discretion.

4.2 Prescreening eligibility criteria

1. Signed informed consent form 1 (IC)
2. Age > 18 years
3. Histologically confirmed prostate cancer
4. Scheduled for RP as primary treatment with intention of at least a one-sided nerve-sparing procedure.
5. Non-metastatic disease (cN0M0)
6. Willing to provide blood samples to determine testosterone level
7. A pre-operative minimal sexual function defined as 40 points (out of 100) for the EPIC-26 sexual functioning domain.

Prescreening **exclusion** criteria:

1. Any previous treatment for prostate cancer, for example but not limited to: anti-hormonal therapy, radiotherapy or brachytherapy (active surveillance is allowed).
2. Previous use of testosterone therapy for any reason
3. History of male breast cancer
4. History of liver tumor
5. Uncontrolled hypertension
6. Allergy for components in the testosterone therapy agent or placebo
7. Use of vitamin-K antagonists (acenocoumarol or fenprocoumon)
8. BMI > 30

4.3 Inclusion criteria

1. All of the above prescreening eligibility criteria
2. Signed informed consent form 2 (ICF)
3. Undetectable PSA level within six weeks after RP
4. At least one-sided nerve-sparing procedure

4.4 Exclusion criteria

1. pT3b or pT4
2. Positive surgical margin (PSM) and ISUP 4 or 5
3. Metastatic lymph nodes if a PLND has been done

Following medical conditions require extra consideration regarding TRT:
Inclusion at discretion of the caregiver.

- Heart failure, history of ischemic cardiac disease, altered renal- or liver functioning,

epilepsy, migraine (risk of fluid retention)
- Diabetes mellitus (risk of increased glucose tolerance)
- Obesity or COPD (risk of induction or worsening of sleep-apnea syndrome)
- Thrombophilia or high-risk for DVT

4.5 Sample size calculation

To calculate the sample size, the clinical minimally important difference for the EPIC-26 within the domain of sexual functioning was used. Based on the Dutch ProZIB report on prostate cancer in 2019 the mean score [0-100] within the sexual functioning domain for patients who underwent RARP at T0 was 63, with a standard-deviation of 26. At T12 for the same group, the mean was 26 with an SD of 22[6]. Skolarus et al demonstrated in previous research that a clinical relevant difference (minimal important difference, MID) in the domain of sexual functioning is considered 12 points or more[23]. This means that we expect patients who receive TRT who have clinically relevant improvement will have a mean score of at least 38. A sample size calculation using the following parameters was performed:
Power (β-1) = 0.80
Significance level (α) = 0.05
Two-sided testing
Group 1: mean 26 SD: 22 Group 2: mean 38
This results in a sample size of 53 patients in each group.

The university of Michigan, who developed the EPIC-26 questionnaire, suggests when studying one domain as primary endpoint, a sample size of 64 patients per treatment group should be used[24].
We assume that 10% of our patients will discontinue treatment, therefore we establish the sample size for each group at 70 patients, 140 in total. To reach inclusion of 140 testosterone deficient patients, we will prescreen 700 patients who are scheduled for RP, assuming that 25% of our population meets the criteria for TD and 80% will be eligible for inclusion after RP (700*0.25*0.8 = 140 patients).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will be randomized 1:1 between receiving testosterone gel (TRT) or placebo.
Testosterone gel (Androgel®) will be given as a gel for topical application.

Placebo gel will contain the same components as testosterone gel, except for the testosterone.

5.2 Use of co-intervention

Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing edema. As a result, these medicinal products should be administered cautiously, particularly in patients suffering from cardiac, renal or hepatic disease.

Interactions with laboratory tests: androgens may decrease levels of thyroxin binding globulin, resulting in decreased T_4 serum concentrations and in increased resin uptake of T_3 and T_4. Free thyroid hormone levels, however, remain unchanged and there is no clinical evidence of thyroid insufficiency.

Changes in insulin sensitivity, glucose tolerance, glycemic control, blood glucose and glycosylated hemoglobin levels have been reported with androgens. In diabetic patients, antidiabetics' medication might need reduction.

Application of sunscreen or lotion does not reduce efficacy.

Washing 2 hours after application does not have significant effect on blood testosterone levels.

Patients are allowed to use 5-alpha-reductase inhibitors (sildenafil, tadalafil) if requested.

5.3 Escape medication

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Androgel 16.2 mg/g gel. One gram of gel contains 16.2 mg testosterone. One pump actuation delivers 1.25 g of gel containing 20.25 mg of testosterone.

6.2 Summary of findings from non-clinical studies

Please see section 5.3 of the attached Summary of Product Characteristics (SPC) of Testosterone gel.

6.3 Summary of findings from clinical studies

Several clinical studies have demonstrated the efficacy and safety of TRT in patients with TD. Several testosterone formulations are available; oral, topical gel and through intramuscular injection. The use of testosterone gel is the most frequent used. After absorption by the stratum corneum, creating a reservoir, from which testosterone is continuously is delivered for 24 hours after daily application. Topical applications have shown to normalize testosterone levels with an excellent safety profile[26]. A recent multicenter, randomized, double-blind placebo-controlled trial studied the efficacy and safety of testosterone gel in several dosages compared to placebo (6:1 ratio) in 274 hypogonadal men[27] over 182 days. They found that over 80% over the men treated had an adequate testosterone level after titration with a good safety profile.

6.4 Summary of known and potential risks and benefits

Testosterone replacement therapy is associated with an elevation of the serum PSA and increased prostate volume. However, before inclusion there must be no sign of residual prostate cancer following RP. Therefore, we consider it safe to treat patients who have been successfully treated with RP, as mentioned before. The potential risks include known side-effects, as listed below.

Undesirable effects
Most frequent undesirable effects are skins reactions (10%), reaction at the application side, erythema, dry skin.
Adverse drug reactions reported in 1 - <10% of patients treated with Androgel in the controlled clinical trials are listed in the following table:

Organ system class	**Common adverse reactions (>1/100,<1/10)**
Blood and lymphatic system disorders	Changes in laboratory tests (polycythaemia, lipids), Haematocrit increased, Red blood cell count increased, Haemoglobin increased
General disorders and administration site conditions	Headache
Renal and urinary disorders	Prostatic disorders
Reproductive system and breast disorders	Gynaecomastia, mastodynia
Nervous system disorders	Dizziness, paraesthesia, amnesia, hyperaesthesia

Psychiatric disorders	Mood disorders
Vascular disorders	Hypertension
Gastro-intestinal disorders	Diarrhoea
Skin and subcutaneous disorders	Alopecia, urticaria

Gynaecomastia, which may be persistent, is a common finding in patients treated for hypogonadism. Because of the alcohol contained in the product, frequent applications to the skin may cause irritation and dry skin.

6.5 Description and justification of route of administration and dosage

Transdermal use.

The application should be administered by the patient himself, onto clean, dry, healthy skin over right and left upper arms and shoulders.

The gel should be simply spread on the skin gently as a thin layer. It is not necessary to rub it on the skin. Allow to dry for at least 3-5 minutes before dressing. Wash hands with soap and water after application, and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. For more information regarding post dose washing see section 4.4 (subsection Potential for testosterone transfer).

Do not apply to the genital areas as the high alcohol content may cause local irritation.

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for delivering 1.25 g of ANDROGEL 16.2 mg/g into the palm of the hand and then apply to the upper arms and shoulders.

6.6 Dosages, dosage modifications and method of administration

The recommended dose is two pump actuations of gel (*i.e.* 40.5 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding four pump actuations or 81 mg testosterone per day. The adjustment of posology should be achieved by increments of one pump actuation of gel.

The dose should be titrated based on the pre-dose morning testosterone blood levels. Steady state blood testosterone levels are reached usually by the second day of treatment with ANDROGEL 16.2 mg/g. In order to evaluate the need to adjust the testosterone dosage, blood testosterone levels should be measured in the morning before application of the product, after the steady state is reached. Testosterone blood levels should be assessed periodically. The dose may be reduced if the testosterone blood levels are raised above the desired level. If the levels are low, the dosage may be increased stepwise, to a daily administration of 81 mg of testosterone (four actuations of gel) per day.

Therapy should be discontinued if the blood testosterone levels consistently exceeds the normal range at the lowest daily dose of 20.25 mg (1.25 g gel, equivalent to one pump actuation) or if blood testosterone levels in the normal range cannot be achieved with the highest dose of 81 mg (5 g gel, equivalent to four pump actuations).

6.7 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products will be done according to GMP

guidelines.

6.8 Drug accountability

At start of the study, the local the investigational products will be delivered to the principal investigator authorized designee of the participating hospital. The designee will check and record the amount and condition of the received products. The products will come with an enclosed packing slip, which must be signed and returned to the delivered to verify the reception of the investigational product. An investigational product dispensation record will be kept, which will contain the following information:

- Patient record id
- Date and quantity of product dispensed
- Date and quantity of product returned to pharmacy/investigator (if applicable)
- Date and quantity of accidental loss or damaged product (if applicable)

These logs must be kept for inspection of the study. At the end of the study these the monitor will collect these records as well.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

Most of the study's endpoints will be functional outcomes, which will be registered with Patient Reported Outcome Measures (PROM).

8.1.1 Main study parameter/endpoint

The main endpoint for this study is the total sexual domain score coming from the EPIC-26 questionnaire, 12 months after RP. Calculation of this domain score is done by calculating the average of the Standardized Values for items 57-60, 64 and 68 (with 5 non-missing items needed to compute score). Corresponding with questions 8a, 8b, 9, 10, 11 and 12. This results in a number between 0 and 100. A change of 12 points in this domain is considered clinically relevant.
Calculation of the different domain scores is done according to the instructions provided by University of Michigan[28].

8.1.2 Secondary study parameters/endpoints

1. EPIC-26 sexual functioning domain score [0-100] at 3 months after RP. A difference of 12 points or more is considered clinically relevant.
2. EPIC-26 sexual functioning domain score [0-100] at 24 months after RP. A difference of 12 points or more is considered clinically relevant.
3. EPIC-26 urinary incontinence domain score [0-100] at 12 months after RP. A difference of 9 points or more is considered clinically relevant.
4. EPIC-26 urinary incontinence domain score [0-100] at 24 months after RP. A difference of 9 points or more is considered clinically relevant.
5. EPIC-26 hormonal functioning domain score [0-100] at 12 months after RP. A difference of 6 points or more is considered clinically relevant.
6. EPIC-26 hormonal functioning domain score [0-100] at 24 months after RP. A difference of 6 points or more is considered clinically relevant.
7. Occurrence of biochemical recurrence (two times detectable PSA > 0.2 ng/ml)
8. In case of biochemical recurrence, time to recurrence in months.

8.1.3 Other study parameters

Baseline characteristics:

- Date of birth
- Age at time of surgery
- Date of histological diagnosis
- Weight
- Height
- BMI
- Family history of prostate cancer
- History of hereditary prostate cancer
- ECOG performance status
- ASA classification
- Comorbidities
- Charlson Comorbidity index (CCI)
- Marital status

- Smoking
- EPIC-26 domain scores [0-100] at baseline

Physical diagnostic parameters:
- Digital rectal exam outcome and side

Biopsy parameters:
- Date of biopsy
- Route of biopsy (transperineal or transrectal)
- Random and/or target biopsy
- If target what method (cognitive fusion, MRI/TRUS fusion, in-bore MRI guided)
- Number of random biopsies
- Number of positive biopsies and location
- Number of target biopsies
- Number of positive biopsies
- Gleason score
- ISUP grade

Risk group:
- EAU risk group classification

Serum tests:
- PSA
- Hemoglobin
- Creatinine and eGFR
- Free Testosterone
- Total Testosterone
- Sex Hormone Binding Globulin, LH, FSH, prolactin
- Lipid spectrum (Total Cholesterol, HDL-C, TC-HDL ratio, LDL-C, Triglycerides)
- Glucose
- Liver function tests (ASAT, ALAT, gGT, AF)

MRI prostate:
- Date of MRI
- Hospital of acquisition
- Number of lesions
- PIRADS score per lesion
- Extracapsular extension (ECE)
- Prostate volume
- Suspicion of metastatic lymph nodes
- Suspicion of bone or visceral metastases

Other imaging modalities to asses metastatic status. For example: PSMA PET-CT, Bone scintigraphy, CT-scan.
- Date of acquisition
- Imaging parameters like contrast fluid or agents used
- Metastatic lymph nodes
- Bone or visceral metastases

Radical prostatectomy:
- Date of surgery
- Surgeon
- Surgery time in minutes
- Estimated blood loss in mL
- PLND performed
- Nervesparing procedure (no/unilateral/bilateral)

Pathology:

- Tumor type
- Tumor side
- Gleason score
- pT stage
- Positive surgical margin (if yes, location and size in mm)
- In case of PLND:
    - Number of regional lymph nodes dissected
    - Number of regional of metastatic lymph nodes
    - Number of extra-regional lymph nodes dissected
    - Number of extra-regional metastatic lymph nodes
    - N stage

Treatment/follow-up items:

- Laboratory test results
- EPIC-26 domain scores and subquestions
- MACE
- PSA values at each follow-up moment
- Occurrence of biochemical recurrence
- Use of additional medication for penile rehabilitation.
- Continuation of testosterone therapy after the treatment phase on patients request.

8.2 Randomization, blinding and treatment allocation

Patients will be randomized to TRT:placebo in a 1:1 ratio. Randomization will be done centrally and computer generated with stratification per hospital in random block of 2, 4 and 6.
Patients will be blinded for treatment; investigators will not be blinded. In case of serious adverse events, the participant can be unblinded at any time after consultation with the investigator or the physician. After the collection of the last assessment of functional outcomes (24 months) patients will receive an email with information about the intervention they have had (TRT/placebo).

8.3 Study procedures

Before inclusion:

- Patients diagnosed with prostate cancer who have chosen for RP, will be informed about the study by their treating urologist, (research) physician, physician assistant or nurse practitioner. Patients will be informed in person during on the outpatient clinic or by phone.
- Patients who are interested receive additional study information (including Informed Consent Form) for the prescreening phase.
- After signed informed consent, a blood sample will be drawn and patients will be invited to complete the baseline PROMS online.

After RP:

- Within 6 weeks after RP patients will have another blood sample drawn for the screening phase
- Eligibility for inclusion will be checked using an eCRF.
- If patients are eligible for inclusion, they will be asked to sign another informed consent form. Included patients in will be centrally randomized for TRT/placebo.

After randomization:

The researcher/research nurse will prepare the study medication according to randomization outcome and the guideline provided. A second person will check if the right medication is prepared. Patients will be given written and spoken instructions about the application of TRT/placebo.

Except for the administration of TRT or placebo, patients will not undergo any other invasive procedures for study purposes.

Participation in this study could potentially be a contra-indication for inclusion in other study (such as studies evaluating oncological or functional follow-up after RP).

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Withdrawal criteria for study drug:

- Detectable PSA at any time point during follow-up
- No compliance with therapy
- Clinical sign of local recurrence or metastatic disease
- Any AE that leads to substantial changes in risk-benefit consideration
- Delay of drug administration of more than 28 days.
- Death
- New medical condition that does not allow continuation of study drug compliance
- Protocol deviation, including non-compliance with dosing regimen and retroactive failure to fulfill study entry criteria
- Lost to follow-up (defined as no contact after 3 documented attempts by telephone followed by 1 attempt via certified letter)
- Subject request
- Investigator request

8.5 Replacement of individual subjects after withdrawal

Patients that withdraw will not be replaced with new patients. Patients will not change groups after original assignment.

8.6 Follow-up of subjects withdrawn from treatment

Patients that withdraw from treatment will be followed as usual.

8.7 Premature termination of the study

After inclusion of 70 patients an interim analysis will be done to evaluate the safety of TRT. If a significant higher BCR rate in the TRT group is found, the study will be terminated. If a significant higher rate of cardiovascular events in the TRT group is found the study will be terminated.
The final decision is with the sponsor.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

Information on all AEs should be recorded at each contact on the AE-module of the CRF. Grading will be done according to the NCI-CTCAE version 5.0. AEs will be graded mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5). All AEs will be documented at every visit.

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Patients will be asked about the occurrence of AEs during every doctor visit. In case of an AE, dependent on the symptoms of the patient, he will be contacted by the investigator and if necessary, admitted to the hospital. The condition of the patient will be evaluated by the physician.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.
The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death

or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorized medicinal product;
   - Investigator's Brochure for an unauthorized medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB)

A DSMB will be established prior to start of the trial. Prior to the start of the trial the DSMB will define criteria to terminate the trial prematurely.
An interim analysis will be performed after the inclusion of 70 patients. The interim analysis will be done by a safety and monitoring board (DSMB) for safety and relevance.
The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

The collected data will include nominal, categorical, ordinal and continuous variables. Continuous measures will be summarized using their means and standard deviations; ordinal data will be presented with the median and range; categorical data by portions (percentages).

10.1 Primary study parameter(s)

The primary outcome parameter is sexual functioning score at 12 months after RP.
At prescreening (T0) we will collect questionnaire-based information on sexual functioning (PROMS). A baseline analysis will be done to identify equal distribution of patients between groups. Baseline parameters such as age, BMI, Charlson Comorbidity Index, marital status, initial PSA, ISUP score, clinical t-stage and EAU risk group will be evaluated with a student's t-test (for continuous variables) or chi-square test (categorical variables) for equal distribution among groups.
For the analyses, we will conduct a linear regression analysis in which we use sexual functioning at T12 as outcome variable. Sexual functioning at baseline (T0) will be included as a determinant in order to decrease the effect of intraindividual variability and increase power. The effect of testosterone replacement therapy will be estimated by the coefficient (along with its 95% confidence interval) of the dichotomous variable indicating intervention versus control group. Any important prognostic characteristic for sexual functioning that will appear not to be equally distributed in both treatment groups after randomization will also be included in the model.

10.2 Secondary study parameter(s)

The same procedure as described in paragraph 10.1 will be performed for the secondary study outcomes.
Five years following RP, a final oncological analysis will be done to assess the biochemical recurrence rate (BCR) in the TRT and placebo group. This will be done by using the data from the Dutch Cancer Registry (Nederlandse Kanker Registratie, NKR). From this registry we will conduct the PSA level and in case of BCR, the date of BCR. To assess the rate of BCR, a Kaplan-Meier analysis with log-rank test will be done. Secondly a Cox regression analysis will be done to assess if multiple variables influence the BCR rate.

10.3 Other study parameters

To gain insight in the prevalence of testosterone deficiency and on the effect of RP on the T level we will compare the T level of all patients in all groups before the RP and within 6 weeks following RP.

10.4 Interim analysis

After inclusion of 70 patients an interim analysis will be done to evaluate the safety of TRT. If a significant higher BCR rate in the TRT group is found, the study will be terminated. If a significant higher rate of cardiovascular events in the TRT group is found the study will be terminated.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 8, 19 October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO), the personal data protection act (Wet Bescherming Persoonsgegevens), and the Medical Treatment Agreement Act (WGBO).

11.2 Recruitment and consent

Patients will be approached for study participation by their treating urologist. Eligible patients will be informed about the study by an investigator. After being informed, patients will be given at least one week to consider their participation. All subjects must sign and personally date an approved informed consent form after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the study agent. This will be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for GCP, and requirements of Title 21 CFR 50.20 through 50.27.

The subject must be made aware and agree that personal information may be scrutinized during audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The number of visits and blood drawings are equal to standard of care follow-up after RP, with the exception of one extra blood sample at inclusion and six weeks after RP. We ask patients to remain with the study hospital for 24 months after RP for follow-up and to complete online questionnaires for the given visits.
The patients who receive TRT can experience local and systemic side-effects. Local side-effects can express themselves as itching, rash and/or irritation at the site of application. Systemic side-effects are gain of weight, hot flashes, acne and a change in red blood count level.
TRT might improve sexual functioning, urinary continence, hormonal functioning, quality of life and BCR-free survival, but this is not certain and is subject of research in this study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Patients will not be compensated for participating in this study. Damage to subjects through injury or death, caused by the study or negligence of local study investigators, is not accountable to the principle investigator. The participating centers will provide appropriate insurance which is in accordance with the legal requirements.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be collected using an electronic Case Report Form (eCRF).
Research nurses and local investigators in each of the participating centers will do data monitoring. Participants will be given a computer-generated numeric code. Data handling will be done anonymously, with the patient code only available to the local investigator and the research nurse working in the local center. A validated data management system will be used for storing all data.

12.2 Monitoring and Quality Assurance

We classify this trial as a low risk study 'laag-risico onderzoek', with a negligible risk 'verwaarloosbaar risico' in terms of the risk classification table provided, because the intervention is already registered. Monitoring of the trial will be done by the Research Support Office of the main study site.

The first monitor visit will take place before inclusion of the first study participant. During this visit the presence and completeness of the relevant Study Files will be checked. Additionally, the quality and competence will be evaluated of the personnel that will perform the informed consent and who will administer the research medication. After inclusion of 10 participants at the participating site, the site will be monitored with a check of the completeness of 3 informed consent forms and the accuracy of the eligibility criteria. If there are errors in this, more intensive monitoring will take place.
Thereafter, monitoring will be performed centrally by checking the completeness of follow-up data from participants with the mobile application. At the closing visit, the presence and completeness of the relevant Study Files will be checked.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of

subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The results will be prepared for publication in a peer-reviewed journal.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

See 13.2

13.2 Synthesis

Considering that TRT is a well-established treatment for men with late-onset hypogonadism, we deem a structured risk-analysis is not necessary.

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