
Short title: MR PROPER-study (Magnetic Resonance Imaging of the PROstate with Prior individual Risk Assessment).

Dutch title: Risicostratificatie en een MRI-gedreven zorgpad voor het diagnosticeren van prostaatkanker: een impactanalyse.

Dutch title used in the patient information form: Een evaluatiestudie om te bepalen welk effect het gebruik van de risicowijzer op prostaatkanker en het maken van een MRI heeft op het vaststellen van prostaatkanker.

Research Protocol
Version 1.0
1st June 2017
**PROTOCOL TITLE**  'Risk assessment and MR imaging in prostate cancer diagnosis: an impact analysis'

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## PROTOCOL SIGNATURE SHEET

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# TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE .......................... 8
2. OBJECTIVES ........................................... 12
   2.1 Primary objective: .................................. 12
   2.2 Secondary objective: ................................. 12
3. STUDY DESIGN ......................................... 13
4. STUDY POPULATION .................................... 15
   4.1 Population (base) .................................... 15
   4.2 Inclusion criteria .................................. 15
   4.3 Exclusion criteria .................................. 15
   4.4 Sample size calculation ............................. 16
5. METHODS .................................................. 17
   5.1 Study parameters/endpoints ......................... 17
      5.1.1 Main study parameter/endpoint ............... 17
      5.1.2 Secondary study parameters/endpoints ...... 17
   5.2 Randomisation, blinding and treatment allocation 17
   5.3 Study procedures .................................. 17
   5.4 Withdrawal of individual subjects ................. 19
      5.4.1 Specific criteria for withdrawal ............. 19
   5.5 Replacement of individual subjects after withdrawal 20
   5.6 Follow-up of subjects after withdrawal .......... 20
   5.7 Premature termination of the study ............... 20
6. SAFETY REPORTING .................................... 21
   6.1 Temporary halt for reasons of subject safety .... 21
   6.2 AEs and SAEs ....................................... 21
      6.2.1 Adverse events (AEs) ......................... 21
      6.2.2 Serious adverse events (SAEs) .......... 21
   6.3 Follow-up of adverse events ....................... 22
7. STATISTICAL ANALYSIS ................................. 23
8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

8.2 Recruitment and consent

8.3 Compensation for injury

8.4 Incentives

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

9.2 Monitoring and Quality assurance

9.3 Amendments

9.4 Annual progress report

9.5 Temporary halt and (prematurely) end of study report

9.6 Public disclosure and publication policy

10. REFERENCES
LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
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<td>EPIC</td>
<td>Expanded Prostate cancer Index Composite</td>
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<td>ERSPC</td>
<td>European Randomised study of Screening for Prostate Cancer</td>
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<td>GS</td>
<td>Gleason score</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>IIEF</td>
<td>International Index of Erectile Function</td>
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<td>IPSS</td>
<td>International Prostate Symptom Score</td>
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<td>METC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>PCA</td>
<td>Prostate cancer</td>
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<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<td>QALY</td>
<td>Quality-adjusted life year</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>RC</td>
<td>Risk Calculation</td>
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<td>(S)AE</td>
<td>(Serious) Adverse Event</td>
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<td>Sponsor</td>
<td>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation 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 subsidising party.</td>
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<td>STAI</td>
<td>State Trait Anxiety Inventory</td>
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<td>STARD</td>
<td>STAndards for the Reporting of Diagnostic accuracy studies</td>
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<td>TBx</td>
<td>Targeted prostate biopsy</td>
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<td>TRUS</td>
<td>Transrectal ultrasound</td>
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<td>TRUS-Bx</td>
<td>Transrectal ultrasound guided systematic prostate biopsy</td>
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<td>WMO</td>
<td>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</td>
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SUMMARY

PURPOSE / RESEARCH QUESTION: To evaluate the diagnostic performance and cost-effectiveness of the MRI-driven diagnostic pathway of prostate cancer, with upfront individual multivariate risk stratification.

HYPOTHESIS: The combination of upfront risk stratification for prostate cancer and the MRI-driven diagnostic pathway (intervention) provides a greater diagnostic (and cost-) effectiveness as compared to the current standard care of the TRUS-guided prostate biopsies (control).

STUDY DESIGN: Multicenter, non-randomized, prospective, clinical efficacy study. The individual risk of prostate cancer will be calculated with the Prostaatwijzer (current diagnostic pathway). Low-risk men will undergo yearly clinical follow-up (no direct biopsy intervention; is standard care), high-risk men will undergo prostate biopsies (initially TRUS-driven or MRI-driven; existing clinical algorithms). Furthermore, during the diagnostic process, the quality of life will be measured.

STUDY POPULATION: Men (> 50 years, with no history of prostate cancer or biopsies) with suspicion of prostate cancer (elevated PSA and/or abnormal DRE) will be included.

INTERVENTION: In intermediate/high-risk men the MRI-driven diagnostic pathway will follow. This pathway is either 1) a TRUS-'first' diagnostic approach or 2) a MRI-'first' diagnostic approach depending on the clinical practice in the participating medical centers.

USUAL CARE / COMPARISON: In intermediate / high-risk men the standard care comprises the TRUS-guided biopsies (without MRI) will follow, according to the Dutch and European guidelines 2016.

OUTCOME MEASURES: 1) the detection of high-grade prostate cancers, 2) the number of prostate biopsy procedures, in relation to 1), 3) reduced detection of low-grade prostate cancers, 4) quality of life, and 5) cost-effectiveness.

SAMPLE SIZE CALCULATION / DATA ANALYSIS: To detect an increase from 25% Gleason sum Score =7 detected prostate cancers by TRUS-'only' driven diagnostic pathway (control arm), to 32% by the MRI-driven diagnostic pathway (intervention arm), with 80% power at a significance level of 0.05, we would require 648 patients in each arm, in total 1944 intermediate/high-risk patients.

COST-EFFECTIVENESS ANALYSIS / BUDGET IMPACT ANALYSIS: The economic evaluation (health care and social perspective) will evaluate short term costs and effectiveness based on observed outcomes measured in this study. Long term outcomes will be calculated with a semi-Markov model (MISCAN).

TIME SCHEDULE: Inclusion (M1-24); follow-up (M3-36), analysis and reporting (M25-36) (=36M).
1. INTRODUCTION AND RATIONALE

Screening for prostate cancer (PCa) remains one of the most controversial issues in urological practice. Although robust data from the European Randomised study of Screening for Prostate Cancer (ERSPC) suggest a disease specific survival benefit in favor of prostate-specific antigen (PSA)-based PCa screening, the coinciding unfavorable harm-benefit precludes that PCa screening can be adopted as a public health policy [1, 2]. The diagnostic pathway needs to be optimized to reduce unnecessary testing and to avoid diagnosing those cancers that will never harm a patient if not detected through screening. Some men may thus benefit from PCa screening, but with the currently used diagnostics (i.e. the PSA test and systematic TRUS-guided prostate biopsy) many more men are harmed by unnecessary testing and the cascade of diagnostic and treatment related events that follow. Men themselves, the healthcare system, and society-at-large bear the financial costs of this screening cascade. Over- and underdiagnosis, as well as over- and undertreatment are difficult manageable problems in PCa diagnostics, for patient, urologist, hospital, and health insurance. Further refinements to screening strategies, focusing on detecting only those PCa that are potentially life threatening (clinically significant) are needed to become acceptable to the general population and health care providers (Figure 1). We propose such a refinement within this protocol, with upfront individual risk prediction and in addition a MRI-driven diagnostic pathway in only those men that are considered to be at intermediate/high-risk of having a potentially life threatening PCa (in general defined as Gleason sum Score (GS) = 7).

Clinically significant prostate cancer
In contrast to clinically insignificant prostate cancer, men with clinically significant prostate cancer may die from the disease through metastasis. Insignificant prostate cancer will not metastasise, and will never become symptomatic throughout life. The difference between significant and insignificant prostate cancer is in general based on histopathological criteria from transrectal ultrasound (TRUS)-guided biopsies [3, 4]. It is of utmost importance to detect and treat significant prostate cancer and to avoid overtreatment of insignificant prostate cancers.

Current diagnostic pathway: PSA test, risk calculator and TRUS-biopsy
The current diagnostic work-up, as recommended by the Dutch Guidelines (2014) and European Association of Urology Guidelines on Prostate Cancer (2016) consists of the following [5, 6]:

1) History, physical exam/DRE (clinical staging), PSA blood analysis, and risk prediction using e.g. the “Prostaatwijzer” (www.prostaatwijzer.nl). Risk calculators (or nomograms) for the
prediction of a positive prostate biopsy have been developed to support physicians in clinical decision-making with respect to the individual patient and reduce the number of unnecessary biopsies. Risk calculators improve the diagnostic value of PSA by increasing its sensitivity and specificity by adding other potential predictive risk factors to the decisional process and as such provide an individual risk estimation of having a biopsy-detectable PCa [7]. Risk prediction using the Prostaatwijzer can avoid 33% of unnecessary TRUS-Bx at initial biopsy, without missing significant PCa, as previously shown in our ZonMW project 2008 – 2011 [8]. Validation of the Prostaatwijzer in a Dutch patient population (2016) demonstrated that unnecessary TRUS-Bx could safely be avoided in 24% [9].

2) Transrectal ultrasound (TRUS)-guided biopsy procedure (TRUS-Bx). TRUS-Bx, using 18G needle and a periprostatic block is the standard of care in western world in which the peripheral zone of the prostate is randomly sampled, generally by 10 to 12 systematic TRUS-Bx cores, depending on the size of the prostate. A TRUS is performed primarily for anatomic guidance, as suspicious lesions for PCa in general cannot be visualized by ultrasound. This approach may therefore result in random and systematic errors, which leads to sampling insignificant lesions while missing significant lesions [10]. The estimated false negative rate of TRUS-Bx is 30-45% [11]. Also misclassification occurs by not sampling the cancer lesion at its greatest diameter or highest grade, as reclassification is seen in almost half of men when a more accurate biopsy test is applied [12-15]. In addition, TRUS-Bx is associated with the risk of infection (1-8%) and an increasing risk of life-threatening sepsis (1-4%), as a consequence of increasing antibiotic resistance [16]. Other morbidities include dysuria, haematospermia, haematuria, rectal bleeding, vasovagal episodes and urinary retention [16, 17]. The performance of the current diagnostic work-up is therefore not optimal. Uncertainty about test results, layered testing, delayed or inaccurate diagnoses and under-/overtreatment, all have a negative effect on patient well-being. In addition, inefficient patient care is costly, in terms of health care related expenses as well as productivity losses.

**Potential diagnostic pathway: MRI and MRI-guided targeted biopsy**

The multi-parametric MRI approach that combines anatomic T2-weighted imaging with functional data appears to be one of the most promising techniques for prostate cancer detection [18-21]. Pooled data from a meta-analysis showed high specificity of 0.88 (0.82–0.92) with variable but high sensitivities of 0.74 (0.66–0.81) and negative predictive values ranging from 0.65 to 0.94 [22]. These results imply a strong role for MRI before biopsy in detecting prostate cancer. Several MRI guided targeted biopsy (TBx) methods have been discussed to diagnose prostate cancer [23, 24]. We have shown in a meta-analysis the extra yield in terms of significant prostate cancer detection and reduction of insignificant prostate cancer by the MRI-
targeted biopsy approach [25]. MRI-targeted biopsy compared to TRUS biopsy improved the
detection of significant prostate cancer in men with a previous negative biopsy by a factor of
1.56. Thus, using MRI and MRI targeted biopsy instead of TRUS biopsy would theoretically lead
to a) fewer men biopsied overall, b) a greater proportion of men with clinically significant
prostate cancer biopsied, and c) fewer men attributed a diagnosis of clinically insignificant
prostate cancer. However, with a sensitivity of 0.87 (0.71-0.95), still 13% significant cancers
were missed. Therefore, MRI and MRI targeted biopsy is still advocated in addition to TRUS
biopsy.

Relevance and importance of this project for healthcare and society
The diagnostic accuracy of TRUS-Bx after upfront risk prediction in detecting high-grade PCa's
in Dutch men with initial TRUS-Bx is expected to be 23%-26% [8, 9]. A retrospective analysis
(2016) of upfront risk prediction in men with previous negative TRUS-Bx and subsequent MRI
showed similar results, safely avoiding one third of unnecessary TRUS-Bx [26]. However, no
data is available yet about the MRI-driven strategy following multivariate risk prediction in men
with no history of prostate cancer or (negative) prostate biopsies. In this project the MRI
diagnostic pathway using MR imaging of the prostate and if indicated additional MRI-guided
targeted biopsy after upfront individual risk prediction using the Prostaatwijzer will be evaluated
in biopsy naïve men within existing clinical algorithms (Figure 2) labelled as the MRI-‘first’ or the
TRUS-‘first’ diagnostic pathway. The MRI-driven strategy is expected to result in efficiency gain
of the diagnostic approach of prostate cancer detection. The gain is anticipated to be primarily in
1) improved detection of high-risk PCa, 2) more secure of final diagnosis of low-risk or no PCa,
due to reduction of misclassification, and 3) less biopsies and less significant diagnosis in
further follow-up, resulting in an improvement of quality of life of eligible men and a decrease of
health economic costs.

In 2011 the total costs of prostate cancer care was 254 million [27]. This corresponds to 0.3% of
the total Dutch healthcare costs, and to 5.3% of costs incurred for all malignancies. The
incidence of PCa was 10.977 men and the 10-year prevalence was 74.474 men in the
Netherlands in 2013 [28]. Number of new cases of PCa will continue to increase by 49% in
2030. The importance of an effective diagnostic algorithm in PCa is therefore high. This study
will demonstrate the impact of a risk-based MRI-driven diagnostic pathway, a procedure that will
increase in the coming years due to ageing of the population. Implementation into clinical
practice will achieve a more evidence-based and stringent application of diagnostic
interventions.
Figure 1: Flowchart of three diagnostic pathways on prostate cancer detection. 1) Current standard practice, with TRUS-guided biopsy (TRUS pathway); 2) practice of MRI with MRI-guided targeted biopsy and TRUS guided biopsy (MRI-TRUS pathway) if available in hospital; 3) proposed practice of the combination of risk stratification (using Prostaatwijzer) and MRI-TRUS pathway. We hypothesize that additional MRI and biopsies can be avoided in men with a low risk of significant prostate cancer following risk stratification (middle right column). Furthermore, the diagnostic effectiveness of the combined test in men with intermediate/high risk of significant prostate cancer may increase.

RC, risk calculation; PCa, prostate cancer; TRUS-Bx, transrectal ultrasound-guided biopsies; MRI-TBx, magnetic resonance imaging-guided targeted biopsies, Bx, biopsies; +DRE, positive digital rectal examination; PSA, prostate specific antigen; (-) no PCa; (±) insignificant PCa; (+) significant PCa.
2. OBJECTIVES

2.1 Primary objective:
Evaluation of the diagnostic performance of the diagnostic MRI-driven pathway in diagnosing high-grade prostate cancer in comparison to standard care of the TRUS-driven diagnostic pathway of prostate cancer, both following upfront risk stratification, in biopsy naïve men.

2.2 Secondary objective:
Does MRI-driven diagnostic pathway in combination with upfront risk stratification by Prostaatwijzer result in:
- reduction of the number of biopsies,
- reduction of MRI scans,
- decreased detection of insignificant prostate cancer,
- decreased misclassification and adverse events,
- improvement of the quality of life of prostate cancer patients,
- reduction of diagnostic health care costs,
when compared to the current/classical diagnostic TRUS-driven pathway in biopsy naïve men with a suspicion for prostate cancer?
3. STUDY DESIGN

The design of this observational study is a multicenter, non-randomized, clinical efficacy study. High volume peripheral hospitals are participating in this project, together with the Dutch Cancer Institute and two Prostate Centers (with two academic medical centers involved). Each center has proven experience in prostate MRI (>250) and MRI targeted biopsy (>100). Within this study design we do not attempt to randomise patients to each arm. Participating medical centers will include men in the arm that reflects their current clinical practice. The flowchart of the study design is shown in Figure 2. The study has been designed to ensure compliance with STARD (STAndards for the Reporting of Diagnostic accuracy studies) reporting and to ensure avoidance or minimisation of a number of biases that are inherent in the current literature [29].

Following enrolment in the study and signing informed consent, individual risk prediction (= standard care according to the guidelines) will be performed with the Prostaatwijzer-3 (± DRE and/or TRUS) in men with no prior biopsies. The cut-off for stratifying men into intermediate/high-risk prostate cancer will be a) = 20% for any prostate cancer or b) > 12.5% risk for any cancer in combination with a > 3% risk for high-grade prostate cancer. Low-risk men will undergo yearly clinical follow-up (no direct biopsy intervention; is standard care), intermediate/high-risk men will undergo prostate biopsies (initially TRUS-driven or MRI-driven; existing clinical algorithms).

The usual standard care comprises the TRUS-‘only’ diagnostic pathway (without MRI), according to the Dutch (2014) and European (2016) guidelines. This dataset will be created from participating medical centers that strictly follow the guidelines, not incorporating MRI at primary diagnosis.

We propose a Dutch multicenter efficiency study of the MRI-driven diagnostic pathway of prostate cancer, with upfront individual multivariate risk stratification. This study is unique at the present time. We hypothesize that upfront risk stratification with the combined use of MRI may:
- select more accurately the population to be tested,
- increase the diagnostic performance of the MRI-‘first’ and TRUS-‘first’ pathway in significant prostate cancer detection,
- reduce the number of the unwanted detection of insignificant prostate cancer,
- reduce the number of MRI scans,
- reduce the number of unnecessary TRUS biopsies,
- decrease diagnostic health care costs.
The departments of Urology and Radiology in the participating centers are responsible for patient inclusion, risk calculation (RC), TRUS biopsy, and MRI/MRI targeted biopsy in this diagnostic and cost-effectiveness study. The departments of Public Health and Epidemiology of Erasmus Medical Center will provide guidance in the diagnostic and cost-effectiveness analyses. The results of this project should lead to a clinical protocol or algorithm, as shown in Figure 1.

Figure 2: Flowchart of study design of multicenter prospective cohort study. Outcome will be analysed based on significant (+), insignificant (±) and no (-) prostate cancer in the low risk and intermediate/high risk group, based on risk stratification (using Prostaatwijzer).
4. STUDY POPULATION

4.1 Population (base)

The departments of Urology and Radiology in the participating centers are responsible for patient inclusion. Men are eligible for the study if there is a clinical suspicion that they may be harbouring prostate cancer without previous prostate biopsies. This essentially includes men with an elevated PSA (≥ 3 ng/ml) and/or a suspicious digital rectal examination, or family history of prostate cancer. These men are referred to a urology department for further diagnostic work-up. All men should have the ability to undergo protocolled diagnostic procedures, and must have signed the informed consent. Based on clinical parameters, all eligible men will be stratified with the Prostaatwijzer, into low-risk or intermediate/high-risk prostate cancer (= standard care according to the guidelines).

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- men ≥ 50 years,
- no prior prostate biopsies,
- suspected of having prostate cancer based on regular PSA blood test (≥ 3 ng/ml) and/or digital rectal examination and/or family history of prostate cancer,
- fit to undergo all protocol procedures,
- signed informed consent.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- previously detected or treated prostate cancer,
- previous (negative) prostate biopsies,
- contra-indications to MRI (e.g. claustrophobia, pacemaker, eGFR ≤ 30, known or expected allergy to contrast media) or TRUS biopsy procedures,
- previous history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work,
- any other medical condition precluding procedures described in the protocol.
4.4 Sample size calculation

The null hypothesis is that the MRI-driven pathway following the Prostaatwijzer is not related to clinically significant prostate cancer detection. Based on pooled data the additional diagnosed high-grade prostate cancers by the MRI-driven strategy is expected to be 7% (range 2-13%) [25, 30]. This rate will be the probabilistic estimate for the studied population. So to detect an increase from 25% of Gleason score = 7 prostate cancers by the TRUS-‘only’ pathway (control arm), to 32% by the MRI-driven pathway (intervention arm), with 80% power at a significance level of 0.05 (2-sided), we would require 648 patient in each arm, in total 1944 patients are required. This analysis will recruit at least 2558 patients to account for low-risk (24%) and losses (10%). The total enrolment period will be 24 months.
5. METHODS

5.1 Study parameters/endpoints
The outcomes in this study are of fundamental importance to decisions regarding the future use of risk stratification prior to any intervention in order to reduce the use of MRI and the number of biopsy sessions in the diagnostic pathway for significant prostate cancer. For the outcomes the following criteria will be used to set the target definition of clinically significant prostate cancer on MRI-guided targeted and TRUS-guided biopsies: at least one core with a Gleason score (GS) of ‘7’ (3+4) or ‘6’ with a maximum cancer core length ≥6 mm [4, 31].

5.1.1 Main study parameter/endpoint
Proportion of study population with clinically significant prostate cancer, correctly identified by the “Prostaatwijzer-MRI-driven” pathway.

5.1.2 Secondary study parameters/endpoints
- Number of prostate biopsy procedures in relation to the detection of clinically significant prostate cancer.
- Proportion of study population with clinically insignificant or no prostate cancer, correctly identified by the “Prostaatwijzer-MRI-driven” pathway.
- Proportion of MRI scans that could have been avoided.
- Proportion of (TRUS-guided) biopsies that could have been avoided.
- Quality of life of the patients.
- Diagnostic health care costs(-effectiveness) of the “Prostaatwijzer-MRI-driven” pathway.

5.2 Randomisation, blinding and treatment allocation
Participants will not be randomized: participants will follow the arm (TRUS-‘only’, TRUS-‘first’ or MRI-‘first’) that reflects the current clinical practice of their medical center. The participants and the investigators performing the biopsy procedures will not be blinded for the results of the prostate MRI.

5.3 Study procedures
Men having PSA levels above >3 ng/ml and/or positive digital rectal examination (DRE), will be eligible for the study. Following enrolment in the study and signing informed consent at
the outpatient clinics, data registration will start and men will be stratified (= standard care) into category of low-risk or intermediate/high-risk of having (significant) prostate cancer (see Figure 2). Low-risk men will undergo yearly clinical follow-up with PSA measurement and DRE (no direct biopsy intervention; is standard care), intermediate/high-risk men will undergo prostate biopsies (initially TRUS-driven or MRI-driven; existing clinical algorithms).

Depending on the standard care/current clinical practice in the recruiting hospital, intermediate/high-risk men will undergo a, 1) TRUS-'first' diagnostic pathway (intervention arm 1), 2) MRI-'first' diagnostic pathway (intervention arm 2) or 3) TRUS-'only' diagnostic pathway without MRI (control). The TRUS-'first' diagnostic pathway will start with TRUS-guided biopsies, and subsequently additional MRI and MRI targeted biopsies will be performed when indicated. MRI-'first' diagnostic pathway will start with MRI, and subsequently additional MRI targeted biopsies and/or TRUS-guided biopsies will be performed when indicated. The TRUS-'only' diagnostic pathway will follow the current standard of care for prostate cancer detection according to the Dutch and European guidelines, using only TRUS-guided biopsies without prostate MRI. Preferably, within 6-12 weeks these diagnostic procedures should be performed.

TRUS-guided biopsy, using 18G needle and (optional) periprostatic block is the standard of care. The biopsy scheme for the primary TRUS-guided biopsy consists of sextant lateral biopsies with a minimum of two additional medial cores in all referring centres, based on prostate volume, and a maximum of 12 biopsies.

The MRI protocol is according to the Guidelines by the European Society of Urogenital Radiology and American Society of Radiology [32]. The MRI protocol consists of T2-weighted imaging, and diffusion weighted imaging with apparent diffusion coefficient reconstructions. Additional dynamic contrast enhanced imaging is optional, based on the preferred hospital protocol. MRI scans are performed on 1.5T or 3-T systems (different vendors: Philips Healthcare, Siemens Healthcare, General Electric Healthcare) using different pelvic phased-array coils. The images are analysed by an expert radiologist (>250). Individual lesions, as well as the whole prostate, are scored with the version 2 of the Prostate Imaging Reporting and Data System (PI-RADS) 5-point likelihood scale for significant PCa. Individual lesions with a PI-RADS score =3 are classified as suspicious. All suspicious lesions are biopsied with an MRI targeted approach. This can be 1) in-bore MRI 2) with MRI-TRUS fusion software (different vendors), or 3) with cognitive (MRI-TRUS) fusion approach [33]. The number of targeted biopsies is at the discretion of the physician performing the biopsies, however, the minimum of 2 and maximum of 4 should be performed. An expert physician
(>100) should perform the targeted biopsy procedure, or supervise inexperienced physicians.

Health-related quality of life (QoL) will be assessed through the use of validated measures. Generic, prostate-specific function and anxiety will be assessed using the EQ-5D, the Expanded Prostate cancer Index Composite (EPIC), the International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), the State Trait Anxiety Inventory (STAI) and the Hospital Anxiety and Depression Scale (HADS). These measures have been chosen, because not all participants will be diagnosed with prostate cancer. Therefore we have chosen, next to the generic EQ-5D, STAI-6 and HADS measures, a majority of prostate-specific measures instead of prostate cancer-specific measures. With respect to timing: for the intermediate/high-risk control arm QoL will be measured directly following TRUS-guided biopsies, and at 6 and 12 months after outcome. In the intervention arm (1) QoL will be measured following TRUS-guided biopsies, following MRI and MRI-targeted biopsies, and at 6 and 12 months after outcome. In intervention arm (2) generic QoL and anxiety will be assessed following the MRI. The prostate-specific function and anxiety will be assessed following the MRI-targeted biopsies and TRUS-guided biopsies, as well as 6 and 12 months after outcome.

To make it possible to use the data and/or residual materials and MRI images from the study subjects for future prostate cancer research, subjects will be asked in the informed consent form whether they agree with the use of their data and/or residual material and MRI images for this purpose.

5.4 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.

5.4.1 Specific criteria for withdrawal

Subjects who are not eligible for MRI (i.e. contra-indications, claustrophobia, obesity) or biopsy procedures and T4 tumors will be withdrawn from the study.
5.5 Replacement of individual subjects after withdrawal
Individual subjects withdrawn from the study will be replaced till two years after their enrolment.

5.6 Follow-up of subjects after withdrawal
All patients in the study will be followed after their inclusion (for a time period of four years). Only patients who have withdrawn consent will be assessed immediately and their records will be closed.

5.7 Premature termination of the study
As this study is part of routine work-up in prostate cancer diagnosis it would be unrealistic to prematurely terminate the study.
6. SAFETY REPORTING

6.1 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 jeopardise 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.

6.2 AEs and SAEs

6.2.1 Adverse events (AEs)
Adverse events are complications as part of the intervention or control diagnostic pathway. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. These events will be reported following each procedure, either TRUS-guided or MRI-targeted biopsy diagnostic approach. Adverse events are hematospermia, rectal bleeding, dysuria, vasovagal episodes, hematuria, urinary retention, prostatitis and sepsis.

6.2.2 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;
- that required medical or surgical intervention.

Any other important medical event that did not result in any of the outcomes listed above due to medical intervention but could have been based upon appropriate medical judgment. An elective hospital admission will not be considered as a serious adverse event.

Serious adverse events will be immediately after coming to notice of the investigator reported to the trial coordinator.
The investigator will report the following SAE occurring in the study period to the sponsor without undue delay of obtaining knowledge of the events: death from sepsis after prostate biopsy.

6.3 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 another medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.
7. STATISTICAL ANALYSIS

Risk stratification will discriminate the study population into two groups, low risk (<12.5%) and intermediate or high risk (>12.5%). We will compare the diagnostic performance and cost-effectiveness of the MRI-driven diagnostic pathway of prostate cancer after upfront individual multivariate risk stratification with the current standard care of the TRUS-guided prostate biopsies (control group). For the diagnostic performances we will calculate the change in sensitivity, specificity, PPV and NPV. Data will be presented using continuous or dichotomous variables, as appropriate. Univariate data will be presented as means with standard deviation or median with interquartile ranges, as appropriate. Differences in the main outcomes will be assessed using the student-t test, chi-square test or Mann-Whitney test according to the distribution of the data.

Furthermore we will perform a cost-utility and cost-effectiveness analysis in accordance with the Dutch guidelines for economic evaluations. For the cost-utility analysis the quality-adjusted life years (QALY) is the outcome measure. For the cost-effectiveness analysis the primary effect measure will be the number of prostate biopsy procedures, in combination with the detection of 1) low-grade or no prostate cancers, and 2) high-grade prostate cancers. The diagnostic healthcare costs will be calculated from diagnostic resources used and the associated costs per resource [34, 35]. If both diagnostic performance improves and costs decrease, simulation of long-term outcomes is unnecessary. If a trade-off needs to be made between effectiveness and costs, a decision model simulating long-term outcomes will be developed analysing costs and QALYs from both the healthcare (participating hospitals) and societal perspectives, using standard recommendations for such analyses [36]. With the decision and Markov/MISCAN models we will calculate the effectiveness in QALYs, the costs, the cost-effectiveness ratios (Euros/QALY), the net health benefit, and the net monetary benefit for a number of societal willingness-to-pay thresholds.
8. ETHICAL CONSIDERATIONS

8.1 Regulation statement
The investigators will ensure that this study is conducted in agreement with the Declaration of Helsinki (version of October 2013, www.wma.net) and all relevant national guidelines and regulations, whichever provides the greatest protection of the patient. The study protocol will be submitted first to the METC Erasmus MC and subsequently to the METCs or board of directors of all participating hospitals.

8.2 Recruitment and consent
Patients who meet the inclusion criteria and none of the exclusion criteria will be informed orally about this study by their treating urologist during a (first) regular visit. A patient information and consent form will be handed over to the patient. When the patient is willing to participate, he will be asked to sign the consent form during a (second) regular visit and from that moment the (study) registration of all patient data obtained from the standard diagnostic pathway in the recruiting hospital will start.

8.3 Compensation for injury
The Erasmus MC has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.

8.4 Incentives
Participants will not receive a reimbursement for their participation in the study. The proposed diagnostic work-ups are part of the daily clinical practice at the participating hospitals. The focus of this study is the diagnostic and cost effectiveness of this diagnostic work-up.
9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents
Data will be handled confidentially. All data will be entered into a web-based database (OpenClinica), by local research personnel. Subject records are coded by a unique study number. The local investigators will keep a list showing codes and names. Stored anonymized data will include patient characteristics at baseline (eg. age, race, PSA levels, DREs and results of the Prostaatwijzer), biopsy and MRI results including storage of the MRI images, answers on QoL questionnaires and follow up data (eg. treatment types and results). Only the study coordinator will be able to extract data resulting from this study to perform analyses. Patients will not be identified by personal information in any publication following this study.

9.2 Monitoring and Quality assurance
Monitoring schedules will be kept as proposed in the NFU position paper “Kwaliteitsborging mensgebonden onderzoek 2.0” [37]. We propose that the trial will be placed in the category “kleine kans-matige schade” (“low likelihood, moderate damage”), i.e. low risk. Following the NFU guidelines, an independent monitor will perform 1 monitoring visit per center per year. The first 3 included patients in each center will be verified concerning their in- and exclusion criteria followed by 1-10% of all subjects. Informed consent and source data verification will also take place for 1-10% of all subjects. The monitored data will comprise: patient characteristics at baseline, biopsy and MRI results and follow up data. A screen for occurrence of study-related SAE, and 3-month assessment of primary outcome will also take place, as well as a verification of the presence of a study log and documentation. All other data will be monitored for completeness and consistency by the study coordinators.

9.3 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

9.4 Annual progress report
The sponsor/investigator will submit a summary of the progress of the study to the accredited METC and subsidising party (ZonMw) once a year. Information will be provided
on the date of inclusion of the first subject, numbers of subjects included, serious adverse events/serious adverse reactions, other problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report
The investigator/sponsor will notify the accredited METC and ZonMw of the end of the study within a period of 8 weeks. The study will end after approximately four years.

The investigator/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 investigator/sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. However, as this study is part of routine work-up in prostate cancer diagnosis we cannot think of any criteria for premature terminating the study.

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 ZonMw.

9.6 Public disclosure and publication policy
The study will be registered with ClinicalTrials.gov.

All relevant results from the study (at least the answers to the primary and secondary research questions) will be written down in one or more publications which will be submitted to peer reviewed journals. Appointments have been made for this between the Dept. of Urology and Dept. of Radiology. The manuscripts will be shared with the financial sponsor(s)/subsidising party one month before submission, but the financial sponsor(s) will have no influence on its contents.

Anonymous data can be requested from the principal investigator with a detailed description containing the aims and methods of the (prostate cancer) study for which the data are intended to be used. Data will be made available for this purpose at least 18 months after publication of the main report. Anonymous data may also be shared with non-commercial parties for scientific purposes, including individual patient meta-analyses, and with commercial parties (eg. for improvement of imaging techniques). Consent will be asked specifically for these purposes (future prostate cancer research).
10. REFERENCES


37. NFU Kwaliteitsborging mensgebonden onderzoek 2.0.