5. Work Program

5.1 Synopsis

Study Title:	Risk-adapted prostate cancer early detection study based on a “baseline” PSA value in young men – a prospective multicenter randomized trial
English Acronym:	PROBASE study
Indication:	Diagnosis of prostate cancer
Study Type:	Interventional
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Primary Endpoint:	• To demonstrate the superiority of a delayed risk-adapted PSA screening according to a baseline PSA value at age 50 (= study arm

	B) versus a risk-adapted PSA screening according to a baseline PSA value at age 45 (= study arm A) with respect to specificity of the screening and non-inferiority in terms of detection of metastatic prostate cancer (M+) up to the age of 60 (composite hypothesis).
Secondary Endpoints:	• To compare the incidence of late metastasis (M+) in both study arms after curative treatment (radical prostatectomy, radiotherapy) of detected prostate cancers up to the age of 60 • To compare the incidence of biochemical recurrences in both study arms after curative treatment (radical prostatectomy, radiotherapy) of detected prostate cancers up to the age of 60 • To compare the incidence of locally advanced prostate cancers (≥ clinical and/or pathological stage T3) detected in both study arms up to the age of 60 • To compare the incidence of high grade prostate cancers (≥Gleason Score 4+3=7) detected in both study arms up to the age of 60 • To compare the prostate cancer mortality rate in both study arms up to the age of 60 • To compare the overall survival in both study arms up to the age of 60
Exploratory Objectives:	• To evaluate the distribution of PSA values in a screening population of young men at age 45 and 50 • To evaluate the time-dependent course of

	a baseline PSA value in a screening population of young men at age 45 and 50 up to the age of 60 • To evaluate the prevalence of prostate cancer in a screening population of young men at age 45 and 50 at a PSA cut-off value of 3.0 ng/ml • To evaluate the positive predictive value of a PSA test in a screening population of young men at age 45 and 50 at a PSA cut-off value of 3.0 ng/ml • To prospectively identify groups at low risk of prostate cancer by their baseline PSA value • To compare quality of life in both screening arms • To evaluate predictive molecular markers for prostate cancer (urine, blood) • To evaluate the cost-benefit ratio of a risk-adapted PSA screening • To evaluate the efficacy of multiparametric MRI for prostate cancer early detection • To evaluate a standardized reporting and scoring scheme for multiparametric MRI examinations of the prostate • To compare targeted prostate biopsies with undirected random prostate biopsies
Study Design:	This is a prospective, multicenter randomized (1:1) open label study comparing a delayed risk-adapted PSA screening according to a baseline PSA value at age 50 (study arm B) versus a risk-adapted PSA screening according to a baseline PSA value at age 45 (study arm A) with the

	primary endpoint of detection of metastatic prostate cancer. Subjects randomized into study arm A undergo a risk-adapted PSA screening beginning at age 45. At enrolment subjects of study arm B will be asked for a blood sample and for family history but no PSA test will be carried out. As standard of care only a yearly digital rectal examination of the prostate up to the age of 50 (pre-screening period) will be offered to subjects of study arm B. In study arm B the risk-adapted PSA screening begins at age 50. Each study participant who meets or exceeds the PSA cut-off value of 3.0 ng/ml at baseline or in one of the following screening rounds will be submitted to a multiparametric MRI examination of the prostate with subsequent stereotactically guided prostate biopsy according to the MRI findings, and additional random biopsy of the prostate. The presence of metastatic prostate cancer is judged by imaging and verified by histological analysis (e.g. bone biopsy). Each study participant will be screened up to the age of 60, until prostate cancer is detected, death of study participant, or study participant refusal.
Study Population:	Approximately 50,000 men at age 45 will be enrolled from 4 study sites within 5 years and randomized (1:1) into study arm A or B.
Main inclusion criteria:	• Men at age 45 • Written informed consent
Main exclusion criteria:	• Known prostate cancer • Prior malignancy. Adequately treated basal cell or squamous cell skin cancer are allowed.

	• Occurrence of other malignancies during the study period that have the potential to metastasize to the bones (e.g. lung cancer)
	• Any serious illness with life expectancy less than 10 years
	• Acute prostatitis within the last 6 months prior to study entry
	• Any contra-indication to MRI
	  ○ Pacemaker or artificial heart valve not permitted for MRI (patient identification card)
	  ○ Cochlear implant
	  ○ Intracranial vessel clip
	  ○ Implanted medication pump
	  ○ Contrast agent allergy
	  ○ Claustrophobia
	  ○ Severe renal dysfunction (glomerular filtration rate <30 ml/min)
	  ○ Narrow-angle glaucoma
	  ○ Phaeochromocytoma
	• Concomitant therapy with drugs with influence on PSA levels
	  ○ 5 α-reductase inhibitor
	  ○ Luteinizing hormone releasing hormone
	  ○ Bicalutamide, nilutamide, flutamide
	  ○ Cyproterone acetate
	  ○ Systemic ketoconazole (or other azole drugs such as fluconazole and itraconazole)

Interventions:	• PSA test (risk-adapted screening intervals) • Multiparametric prostate MRI • Prostate biopsy

Duration of Screening:	Eligibility of subjects will be conducted prior to randomization. Screening starts at age 45 (study arm A) or at age 50 (study arm B). Subjects of both study arms will be screened by PSA testing in a risk-adapted manner up to the age of 60, until prostate cancer is diagnosed as defined in the protocol, death of study participant, or study participant refusal. After diagnosis of prostate cancer or study participant refusal the subjects discontinue the screening period and enter the follow-up period. In the follow-up period subjects with detected prostate cancer will be contacted once every 3 months up to the age of 60. Subjects curatively treated for prostate cancer will be followed by PSA (3-monthly) and imaging (CT scan and isotopic bone scan once per year). In addition to the evaluation for the primary and the secondary endpoints, consecutive treatments for prostate cancer (including active surveillance, surgery, radiotherapy, androgen deprivation therapy, and dose and treatment duration of other systemic therapies) will also be analyzed.
Risk-adapted Screening Intervals:	• PSA <1.5 ng/ml: 5 years • PSA 1.5 - 2.99 ng/ml: 2 years • PSA ≥3.0 ng/ml: MRI and prostate biopsy, if biopsy negative: next PSA test 1 year later
Efficacy Assessment:	The primary efficacy endpoint is incidence of metastatic prostate cancer. • Efficacy assessment for metastasis from prostate cancer (cM stage) will utilize

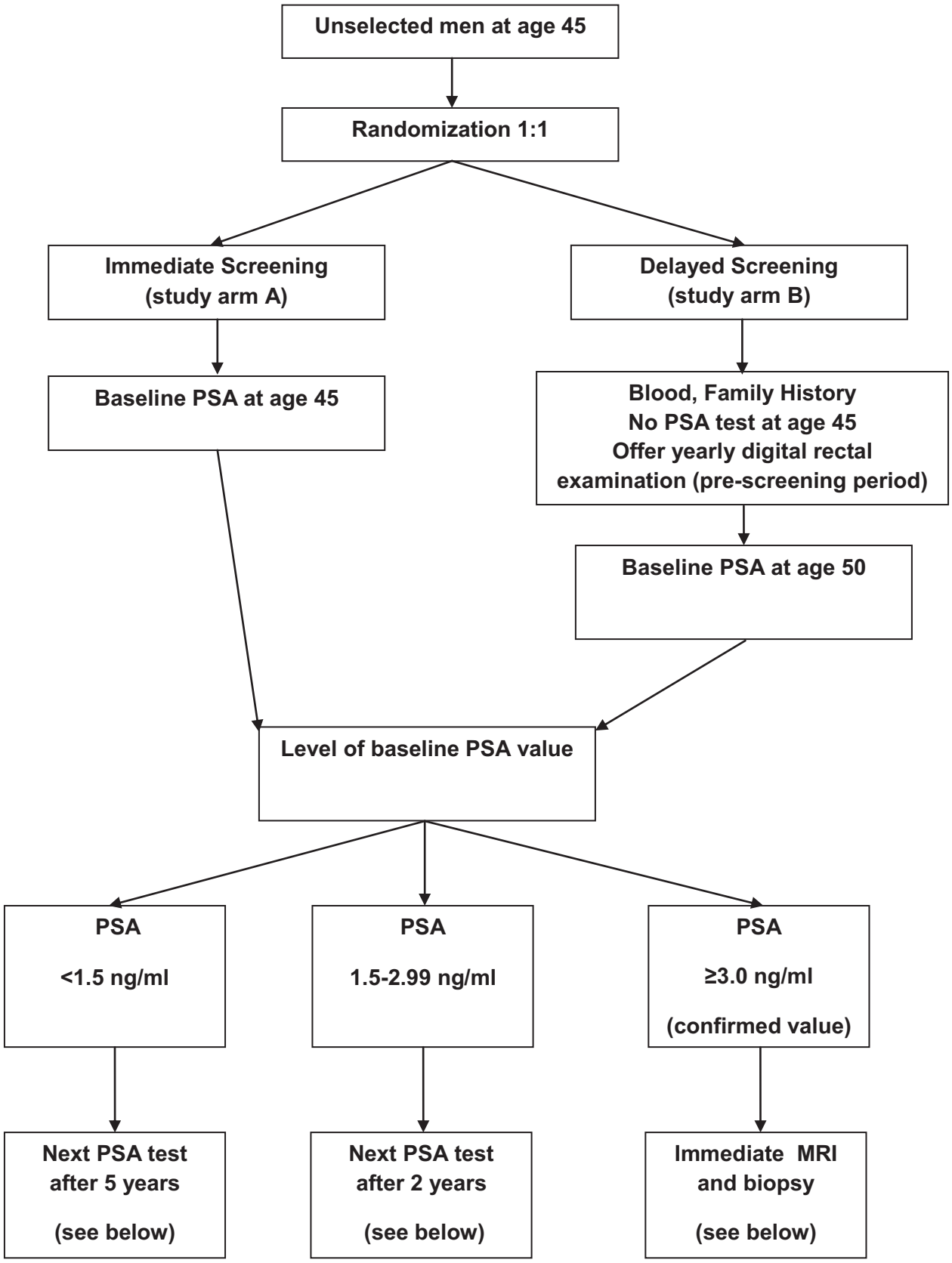
	imaging studies (isotopic bone scan, CT scan; if necessary supplemented by MRI and X-ray) as defined by UICC TNM Classification of Malignant Tumours and RECIST criteria. cM stage is verified by histological analysis (e.g. bone biopsy). In subjects undergoing subsequent surgery after diagnosis of prostate cancer assessment of regional lymph node metastasis from prostate cancer (pN stage) will utilize pathological examination of removed regional lymph nodes according to the recommendations of the International Society of Urological Pathology (ISUP) and of the German national guideline for prevention, diagnosis and treatment of prostate cancer (S3-Guideline). pN stage (regional lymph node metastases) will be recorded but not be considered for analysis of the primary endpoint. Secondary efficacy assessments: • Efficacy assessment for late metastasis (M stage) after curative treatment of detected prostate cancers (radical prostatectomy, radiotherapy) will utilize imaging studies (isotopic bone scan, CT scan; if necessary supplemented by MRI and X-ray). M stage is verified by histological analysis (e.g. bone biopsy). • Efficacy assessment for biochemical recurrence after curative treatment (radical prostatectomy, radiotherapy) of detected

	prostate cancers will utilize post-treatment PSA values (3-monthly).
	• Efficacy assessment for locally advanced prostate cancer:
	  ○ cT stage will be evaluated throughout digital rectal examination and multiparametric MRI.
	  ○ In subjects undergoing subsequent surgery after diagnosis of prostate cancer assessment for locally advanced prostate cancer (pT stage) will utilize pathological examination of radical prostatectomy specimens according to the recommendations of the International Society of Urological Pathology (ISUP) and of the German national guideline for prevention, diagnosis and treatment of prostate cancer (S3-Guideline).
	• Efficacy assessment for high grade prostate cancer:
	  ○ Evaluation of biopsy cores and of radical prostatectomy specimens and assignment of Gleason score will follow the recommendations of the International Society of Urological Pathology (ISUP) and of the German national guideline for prevention, diagnosis and treatment of prostate cancer (S3-Guideline).
	• Prostate cancer mortality and overall survival data will be collected throughout the whole study.

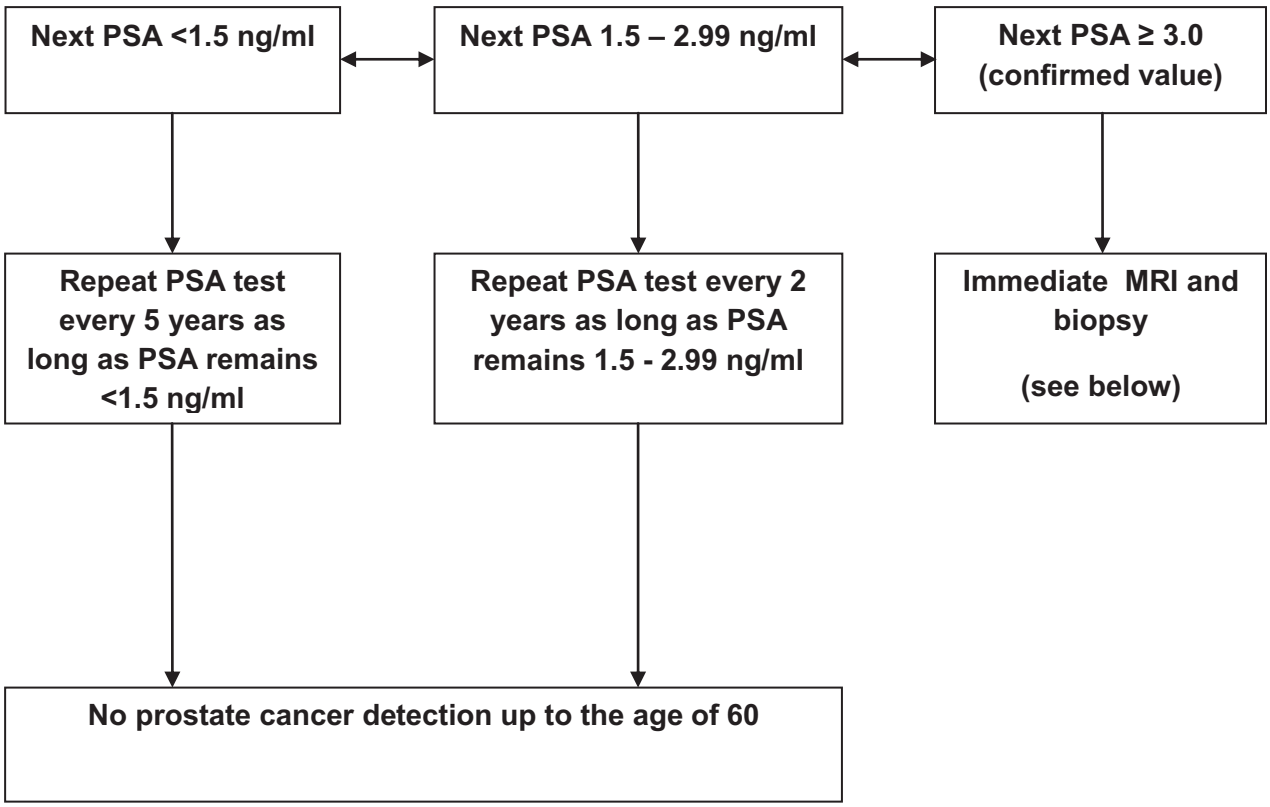
Safety Assessments:	• Medical history • Concomitant therapy and procedures • Adverse events (AEs) and serious adverse events (SAEs) for all invasive study interventions (multiparametric MRI, prostate biopsy, biopsy of metastases, treatment of prostate cancer) will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
Other Assessments:	• PSA values will be assessed at baseline and throughout the study to assess the distribution of PSA values and the time-dependant course of PSA values • Quality of Life (QoL) • Collection of blood and urine samples for translational research • Incidence of prostate cancer in the pre-screening period of study arm B detected only by digital rectal examination of the prostate

5.2 Overall Study Design and Plan

5.2.1 General Flow Chart for Study Arms A and B



5.2.2 Flow Chart for Following Screening Rounds (Study Arms A and B)



5.2.3 Flow Chart for Subjects with PSA Level ≥3.0 ng/ml at Baseline or in one of the Following Screening Rounds (Study Arms A and B)