Universitätsspital Basel

Evaluation of an MRI-based Prostate Cancer Screening Program (VISIONING): 5-year Follow-up Round (VISIONING III)

Research legislation:	Ordinance on human research except for Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects. Follow-up project to VISIONING (2018-01965, ClinicalTrials.gov Identifier: NCT03749993)
Risk Categorisation:	Other clinical trial acc. to Chapter 4 of the Ordinance on Clinical Trials in Human Research, ClinO/KlinV
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PROTOCOL SIGNATURE FORM

Project Title	*Evaluation of an MRI-based Prostate Cancer Screening Program (VISIONING): 5-year Follow-up Round (VISIONING III)*

The project leader has approved the protocol version ***[1.1, dated 14.05.2026]*** and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

The project leader has received the ICF and consider it appropriate for use.

Project leader:

Site *[Universitätsspital Basel]*

Name:

Date: _____ Signature: _____

Sponsor:

Name:

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

Art.	*Article*
BASEC	*Business Administration System for Ethical Committees*
bpMRI	*Biparametric Magnetic Resonance Imaging*
csPCa	*Clinically Significant Prostate Cancer*
CT	*Computed Tomography*
cnsPCa	*Clinically Non-Significant Prostate Cancer*
CRF	*Case Report Form*
DKF	*Department of Clinical Research (Departement Klinische Forschung)*
DRE	*Digital Rectal Examination*
EAU	*European Association of Urology*
eCRF	*Electronic Case Report Form*
ERSPC	*European Randomized Study of Screening for Prostate Cancer*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Human Research Ordinance*
ICF	*Informed Consent Form*
ICMJE	*International Committee of Medical Journal Editors*
IPSS	*International Prostate Symptom Score*
ISUP	*International Society of Urological Pathology*
IQR	*Interquartile Range*
mpMRI	*Multiparametric Magnetic Resonance Imaging*
NIH-CPSI	*National Institutes of Health Chronic Prostatitis Symptom Index*
ORCA	*Orchestrate Your Clinical Research Activities*
PCa	*Prostate Cancer*
PET-CT	*Positron Emission Tomography–Computed Tomography*
PI	*Principal Investigator*
PI-RADS	*Prostate Imaging Reporting and Data System*
PLCO	*Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial*
PSA	*Prostate-Specific Antigen*
PSAD	*Prostate-Specific Antigen Density*
PPI	*Patient and Public Involvement*
QoL	*Quality of Life*
SB	*Systematic Biopsy*
STROBE	*Strengthening the Reporting of Observational Studies in Epidemiology*
TRUS	*Transrectal Ultrasound*
UTI	*Urinary Tract Infection*

1 BACKGROUND AND PROJECT RATIONALE

Prostate cancer (PCa) is the most common cause of cancer-related death among men in Switzerland and Europe [4]. Large screening trials such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) demonstrated a reduction in prostate cancer–specific mortality of up to 30% [5,6]. These landmark trials established prostate cancer screening as a potentially life-saving intervention. However, they also revealed major limitations of prostate specific antigen (PSA) - based screening strategies.

PSA lacks sufficient specificity in the clinically relevant PSA range of 2–10 ng/ml [7,8]. Elevated PSA values may reflect benign prostatic hyperplasia, inflammation, or other non-malignant conditions. Consequently, PSA-based screening is associated with substantial overdiagnosis and overtreatment of clinically insignificant prostate cancer, unnecessary biopsies, and treatment-related morbidity. The limited discriminative ability of PSA between clinically significant and indolent PCa has raised concerns regarding the balance between benefit and harm in population-level screening programs.

Multiparametric MRI (mpMRI) has demonstrated improved diagnostic performance compared with PSA-triggered systematic biopsy strategies [9–12]. MRI-based approaches improve the detection of clinically significant prostate cancer (csPCa) while reducing the detection of indolent International Society of Urological Pathology (ISUP) grade group 1 tumors. Standardized Prostate Imaging Reporting and Data System (PI-RADS) classification correlates strongly with histopathological outcomes and provides structured risk stratification of MRI-visible lesions. Biparametric MRI (bpMRI), using T2-weighted and diffusion-weighted imaging without dynamic contrast enhancement, has demonstrated diagnostic performance comparable to mpMRI [10], while reducing acquisition time, costs, and potential contrast-related risks.

Based on this evidence, the VISIONING study was designed as a prospective cohort study evaluating an opportunistic bpMRI-based prostate cancer screening strategy. In VISIONING (consisting of phases I and II), bpMRI served as the primary screening modality, with biopsy performed only in men with suspicious imaging findings according to predefined criteria [13]. The VISIONING study demonstrated that bpMRI-based screening in an opportunistic setting is feasible and diagnostically efficient. Among 229 screened participants, approximately eleven bpMRI examinations and four targeted biopsies were required to detect one case of clinically significant ISUP grade group ≥2 prostate cancer [13]. Most recently, in the PRIME Diagnostic Clinical Trial, biparametric MRI was found to be noninferior to multiparametric MRI for the detection of clinically significant prostate cancer in biopsy-naive men, with nearly identical cancer detection rates and no increase in detection of clinically insignificant cancer [14].

While these findings confirm the efficiency of bpMRI as a screening tool in identifying clinically significant prostate cancer, considerably less is known about the long-term outcomes of men who did not receive a csPCa diagnosis or undergo active treatment as part of the initial screening round. Importantly, even less is known in the context of screening strategies based on biparametric MRI, where systematic long-term follow-up data after a negative initial screening round are lacking.

Most recently, Yun Ng et al. [15] reported outcomes of the UK RAPID pathway, which evaluated men with elevated PSA using upfront mpMRI, with prostate biopsy performed only for PI-RADS ≥4, or PI-RADS 3 with PSA-density ≥0.12. In their cohort of 1,266 men who had either a negative MRI or a benign biopsy during the first diagnostic round, the median follow-up was 3.4 years (IQR 2.4–4.9). Fewer than one in thirteen men (8.1%) were subsequently diagnosed with csPCa, and only one in twenty (5.8%) required active treatment by the five-year mark. The trigger for re-referral in the RAPID pathway was PSA dynamics: the PSA threshold was either a 20% increase from the patient's initial PSA if their baseline PSA-density was >0.12 ng/ml², or the PSA level at which their PSA-density would reach 0.12 ng/ml². The interpretation of these findings is limited

by the substantial number of men who were not re-referred for follow-up assessment: 647 had a negative MRI or a PI-RADS 3 lesion with non-suspicious PSA-density (<0.12), and 252 were discharged after a benign biopsy. Consequently, the clinical trajectories of a large proportion of the cohort (899/1568, 57.3%) remain unknown. Furthermore, the RAPID data underline the importance of systematic reassessment in men with initially benign biopsy results. Among the subset of 87 men who underwent repeat MRI, 44 again demonstrated suspicious PI-RADS findings, and 17 (38.6%) were subsequently diagnosed with csPCa despite previously benign biopsy results. In the group initially discharged with a negative MRI (PI-RADS 1–2 or PI-RADS 3 with PSAD <0.12), 280 patients underwent repeat MRI and 107 proceeded to biopsy, yielding a csPCa detection rate of 53% (57/107).

Similarly, a retrospective study by Itatani et al. [16] evaluated 193 men with a negative initial MRI who underwent systematic biopsy despite negative imaging. After five-year follow-up including repeat MRI and biopsy, 165 remained free of prostate cancer. Eight patients were classified as harbouring clinically insignificant prostate cancer according to their definition, resulting in a reported 5-year MRI negative predictive value of 89.6%. When considering only truly cancer-free outcomes (165/193), the negative predictive value would be 85.5%.

The follow-up round of VISIONING III is designed to directly address these limitations.

All eligible participants from the original VISIONING cohort will be re-invited approximately five years after their initial screening round. Eligible participants are defined as (i) men with a negative biopsy result, (ii) men with a negative bpMRI and who did not meet biopsy indication criteria, and (iii) men diagnosed with prostate cancer who did not undergo definitive treatment and were managed with active surveillance as part of the first VISIONING screening round (VISIONING I and II). Participants will be excluded from the follow-up round if they are deceased or if they received definitive active treatment for prostate cancer after the initial screening round.

All enrolled participants in VISIONING III will undergo repeat bpMRI and baseline clinical testing including PSA and PSA-density.

- Biopsy will be performed only when predefined triggers according to the European Association of Urology (EAU) are met (PSA-density ≥0.15, PSA >10 ng/ml, or PI-RADS ≥4) [17].
- For PI-RADS 3 lesions, the adapted protocol from VISIONING II will be applied, with repeat multiparametric mpMRI at six months and biopsy indicated only if the lesion is upgraded or persistent.

In VISIONING III, a targeted plus perilesional biopsy strategy will be adopted for suspicious MRI-lesions, replacing the targeted-only approach used in the initial VISIONING protocol. This adaptation aims to reduce the risk of targeting error and to align the study protocol with contemporary evidence and the current EAU guidelines [17,18]. Hagens et al. [19] demonstrated that adding perilesional sampling to targeted biopsy significantly increases the detection of clinically significant prostate cancer compared with targeted biopsy alone, while still resulting in fewer ISUP grade group 1 diagnoses than when full systematic biopsy is added. Importantly, the number of the additional perilesional cores is low and is not expected to increase morbidity. Complication rates for transperineal prostate biopsy are already very low, as demonstrated in the PREVENT randomized clinical trial, so the addition of limited perilesional cores is not expected to affect this risk profile [20].

Further protocol modifications are introduced in VISIONING III to reduce participant burden and improve adherence. Routine digital rectal examination (DRE) will be omitted from standard study visits, and routine administration of quality-of-life and distress questionnaires prior to knowledge of biopsy results will no longer be performed. DRE will remain available only in selected cases with clinical suspicion of inflammatory conditions, such as prostatitis, where it may contribute to clinical assessment. Furthermore, DRE will be performed at the time of prostate biopsy in all patients undergoing biopsy, in order to provide information on local clinical T stage in case of confirmed prostate cancer. Likewise, questionnaires assessing quality of life and psychological distress will be administered selectively in participants diagnosed with prostate cancer. These adaptations are based on observations from the initial VISIONING rounds. Specifically, in the

original VISIONING cohort, 0 men had a suspicious DRE that led to prostate biopsy in the setting of a non-suspicious MRI and resulted in a prostate cancer diagnosis. This observation is consistent with contemporary literature questioning the role of routine DRE in prostate cancer screening [21]. In a systematic review and meta-analysis of four prospective cohort studies and three retrospective studies including 9,241 patients who underwent DRE and prostate biopsy, the pooled sensitivity of DRE was 51% and the pooled specificity was 59%, highlighting its limited diagnostic accuracy as a screening tool [22]. Importantly, omission of routine DRE does not introduce a diagnostic disadvantage, as biopsy indications within VISIONING III will continue to be driven by PSA levels, PSA-density, and MRI findings. In addition, in the initial VISIONING round, adherence to repeated quality-of-life and distress questionnaires prior to knowledge of biopsy results was low, with evidence of survey fatigue and no signal suggesting a negative impact of MRI-based screening on quality of life. Based on these observations, routine administration of QoL and distress questionnaires before biopsy results are known will be omitted in the follow-up round. Questionnaires will instead be administered selectively in participants with a positive biopsy result, in accordance with the certification requirements of the German Cancer Society, where systematic assessment of psychosocial burden is clinically relevant. By omitting procedures with limited diagnostic or scientific yield in the screening setting, while retaining them where clinically indicated, VISIONING III aims to streamline diagnostic pathways, reduce unnecessary patient burden, and improve participation and adherence throughout the follow-up process.

By applying uniform re-screening and biopsy criteria in an unselected, real-world opportunistic bpMRI-first screening cohort, VISIONING III will provide a reliable estimate of the five-year incidence of clinically significant prostate cancer in men whose first screening round was negative or did not result in active treatment. In addition, the follow-up will generate valuable longitudinal data on PSA kinetics, PSA-density evolution, and dynamics of prostate morphology and MRI-lesions over time, thereby allowing detailed characterization of radiological and biochemical changes between the initial screening round and the five-year reassessment.

The planned measures (bpMRI and PSA testing) entail only minimal risks and burdens. bpMRI is non-invasive and does not involve ionizing radiation. Blood sampling represents minimal burden. Prostate biopsy is performed only when clinically indicated and follows established standard-of-care procedures with low complication rates [18].

The overall risk profile of the project is therefore minimal and consistent with Category A classification.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

We hypothesize that men who underwent bpMRI-based opportunistic screening within the VISIONING cohort and had either:

i. a negative bpMRI and no biopsy indication
ii. a negative biopsy result
iii. a prostate cancer diagnosis managed with active surveillance

will demonstrate a low five-year incidence of clinically significant prostate cancer (ISUP grade group ≥2). We further hypothesize that a bpMRI-first screening strategy provides durable negative predictive performance over a five-year interval.

Based on the data from the UK RAPID pathway, we additionally hypothesize that in participants who meet predefined biopsy triggers at follow-up, clinically significant prostate cancer will be detected in a relevant proportion of cases. Accordingly, systematic re-evaluation at five years is expected to identify men harbouring clinically significant PCa at an early stage, thereby enabling early diagnosis and allowing these men to benefit from timely therapeutic intervention.

The primary objective of the follow-up round is to determine the five-year risk of clinically significant prostate cancer in men who previously underwent bpMRI-based screening, which was negative or without receiving definitive treatment, thereby assessing the long-term safety and negative predictive performance of bpMRI in an opportunistic screening setting.

2.2 Primary and secondary endpoints

The purpose of this 5-year follow-up round is to evaluate the long-term diagnostic performance of a bpMRI–based prostate cancer screening pathway by determining how many men develop clinically relevant prostate cancer (ISUP ≥ 2) after an initially negative screening round (VISIONING phases I and II). The initially negative screening round cohort consists of men:

1) with a negative MRI, who did not receive biopsy
2) who received biopsy, but biopsy was negative
3) who had a positive biopsy with low-risk prostate cancer and were managed with active surveillance.

The primary outcome is ISUP ≥ 2 diagnosis-free-survival 5 years after an initial negative screening round.

- Patients with a positive finding on repeat bpMRI (PI-RADS 4–5) will undergo targeted biopsy with additional perilesional sampling.
- Patients with a PI-RADS 3 lesion will undergo a repeat multiparametric MRI after six months and will be biopsied only if the lesion persists or upgrades (i.e. becomes PI-RADS 4 or 5).
- Patients with a negative bpMRI finding (PI-RADS 1–2) may undergo template prostate biopsy only in case of very suspicious PSA values: PSA-density ≥0.15 or PSA >10 ng/ml or may continue with classical PSA-based screening if clinically indicated.

In the 5-year follow-up round of VISIONING, all clinical outcomes observed after the initial screening round will be systematically evaluated.

- First, we will assess **five-year treatment-free survival**, both overall and by diagnostic category at baseline (MRI-negative, MRI-positive/biopsy-negative, active surveillance). Treatment-free survival events are defined as:
    1. radical prostatectomy
    2. prostate radiotherapy
    3. prostate focal therapy
    4. death

The outcome will be assessed at the first consultation of VISIONING III, and patients without retreatment will be considered treatment-free.

- In addition, we will determine **biopsy-free survival and re-MRI-free survival** and analyse the timing and clinical indications that led to reassessment.
    - Biopsy-free survival events are defined as: performed prostate biopsy at any time after the conclusion of the initial screening round (VISIONING phases 1 and 2) and enrolment in the current study or death.
    - Re-MRI-free survival events are defined as: performed Prostate MRI at any time after the conclusion of the initial screening round and enrolment in the current study or death. The outcome will be assessed at the first consultation of VISIONING III, and patients without a biopsy or re-MRI will be considered biopsy-free and re-MRI-free.
- The diagnostic performance of the repeat screening round will be examined by evaluating the yield of the 5-year re-screen MRI, including **detection rates of clinically significant (csPCa) and clinically non-significant prostate cancer (cnsPCa).**
- We will also calculate the per-MRI and per-biopsy productivity, expressed as the **number of MRIs or biopsies needed to detect one case of csPCa**. These measures will be

compared with corresponding metrics from the first VISIONING round (VISIONING I and II).

- Longitudinal **changes in PSA-density and PI-RADS categories over the five-year interval** will be analyzed to determine their predictive value for clinically significant cancer at re-screen.
- Safety outcomes including **metastasis-free survival and prostate cancer–specific survival** between the first screening round and the first consultation of VISIONING III will also be evaluated. Metastasis-free survival events are defined as: any new radiographic suspicion of metastasis (in CT, MRI, or PET-CT) or any new histologically proven metastasis after the first screening round or death. Prostate cancer-specific survival events are defined as: death directly attributable to prostate cancer, including death resulting from metastatic progression or complications of prostate cancer or its treatment at any time after the initial screening round. Special attention will be given to the evolution of PI-RADS 3 lesions, distinguishing inflammatory from non-inflammatory appearances and assessing their relationship to PSA-density.
- Furthermore, we will characterize the anatomical evolution of the prostate, including total **prostate volume, transition-zone volume, and relevant morphological features** and investigate their **associations with PSA and age**.
- Finally, for participants who underwent **definitive treatment** during the five-year period (radical prostatectomy, radiotherapy, focal therapy), we will document available **outcomes**.

2.3 Independent variables

1. Baseline screening status (VISIONING I/II)

Participants will be categorized according to their status in the initial screening round as described in Section 2.2. This categorical variable will allow stratified analysis of five-year outcomes according to baseline risk profile.

2. Repeat biparametric MRI findings

All participants will undergo repeat bpMRI at follow-up. MRI findings will be assessed according to the Prostate Imaging Reporting and Data System (PI-RADS).

- Variable type: ordinal categorical variable
- Scale: PI-RADS 1–5
- Time point: approximately five years after baseline screening
- Additional parameters: lesion size, lesion location, and presence of new or progressive lesions

MRI-visible lesions will be documented and compared longitudinally with baseline imaging where available.

3. PSA and PSA-density

Serum prostate-specific antigen (PSA) levels will be measured at follow-up. PSA-density (PSAD) will be calculated as PSA divided by MRI-derived prostate volume.

- Variable type: continuous variable (ng/ml for PSA; ng/ml² for PSAD)
- Time point: at follow-up visit
- PSA kinetics: change from baseline PSA will be calculated

PSA and PSAD serve as predefined biopsy triggers in accordance with current EAU guideline criteria.

4. Biopsy indication and biopsy findings
Biopsy will be performed only if predefined triggers are met (PSAD ≥0.15, PSA >10 ng/ml, or PI-RADS ≥4; persistent or upgraded PI-RADS 3 at 6-month repeat multiparametric MRI).

- Variable type: categorical (biopsy performed: yes/no)
- Histopathological outcome: ISUP grade group (1–5)
- Primary outcome definition: clinically significant prostate cancer defined as ISUP ≥2

2.4 Project design

VISIONING III is designed as a prospective, single-center, longitudinal cohort follow-up study.

The project represents the five-year follow-up round of the previously conducted VISIONING I and II screening phases and evaluates long-term oncological outcomes after an opportunistic biparametric MRI (bpMRI)-first prostate cancer screening strategy.

The study is conducted at a single tertiary referral center and includes participants from the original VISIONING cohort. The project is national in scope and does not involve international study sites.

VISIONING III is a confirmatory longitudinal cohort study designed to assess long-term safety and negative predictive performance of bpMRI-based screening. The study is observational in nature, as no experimental intervention is introduced. All diagnostic procedures follow predefined criteria based on contemporary European Association of Urology (EAU) guidelines.

The study includes two principal time-points:

- Baseline screening (VISIONING I/II; already completed)
- Five-year follow-up assessment (VISIONING III)

During the follow-up round, all eligible participants undergo repeat bpMRI and serum PSA testing including PSA-density calculation.

- Biopsy is performed only if predefined triggers are met (PSA-density ≥0.15, PSA >10 ng/ml, or PI-RADS ≥4)
- In case of PI-RADS 3 lesions a repeat multiparametric MRI will be performed 6 months later. Biopsy is performed only in case of:
    - lesion persistence (i.e. still PI-RADS 3)
      or
    - lesion upgrading (i.e. PI-RADS ≥4).

These biopsy indications are identical to those in the previous VISIONING II protocol.

The longitudinal design is justified by the primary objective of determining the five-year incidence of clinically significant prostate cancer in men who had a negative bpMRI-directed PCa screening or did not undergo definitive treatment after the first screening round. Only a structured prospective follow-up allows reliable estimation of delayed csPCa diagnosis, biopsy-free survival, and treatment-free survival.

By applying uniform re-screening criteria and prostate biopsy indications within the same cohort, the project ensures internal consistency and minimizes confounding related to heterogeneous diagnostic pathways.

The overall duration of VISIONING III corresponds to the five-year interval between the initial screening round and the structured follow-up assessment, with additional follow-up for participants undergoing biopsy or cancer diagnosis according to standard clinical care.

2.5 Patient and public involvement

Patients or formal public representatives were not directly involved as PPI-contributors in the design of the VISIONING III protocol.

However, VISIONING III has been substantially informed by observations and participant experience from VISIONING I and II. Informal feedback from participants during the previous screening rounds was considered when optimizing visit structure and follow-up procedures.

Specifically, procedural adaptations in the follow-up round were implemented to reduce participant burden and improve adherence. These adaptations include:

- Omission of routine digital rectal examination (DRE) during standard study visits
- Omission of routine quality-of-life and distress questionnaires prior to knowledge of biopsy results

These modifications were based on participant adherence data, observed survey fatigue, and the limited additional diagnostic value of DRE in the initial screening rounds.

Participants will continue to receive comprehensive information and have the opportunity to discuss study procedures with the responsible doctors before providing informed consent.

3 PROJECT POPULATION AND PROJECT PROCEDURES

3.1 Project population, inclusion and exclusion criteria

The project population consists of men who previously participated in the VISIONING I and II screening phases and who fulfill eligibility criteria for the five-year follow-up round (VISIONING III).

VISIONING III is a single-center follow-up cohort study. All eligible participants from the original VISIONING cohort will be invited for re-assessment approximately five years after their initial screening visit.

The total number of potential participants corresponds to the number of men enrolled in VISIONING I and II and had no biopsy (n=150), had a negative biopsy (n = 50), or were enrolled in active surveillance (n=8) minus those who are deceased or who received definitive active treatment for prostate cancer. The final number of participants is expected to depend on survival, treatment-free-survival status and willingness to participate in follow-up.

No separate control group is included, as this is a longitudinal within-cohort follow-up study.

Sex and Gender Considerations:

Prostate cancer is a male-specific disease. Therefore, the study population consists exclusively of men.

Inclusion Criteria:

Participants must meet all of the following criteria:

- Prior participation in VISIONING I or II
- One of the following baseline screening outcomes during VISIONING I or II:
  - Negative bpMRI, no biopsy indication
  - Negative prostate biopsy result
  - Prostate cancer diagnosis managed with active surveillance and no definitive treatment
- Signed informed consent for participation in VISIONING III

Exclusion Criteria:

Participants will be excluded if any of the following criteria apply:

- Deceased at the time of follow-up
- Receipt of definitive active treatment for prostate cancer (e.g., radical prostatectomy, radiotherapy, or focal therapy) after the initial screening round

- Severe comorbid condition precluding MRI examination or prostate biopsy (if biopsy becomes indicated)
- Contraindications to MRI (e.g., incompatible implanted medical devices)
- Inability to provide informed consent or refusal

3.2 Recruitment, screening and informed consent procedure

Recruitment:

Eligible participants will be identified from the database of the original VISIONING I and II screening cohort conducted at the University Hospital Basel. All potentially eligible participants will be contacted by mail and/or telephone and invited to participate in the five-year follow-up round (VISIONING III). Recruitment is therefore conducted through re-contact of previously enrolled study participants and not through public advertisement.

VISIONING III is a single-center study conducted at a tertiary referral university hospital. No external recruitment sites are involved.

The study population consists exclusively of men, as prostate cancer is a male-specific disease. All eligible participants from the original cohort will be invited irrespective of age, socioeconomic background, or other demographic factors. Therefore, recruitment reflects the original screening cohort and ensures appropriate representation of age distribution relevant to prostate cancer screening.

Screening:

Eligibility will be assessed based on the documented outcomes of VISIONING I and II. Screening procedures consist of verification of:

- Prior participation in VISIONING I or II
- Baseline screening outcome (negative bpMRI without biopsy indication, negative biopsy result, or prostate cancer managed with active surveillance)
- Survival status
- Absence of definitive active treatment for prostate cancer

Informed Consent Procedure:

The study information and informed consent documents are prepared using the current swissethics templates and comply with Swiss legal requirements. The patient information is written in clear and comprehensible language.

The project leader explains to each participant the nature of the research project, its purpose, the procedures involved, the expected duration, the potential risks and any discomfort it may entail. Each participant is informed that the participation in the research project is voluntary and that he/she may withdraw from the research project at any time and that withdrawal of consent will not affect their subsequent medical assistance and treatment. The participants are informed that they can ask any question. Enough time is given to the participant. Participants receive the written study information prior to the study visit whenever possible. At the study visit, participants have the opportunity to discuss the project in detail with the investigator and to ask questions. Adequate time for consideration is provided in accordance with the swissethics guidance on time for consideration between information and consent. All participants are given an information document and a consent form describing the research project. The formal consent of a participant, using the approved consent form, is obtained before the participant is enrolled in the research project. The participant should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the participant and the project leader (or her/his designee). The signed consent form it is retained as part of the investigation records. Electronic informed consent is not planned for this study.

Compensation:

Participants will not receive financial compensation for participation.

Pregnancy and Genetic Testing:

This study does not involve genetic testing, presymptomatic testing, or prenatal risk assessment. Contraception requirements are not applicable, as the study population consists exclusively of adult men and no investigational medicinal product is administered.

Overall Project Duration:

VISIONING III represents the five-year follow-up round of the original VISIONING I and II screening phases. The recruitment period is expected to last approximately 12–18 months, depending on response rate and scheduling availability. For each participant, the follow-up phase consists of up to five visits within a timeframe of approximately 3–5 weeks.

Study visits and timeline:

The study schedule includes the following visits:

- Visit 1 (Consultation): Day 1
- Visit 2 (Imaging): Day 7–14
- Visit 3 (Counseling): Day 14–21
- Visit 4 (Biopsy / Tumorboard, if indicated): Day 14–21
- Visit 5 (Consultation / Results discussion): Day 21–35

Not all participants will undergo all five visits.

- Participants without biopsy indication will complete the study after the imaging and counseling phase.
- Participants with biopsy indication will undergo biopsy and a final consultation for result discussion within the specified timeframe.
- Participants with PI-RADS 3 lesions requiring repeat imaging will follow the predefined protocol timing as described in Section 2.2.

The duration of participation per individual participant is therefore approximately:

- Three visits, two to three weeks (if no biopsy is indicated)
- Five visits, three to five weeks (if biopsy is indicated)
- Up to seven – eight months (if repeat imaging is required)

Long-term oncological follow-up after diagnosis of prostate cancer follows standard clinical care and is not considered a study-specific intervention.

Schedule of assessments

A detailed schedule of assessments, including procedures performed at each visit, is provided in Appendix 1.

Description and Sequence of Procedures

All eligible participants will undergo the following procedures at the five-year follow-up round:

1. Clinical assessment

- Review of medical history since initial screening
- Documentation of interim prostate cancer diagnostics or treatment (if applicable)

- Assessment of relevant comorbidities

2. Serum PSA testing
- Blood sampling for PSA measurement
- Calculation of PSA-density (PSA divided by MRI-derived prostate volume)

3. Biparametric MRI (bpMRI)
- T2-weighted imaging
- Diffusion-weighted imaging
- No dynamic contrast enhancement
- PI-RADS classification (1–5)
- MRI findings will be compared with baseline imaging where available.

4. Biopsy Procedures (if indicated)

Prostate biopsy will only be performed if predefined criteria are met:
- PSA-density ≥0.15
- PSA >10 ng/ml
- PI-RADS ≥4
- Persistent or upgraded PI-RADS 3 at six-month repeat MRI

Biopsy method:
- Transperineal targeted plus perilesional biopsy (minimum of 3 targeted cores and 3 perilesional cores).
- Histopathological assessment including ISUP grading

Biopsy is part of standard-of-care diagnostic practice and not an experimental intervention.

Material Sampled and Stored

The following biological material will be collected: Blood sample, serum for PSA measurement

standard clinical laboratory analysis. No genetic testing. No biobanking beyond routine clinical documentation. Prostate biopsy tissue (if indicated). Histopathological examination. No additional research-only tissue sampling beyond clinically required cores. No additional biological material will be stored for future unspecified research.

Qualitative Methods

This project does not include qualitative interviews, audio or visual recordings, or field notes.

Potential Sources of Bias and Mitigation Measures

The following potential biases are acknowledged:

1. Attrition bias

Participants lost to follow-up may differ systematically from those who participate.

Mitigation: All eligible participants will be actively contacted and re-invited.

2. Selection bias

The cohort reflects an opportunistic screening population rather than a population-based sample.

This is inherent to the study design and will be considered in interpretation of results.

3. Observer bias in MRI interpretation

Mitigation: MRI assessment is performed by two blinded radiologists and according to standardized PI-RADS criteria.

3.4 Withdrawal and discontinuation

A participant may be withdrawn from the project under the following circumstances:

- Withdrawal of informed consent at any time without providing a reason
- Medical contraindication to MRI or biopsy arising during the study
- Severe intercurrent illness preventing continuation
- Investigator decision in case continuation is not in the participant's best medical interest

Participants may withdraw from the study at any time without any negative consequences for their subsequent medical care.

If a participant withdraws consent: no further study-specific procedures will be performed. No additional data will be collected. A final study visit is not mandatory upon withdrawal. If withdrawal occurs during an ongoing diagnostic process, clinically indicated examinations will be completed as part of routine medical care. In longitudinal follow-up, participants who discontinue participation will be considered drop-outs. Available data collected prior to withdrawal will be retained in coded

All study data are recorded in coded (pseudonymised) form. Each participant is assigned a unique identification number. The key linking the study identification number to personal identifiers is stored separately and securely at the study site, accessible only to authorized personnel. Items of data which allow direct identification of a specific person (such as name, address, and date of birth) are stored separately from study data.

Complete anonymisation during the study is not performed, as longitudinal follow-up and outcome verification require maintenance of coded linkage.

If a participant explicitly requests destruction of biological material: no further biological material will be stored. Any stored study-specific biological material not required for routine clinical care will be destroyed where feasible

In this study, no additional research biobank material is stored beyond clinically indicated samples.

At the end of the legally required data retention period, data may be anonymised in accordance with Art. 25 HRO. Anonymisation will be performed by permanently deleting the identification key linking study codes to personal identifiers. The anonymisation process will ensure that re-identification is no longer possible without disproportionate effort. The procedure will be documented according to institutional data protection standards.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

MRI-based opportunistic screening using a biparametric MRI-first strategy with targeted-only biopsy during the initial round represents a novel screening approach. Currently, there are no longitudinal data describing the five-year outcomes of such a population. In particular, it is not known what proportion of men undergoing bpMRI-based screening will subsequently be diagnosed with clinically significant prostate cancer during structured long-term follow-up. VISIONING III is therefore designed to provide the data necessary to estimate the five-year incidence of clinically significant prostate cancer and to characterize the negative predictive performance of bpMRI-based screening. The study is primarily descriptive and exploratory in nature.

VISIONING III represents a longitudinal follow-up of a fixed cohort of participants from VISIONING I and II (n = 229). The sample size is therefore determined by the number of surviving and eligible participants available for re-invitation and consenting to follow-up.

Assuming approximately 180–200 evaluable participants at follow-up, this cohort size allows estimation of the five-year incidence with acceptable precision using exact confidence intervals.

Because this is not a randomized interventional trial and no formal comparison between independent treatment groups is planned, a formal power calculation is not applicable.

The data generated in VISIONING III will provide the basis for future statistical considerations in potential MRI-based screening strategies.

Analysis Populations:

All participants from the original VISIONING I and II cohort who meet eligibility criteria and undergo follow-up assessment will be included in the analyses.

Subgroup analyses will be performed according to baseline diagnostic category:

- MRI-negative without biopsy
- MRI-positive with negative biopsy
- Active surveillance

Primary Analysis:

Statistical analysis will be performed upon completion of the study by Stefanie Hayoz, Statistician at the Swiss Cancer Institute, Bern.

The primary outcome is ISUP ≥ 2 diagnosis-free-survival 5 years after an initial negative screening round.

Categorical variables will be summarized with frequency and percentage and may be compared between subgroups using Fisher's exact tests.

Confidence intervals for proportions will be calculated using the Clopper-Pearson method.

Continuous variables will be summarized using median and range and may be compared between subgroups using Wilcoxon rank sum tests. Linear regression models may be used to investigate the effect of the parameters of interest on these variables. for time-to-event endpoints, Kaplan-Meier estimated will be used to describe and visualize the data, using Kaplan-Meier plots, calculating medians together with 95% confidence intervals and evaluating the curves at 5 years. Cox regression models may be used to investigate the effect of the parameters of interest on these variables. If the assumption of proportional hazards is seriously violated, other methods may be applied.

Secondary Analyses:

The same statistical methods as described in the primary analysis will be applied.

In the 5-year follow-up round of VISIONING, all clinical outcomes observed after the initial screening round will be systematically evaluated.

- First, we will assess five-year treatment-free survival, both overall and by diagnostic category at baseline (MRI-negative, MRI-positive/biopsy-negative, active surveillance). Treatment-free survival events are defined as: 1) radical prostatectomy, 2) prostate radiotherapy, 3) prostate focal therapy, 4) death. The outcome will be assessed at the first consultation of VISIONING III, and patients without retreatment will be considered treatment-free.
- In addition, we will determine biopsy-free survival and re-MRI-free survival and analyse thetiming and clinical indications that led to reassessment. Biopsy-free survival events are defined as: performed prostate biopsy at any time after the conclusion of the initial screening round (VISIONING phases 1 and 2) and enrolment in the current study or death. Re-MRI-free survival events are defined as: performed Prostate MRI at any time after the conclusion of the initial screening round and enrolment in the current study or death. The outcome will be assessed at the first consultation of VISIONING III, and patients without a biopsy or re-MRI will be considered biopsy-free and re-MRI-free.
- The diagnostic performance of the repeat screening round will be examined by evaluating the yield of the 5-year re-screen MRI, including detection rates of clinically significant (csPCa) and clinically non-significant prostate cancer (cnsPCa).
- We will also calculate the per-MRI and per-biopsy productivity, expressed as the number of MRIs or biopsies needed to detect one case of csPCa. These measures will be compared with corresponding metrics from the first VISIONING round (VISIONING I and II).

- Longitudinal changes in PSA-density and PI-RADS categories over the five-year interval will be analyzed to determine their predictive value for clinically significant cancer at re-screen.
- Safety outcomes including metastasis-free survival and prostate cancer–specific survival between the first screening round and the first consultation of VISIONING III will also be evaluated. Metastasis-free survival events are defined as: any new radiographic suspicion of metastasis (in CT, MRI, or PET-CT) or any new histologically proven metastasis after the first screening round or death. Prostate cancer-specific survival events are defined as: death directly attributable to prostate cancer, including death resulting from metastatic progression or complications of prostate cancer or its treatment at any time after the initial screening round. Special attention will be given to the evolution of PI-RADS 3 lesions, distinguishing inflammatory from non-inflammatory appearances and assessing their relationship to PSA-density.
- Furthermore, we will characterize the anatomical evolution of the prostate, including total prostate volume, transition-zone volume, and relevant morphological features and investigate their associations with PSA and age.
- Finally, for participants who underwent definitive treatment during the five-year period (radical prostatectomy, radiotherapy, focal therapy), we will document available outcomes.

4.2. Handling of missing data

A row denoted “Missing” will be included in count tabulations if necessary to account for drop-outs and missing values. For continuous variables, a column with the number of available observations will be added. Participants who withdraw informed consent or are lost to follow-up will not be replaced. As VISIONING III represents a follow-up of a fixed cohort from the original screening round, replacement of participants is not possible. All eligible participants from the original cohort will be systematically re-invited in order to minimize drop-outs and ensure that an adequate number of participants can be evaluated. All data of patients withdrawing informed consent will be handled according to the provisions described in section 3.4.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Swiss Human Research Act (HRA) and the Swiss Ordinance on Clinical Trials in Human Research (ClinO/KlinV) [1] as well as other locally applicable legal and regulatory requirements [1]. The project leader acknowledges his responsibilities as both the project leader and Sponsor-Investigator.

5.2 Notification of safety and protective measures (ClinO/KlinV Art. 37)

If, during the conduct of the clinical trial, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the expected benefits, all measures required to ensure the protection of the participants will be taken without delay.
The project leader/Sponsor-Investigator will be informed promptly, within 24 hours, if immediate safety and protective measures must be taken during the conduct of the clinical trial. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days, in accordance with ClinO/KlinV Art. 37.
Furthermore, a yearly safety- and progress report will be submitted to the Ethics Committee.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

The project leader reports to the ethics committee on the connection between the event and the collection of health-related personal data or the sampling of biological material. At the same time, the project leader submits proposals concerning the next steps to be taken.

Any new relevant information and the outcome to the original Serious Event is reported to the ethics committee via BASEC.

Given that the study procedures correspond to standard-of-care diagnostic procedures and entail minimal risk, serious events are not expected to exceed those known from routine clinical practice. Nevertheless, any such event temporally associated with study participation will be evaluated and reported in accordance with Art. 21 HRO

5.4 Procedure for investigations involving radiation sources

Not applicable.
This research project does not involve the use of ionising radiation, radiopharmaceuticals, medical devices capable of emitting ionising radiation, or any sealed or unsealed radioactive sources. Therefore, the additional requirements according to HRO Annex 2 and Art. 19 and 23 HRO are not applicable.

5.5 Amendments

Substantial changes to the authorised clinical trial, the protocol and relevant trial documents will be submitted to the Ethics Committee for approval according to ClinO/KlinV Art. 29 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

The following are considered to be substantial changes:

a. changes affecting the participants' safety and health, or their rights and obligations
b. changes to the protocol, in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis
c. a change of trial site, or conducting the clinical trial at an additional site
d. a change of Sponsor, coordinating investigator or investigator responsible at a trial site.

Other changes that are not considered substantial will be documented and notified to the Ethics Committee as applicable in accordance with ClinO/KlinV Art. 29.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

The completion of the research project is defined by the last collection of health-related personal data or the last sampling of biological material.

All study data are recorded and stored in coded (pseudonymised) form. Each participant is assigned a unique study identification number. The key linking this study identification number to personal identifiers is stored separately and securely at the study site and is accessible only to authorized personnel. At project completion, health-related personal data will remain coded and stored in accordance with institutional and legal retention requirements. No additional research-specific biobanking of biological material is performed in this project. Biological material (e.g.,

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

blood samples, biopsy tissue) collected during the study corresponds to routine clinical diagnostics and is handled according to institutional standards for clinical material. If anonymisation of study data is performed after the legally required retention period, this will be done by permanently deleting the identification key linking coded data to personal identifiers. Anonymisation will be performed using a method based on the current state of the art, ensuring that re-identification is no longer possible without disproportionate effort. Items of data which, individually or in combination, allow the association with a specific person to be re-established (such as name, address, date of birth, or unique identification numbers), will be deleted or modified accordingly. The anonymisation procedure will be documented in accordance with Art. 25 HRO.

Radiation-Specific Reporting: Not applicable. This project does not involve investigations with unsealed or sealed radioactive sources and does not require FOPH approval.

5.7 Insurance

This research project is classified as Category A according to the Ordinance on Clinical Trials in Human Research, ClinO/KlinV. In the event of project-related damage or injuries, the liability of the institution University Hospital Basel provides compensation.
No separate project-specific insurance policy is required.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Prostate cancer screening remains a subject of ongoing scientific debate, particularly with regard to balancing early detection of clinically significant disease against the risks of overdiagnosis and overtreatment. The VISIONING III follow-up addresses an important and currently insufficiently studied question: the long-term implications of an opportunistic biparametric MRI (bpMRI)-based screening strategy.

The social and scientific value of the project lies in generating longitudinal data on men who underwent bpMRI-based screening and either had a negative result, a negative biopsy, or were managed with active surveillance. Currently, long-term data on such cohorts, particularly in the context of bpMRI-based screening, are lacking. The results of this study will contribute to evidence-based evaluation of MRI-based screening strategies and may inform future screening recommendations, including the definition of safe re-screening intervals and follow-up algorithms.

The project design is observational and longitudinal. All diagnostic procedures performed during the follow-up round correspond to established clinical standard-of-care procedures. bpMRI is non-invasive and does not involve ionizing radiation. PSA testing requires routine venous blood sampling. Prostate biopsy is performed only when predefined clinical and radiological criteria are met and follows established EAU guideline recommendations. The overall time effort for participants is limited to scheduled study visits and corresponds largely to routine urological follow-up. Participation is entirely voluntary. Eligible participants are re-invited and may decline participation without any consequences for their medical care. Participants may withdraw consent at any time without providing reasons and without any impact on subsequent treatment.

Handling of incidental findings: MRI examinations may reveal incidental findings unrelated to prostate cancer (e.g., pelvic or adjacent organ abnormalities). In accordance with institutional policy and the swissethics guideline on incidental findings, clinically relevant incidental findings will be communicated to the participant and, where appropriate, further diagnostic clarification will be recommended. Surplus information not relevant to participant health or to the scientific objectives of the project will not be actively pursued.

Right to information: Participants are informed about clinically relevant findings that may affect their health. This includes prostate cancer diagnoses or other clinically significant incidental findings detected during the study procedures.

The project does not involve genetic testing, radiation exposure, experimental drugs, or invasive procedures beyond clinically indicated prostate biopsy. No vulnerable populations are included. Given the minimal additional burden beyond routine clinical practice and the significant potential societal benefit in improving prostate cancer screening strategies, there is an overall fair balance between participant burden and scientific value.

6.2 Risk-Benefit Assessment

The risks associated with participation are minimal and correspond to routine diagnostic procedures:

- bpMRI: Non-invasive, no ionizing radiation. Potential minor discomfort due to examination duration or confined space.
- PSA blood sampling: Minimal risks such as transient pain or minor hematoma.
- Prostate biopsy (if indicated): Risks include pain, transient hematuria, hematospermia, urinary retention, and rarely infection. Transperineal biopsy significantly reduces infectious complications compared to transrectal approaches.

Psychological burden may arise from anxiety related to screening results or prostate cancer diagnosis. However, omission of routine distress questionnaires prior to biopsy results (as adapted in VISIONING III) reduces unnecessary psychological burden in participants without clinically relevant findings. There is a theoretical risk of unauthorized access to health-related personal data. This risk is minimized through coded data storage, restricted access, secure institutional IT infrastructure, and compliance with Swiss data protection regulations.

Risk minimization: All procedures follow established clinical standards and EAU guideline recommendations. Biopsy is performed only when predefined criteria are met. Data are coded and stored securely. Participants may withdraw at any time. Clinically relevant incidental findings are managed according to institutional standards.

Potential benefits: Participants may benefit from early detection of clinically significant prostate cancer at a potentially curable stage through systematic five-year re-evaluation. Although direct individual benefit cannot be guaranteed, men diagnosed with clinically significant disease during follow-up may benefit from timely therapeutic intervention. In addition, participants may gain clinically relevant information derived from secondary outcome analyses, including detailed assessment of prostate volume, prostate morphology on MRI, and longitudinal PSA and PSA-density dynamics. These data may support individualized clinical decision-making beyond the scope of the primary endpoint, particularly with regard to the management of lower urinary tract symptoms secondary to benign prostatic enlargement. Furthermore, longitudinal PSA kinetics and MRI findings may inform future prostate cancer surveillance strategies and guide individualized follow-up planning extending beyond the five-year study horizon. In addition, the project has substantial societal benefit. It will generate long-term safety data on bpMRI-based screening strategies and may contribute to improved, more precise, and less burdensome prostate cancer screening pathways for future patients.

Overall assessment: Given that all procedures are either non-invasive or clinically indicated, and given the limited additional burden compared to routine urological care, the overall risk is minimal. The potential individual and societal benefits justify the conduct of the project. The risk–benefit ratio is therefore favorable and consistent with the Category A classification.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Quality assurance measures are implemented to ensure protocol adherence, data integrity, and compliance with applicable legal and institutional requirements. All project personnel involved in recruitment, data collection, MRI interpretation, biopsy procedures, and data entry are appropriately trained and qualified. Study procedures are conducted in accordance with the approved protocol and institutional standard operating procedures. MRI examinations are performed according to standardized institutional protocols. MRI interpretation is conducted by experienced radiologists with expertise in prostate imaging. Prostate biopsies are performed by experienced urologists using standardized transperineal techniques. Data are entered into secure institutional systems (the clinical research management system ORCA - Orchestrate your clinical research activities - and Redcap). Plausibility checks and consistency controls are implemented where appropriate. Data validation is performed by the Principal Investigator (PI) and Co-Investigators through review of entered data and comparison with source documents where necessary.

Due to the non-interventional design and minimal risk classification (Category A), no independent data monitoring committee is planned.

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

The project leader has appropriate knowledge and skills in the areas of data security and data protection or can ensure compliance by calling in appropriate expertise (Ordinance on Clinical Trials in Human Research, ClinO/KlinV.).

7.2 Data recording and source data

Project data are recorded using the institutional clinical research management system ORCA (“Orchestrate your clinical research activities”) and the secure electronic data capture system Redcap hosted by the University Hospital Basel. ORCA is the institutional clinical research management platform of the Department of Clinical Research (DKF Basel) and the University Hospital Basel. It is used for structured study management, participant tracking, and documentation within the secure institutional IT infrastructure. For each participant, a study-specific electronic Case Report Form (eCRF) is maintained in Redcap. Participants are identified in the eCRF exclusively by a unique study participant number. Direct identifiers (name, full date of birth, address) are not recorded in the study database. Redcap provides a secure, password-protected environment with user-specific access rights and a full audit trail documenting all data entries, changes, and exports. Data entered into Redcap are derived from source documents and institutional clinical records. Data quality is ensured through predefined validation rules, plausibility checks, and regular review by authorized study personnel. Source data include: institutional electronic medical records, ORCA study documentation, signed informed consent forms, PSA laboratory results, MRI reports and imaging findings. biopsy reports and histopathological results, clinical examination findings, documentation of adverse events. Routinely collected clinical data remain part of the participant’s medical record. Study-specific variables are transferred to Redcap for research purposes. No online questionnaires or home-based electronic data collection are planned.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Coding is done using a method based on the current state of the art that must be based on the current state of the art (Art. 26 HRO). The participant identification list linking the unique participant number to directly identifying information (e.g., name, date of birth) is stored separately from the study database in a secure, access-restricted institutional environment at the University Hospital Basel. Access to this list is limited to the Principal Investigator and specifically authorized study personnel. Study data are recorded and stored in the institutional clinical

research management system ORCA and in the secure electronic data capture system Redcap. Both systems are hosted within the protected IT infrastructure of the University Hospital Basel. Access is role-based and password-protected. Redcap provides a complete audit trail documenting data entry, modification, and export, thereby ensuring traceability of all data processing operations. Appropriate technical and organizational measures are implemented to prevent unauthorized or accidental disclosure, alteration, deletion, copying, or theft of health-related personal data. Data are stored on secure institutional servers with regular back-up procedures. Biological material in this project is not identified by participant name but by a unique participant number. Coding is done using a method based on the current state of the art (Art.26 HRO). Biological material collected as part of routine clinical care (e.g., blood samples for PSA testing or biopsy tissue) is handled according to institutional standards. No additional research-specific biobanking is planned. If biological material were to be used for further research beyond the present project, separate ethical approval and separate participant consent would be obtained. With regard to retention and storage of project data and biological material, reference is made to section 7.4.

7.4 Retention and destruction of project data and biological material

Specify time-period and location of archiving of the project data and documents (electronic and hard copies) and the biological material. All electronic research data stored in Redcap and ORCA will be archived within the secure IT infrastructure of the University Hospital Basel. Access to archived data is restricted to authorized personnel. Institutional back-up procedures are in place to prevent data loss. Paper documents, including signed informed consent forms and any project-specific documentation, will be stored in locked facilities with restricted access at the University Hospital Basel. Health-related personal data are protected by appropriate operational and organizational measures. Handling of such data is restricted to persons who require access to fulfil their duties within the research project. Measures are in place to prevent unauthorized or accidental disclosure, alteration, deletion, or copying of data. Processing operations essential to ensure traceability are documented in accordance with institutional and legal requirements. Biological material collected in the context of routine clinical care (e.g., blood samples for PSA testing or biopsy tissue) is handled and stored according to institutional clinical laboratory standards. No additional research-specific long-term storage of biological material is planned within this project.

The project leader retains all the research project data for a period of at least ten years after the completion or early termination of the research project.

If biological material or data are to be destroyed after expiration of the legally required retention period, destruction will be carried out in accordance with institutional procedures and documented appropriately. If future research use of data or biological material beyond the scope of the present project is planned, separate ethical approval and separate participant consent will be obtained prior to such use.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The VISIONING III study is conducted as an investigator-initiated academic research project at the University Hospital Basel. The project is funded through institutional resources of the Department of Urology and the Department of Radiology. No commercial sponsor is involved. No financial support from industry is received for the conduct of this study.

The results of the study will be analyzed and published in peer-reviewed scientific journals and may be presented at national and international scientific conferences. Publication will occur irrespective of the direction or magnitude of the study findings. Both positive and negative results will be reported in accordance with principles of scientific transparency.

Authorship will follow internationally accepted authorship guidelines (e.g., International Committee of Medical Journal Editors - ICMJE). Data generated within the scope of this project will be analyzed and reported in aggregated, anonymized form. Individual-level data will not be

publicly disclosed. Data sharing with external researchers may be considered upon reasonable request and after approval by the responsible ethics committee, provided that data protection regulations are respected and appropriate data transfer agreements are established. Any secondary use of data beyond the scope of the present protocol will require separate ethical approval where applicable.

Declaration of interest:

The investigators declare that there are no financial or personal conflicts of interest related to this research project. If any potential conflict of interest arises during the conduct of the study, it will be disclosed to the responsible Ethics Committee and in all related publications

Analysis of sex differences is not applicable, as the study population consists exclusively of men due to the disease under investigation (prostate cancer). Therefore, no sex-based comparative analyses are planned.

9 REFERENCES

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Appendix 1: Schedule of assessments

Time (days)	***Day 1***	***Day 7-14***	***Day 14-21***	***Day 14-21***	***Day 21-35***
Visit	*Consultation*	*Imaging*	*Counseling*	*Biopsy / Tumorboard*	*Consultation*
Patient Information & Informed Consent (Study & Biopsy)	+		+		
Demographics	+				
Medical History and questionaires: ***- IPSS*** ***- NIH-CPSI*** ***- QoI,Distress***	 + +				+ *(in case of positive biopsy)*
In- /Exclusion Criteria	+	+			
Physical Examination (DRE)	+ *(in case of suspicion of prostatitis, IPSS >20 , CPSI>19)*			+ *(during biopsy)*	
Laboratory Tests ***- PSA*** ***- Urine sample*** ***- Urine analysis for UTI***	 + + +			 +	+ *(if indicated)*
<u>bpMRI</u>		+			
MRI Targeted + perilesional Biospy / or SB (according to indication)				+	
Discussion of biopsy results and treatment counseling					+
<u>Primary Variables</u>	+	+	+	+	+
<u>Secondary Variables</u>	+	+	+		+

<u>Study-specific examinations appear underlined (essentially only repeat bpMRI for all participants).</u>
The remaining examinations constitute standard urological practice.

**In case of PI-RADS 3 lesions in bpMRI, a repeat mpMRI is performed after 6 months. The schedule of assesements is consequently restarted from the MRI examination and depends on the findings obtained at that time.*