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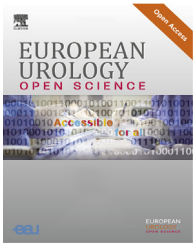

European Association of Urology

Trial Protocol

Risk-stratified Approach to Implementing Population-based Prostate Cancer Screening in Five Pilot Sites in the European Union: A Protocol for the PRAISE-U Project

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Abstract

Prostate cancer (PCa) is a major public health concern for men globally and the most commonly diagnosed cancer among men in the European Union (EU). Despite large trials suggesting benefits from early detection of PCa, risks of overdiagnosis and overtreatment are evident. In 2022, the EU Commission proposed introducing prostate-specific antigen (PSA) testing for men in an organised setting, in combination with magnetic resonance imaging (MRI) scanning as a follow-up test to minimise these risks. PRostate cancer Awareness and Initiative for Screening Europe (PRAISE-U) is a pilot study evaluating the implementation of a risk-stratified population-based approach to PCa screening in Ireland, Lithuania, Poland, and two areas in Spain (Galicia and Manresa) for feasibility, efficacy, and cost effectiveness. As per the protocol designed for the pilots, men aged 50–69 yr residing within the catchment area of the study sites will be invited to participate. Those consenting to participate will undergo PSA testing, and men with PSA >3 ng/ml will undergo risk stratification before MRI and, if necessary, after MRI before undergoing biopsy. A collaborative user board comprising health care

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professionals, patients, and decision-makers will be formed to provide stakeholder input throughout the study. PRAISE-U will be evaluated on three major pillars: analysis of clinical and programme outcomes, psychosocial impact, and cost effectiveness. A set of key performance indicators (KPIs) has been developed to be piloted in the PRAISE-U pilot sites. The KPIs will serve to assess the performance and outcomes of risk-stratified PCa screening at each site. A REDCap database will be used to collect and manage pseudoanonymised data from the pilot sites. Ethics approval was obtained from each pilot site. The PRAISE-U pilot implementation is expected to commence in the 3rd quarter of 2024 for 12 mo and provide valuable data on the implementation outcomes of a risk-stratified screening approach across Europe. The findings is expected to inform the development of an optimised screening strategy with an acceptable benefit to harm ratio.

1. Introduction

Prostate cancer (PCa) is the second most common cancer among men globally and the most commonly diagnosed cancer among men in the European Union (EU) [1]. Controversies surrounding screening for PCa has resulted in frequent changes in recommendations [2–4]. Despite large trials demonstrating significant mortality reduction from early detection of PCa through screening with prostate-specific antigen (PSA), the risks of overdiagnosis and overtreatment are evident [5]. The European Association of Urology (EAU) recommends individualised risk-adapted strategies to be implemented within the framework of a population-based organised screening programme [6]. In 2022, the EU Council recommended introducing PSA testing for men, with magnetic resonance imaging (MRI) of the prostate for men with high PSA before making a decision for prostate biopsy [7]. Using risk calculators that consider other factors in addition to PSA levels may further improve the positive predictive value of screening to detect clinically significant PCa and reduce unnecessary diagnostic procedures. These proposed interventions are largely based on controlled screening trials, and their effectiveness in population-based screening programmes in different health systems is yet to be established.

Population-based, quality-assured screening programmes are instrumental in achieving the desired outcomes of screening in terms of mortality reduction with a positive benefit to harm ratio. The PRostate cancer Awareness and Initiative for Screening Europe (PRAISE-U) project (co-funded by EU4health programme of the European Commission) is designed to address the knowledge gap that exists in understanding the impact of PCa screening while translating from research to real programmatic setting. In this paper, we detail the design of a multicentric study that aims to pilot the implementation of a risk-stratified population-based PCa screening algorithm in different health systems to generate evidence for feasibility, efficacy, and cost effectiveness at the EU level [8]. In addition to risk stratification, the pilot utilises MRI to refine patient selection for biopsy and is designed to address various aspects of delivery of PCa screening within an organised framework, including evidence-based management of the PCa cases detected through the project. This initiative will identify implementation strategies that are appropriate in local context in the five pilot sites. The study will also evaluate acceptability of the programme among the beneficiaries as well as the service providers through a collaborative stakeholder engagement approach. In addition, we will evaluate the cost effectiveness and user attitudes towards the proposed intervention strategy in each pilot.

2. Methods

2.1. Protocol development

As a first step, we performed a desk review of documents related to the requirements for provision, access, and performance of PCa screening in the selected region. We modified the Cancer Screening in Five Continents (CanScreen5) qualitative questionnaire developed by the International Agency for Research on Cancer (IARC) for breast, cervical, and colorectal cancer for this purpose. A background report was prepared based on the desk review and was shared with the local teams for verification. Information collected online through the questionnaire was cross verified during facility visits and stakeholder consultations. Next, a facility assessment visit was carried out in the pilot sites to assess selected health facilities in the region. The following dimensions were assessed: general information, governance, cost of care, infrastructure, human resources, consumables and supply chain, monitoring and evaluation, and infection control. Facility assessment was followed by consultations with stakeholders. The stakeholders selected for engagement depended on the organisation and implementation of the programme. The stakeholder consultation covered the World Health Organization building blocks for efficient health systems, and questions related to PCa delivery and implementation of evidence-based interventions were included. All information was triangulated and developed into a protocol by a multidisciplinary team within PRAISE-U and reviewed by a set of external reviewers.

2.2. Pilot sites

The study will be conducted in five pilot sites: namely, in Ireland, Lower Silesian region in Poland, Lithuania, and two areas (Manresa and Galicia) in Spain (Fig. 1). The sites were selected due to the difference in status and organisation of screening programmes between them. Lithuania is the only country that has an on-going PCa screening programme. Organisation of

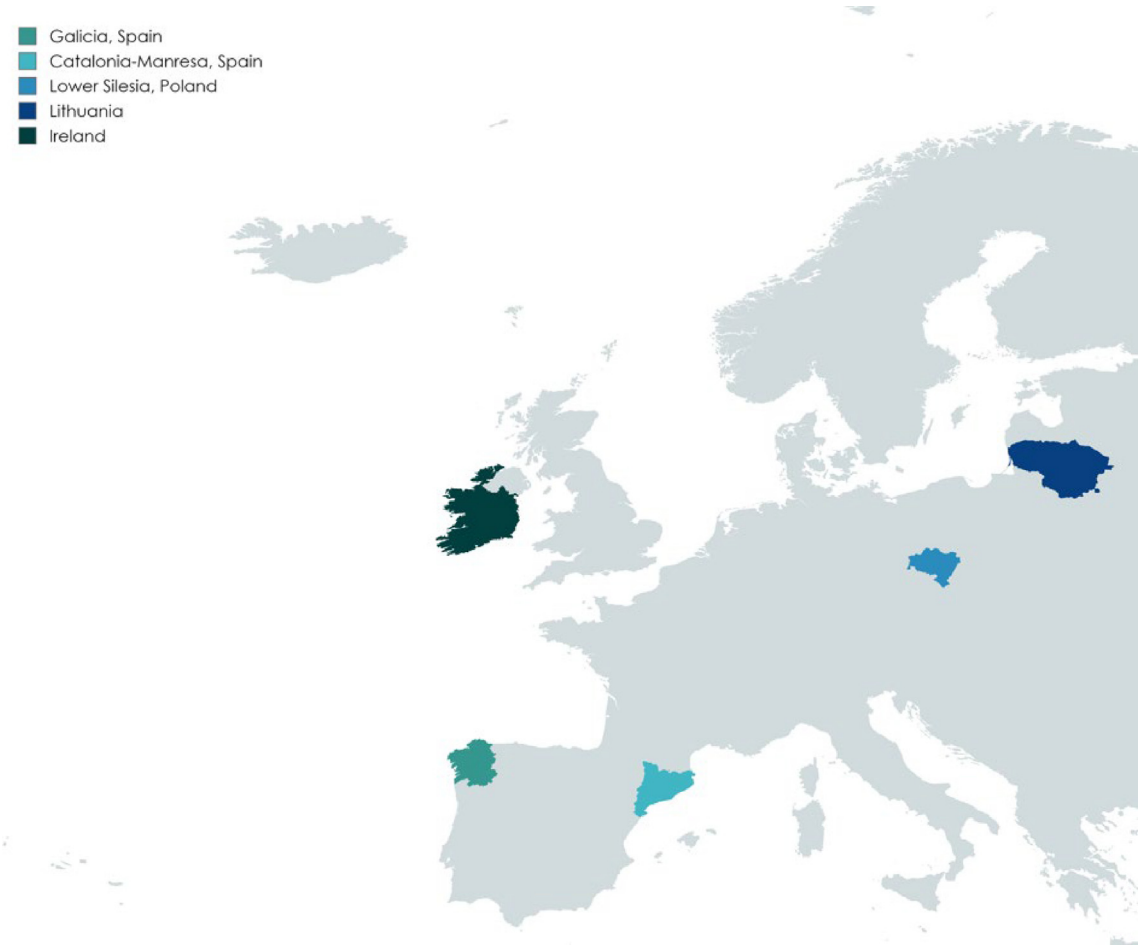

Fig. 1 – PRAISE-U pilot sites. PRAISE-U = PRostate cancer Awareness and Initiative for Screening Europe.

screening programmes for other cancers (breast, cervical, and colorectal cancer) is quite different across Ireland, Lithuania, Poland, and Spain. In addition, PRAISE-U will also collaborate with advisory and knowledge-sharing sites such as Sweden, Czech Republic, and Estonia.

2.3. Study size

Due to the 1-yr intervention phase of PRAISE-U to assess the feasibility of the screening strategy, we estimated the minimum required number of PCa patients for the project. We factored in local health system resources, constraints, and response rates from other screening programmes to determine the necessary recruitment size. The sample size needed in a pilot study, considering participant flow, budgetary constraints, and the number of participants needed to reasonably evaluate feasibility goals in quantitative studies, is estimated to be 30 patients [9]. Based on the total number of invitations, expected participation rate, and an estimated PCa detection rate of 12.8 PCa cases per 1000 participants, we estimate that we would diagnose between 36 and 77 PCa cases across study sites. This range is consistent with the guidelines for designing and evaluating feasibility pilot studies, ensuring that we can reasonably assess the study's feasibility within the constraints of a 1-yr period [10].

2.4. Timeline for implementation

The pilot study is expected to commence in the third quarter of 2024 and is expected to be completed in 12 months after the first invitation.

3. Strategies for recruitment of eligible men

Men aged 50–69 yr residing within the catchment area of each pilot site will be invited to participate. The recruitment strategies by the study sites are described in Table 1. In Galicia, Spain, up to 12 000 eligible men will be invited from Ferrol Sanitary district, with an expected response rate of 50%. The programme will utilise a two-step invitation process—a short message service (SMS) will initially be sent to the men with subscription telephone number (or letter, in case it is not available), and this will be followed up by an SMS reminder to encourage participation. Galicia will leverage on existing health care databases with unique identifiers for participants to facilitate programme monitoring and evaluation. Men will be invited to register in a specific website.

In Manresa, Spain, 5640 men will be invited via letters from the catchment population of two GP networks managed by Althaia Foundation. The letter will contain a pre-

Table 1 – Recruitment strategy for PRAISE-U pilot sites

	Galicia, Spain	Manresa, Spain	Lower Silesia, Poland	Lithuania	Ireland
Invitation method	SMS (or letter) + hotline support. Website for registration	Letter with appointment details + SMS before appt, hotline support	Letter, hotline support	E-mail + SMS + hotline support	Letter, website for registration
Number of invitations	12 000	5640	30 000	10 000	8000
Sampling frame	Eligible men from Ferrol sanitary district	Catchment population of 2 GP networks	All communities (of 169) in Lower Silesia distributed evenly	Catchment population of 2 GP networks	Population registry
Expected response rate (%)	50	50	10	50	60
Existing data infrastructure	NASI (“número asistencial”) unique ID and CRIIS database	Network EMR	Unique ID, hospital EMR	Unique ID, MED.I.S. information system monitored by NHIS	No unique ID; hospital ID

appt = appointment; EMR = electronic medical record; GP = general practitioner; NHIS = national health insurance scheme; PRAISE-U = PRostate cancer Awareness and Initiative for Screening Europe.

booked appointment and details with a hotline support. An SMS will be sent to the registered participants prior to the appointment date.

In Poland, a screening centre and a number of satellite screening centres will invite evenly distributed 30 000 men from all communities in the Lower Silesian region via letters supported by a central hotline. The expected participation is 10% of the invited men.

The pilot to be implemented in Ireland aims to invite 8000 men with urban and rural representations. Letters will be sent inviting men to register in a website to receive home-based test kits. The expected participation rate is approximately 60%. Ireland will utilise a national population registry from the Department of Social Protection for its sampling frame.

In Lithuania, 10 000 men will be invited via two GP networks with an expected response rate of 50%.

4. Information sheet and informed consent

Participants who are invited will be informed that this is a pilot study in which their participation is purely voluntary and their refusal to participate will not affect their routine care. They will be informed about the study details using predeveloped participant information sheet, and consent will be sought from each participant. The informed consent obtained from the participants include explicit consent for the collection, storage, and use and future use of personal data, and for the investigator to allow access to their medical records for study-related monitoring. The consent also informs the participant about the transfer of data to other entities and other countries, and how data confidentiality will be ensured.

Information sheet and informed consent forms will be sent along with the invitation. It includes information explaining the nature of the study, its purpose, procedures involved, expected duration, potential discomfort that they may endure, potential risks and benefits, alternative treatments, and specific study requirements.

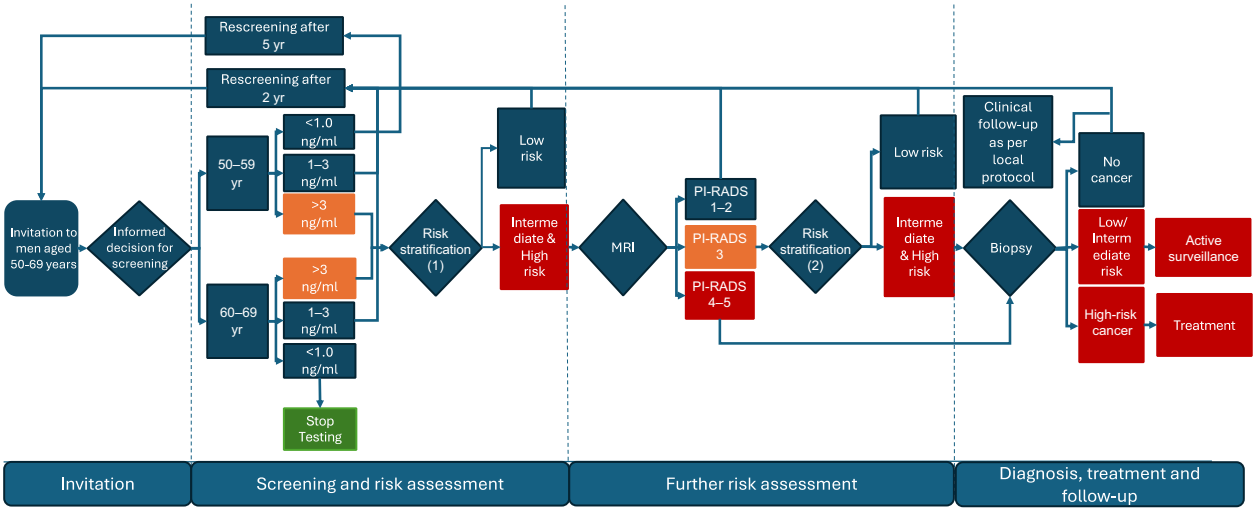

Fig. 2 – PRAISE-U screening algorithm. MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PRAISE-U = PRostate cancer Awareness and Initiative for Screening Europe.

Table 2 – Strategy for implementation in five PRAISE-U pilot sites

	Galicia, Spain	Manresa, Spain	Poland	Lithuania	Ireland
First contact point after recruitment	GPs of Ferrol district	GP network (Althaia Foundation)	Central and satellite screening centres	GPs in 2 networks	Website to receive home-based PSA test kit
Risk stratification (1)	DRE and suprapubic US + RPCRC 3/4 calculator by urologist	Transabdominal US + PSA density calculation by advanced care nurse	DRE + transabdominal US + RPCRC 3/4 calculator by urologist	DRE + transabdominal US + RPCRC 3/4 calculator by urologist	DRE + RPCRC 3/4 calculator by urologist at rapid access prostate clinic
MRI	mpMRI 3T	bpMRI 3T	bpMRI 1.5T	mpMRI 1.5T	mpMRI 3 and 1.5T
Risk stratification (2)	RPCRC 3 and 4 risk calculator	RPCRC 3 and 4 risk calculator	RPCRC 3 and 4 risk calculator	RPCRC 3 and 4 risk calculator	RPCRC 3 and 4 risk calculator
Biopsy	Transperineal/TRUS-guided cognitive fusion biopsy by urologist Targeted/systematic biopsy Type of anaesthesia depends on consensus between clinician and participant	TRUS-guided cognitive fusion biopsy by radiologist Targeted/systematic biopsy performed under sedation	TRUS-guided fusion biopsy by urologist Targeted/systematic biopsy performed under local anaesthesia	Transperineal/TRUS-guided biopsy Targeted/systematic biopsy performed under sedation	Transperineal/TRUS-guided biopsy by radiologist Targeted/systematic biopsy performed under local anaesthesia
Treatment decision	Local clinical protocol MDT	Local clinical protocol At RPCD unit + MDT	Local clinical protocol Hospital tumour board	Local clinical protocol + MDT	Local clinical protocol MDT

bpMRI = biparametric MRI; DRE = digital rectal examination; GP = general practitioner; MDT = multidisciplinary team; mpMRI = multiparametric MRI; MRI = magnetic resonance imaging; PRAISE-U = PRostate cancer Awareness and Initiative for Screening Europe; PSA = prostate-specific antigen; RPCD = rapid prostate cancer diagnostic; RPCRC = Rotterdam Prostate Cancer Risk Calculator; TRUS = transrectal ultrasound; US = ultrasound.

5. Screening and risk assessment pathway

The screening algorithm includes PSA testing, followed by risk stratification before and, if necessary, after MRI, after which a decision for biopsy is made (Fig. 2). The diagnostic pathway for each pilot will be the same; however, the implementation strategy at each step will vary, primarily to align with the current standard of care and health system capacity in each pilot site. The implementation strategies for the pilots incorporating the screening algorithm by the study sites are summarised in Table 2.

5.1. *PSA testing*

After consenting to participate, men will undergo PSA testing at a health facility in all pilots, except in Ireland. In the Irish pilot, a home-based PSA testing kit will be sent to registered men. Men with PSA levels >3 ng/ml will be referred for first-level risk stratification. Men with PSA levels of 1–3 ng/ml will be advised to repeat PSA testing in 2 yr. Men with a PSA result of <1 ng/ml will be advised to retest in 5 yr unless they are in the 60–69 yr age range, then they will be advised to stop testing.

5.2. *Risk stratification (1)*

The Rotterdam Prostate Cancer Risk Calculator (RPCRC) 3 and 4 will be utilised for first-level risk stratification in all pilot sites, except in Manresa. The RPCRC requires information on PSA, history of biopsy and digital rectal examination (DRE), and prostate volume estimation [11]. Prostate volume will be assessed via ultrasound (transrectal or transabdominal) in all sites except in Ireland, where volume will be assessed only by DRE. Those with intermediate and high risk will be referred to MRI. Men with a low risk will be advised to repeat PSA after 2 yr. The Manresa site will utilise PSA density (PSA-D) for first-level risk stratification. A PSA-D cut-off of $\leq$0.15 indicates a low risk, while PSA-D >0.15 indicates a high risk. High-risk participants will be referred for MRI.

5.3. *MRI for intermediate- and high-risk men*

Following the first risk stratification, all sites will utilise MRI as a next step in the screening pathway. The pilot sites in Lithuania, Galicia, and Ireland will utilise multiparametric MRI (mpMRI). The sites in Manresa and Poland will use biparametric MRI (bpMRI). Men with Prostate Imaging Reporting and Data System (PI-RADS) score of 1–2 will be advised for rescreening in 2 yr, and those with PI-RADS 4–5 will be advised to undergo prostate biopsy. For those with PI-RADS 3, additional risk stratification will be administered.

5.4. *Risk stratification (2)*

This risk stratification moment will be performed only for men with PI-RADS 3. All sites will use RPCRC 3 and 4 for this second-level risk stratification. At this point of risk stratification, MRI results are added to the variables used for first-level risk stratification. Subsequently, those with intermediate and high risk will be referred for prostate biopsy and those who are at a low risk will be advised for screening in 2 yr.

5.5. *Diagnostics and treatment*

Ultrasound-guided prostate biopsy will be performed in eligible men, after which a treatment decision will be made based on histopathology results (Gleason grade and other parameters). Lithuania and Poland will use the transrectal ultrasound (TRUS)-guided software fusion method for prostate biopsy, while Galicia, Manresa, and Ireland will use the TRUS-guided cognitive fusion method. In Lithuania, the approach for biopsy depends on whether it is organ confined (transperineal) or locally advanced (transrectal). The Polish and Manresa sites will use a transrectal approach, whereas the Galician pilot will be performing transperineal biopsies for all. In Ireland, both (transperineal and transrectal) will be performed. In Poland and Ireland, biopsies will be performed under local anaesthesia. In Manresa and Lithuania, it will be performed under sedation. In Galicia,

the type of anaesthesia will depend on the consensus between the clinician and the participant. Prostate biopsies will be performed by urologists (Galicia, Poland), radiologists (Manresa, Ireland), or urologist and interventional oncologist (Lithuania).

The difference in diagnostic and treatment protocol is also highlighted in Table 2.

6. Management after histopathology

All participants of the pilot will be informed of their histopathology results. Those with cancer detected on histopathology will be referred to oncology centres for treatment decisions. The decision for active surveillance and active treatment will be offered to men based on clinical assessments.

7. Stakeholder involvement

A collaborative user board (CUB) will be formed in every pilot site to provide stakeholder input throughout the pilot implementation. The CUB will include clinicians (urologists, oncologists, radiologists, pathologists, and primary care physicians), service users (men, patients, family members, and patient advocacy groups), and decision-makers (public health officials and policymakers). The CUB will meet to discuss barriers and facilitators to implementation, and may be consulted throughout the project.

Focus group sessions will be held with clinicians (those who are actively involved with screening the men), support staff (nurses, medical assistants, and administrative staff, whose work will be impacted by the implementation), and decision-makers (working with screening) to gather information about their perspectives on the screening protocol. In addition, clinicians and support staff will be surveyed before and during the screening process about their experiences with the intervention.

8. Monitoring and evaluation

8.1. Codebook

A codebook was developed to describe the variables that will need to be collected across the screening and management continuum. To facilitate an evaluation of the programme across the pilot sites in a harmonised manner, a list of minimal requirements was created, consisting of clinical, psychosocial and cost-effectiveness variables in addition to a full data requirement. A set of key performance indicators (KPIs) were also developed to be piloted in the PRAISE-U pilot sites.

8.2. Database

The REDCap database will be used to collect and manage pseudoanonymised data from each pilot site. This database will be hosted by the EAU, and data will be stored in a secure server. Every pilot will assign data entry personnel, and data will be entered prospectively. Data managers at the Erasmus University Medical Centre, the Netherlands, will perform data quality control in several ways. Scripts will be created to identify data entry errors and illogical data combinations, which will be scheduled to run at regular intervals based on data inflow. Prior to the start of the pilots, all data entry persons will be trained by the data managers. Within this session, the basics of REDCap will be explained, and the different ways of data import and different test cases will be shown to the data entry persons. In addition, on-site data quality control will be conducted and compared with all sources of data. PRAISE-U will be evaluated on three major pillars: clinical analyses, psychosocial analyses, and cost-effectiveness analyses. Two sites (Poland and Galicia) will develop the database in their internal database systems, and all the necessary data will then be transmitted in packages to REDCap and handled in the same manner as the remaining sites. This allows better data protection at those sites and aims at proving that all screening activities can be settled in already existing medical data systems available commercially to hospitals and outpatient clinics.

8.3. Programme, clinical assessment, and psychosocial assessment

For the assessment of feasibility and effectiveness, clinical parameters and programme indicators will be collected on the following parameters: invitation, participation, sociodemographic characteristics of participants, PSA results, medical history, DRE/TRUS details, risk stratification, MRI, biopsy, treatment details, and follow-up.

Our main outcome measure of interest is the incidence of clinically significant PCa (defined as International Society of Urological Pathology score of $\geq$2). The secondary outcome measures involve measures of feasibility and effectiveness that include invitation coverage, participation rates, compliance to diagnostic steps, risk stratification outcomes, PCa detection rates, and intervals of care pathway. The set of KPIs developed will also be tested in this pilot.

For the psychosocial assessment, a combination of questionnaires will be sent to the participants at different touch points during the screening and care pathway. The questionnaire includes the following: PROCASE Knowledge Index [12], Attitude scale [13], Risk Perception [14], Brief Health Literacy Scale for Adults (B-HLA) [15], Perceived Stress Scale 10 (PSS-10) [16], State and trait anxiety Inventory short form (STAI-6) [17], and European Quality of Life-5 Dimensions (EQ-5D-5L) [18]. All questionnaires used are validated in English. PROCASE, Attitude, Risk Perception, and B-HLA have been translated into Spanish, Polish, and Lithuanian by two independent health researchers, and the translations were cross-verified with each other and the original English versions. The STAI-6, PSS-10, and EQ-5D-5L questionnaires have been validated in previous studies across all target languages.

To ensure adequate response rates and minimise response bias, questionnaires will be sent to all men invited for screening, including both those who accept and those who decline participation. Participants will receive up to two reminders, spaced 7 d apart, if they have not completed

the questionnaires. For participants without electronic devices, we will provide the option to complete the questionnaires in paper form or on tablets at the clinic during their screening visit.

Medians and quartiles or absolute and relative frequencies will be used to describe quantitative and categorical variables, respectively. Likert scale responses corresponding to the outcome measures will be analysed as ordered categorical data, with frequencies and proportions represented for outcome measures.

Baseline characteristics (sociodemographic variables, knowledge, attitudes towards PCa screening, health literacy, and psychosocial levels) will be compared between participants and nonparticipants using descriptive statistics and nonparametric tests. The psychosocial impact of screening at different touch points will be analysed using uni- and multivariate regression models.

8.4. Cost-effectiveness analysis

We will evaluate the cost and effects of this screening strategy compared with no screening, opportunistic screening, or non–risk-tailored PSA-based screening (current standard of care). Unit costs will be collected from local official sources. Information on local official sources and any possible translations should be provided by the pilot sites. The effects will be expressed as quality-adjusted life years (QALYs) to express participants' quality-adjusted life expectancy. QALYs will be used to measure the effectiveness, combining both the quality of life (ie, utility scores) and the quantity of life lived (ie, numbers of years lived in a certain health state). A decision-analytical model (ie, Markov model or discrete event model) will be used to predict costs and health outcomes of the PRAISE-U screening strategy and to compare this with the current standard of care.

The outcome of this cost-effectiveness analysis will be expressed as incremental cost-effectiveness ratios (ICERs), which quantifies the cost per QALY gained. ICERs will evaluate the ratio between the differences in costs and effects of the PRAISE-U algorithm and the current standard of care. Direct medical and indirect costs will be considered, which means that these analyses will be performed from a societal perspective. Data on health outcomes, health care use, and costs will be collected at different time points of the screening algorithm. Additional information will be obtained from local cancer registries. To account for uncertainties in the cost-effectiveness model, a sensitivity analysis will be performed to obtain the best possible estimation of the cost effectiveness of the PRAISE-U screening algorithm. These parameters will serve as critical inputs for the comprehensive evaluation of the cost effectiveness of the PRAISE-U screening algorithm in comparison with the existing standard of care. Country-level pre- and postmeasurement cost effectiveness will be evaluated for some key parameters, such as the annual number of patients diagnosed with PCa per country, tumour stage at diagnosis, and treatment patterns.

8.5. Quality assurance

Regular audits of the sites' progress will be led by the EAU and governed by the PRAISE-U management board. The management board will also conduct site visits periodically to check protocol compliance, quality of documentation, and updating of data entry. IARC will also collect aggregate data at the end of the pilots (after 12 months from the starting date of screening implementation) to estimate the programme KPIs. Each site will organise a stakeholder meeting to disseminate the findings based on an analysis of the KPIs.

Rigorous quality assurance measures will be implemented to address the quality and variability of magnetic resonance (MR) images. During the preintervention phase, The European Society of Urogenital Radiology conducted expert assessments of MR images to ensure the quality of MRI in all sites using the PI-QUAL criteria. Additionally, PRAISE-U has established a data monitoring committee comprising external experts who will oversee quality control of both biopsy and MR images during the pilot phase. PRAISE-U is also developing a standard operating procedure for maintaining consistent quality control in MRI and biopsy processes.

9. Ethics declaration and trial registration

The study has been approved by the institutional review board and ethics committee of the following institutions: IARC (conditional approval IEC 23-25, 03/07/2023) and Komisja Bioetyczna by Lower Silesian Chamber of Physicians (approval no. 02/05/2024, dated May 8, 2024). At the time of manuscript preparation, the protocol was under review by the ethics committees in Galicia and Manresa, Spain, Ireland, and Lithuania. The trial was also registered at ClinicalTrials.gov (NCT06424275).

10. Discussion and conclusion

The protocol of the pilots designed jointly by a large multidisciplinary team within the framework of the PRAISE-U study will guide implementation of a risk-stratified approach to PCa screening across a geographically diverse European population. The approach incorporating several key elements to optimise screening accuracy and minimise unnecessary diagnostic and treatment procedures is well aligned with the latest European Council recommendations to expand population-based PCa screening in the member states.

Designing of the protocol and implementation of the pilots have several strengths. The overall approach to risk-stratified PCa screening and management was described by several European experts and IARC investigators following an evidence review [19]. Planning the details of implementation in a real public health care setting required an in-depth understanding of the functioning of the local health care services as well as availability of infrastructure and resources. We incorporated a health system assessment and stakeholder feedback to develop implementation

strategies for the proposed intervention. The proposed CUB will play a vital role in providing continued practical guidance and ensuring the programme's acceptability to all stakeholders, including health care providers, patients, and policymakers. This is expected to have a major implication on scaling up PCa screening in the target countries as well as the rest of the EU member states. The diverse implementation strategies across the pilot sites, such as initial contact through general practitioners or dedicated screening centres, reflect the need for adaptability to existing health care structures. This pragmatic approach strengthens the generalisability of the study's findings across future scalability plans.

The multitier diagnostic pathway for PCa is documented widely in scientific literature. The one used in the current project mirrors the EAU clinical guidelines with several adaptations. The decision to utilise a PSA value of >3 ng/ml as a threshold for further workup acknowledges the limitations of PSA as a standalone biomarker. This value balances sensitivity and specificity, aiming to optimise the programme's ability to detect clinically significant cancers while minimising unnecessary biopsies.

Implementation of risk stratification via a calibrated risk calculator (RC), tailored to the target population, provides an enhancement to the algorithm. This approach has been shown to outperform traditional diagnostic algorithms [20]. For PRAISE-U, the rationale behind this algorithm is twofold. First, by incorporating a calibrated RC both before and after MRI, the stratification accuracy is improved by refining participant selection, ensuring that only those with a significant likelihood of PCa proceed to biopsy. Second, this dual-step risk stratification is expected to reduce the number of unnecessary biopsies, mitigating associated risks and costs. However, even though this hypothesis regarding the reduction in biopsy numbers through this method is promising, it warrants evaluation to establish its effectiveness, which is the aim of this project.

While there are multiple different risk stratification tools for PCa screening, in a systematic review, Denijs et al [21] identified 96 unique RCs, with 45 of these having been validated externally. For the purpose of the study, we aimed to utilise a simple to use RC that would be feasible at a population level and at low cost. The RPCRC was developed based on the data of the Rotterdam section of the European Randomised study of Screening for Prostate Cancer. Using the RPCRC, we can estimate the risks of having biopsy-detectable and potentially indolent PCa. Using clinical variables such as PSA, outcome of DRE and TRUS, prostate volume, and outcome of MRI, an individual risk is calculated. If the individual risk is $\geq$20% for any PCa and/or >4% for clinically significant PCa, a prostate biopsy is recommended. In a population-based biopsy-naïve cohort, it has been shown that using the RPCRC approach as compared with conducting biopsy in all men with PSA $\geq$3.0 ng/ml could lead to a reduction of 33% of all prostate biopsies performed, at the cost of missing 14% of all PCa cases and 7% of all clinically significant PCa cases [22,23]. In addition, RPCRC has also been validated externally in different populations [24]. The EAU currently proposes the RPCRC and the PCPTRC 2.0 as options. Considering the regulatory requirements in the EU, it is important that RCs have obtained approval for clinical use as medical devices. To our knowledge, only the RPCRC and the Stockholm 3 model have obtained a CE mark, signifying compliance with stringent regulatory EU standards (Medical Device Regulation).

In the Manresa pilot site, we are unable to perform the DRE/TRUS that will allow the use of RPCRC as it is a primary care–based screening strategy with unavailability of urologists before first-level risk stratification. For this site, we have opted to perform first-level risk stratification with PSA-D using prostate volume estimates obtained from transabdominal ultrasound, with a cut-off of 0.15, considering the health system considerations and limitations. Since PSA-D is one of the strongest predictors of an RC and several studies found a PSA-D of over 0.1–0.15 ng/ml/cc to be predictive of PCa, we have opted for a cut-off of 0.15.

Following the recommendations from the EU Council and the EAU, the pilot sites will employ either bpMRI or mpMRI for further risk assessment. This reflects a measured approach, acknowledging the potential reduced cost of bpMRI while leveraging the additional information provided by mpMRI. Rigorous quality assurance measures, including expert assessment of MR images by the European Society of Urogenital Radiology, ensure the validity of MRI data within the study.

In addition to generate data on efficacy and cost effectiveness, the PRAISE-U pilots will provide valuable data on the implementation outcomes of this risk-stratified screening approach. Such implementation outcomes (acceptability, adoption, adaptation to pilot setting, and sustainability) will inform further development of optimised screening protocols that would balance early detection of PCa with patient well-being.

The PRAISE-U study is a 3-yr project aiming to design, implement, and evaluate pilot PCa screening within a total 3-yr timeframe. The initial year focused on health systems' assessment, followed by planning and finalising the protocol. The first pilot is expected to initiate participant recruitment in the third quarter of 2024. All the pilots are expected to complete screening of the target population within 1 yr. The final year will be dedicated to data management, analysis, and evaluation of the project. This limited timeframe restricts the study's ability to assess the long-term effectiveness, sustenance, and scalability of the implemented screening programme on patient outcomes, including PCa mortality rates. Future research endeavours informed by the PRAISE-U pilot data can address this limitation by incorporating a longer follow-up period to evaluate the programme's long-term impact.

Author contributions: Arunah Chandran had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Chandran, Singh, Basu, van Harten
Analysis and interpretation of data: Chandran, Singh, Basu, van Harten.
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