Supplementary Appendix 1. ProScreen power calculation and statistical analysis plan

The main outcome of the trial is prostate cancer mortality. An intention to screen analysis will be performed, with all men in the groups defined by random allocation, regardless of compliance. This is the gold standard for randomized trials, as it gives an unbiased effectiveness estimate, which is realistic for application (though lower and 'diluted' compared with an efficacy estimate based on compliers only). The only post-randomization exclusions will be based on prostate cancer diagnosis prior to entry, as inevitably some recent cases will be found out only after randomization. Follow-up starts at randomization and ends at death. Dates of death are registered also for men who have emigrated, but in case of a missing cause of death, the event will be censored. Cox regression will be used with prostate cancer death as the outcome. Randomization is expected to result in balanced distribution of age, with no need for adjustment.

Based on the most recent age-specific population rates (2010-2014) and the age structure of the male population, the expected number of prostate cancer deaths in the control arm is 222 at 10 years, with sufficient statistical power (1-β=0.8, α=0.05 two-sided) to detect a 33% reduction (hazard ratio, HR≤0.67 for the screening arm, cumulative mortality 29 vs. 44 per 10,000 men) in prostate cancer mortality. This is calculated considering the overall mortality from other causes (ranging from 7 per 100,000 at age 55 to 210 per 100,000 at age 75), yielding a total of 475,000 person-years of follow-up. At 15 years of follow-up, the expected number of deaths in the control arm is 451, with a minimal detectable effect size of 26% (HR≤0.74, 67 vs. 90 deaths per 10,000 men, based 912,800 person-years of follow-up). Covid-19 pandemic has slowed down the conduct of the trial and may influence the recruitment rate. Therefore, we are actively monitoring recruitment rate and are prepared to respond accordingly by inviting additional 45.000 men (1:4 ratio, i.e., 11.000 to screening arm and rest to control arm).

We will collect data on previous PSA test and biopsies among men participating in the study by questionnaires. For all men, record linkages with laboratory databases od service providers of PSA test will be used for both arms (HUSlab, FimLab and if possible, also private laboratories). A secondary analysis of prostate cancer mortality will be performed using the Cuzick method to correct for non-compliance and contamination (Cuzick 1997, Roobol 2009, Kilpeläinen 2015).

Intermediate outcomes include cumulative incidence of advanced (T3-T4 or M1) prostate cancer (number of cases relative to population size, not using incidence density to avoid the lead-time bias due to early detection by screening), and cumulative incidence of low-risk cancer (Gleason<7) as an indicator of overdiagnosis.

Analysis of screening test performance, including sensitivity and specificity, positive and negative predictive value will be conducted, assessing also the accuracy of 4Kscore and MRI. Interval cancer incidence will be analyzed as an indicator of program sensitivity, besides participation and its determinants. Cancer detection and screening test performance will also be evaluated by major risk factors including family history, genetic risk and major lifestyle determinants.

Short-term quality of life impact of screening will be evaluated among screening participants, and adverse effects of prostate biopsy analyzed as outlined above. Quality of life and psychosocial impacts among men diagnosed with prostate will be assessed using the EPIC instrument and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC), enrolling screen-detected and interval cases, as well as those diagnosed among non-participants and in the control arm. Follow-up will be carried

out at diagnosis and 6, 12 and 48 months after it. A mobile phone app is used to collect data on patient-oriented outcomes.

Economic evaluation will commence with cost analysis, and the final analysis of incremental cost effectiveness ratio (with a decision analysis) can be conducted only once data on both long-term cost and real outcome data on both utilities (quality-adjusted life-years) and mortality are available. However, early assessment can give some predictions about potential effects size required for the intervention to be regarded as cost-effective.