

UNICANCER Group Tumour: UCBG - SCREENING

Protocol n°: UC-0109/1805

ID RCB: 2018-A00535-50

<p>MyPeBS International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70</p>
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Abbreviated title: MyPeBS (My Personalized Breast Screening)

Version n°1.2 – 27 July 2018

PROTOCOL	VERSION N° - DATE	CPP approval	ANSM authorisation
INITIAL	V1.2 – 27 July 2018	30 August 2018	31 July 2018

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CLINICAL STUDY AUTHORISATION FOR PROTOCOL N°: UC-0109/1805

Study Title: *MyPeBS - International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70*

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ECONOMICS	DE KONING	

APPROVAL AND SIGNATURE FOR PROTOCOL N°: SCR-01_UC-0109/1805

Study Title: *MyPeBS - International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70*

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LIST of ABBREVIATIONS

ABUS	Automated Breast Ultrasound Screening
ANSM	Agence Nationale De Sécurité Du Médicament Et Des Produits De Santé
BCSC	Breast Cancer Surveillance Consortium
BI-RADS	Breast Imaging Reporting and Data Systems
CA	Competent authority
CBE	Clinical Breast Examination
CISNET	Cancer Intervention and surveillance Modeling Network
CPP	Comité De Protection Des Personnes
CRA	Clinical research associate
CRF	Case Report Form
CSR	Research Strategy Committee, Unicancer
CTSC	Clinical Trial Steering Committee
CV	Curriculum Vitae
DCF	Data Correction Forms
DBT	Digital Breast Tomosynthesis
DCIS	Ductal Carcinoma In Situ
EC	Ethics Committee
ECIBC	European commission initiative on breast cancer
eCRF	Electronic Case Report Form
EDI	European Deprivation Index
EDMC	Ethics And Data Monitoring Committee
EQ-5D	Euroqol 5D questionnaire
EMA	European Medicines Agency
FDA	Food And Drug Administration
FFDM	Full Field Digital Mammography
GCP	Good Clinical Practice
GP	General Practitioner
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International conference on harmonisation
ID	Identification
IMF	Investigator master file
INN	International non-proprietary name
INR	International normalised ratio
IRB	Institutional Review Board

ITT	Intent-to-treat
LNCC	Ligue Nationale Contre Le Cancer
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NHSBP	National Health Service Breast Screening Programme
NSP	National Screening Program
OBSS	Organized Breast Screening Structure
OS	Organized Structure
PIS	Patient Information Sheet
PRO	Participants' Related Outcomes
PRS	Polygenic Risk Score
QoL	Quality of Life
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SNP	Single-Nucleotide Polymorphism
TMF	Study Master File
TS	Tomosynthesis
UK	United Kingdom
US	Ultrasound/Ultrasonography

STATEMENT OF COMPLIANCE

UNICANCER, the study sponsor, certifies that the MyPeBS study will be conducted in compliance with the protocol, and in accordance with the Declaration of Helsinki and the relevant principles of International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP), and the national legal requirements in each country.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the concerned ethics committee (EC) for review and approval, in compliance with local regulations. Approval of both the protocol and the consent form will be obtained before any participant is included. Any amendment to the protocol will require review and approval by the EC before the changes are implemented in the study. In addition, all changes to the consent form will be EC-approved. Depending on the modifications a decision will be made whether or not a new consent is required for women who have already consented.

PROTOCOL SUMMARY

1.1 Synopsis

A) STUDY IDENTIFICATION	
SPONSOR – PROTOCOL CODE NUMBER:	
VERSION (NUMBER & DATE):	
STUDY TITLE: MYPeBS - INTERNATIONAL RANDOMIZED STUDY COMPARING PERSONALIZED, RISK-STRATIFIED TO STANDARD BREAST CANCER SCREENING IN WOMEN AGED 40-70	
ABBREVIATED TITLE: MYPeBS – MY P ersonalized B reast S creening	
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NUMBER OF CENTERS: 852	NUMBER OF RANDOMIZED WOMEN REQUIRED: 85 000 IN EUROPE WITH THE FOLLOWING INCLUSIONS BY COUNTRIES: - 20 000 IN FRANCE - 10 000 IN BELGIUM - 30 000 IN ITALY - 15 000 IN ISRAEL - 10 000 IN UNITED KINGDOM

B) SPONSOR IDENTIFICATION	
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C) STUDY GENERAL INFORMATION
INDICATION: Breast cancer screening in women from the general population aged between 40 and 70 years.

STUDY DESCRIPTION/DESIGN:

MyPeBS is a European randomized, open-label, multicentric, study assessing the effectiveness of a risk-based breast cancer screening strategy (using clinical risk scores and polymorphisms) compared to standard screening (according to the current national guidelines in each participating country), in detecting stage 2 or higher breast cancers.

Women, will be differentially screened for 4 years and then, after an end-of-study mammogram, they will return to the routine screening practice. The main study endpoint will be measured at the end of the four years of intervention.

Furthermore, follow up data will be collected for 15 years from study entry for evaluation of long-term cumulative breast cancer incidence and breast cancer-specific survival (refer to the scheme p 24 and 58).

SUBJECTS

Women from the general population aged 40-70 years old, without personal history of breast cancer or of a high-risk breast cancer condition.

PRIMARY OBJECTIVE:

The study primary objective is to show non-inferiority of the risk-stratified screening strategy in terms of incidence rate of breast cancer of stage 2 and higher (2+) (also referred to as stage 2+ throughout the protocol), compared to standard screening.

SECONDARY OBJECTIVES:

(all at 4 years/during intervention period unless otherwise indicated):

1. The key secondary objective, if non-inferiority is shown, is **to demonstrate superiority** of the risk-based screening arm to reduce the incidence rate of stage 2+ breast cancer, compared to standard screening.
2. To compare the rate of morbidity between the two arms, in terms of false positive imaging findings and benign biopsies
3. To describe the psycho-social characteristics of the population accrued and evaluate the psycho-social impact of each strategy (acceptance, observance, anxiety, distress, satisfaction, decisional regret, etc.)
4. To evaluate the costs and cost-effectiveness of each strategy
5. To evaluate the stage-specific incidence of breast cancer of any stage in each arm
6. To estimate overdiagnosis and overtreatment rates in risk-based screening and standard screening arms
7. To compare the rate of false negative mammograms and interval cancers between arms
8. To evaluate superiority of risk-based screening in terms of breast cancer-specific mortality at 10-years and 15-years in MyPeBS and in a combined analysis of the Wisdom and MyPeBS studies
9. To evaluate the added value of tomosynthesis (TS) in the detection of stage 2+ breast cancers
10. To evaluate the incidence of all stage and stage 2+ breast cancers at 10- and 15-year follow-up
11. To evaluate the incidence of stage 2+ breast cancer in risk-based screening in women aged 40-50 years old as compared to standard screening
12. To evaluate the rate of breast cancers discovered at second reading in each arm
13. To evaluate false positive imaging findings and benign breast biopsy rates in women classified in the low risk category in risk-based arm

EXPLORATORY OBJECTIVES (all at 4 years/during intervention period unless otherwise indicated):

1. To evaluate the added value of ultra-sound in the detection of stage 2+ breast cancers in each arm
2. To describe and compare between the arms, the rates of breast cancer predicted at 10- and 15-year, metastatic risk >10% using validated clinical-pathological predictors and the rates of cancers requiring chemotherapy
3. To explore the efficacy and morbidity of risk-based screening versus standard screening in subgroups (including country, risk and age categories)
4. To refine long-term breast cancer risk prediction scores through improvement of existing scores and/or description of new risk scores including clinical, imaging and/or genotyping characteristics and prediction of different breast cancer subtypes
5. To refine the breast cancer risk prediction value of mammographic and other images
6. To evaluate our ability to predict for poor psycho-social impact and low compliance to screening
7. To evaluate the accuracy (sensitivity and specificity) of single-nucleotide polymorphism (SNPs) to predict for the presence of a founder mutation of BRCA1 or BRCA2 ((BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT))

DIAGNOSIS AND INCLUSION CRITERIA:

Women from the general population of a participating region, in a participating country are eligible for the study if they meet all of the following criteria (this will be verified during the baseline phase and before randomization):

1. Female (whether born female or not)
2. Aged 40 to 70 years old (inclusive)
3. Willing and able to comply with scheduled visits, laboratory tests, and other trial procedures
4. Able to provide written informed consent obtained prior to performing any protocol-related procedures
5. Sufficient understanding of any of the languages used in the study
6. Affiliated to a social security/national healthcare system

NON-INCLUSION CRITERIA:

Women are not eligible to participate in the study if they meet any of the following criteria:

1. Personal history of breast carcinoma, either invasive or ductal carcinoma in situ (DCIS)
2. Prior history of atypical breast lesion, lobular carcinoma in situ or chest wall irradiation
3. Known condition or suspicion of a very high risk predisposition to breast cancer: germline mutation of BRCA1/2, PALB2, TP53 or equivalent
4. History of bilateral mastectomy
5. Recent abnormal breast finding under work-up (clinically suspect lesion or BI-RADS 4 or 5 image)
6. Psychiatric or other disorders that are not compatible with compliance to the protocol requirements and follow-up
7. Women who do not intend to be followed-up for 4 years

PRIMARY ENDPOINT:

The primary endpoint is the **incidence rate of stage 2 + breast cancers at 4 years** (UICC 2010)

SECONDARY ENDPOINT(S):

(all at 4 years/during intervention period unless otherwise indicated):

1. Rates of false positive imaging findings and benign biopsies in each study arm
 - False positive imaging findings include BI-RADS-ACR 3, 4 and 5 (or equivalent) lesions identified on screening images and leading to the need of additional images (US, MRI...), later control or breast biopsy
 - Benign biopsies include any percutaneous or surgical breast diagnostic procedure aimed at identifying the nature of a breast image
2. Socio-psychological assessments at baseline, and then at 1 and 4 years including evaluation of: comprehension of information, acceptance of proposed screening strategy, observance, persistence, anxiety, distress, satisfaction, decisional regret (see questionnaires in table 1)
3. Crude costs, comparison of cost-effectiveness, and budget impact of each strategy
 - Crude costs are defined as full real costs per stage 2 cancer diagnosis in each arm
 - The cost-effectiveness of mammographic screening will be calculated by comparing estimated life-years and costs of breast cancer in each arm
4. Incidence of stage-specific breast cancer in each arm (including DCIS)
5. Estimates of overdiagnosis and overtreatment rates in each study arm
 - Overdiagnosed breast cancer cases are defined as cancers that would never have been diagnosed, if women had not been screened. Differential overdiagnosis can be measured comparing the cumulative incidence of breast cancer from recruitment to a reasonably long period after the end of the study intervention, i.e. longer than the expected sejour time of screen-detected cancers. Breast cancer incidence rates in each arm will be determined approximately 10 - 15 years after the end of the interventional period of the study via interrogation of databases from national health insurances and/or organized breast screening structures.
6. Rate of false negative images and interval cancers in each arm
 - False negative images: in case of diagnosis of breast cancer in women whose last screening images (including mammogram +/- US and MRI) were considered as Breast Imaging- Reporting and Data System 1 or 2 (BI-RADS 1 or 2) at 6 months maximum before diagnosis
 - Interval cancers are defined as a breast cancers diagnosed between a negative screening episode - [mammogram classified as normal (BI-RADS ACR 1 or 2 or equivalent) or abnormal mammogram but negative assessment] and the next planned mammogram
7. 10- and 15-year breast cancer specific survival in MyPeBS and in a combined analysis of the Wisdom and MyPeBS studies
8. Detection rate of stage 2+ breast cancer in women who had screening tomosynthesis (where and when available) and the rate without tomosynthesis
9. Incidence of all stage and stage 2 + breast cancers at 10- and 15-year follow-up
10. Incidence of stage 2 + breast cancer in each arm, in women aged 40-49 at inclusion
11. Rate of breast cancers identified at second reading in each arm
12. Rate of false positive imaging findings and benign breast biopsies in women classified at low risk in risk-based arm

EXPLORATORY ENDPOINTS (all at 4 years/during intervention period unless otherwise indicated):

1. Percentage of breast cancers and stage 2 + cancers that were detected solely by ultrasound in each arm
2. Rate of high metastatic risk breast cancers in each arm using a validated clinical predictor
3. Subgroups analyses of incidence of stage 2 + breast cancers and any stage breast cancer, as well as false positive findings and benign biopsies in each arm (including country, risk and age groups)
4. Updated/new breast cancer risk prediction scores including clinical variables, imaging parameters and genotyping
5. Identification of updated/new imaging parameters to predict breast cancer risk
6. Identification of predictors of poor psycho-social impact and/or compliance to screening

7. Accuracy (sensitivity and specificity) of SNPs to predict for the presence of a founder mutation of BRCA1 or BRCA2 ((BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT)).

TABLE 1 – SOCIO-PSYCHOLOGICAL QUESTIONNAIRES

VISITS	Baseline	Risk-based screening arm	Follow-up	
Visits n°	Visit (V0)	V1	NA	NA
Visit Dates	D0	V0 + 8-12 weeks	M12 +/-6 months	M48 +/-6 months
Type of visit	physical	physical or telephone call	On-line	On-line
QUESTIONNAIRE				
1. STAI short form (state anxiety)	X	X	X	X
2. Comprehension questionnaire	X	X		X
3. Information seeking-behavior questionnaire		X		X
4. Quality of life (EQ-5D)	X			X
5. Satisfaction			X	X
6. Socio-demographic and economical status questionnaire	X			X

D) STATISTICAL ANALYSES

REQUIRED NUMBER OF WOMEN TO BE INCLUDED: 85,000 IN EUROPE

RANDOMIZATION

Women who have signed the informed consent will be assigned a unique participant identifier and will be randomized 1:1 to either standard screening or the risk-based screening strategy. Randomization will be performed through an automated real-time online system (permutation blocks).

STRATIFICATION

Randomization will be stratified by country, age (women aged <50 vs ≥50), and prior mammogram (yes or no). This will ensure to balance screening modalities, global population risks, and the rate of prevalent breast cancers at entry.

METHODOLOGY OF THE RISK-BASED BREAST CANCER SCREENING STUDY

Women who consent to participate will be randomized 1:1 to either standard screening or the risk-based screening strategy.

HYPOTHESES

The incidence rate of stage 2 + breast cancer in the MyPeBS standard arm is expected to be around 120 cases per 100,000 women per year. This number is derived from what is observed in the screened populations of European countries and including women aged 40 to 50 years for whom the incidence rate is lower :

- Incidence in women aged 50-74 years old is 140 cases/100,000 women/year on average in screened populations taking into account interval cancers and cancers not detected in women who are not screened
- We expect to include 25% of women aged between 40-49 years old
- Incidence in women aged 40-49 years old is half than older women
- Expected incidence of stage 2+ breast cancers for 100,000 women followed up for 1-year in the standard arm of MyPeBS is therefore: $(140 \times 0.75) + (0.25 \times 0.5 \times 140) = 105 + 17.5 = 122.5$. A slightly conservative estimate is therefore 120.

We anticipate a drop-out rate lower than 5% in both arms, and non-compliance rates of 10% in the risk-based screening arm and of 30% in the standard arm. These women will not be included in the per-protocol analysis due to non-compliance, in the 4-year period after inclusion.

The primary hypothesis is that the risk-based screening arm will be non-inferior to the standard screening arm in terms of cumulative hazard rate in the per-protocol population. The cumulative hazard functions of cancers of stage 2 + will be compared between the 2 study arms.

Further assumptions are a non-inferiority margin of a 25% relative increase in the risk-based arm (null hypothesis $H_0: \lambda_e/\lambda_c \geq 1.25$ with t and c standing for experimental and standard arm, respectively; it corresponds to an absolute increase in the cumulative hazard rate of stage 2 cancer or higher after 4 years up to 120/100000 stage 2 cancers the risk-based arm under H_0), 80% power, 2.5% significance level, 1-sided test. If we assume that under the alternative hypothesis a 10% relative improvement can be expected by the experimental risk-based-stratified screening arm (i.e. $\lambda_e/\lambda_c = 0.9$) due to our anticipated increase in the average numbers of mammograms in the experimental arm, a total of 298 stage 2 breast cancers are required for the non-inferiority assessment using a logrank test. We assume a total of 85,000 participants, 42,500 in each arm, to be included over a 2.5 years period.

For the primary and key secondary endpoint analysis, each participant will be followed for four years, in order to compare cycles of mammograms between the 2 screening arms. Later updates of the study analyses will be performed using longer follow-up.

STATISTICAL ANALYSES:

A statistical analysis plan (SAP) describing in detail all statistical analyses performed will be elaborated. An intermediate progress report will be made after 1 year of inclusion to evaluate the robustness of the study with regards to estimated initial inclusion rates, expected age categories, risk predictions, and compliance to screening recommendations, on the overall population and at the country level to recommend potential changes to the protocol and/or study management. Indeed if the age and risk structure of the population appeared significantly different from those expected, with potential important influence on the study's power or ability to conclude, amendments may be proposed by the Clinical Trial Steering Committee, upon advice of the Ethics and data Monitoring Committee.

This progress report will be updated after 2 years of inclusion and during the follow-up period after the last woman randomization.

Beside this, the spread of SNPs chosen and harmonious population repartition will be verified after 5,000 women are included.

All the analyses for the progress reports will be conducted blinded from the efficacy outcomes of the study (breast cancer incidence). Once all participants have been followed-up for 4 years, the cleaned database will be locked and a final statistical report prepared.

The primary analysis will compare the cumulative hazard functions of cancers of stage 2 + between the two randomized groups of women using a logrank test. The rate of cancers of stage 2 + for each arm will be estimated as the number of cancers of stage 2 + detected either clinically or by screening out of the total person-years of follow-up.

The primary non-inferiority analysis will be performed on the per-protocol (PP) population, which will include all randomized and eligible women in the arm they were randomized to, who complied with their screening recommendation in terms of number of mammograms. The analyses will be repeated in the intention-to-treat (ITT) population for sensitivity. An additional sensitivity analysis will be performed using causal inference methods to estimate the average effect of risk-based screening versus standard screening on stage 2 incidence as if all participants who will have complied with the protocol.

If non-inferiority of the risk-stratified screening arm relative to the control arm is concluded for the primary endpoint, then superiority of the risk screening arm will be tested against the standard arm (closed testing procedure). The inferential superiority analysis will be performed in the ITT population, with the PP and causal inference analysis for sensitivity. We estimate that for the superiority analysis we will have at least 80% power to detect a 30% relative decrease in the risk-based arm.

In another additional sensitivity analysis, we will exclude all prevalent cases (cancer detected 2 months after the first mammography) from the analysis and focus on women with no cancer at study entry in order to re-evaluate the benefit of risk-adapted screening thereafter.

Standard statistical methods as Kaplan-Meier analyses, Cox proportional cause-specific hazards regression will be used to compare the time-to-event variables between the 2 study arms and estimate hazard ratios adjusted for the stratification factors at a one-sided 0.025 significance level

A multivariable model will also be constructed using relevant key risk factors of breast cancer on the different time-to-event endpoints. A competing risk cumulative incidence approach will also be applied.

The overall excess overdiagnosis with risk-stratified screening compared to standard screening will be estimated from the study. Different lead time models will be applied to obtain a range of mode-based estimates of overdiagnosis; a microsimulation model will be calibrated to the study population for overdiagnosis estimates, and cost and cost-effectiveness evaluations.

E) STUDY PROCEDURES, INTERVENTION AND CONDUCT

SELECTION, INCLUSION AND RANDOMIZATION PROCESSES:

SELECTION

Women meeting eligibility criteria in a region participating in the study will be invited by the regional referral screening organization. Some women may self-refer to an including center or will be proposed the study while consulting for a pre-planned screening event or for a regular clinical visit to a general practitioner (GP) or radiologist.

ACCRUAL VISIT

Women interested in participating in the study will have a dedicated visit with an investigator in a participating center. During this visit, women will get all necessary oral and written information regarding current breast cancer screening (benefits and disadvantages), and regarding breast cancer risk, as well as the motivations, objectives, methodology, organization and logistics of the MyPeBS clinical study. They will be provided written information regarding both breast cancer screening and MyPeBS study. They will have a 2 weeks' reflection time interval before signing the informed consent if they wish so.

Women who meet the inclusion criteria and are willing to participate, will electronically sign a written informed consent form. They will be asked to complete baseline questionnaires online (see Table 1 and I, schedule of activities), before the result of the randomization.

RANDOMIZATION

Women who have signed the informed consent and fulfill all eligibility criteria will be randomized directly online by the investigator.

The results of the randomization will be immediately provided. See the study scheme in Section H) of the synopsis.

Women randomized to the standard arm will immediately receive their personal "standard" screening schedule for the next 4 years. No other study visits with the investigator are formally planned.

Women randomized to the risk-based arm will be asked to provide a saliva sample (see below). Their breast density will be evaluated. They will be scheduled for a second visit, during which they will be communicated their risk estimation and their personalized, risk-based, screening schedule/plan for the next 4 years.

TRIAL CONDUCT IN THE STANDARD ARM

In the standard arm of MyPeBS, women will be screened for breast cancer according to the current national guidelines and procedures: with a mammogram and/or tomosynthesis (TS) every two or three years starting at age 40-50 years, up to age 69-74 years according to countries, with or without ultrasound (US) according to breast mammographic density and ongoing guidelines. The current national/regional guidelines in use in the including center may be subjected to changes during the study. Guidelines and procedures in the standard arm will be updated accordingly. Current guidelines by country and age, applicable to the standard arm are described in Table 2.

BREAST CANCER RISK REDUCTION MEASURES

Participants in the standard arm will be informed of potential risk-reducing strategies. They will be provided written and on-line information material and encouraged on follow these predefined measures.

Participating women will receive standardized self-awareness recommendations, although they will remain free to comply with them or not.

STUDY CONDUCT IN THE RISK-BASED ARM

Women in the risk-based arm will provide a saliva sample during visit 0 (baseline). This sample will be sent out for centralized genotyping.

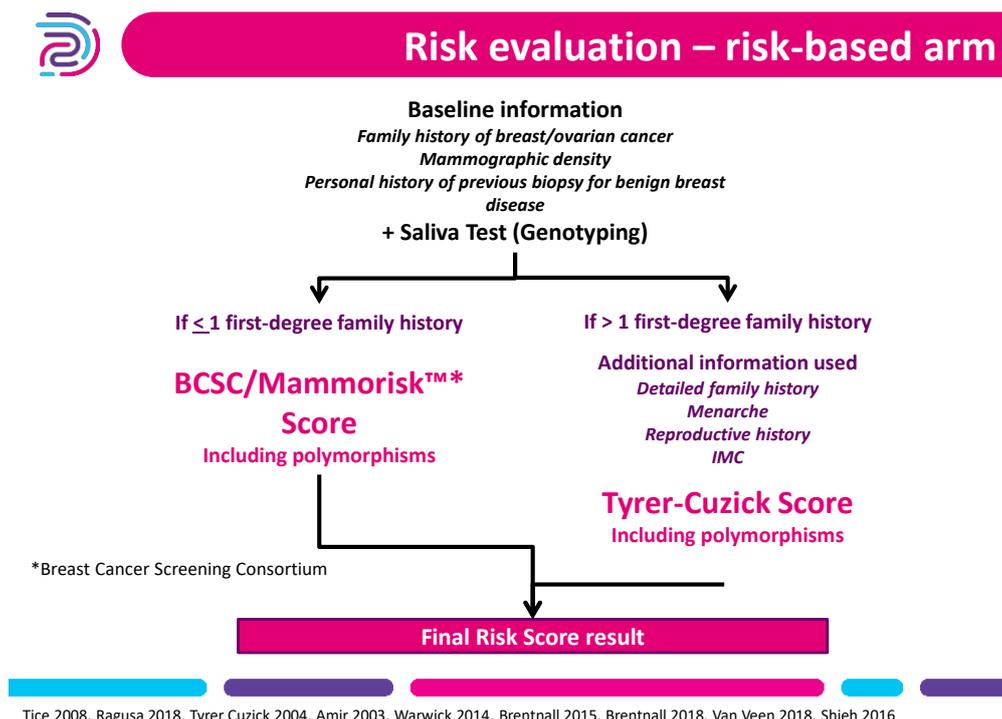
During a second dedicated visit (8-12 weeks after the initial visit) risk-estimation will be delivered and explained to women. This is the moment when they will be proposed their personal screening program. This visit may be physical or by telephone interview depending on the countries.

ESTIMATION OF 5-YEAR BREAST CANCER RISK FOR WOMEN RANDOMIZED IN THE RISK-BASED ARM / RISK STRATIFICATION

Risk stratification will be done using an algorithm defined by the Clinical Trial Steering Committee and which is based on the most recent literature (clinical risk scores and relevant polymorphisms). Risk assessment will be conducted using a dedicated centralized risk-evaluation software. The following variables will be used: age, family history, previous history of benign breast biopsy, personal hormonal and reproductive history, breast mammographic density, and genotyping results (polygenic risk score). As shown in Fig 1, for women with at most one first-degree relative with breast or ovarian cancer, risk assessment will be conducted using Mammorisk™ with the implementation of the polygenic risk score results. Mammorisk™ uses age, family history, history of a previous benign biopsy, mammographic density. It evaluates 5-year invasive breast cancer risk using a k nearest neighbors' method. It has been derived from and validated on the Breast cancer Screening Consortium cohort and validated on French screening cohorts. It has previously been used for risk stratification in a national prospective trial. The risk assessment requires adjustment for national breast cancer incidence. Each woman's genotyping results (SNP score) will be implemented into the risk calculation as previously described, for a final risk calculation including SNPs results.

As shown in Fig 1, women with more than one first-line first degree relative with breast or ovarian cancer will have their risk estimated using the Tyrer-Cuzick™ risk score implemented with each person's polygenic risk score as previously described. Tyrer-Cuzick™ model has been previously used for risk stratification in prospective trials.

FIG 1: RISK EVALUATION IN MYPEBS, RISK-BASED ARM



BREAST MAMMOGRAPHIC DENSITY EVALUATION is part of both risk assessment algorithms. Baseline breast mammographic density will be evaluated using a standard procedure and classified into 4 Bi-RADS categories. The use of a single automated method for the whole study is planned; such software will be provided to the centers. If it happened not to be available to some investigators, central assessment will be provided. If unavailable or impossible, radiologist's BI-RADS visual assessment will be used. If no baseline breast mammography is available (women younger than 50 years), the maximum risk will be applied.

GENOTYPING PROCESS

During the inclusion visit, women will be given a device to collect saliva DNA so that a saliva sample can immediately be obtained. The sample will be sent to the central laboratory in charge of DNA extractions and genotyping, within one week of the sampling.

GENOTYPING IN RISK-BASED ARM

DNA will be extracted from saliva samples using standard protocols. Genotyping will be carried out using an Illumina dedicated array (around 700,000 SNPs) containing additional preselected variants for the purpose of the study (controls and breast cancer (BC) risk-linked SNPs not already present on the chip). All variants currently known to be associated with breast cancer risk and properly validated will be examined for inclusion in the final designed array. The final SNP score (polygenic risk score) used for the study will be defined by the clinical trial steering committee ahead of the start of accrual and shall contain between 120-150 SNPs. The proper calibration of each SNP in the accrual population will be assessed after 2,000 women have been included in the risk-based arm. Non-calibrated SNPs shall be eliminated.

In case major new variants become available during the conduct of the study, either during the inclusion or follow-up phases, they will be implemented in the SNP score and individual risk reassessed. The likelihood of such event will be limited by the proper initial selection of SNP score.

DNA STORAGE

DNA leftovers will be stored pseudonymously in a specific dedicated biobank.

RISK SCORE ASSESSMENT

As mentioned before, the individual breast cancer risk will be estimated using the modified Mammorisk™ (by inclusion of SNPs) or, as indicated, by the modified Tyrer Cuzick™ scores, both including polymorphisms, under a pre-defined algorithm, developed by the project consortium. Both scores will be adjusted for national breast cancer incidences and will incorporate genotyping results for all participants randomized in the risk-based arm.

Breast cancer risk levels will then be classified into 4 meaningful categories, which have been defined by the clinical trial steering committee, according to available guidelines and published literature. Screening procedures will be scheduled accordingly, based on the pre-defined screening decision tree (Table 3).

BREAST CANCER SCREENING IN THE RISK-BASED ARM

In the risk-based arm, women are screened based on their risk category:

Screening recommendations in each risk category are as described in the Table 3 below. The whole set of recommendations has been elaborated by the steering committee of the trial.

RISK LEVEL ASSIGNMENT MODIFICATION IN RISK-BASED ARM

These risk-based screening recommendations might be subject to evolution during the trial, both at a individual participant level and at the level of the whole trial

At the personal level, a web-based yearly update will be organized for all women in this risk-based arm to better adapt their risk profile if required (only in case off change in family history, personal benign breast biopsy, or identification of a germline high-risk mutation).

At the study level, the re-evaluation will take into account published evidence-based knowledge notably based on SNPs

OTHER MEASURES ASSOCIATED WITH RISK LEVEL

GERMLINE GENETIC TESTING

Of note, for the women identified as having a high-risk family-history, genetic counseling might be advised, according to national and international guidelines. This advice will be part of the recommendations produced by the risk assessment tool. This genetic counseling will be performed in the standard genetic network of the country, and genetic testing for the search of germline BRCA1/2 mutations (or panel testing) usually performed in a cancer-affected relative rather than in the healthy consultant. Such women will of course remain within the trial, and be assigned high or very high-risk categories, with the adequate proposed follow-up.

In Israel specifically, it has been planned that women who have signed a dedicated informed consent (proposed to all participants at study entry) will have an additional evaluation of polymorphisms together with their SNP score, aiming at identifying the presence of one of the three Ashkenazi founder mutations. Such finding will prompt genetic testing for confirmation, as described previously.

BREAST CANCER RISK REDUCTION MEASURES

Participating women will receive standardized self-awareness recommendations, although they will remain free to comply with them. They will be informed on potential risk-reducing strategies associated with their individual breast cancer risk level and individual risk factors. Upon risk calculation, they will receive a printed + online document summarizing all their personal information, risk category assignment, proposed screening strategy, but also suggested personalized risk-reduction measures (such as avoidance of certain endocrine therapies, dietary and exercise recommendations, etc). These measures have been predefined by the trial steering committee.

Participants will be able to retrieve all their personal information from their personal account on the study's web-platform. They also will be able to consult more general information on the project's website.

Table 2: **BREAST CANCER SCREENING SCHEME IN THE STANDARD ARM**

Standard arm (either no mammogram or mammogram(s)/1-2-3 years according to age and country – will be defined individually at study entry in the trial)				
Population	40-49 (France, Belgium, UK and Israel) 40-44 (All women of Italy) 45-49 (for some women depending the region of Italy)	50-70 (UK)	50-70 (France, Belgium, Italy and Israel)	45-49 (Some regions of Italy)
Planned images	No mammogram	Mammogram* every 3 years	Mammogram* every 2 years	Mammogram* every year

* Or Tomosynthesis + synthetic 2D if applicable in the country/center

Table 3: DEFINITION OF RISK THRESHOLDS IN MYPeBS AND **BREAST CANCER SCREENING SCHEME IN THE RISK-BASED ARM**

Risk-based arm				
Risk level	Low risk	Average risk	High risk	Very high risk
Numerical definition (invasive breast cancer risk at 5 years)	<1%	1-1.66%	$\geq 1.67\%$ and <6%	$\geq 6\%$ at 5 years
Mammogram*	1 at end of study	Every 2 years	Yearly	Yearly
Additional	Yearly breast cancer awareness reminder	High density: US or ABUS every 2 years	High density: US or ABUS every year	Annual MRI until age 60

* Or Tomosynthesis + synthetic 2D if applicable in the country/center

F) SAMPLES COLLECTED

SAMPLE TYPES: SALIVA SAMPLES

SAMPLE QUANTITIES: one sample of saliva at baseline for all women randomized into the risk-based screening arm

G) STUDY DURATION

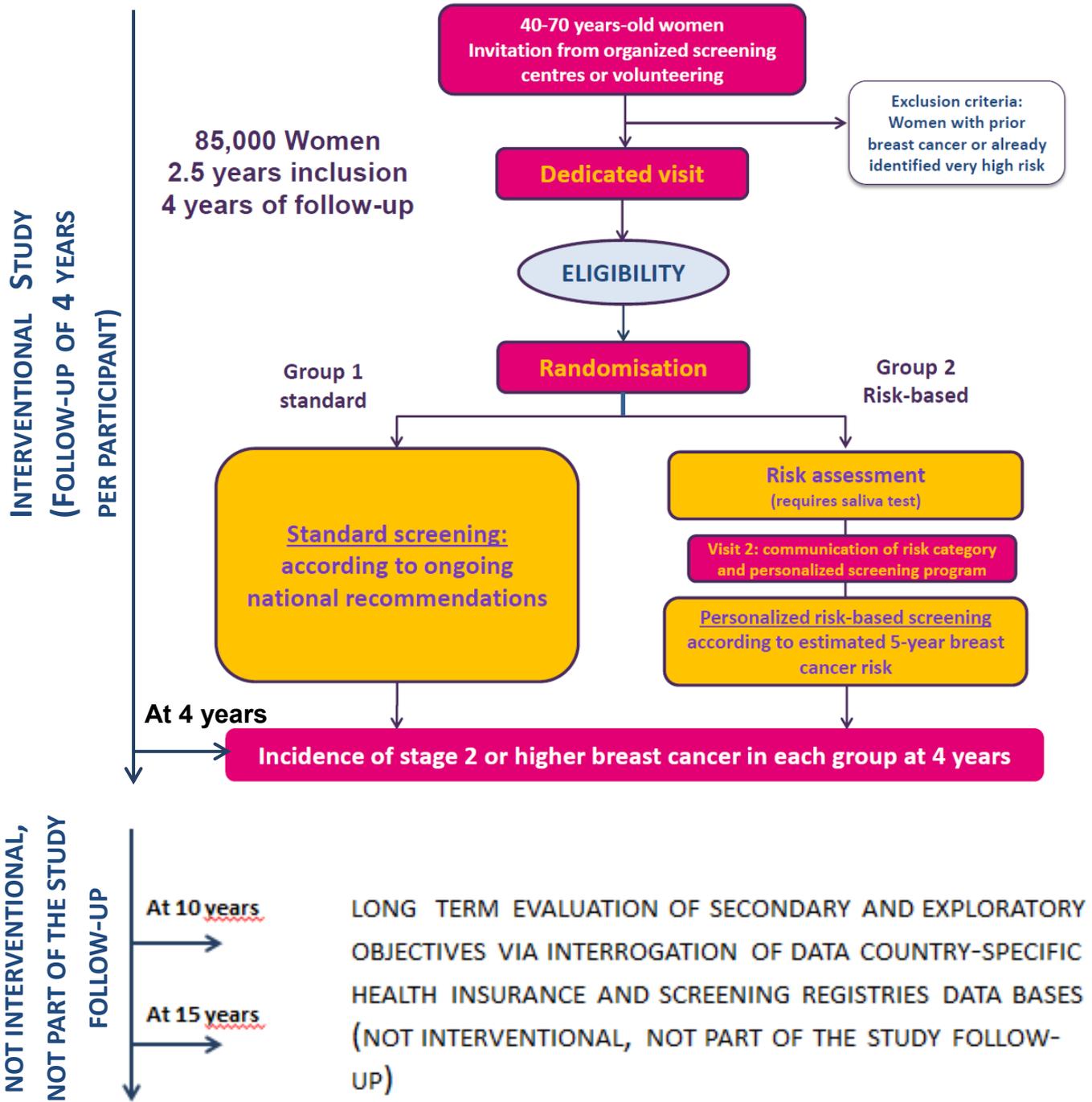
INCLUSION PERIOD: 2.5 YEARS

STUDY FOLLOW-UP DURATION (FOR EACH WOMAN IN BOTH GROUPS): 4 YEARS

LONG TERM DATA COLLECTION FOR THE EVALUATION OF INCIDENCE AND BREAST CANCER SPECIFIC MORTALITY VIA INTERROGATION OF DATA COUNTRY-SPECIFIC HEALTH INSURANCE AND SCREENING STRUCTURES DATA BASES (NOT INTERVENTIONAL, NOT PART OF THE STUDY FOLLOW-UP): UP TO 15-YEARS FROM STUDY ENTRY

DURATION UNTIL PRIMARY ENDPOINT EVALUATION (INCLUSION + FOLLOW-UP) : 6.5 YEARS

H) STUDY SCHEME/OUTLINE



I) SCHEDULE OF ACTIVITIES (SOA)

VISITS	Who will record the data into the web-platform	Baseline	Risk-based screening arm	Follow-up			
				NA	NA	NA	NA
Visits n°		Visit (V0)	V1	M12 V0 + 12 +/- 6 months	M24 V0 + 24 +/- 6 months	M36 V0 + 36 +/- 6 months	M48 V0 + 48 +/- 6 months
Visit / Follow up timepoints Dates		D0	V0 + 8-12 weeks				
Type of visit		physical	physical or telephone call	On-line	On-line	On-line	On-line
Inclusion/non-inclusion criteria	investigator	X					
Signed informed consent form	Investigator/Woman	X					
Baseline mammogram (if applicable)		X*					
Minimal medical data	investigator	X					
Randomization	investigator	X					
Medical history	investigator/Woman	X					
Result of risk score (only for risk-based screening)	investigator		X				
Study visit	NA	X [#]	X [§]				
Study mammogram	NA	(X) [£]	(X) [£]	(X) [£]	(X) [£]	(X) [£]	(X) [£]
BIOLOGICAL TEST (only for women who will be randomized in the risk-based screening arm)							
Saliva test		X					
QUESTIONNAIRES							
1. STAI short form (state anxiety)	Woman	X	X	X			X
2. Comprehension questionnaire	Woman	X	X				X
3. Information seeking-behavior questionnaire	Woman		X				X
4. Quality of life (EQ-5D)	Woman	X					X
5. Satisfaction	Woman			X			X
6. Socio-demographic and economic status questionnaire	Woman	X					X
FOLLOW-UP DATA							
Mammogram yes/no + results	Woman/ OBSS or national security social			X	X	X	X
Breast US (or ABUS) yes/no + results	Woman/ OBSS or national security social			X	X	X	X
Breast MRI yes/no + results	Woman/ OBSS or national security social			X	X	X	X
Breast biopsy or surgery + result and date	Woman/ OBSS or national security social			X	X	X	X
Breast cancer yes/no + date	Woman/ OBSS or national security social			X	X	X	X
Other major medical problem yes/no + date	Woman/ OBSS or national security social			X	X	X	X

* Reference mammograms up to 2 year prior to inclusion are accepted

For woman who will have the standard of care screening program

§ For woman who will have the risk-based screening program

£ According to the woman's individual program of radiological exams (see the section 1.1.14). Concerning the end of study mammogram see the section 1.1.14.

OBSS: Organized breast screening structure

ABUS: Automated breast ultrasound screening

1. INTRODUCTION

MyPeBS addresses the crucial and timely question of the future of breast cancer screening in Europe. Indeed current standard mammographic screening, with entry stratified by age alone, has recently been largely questioned. Despite a demonstrated mean 20% reduction in breast cancer-specific mortality, together with reduction of late-stage disease in women older than 50, mammographic screening is associated with potential harms including false positive recalls and over-diagnosis.

Individual breast cancer risk estimation, through combined risk scores including clinical variables, mammographic breast density and more than 100 genetic polymorphisms, now has substantial clinical and scientific bases. Personalized screening strategies, based on individual risk levels, could potentially improve the individual benefit/harms ratio of screening (earlier cancer detection and less intensive treatments in high risk women, less false positives and over-diagnoses in low risk ones), and increase the cost-efficacy for health insurances [Hood 2011, Burton 2013, Cox 2014, Gagnon 2016, Lee 2017].

MyPeBS will conduct an international randomized study to validate this hypothesis. It will primarily assess the ability of an individual risk-based screening strategy to be non-inferior, and possibly superior, to the standard of care screening, in reducing the cumulative incidence of stage 2+ breast cancers. The study, conducted in 5 countries (France, Italy, UK, Belgium, and Israel) will include 85,000 European women aged 40-70 years, all followed for 4-years. MyPeBS will also evaluate if an individual risk-based screening strategy, compared with the standard screening, reduces screening-related harms such as unnecessary biopsies, overdiagnosis in low-risk women, is overall at least as cost-effective as well as more accepted by women resulting in a larger screening coverage. After analyses of all components, the final objective of MyPeBS is to deliver the best recommendations for the best future breast cancer screening strategy in Europe.

1.1 Study rationale and justification

1.1.1 Current status of breast cancer in western countries

Breast cancer is the most common cancer and the second leading cause of cancer death among women in Western countries. Breast cancer (BC) is a dramatic worldwide issue with almost 1.7 million new BC diagnoses and 521,900 BC deaths estimated worldwide in 2012 <https://www.ncbi.nlm.nih.gov/pubmed/28376154>.

Breast cancer remains a potentially lethal disease. Indeed, 20 to 25% of women developing breast cancer will eventually die, due to the development of metastases. Risk of metastases and global prognosis are linked to both tumor biology and burden at diagnosis (Cardoso 2016).

Although very long survivals are sometimes possible, metastatic breast cancer remains an incurable disease. The median survival after diagnosis of metastases currently ranges from 14 months (triple-negative breast cancers) to 56 months (Her2-positive breast cancers) (Gobbini 2018).

Localized breast cancer currently most of the time still requires aggressive and prolonged treatments associated with long-term consequences (Azim 2011). Treatment intensity and heaviness is clearly deeply linked to the cancer's biology, but also to tumor burden at diagnosis. Tumor burden is the major determinant of the extent of the local therapies, including surgery (partial versus complete mastectomy, axillary surgery) and radiation therapy. Adjuvant medical treatments for breast cancer, including chemotherapy, endocrine and targeted therapies remain difficult for women; they are associated with long-term sequelae, and represent high management costs (Azim 2011).

There is therefore a major need for prevention, including earlier diagnosis (associated with a better prognosis, less treatments needs, less morbidity from the therapies, and lower costs) through secondary prevention, but also, of course, primary prevention.

1.1.2 **Current breast cancer screening in western countries: benefits and potential harms, evaluation, organization**

Current breast cancer screening policies in western countries and known benefits

In Western countries, breast cancer screening is part of national organized screening systems with monitoring of screening quality and with double reading (except in Israel) of the mammograms. Certified radiologists and radiographers are responsible for quality of the diagnostic performance.

Apart from very rare patients at very high-risk, age is currently the only criterion for starting screening. Depending on the country, mammograms are offered every 1 to 3 years, starting from the age of 40-50 years up to 69-74 years.

These screening recommendations are based on large-scale randomized studies (New York, Malmo 1 and 2, Edinburgh, Swedish 2 county, Canada trials 1 and 2, Stockholm, Goteborg, UK age trial) that have globally shown that screening reduced breast cancer specific mortality by about 20% in the intent-to-treat populations (invited women), or 30-40% in the per-protocol populations (participating women).

Several reappraisals of these mammographic screening-associated benefits in the randomized trials have been published in the past 10 years with variable interpretation of data. Indeed, trials' methodologies are somehow heterogeneous most trials dated at times incidence and therapies were quite different. The UK independent panel estimated the benefit of mammographic screening starting at age 50 to be in the range of one breast cancer death prevented for 250 women invited (Marmot et al, 2011).

The benefit and risk-benefit ratio of mammographic screening between the age of 40 and 50 is controversial and each country currently has its own policy. Mammographic screening has also been demonstrated to reduce the number of stage 2 and higher cancers at diagnosis in women older than 50.

Current breast cancer screening by mammography: harms and weaknesses

8,18,87,97,107,127,161,125,128,109,136,161

Current screening by mammography is associated with a number of harms or weaknesses that have been largely debated in the medical literature in the past 10 years:

1. The sensitivity of 2-yearly and furthermore 3-yearly mammogram is not optimal: 1-2 (or more for UK) breast cancers every 1,000 examined women are interval cancers (Blanch, Mandelson, Houssaimi 2017). This turns to 16 to 35% of cancers being interval cancers according to the screening interval. Furthermore, about one fourth of the cancers occurring in regularly screened women are still diagnosed at stage 2 or more.
2. A small percentage of screening mammograms lead to additional check-ups or biopsies for an image that turns to finally be benign: these "false positive" results, according to the way they are estimated concern 3-14% (3% being only cases where biopsies are recommended, whereas higher rates are observed if additional US is considered a check-up) of all screening mammograms (Gøtzsche and Nielsen, 2011; Pace and Keating, 2014; Anon, 2017), causing useless patient's anxiety (Brodersen and Siersma, 2013; Nelson et al., 2016; von Euler-Chelpin et al., 2016).
3. Another criticism is overdiagnosis (screen detection of a cancer that would not have become clinically apparent without screening) which is estimated in average as 10% of all screen-detected cancers (estimates are highly variable; they range from 1% to 30%, depending on the population and estimation methods), leading to an inherent overtreatment.
4. Mammographic screening is associated with a risk of radio-induced breast cancer. This risk appears extremely low (about 1 in 1,000 women screened during 30 years) compared to the benefits of early diagnosis and radiation doses delivered are now very closely monitored. The most pessimistic evaluation of this risk in US women undergoing yearly mammogram from age 40 has led to the following conclusions

(Miglioretti 2016): On average, annual screening of 100,000 women aged 40 to 74 years was projected to induce 125 breast cancers (95% confidence interval [CI]=88–178) leading to 16 deaths (95% CI=11–23) relative to 968 breast cancer deaths averted by early detection from screening. Women exposed at the 95th percentile were projected to develop 246 radiation-induced breast cancers leading to 32 deaths per 100,000 women. Women with large breasts requiring extra views for complete breast examination (8% of population) were projected to have higher radiation-induced breast cancer incidence and mortality (266 cancers, 35 deaths per 100,000 women), compared to women with small or average breasts (113 cancers, 15 deaths per 100,000 women). Biennial screening starting at age 50 reduced risk of radiation-induced cancers 5-fold.

Participation rates

Beside these elements, another problem faced by western countries are the variable participation rates to national organised screening programs: indeed, to be efficient at a public health levels, this type of intervention requires a high (70% or more) participation. Some western European countries or regions currently face decreasing and quite low participation rates (25-30%).

Routine screening guidelines and protocols in the participating countries

In MyPeBS, breast cancer screening activities and breast density assessments follow current updated European and national guidelines regarding methods and indications in the standard arm as well as, while in the exploratory risk-based arm, except regarding screening intervals for the latter.

- European guidelines (standard, good practice, equipment, quality assessments)

We have ensured, and will monitor during the trial, that all screening activities in the standard arm will follow the current European Commission breast cancer screening guidelines (2006 and update 2016) (<http://www.euref.org/european-guidelines>, and <http://ecibc.jrc.ec.europa.eu/-/european-guidelines-for-breast-cancer-screening-and-diagnosis-the-european-breast-guidelines>) and the European Society of Breast Imaging (EUSOBI) recommendations (<http://appliedradiology.com/articles/european-society-of-breast-imaging-s-recommendations-on-breast-cancer-screening>)

The European commission initiative on breast cancer (ECIBC) has developed guidelines platform for all breast cancer processes as well as for quality assessments (several members of the consortium have participated to these initiatives), and we will refer to them and use them as standard throughout the study: <http://ecibc.jrc.ec.europa.eu/-/the-ecibc-guidelines-platform-for-all-breast-care-processes>
<http://ecibc.jrc.ec.europa.eu/documents/20181/22500/EC+Initiative+on+Breast+Cancer.pdf/a586dfb5-83d2-4ee3-a345-9ddf72363fa8>

- National guidelines

In the standard arm of MyPeBS, breast cancer screening has to comply with the current ongoing national guidelines and procedures, while they will follow the same except for screening intervals, in the exploratory arm:

UK: <https://www.gov.uk/government/collections/breast-screening-professional-guidance>

Italy: http://www.ccm-network.it/screening/files/documenti/raccomandazioni_linee_guida.pdf, and http://www.ccm-network.it/screening/files/documenti/raccomandazioni_linee_guida.pdf ,

Israel: http://en.cancer.org.il/template_e/default.aspx?PagelId=7749

Belgium: <https://www.ccref.org/old/pdf/MB25112000.pdf>; <https://www.ccref.org/old/pdf/MB10082001.pdf>; and Royal decree establishing the necessary standards for the accreditation of specialist breast cancer centres in Belgium – January 1st 2008.

France: http://www.has-sante.fr/portail/jcms/c_1741170/fr/depistage-du-cancer-du-sein-en-france-identification-des-femmes-a-haut-risque-et-modalites-de-depistage, <http://www.e-cancer.fr/Professionnels-de-sante/Depistage-et-detection-precoce/Depistage-du-cancer-du-sein/Orienter-vos-patientes>)

The current national/European guidelines in use may vary during the trial, at a national or European level. Guidelines and procedures in the standard arm will be updated accordingly and timely.

All participating countries have specific guidelines for:

- **High-risk women** defined as having had a previous breast cancer or high-risk situations including radiation therapy for Hodgkin's disease or atypical hyperplasia. These women will not be eligible for MyPeBS
- **Very high-risk women** defined as having a germline mutation of either BRCA1 or BRCA2 genes or an equivalent situation. These women will not be included in MyPeBS

1.1.3 “4P medicine” and application to breast cancer screening

Personalized cancer prevention approach (meaning personalized risk assessment together with specific individual screening and primary prevention) is a major public health challenge. However, this approach needs individual risk identification, adequate perception and awareness leading to changes in behaviors towards cancer prevention. It also requires reaching the adequate population and avoiding disparities in health care access. This is included in the so-called P4 medicine (Predictive, Personalized, Preventive, and Participatory) (Hood 2011).

Risk based prevention is highly efficient in other public health models

Several models of the public health impact of risk-based prevention exist, such as in infectious diseases or neonatology. A major model of the medical, sociological and economical efficacy of risk-based prevention (including screening and interventional prevention) is that of cardiovascular diseases. In this setting, computational approaches have led to combine risk factor information for a better individual prediction, and the early development of 10-year absolute cardiovascular risk "Framingham" model designed for routine clinical practice, in 1998. These advances have led to major improvements in specific survival and global survival of the identified individuals, together with eviction of unnecessary interventions among those at low risk. Current guidelines recommend the use of algorithms for cardiovascular risk assessment that combine information of age, sex, together with traditional risk factors (blood pressure, lipids, and smoking), along with other emerging biological factors. Since environmental exposures have a major role to play, constitutional genetics have not yet become a major player in this setting outside of family history.

Proof of concept of breast cancer risk-based screening in very high-risk women

Personalized screening has so far only been used as more intensive screening for very high-risk individuals bearing germline predisposition mutations (mostly of BRCA1/2 until recently). Intensive breast screening, including yearly mammogram and MRI starting at a young age (25-30), have proven to be efficient in these women in terms of drastic reductions in cancer stage at diagnosis and projected reductions in breast cancer-specific mortality. Of note, risk reduction strategies have also proved to be effective for such individuals identified to be at very high hereditary risk of breast cancer. Beside this, women with a past history of breast cancer, atypical lesions or chest wall radiation therapy are also currently identified to be at higher risk of

subsequent breast cancer. National and international guidelines recommend that these women receive increased screening and other prevention measures, which are associated with some suggested benefits.

Modeling of potential benefits of risk based screening in the general population (Yen, Hall, Koitsatu, Onega, Morman)

The vast majority of women is not at increased risk of breast cancer and is recommended to follow general screening guidelines. Only 1 in 9 of these average-risk women will ultimately develop breast cancer. Developing more effective, risk-based screening approaches for this general population requires validated risk-estimation models and assessment of the clinical usefulness of such models. Risk-based screening has indeed recently been recognized by many societies or groups, as a major way to be explored for its ability to lead to a better screening, which would be more effective, less morbid, and health-economically beneficial.

In the absence of randomized controlled trials evaluating the efficacy of risk-based screening protocols in the general population, simulation modeling studies have provided insight into the potential risk/benefit balance of different risk-based screening protocols. These modeling studies suggest that screening regimens should be personalized based on a woman's age, breast density, and other risk factors. One study used several established CISNET (NCI-funded Cancer Intervention and surveillance Modeling Network) simulation models to determine the most efficient screening strategies based on individual breast cancer risk. Biennial screening appeared as the most efficient strategy for most women who are at average risk of breast cancer.

However, for women with 2-fold to 4-fold increase in risk, annual screening beginning at age 40 years had comparable risks and benefits with those of women at average risk undergoing biennial screening between ages 50 and 74 years. Another CISNET study found that women aged 40 to 49 years with a 2-fold increased risk have similar harm/benefit risk ratios compared with average-risk women aged 50 to 74 years undergoing biennial screening.

1.1.4 Breast cancer risk factors

Although deaths from breast cancer have been decreasing in many Western countries, the incidence of breast cancer is continuing to increase. In particular, in countries with historically low incidence, breast cancer rates are rising rapidly making it now the world's most prevalent cancer. The increase in incidence is almost certainly related to changes in dietary and reproductive patterns associated with Western lifestyles. There is evidence from genetic studies in the USA, Iceland and the UK of a 3-fold increase in incidence in the last 80 years, not only in the general population, but also in those with BRCA1 and BRCA2 mutations.

Exploration and description of breast cancer-associated risks through large retrospective and prospective cohorts have allowed a very high amount of data regarding potential individual risk factors of breast cancer.

A number of breast cancer risk factors have been identified, including family history, hormonal exposure, reproductive history and lifestyle.

A family history of breast cancer suggests the presence of an inherited genetic variant such as those in the BRCA1 and BRCA2 genes which confer a high susceptibility (Couch et al. 2014). Recently, additional genetic risk factors have been identified, including rare variants in genes such as PALB2, HEK2, ATM (Lee et al. 2016) associated with moderate to high risk and common low-risk variants (Kurian et al. 2016).

Non-genetic breast cancer risk factors include hormonal factors (e.g. use of hormone replacement therapy, oral contraception), reproductive factors (e.g. age of first pregnancy, breastfeeding, age at menarche, age at menopause) and lifestyle factors (e.g. obesity, physical activity, alcohol consumption) (Dartois et al, 2014, 2015, 2016; Harvie et al. 2015).

Overall, except for true genetic predisposition, each of these factors alone has a limited impact, with relative risks between 1.1 (reproductive factors) and 3.

Beside this, and over the past 20 years, breast density has been explored and validated as an important breast cancer risk factor, together but independently of its other effect (masking effect) (Boyd 1995, 2011, Astely 2018). Many studies have now acknowledged this breast cancer risk effect, which may be seen as a surrogate of both genetic background and lifetime hormonal/other exposures: density is indeed currently regarded as an indicator that summarizes both a woman's genetic background and exogenous exposures to hormones or other risk modifiers (Alexeeff 2017).

1.1.5 Breast cancer risk assessment models

Since individual factors, except for family history, have a limited impact when used alone, several multivariable mathematical models to estimate breast cancer risk in the general population have been developed over the past 25 years. All of these models use clinical variables based on family history, history of benign breast disease, as well as variables that summarize a certain amount of endogenous and exogenous hormone exposure derived from epidemiological studies.

These breast cancer risk models can be separated into those that utilize mainly hormonal and environmental factors and those that focus more on hereditary risk (Cintolo-Gonzalez 2017). Indeed, specific models have been developed in high familial risk populations that are able to predict for the probability of a germline mutation as well as for a woman's individual breast cancer risk in this setting: they include the extended Claus (Claus et al) and more recently, BRCAPRO (Parmigiani et al) and Bodicea (Antoniou et al) models. These models are, however, not suitable for the general population, and have been developed to predict for BRCA1/2 mutations but may be less relevant for other germline alterations [ref].

These models are not suitable for the general population, in which the most accurate models are the three renewed Breast Cancer Risk Assessment Tool (BCRAT/Gail), Tyrer-Cuzick (IBIS) and Breast Cancer Screening Consortium (BCSC) models.

Recent breast cancer risk models are based on screening cohorts and integrate mammographic breast density as a factor. This addition has slightly increased their accuracy in discriminating women who do and do not get breast cancer, with concordance statistics (c-statistics) of about 0.65 compared to 0.58 for models that do not include density.

A crucial point is to use models that are internationally validated. Three such scores/models are currently externally validated: the BCRAT/Gail model, the Tyrer-Cuzick model and the BCSC model (Cintolo-Gonzalez 2017 and subsequent erratum). The teams involved in MyPeBS have experience with two major, recently updated, and well renewed, breast cancer risk assessment models. The American BCSC model has been validated in the Mayo clinic cohort and, more recently, in French general breast screening populations (after adjustment on national incidence, c-statistic 0.61, E/O 1.005) and can be used as such (Ragusa et al).

The Tyrer-Cuzick model has been largely described in general populations as well as high-risk family clinics or clinical trial populations (IBIS1). It has particular relevance for women with a family history: its accuracy is average in the general population (c-statistics between 0.57-0.60), while it is very high in family-risk populations (c-statistics up to 0.70).

As mentioned, it is crucial as well that the model used has been demonstrated to have potential clinical usefulness through relevant, well calibrated, risk reclassification, as defined by Steyerberg et al. In the French validation of the American BCSC model, within the American and French cohorts respectively, 74% and 73% of women who developed breast cancer were considered at sufficient baseline risk to qualify for screening (sensitivity). The use of the BCSC model allows reclassification of 69% of the 40-74 years old individuals into meaningful categories, within the American cohort (40% are reclassified at high risk, 40% reclassified at low risk, below 1%). Use of the same model for the French screening population aged 50-74 allows reclassification of 48% of the women (27% to low risk, 21% to high risk) (Ragusa). In the American cohort of women aged 40-74, only 20% of breast cancers arose in the 41% women with a 5-year risk < 1%.

As well, Tyrer Cuzick model allows such reclassification nicely (Brentnall et al 2014, 2018).

The main characteristics of both BCSC and Tyrer-Cuzick models are summarized in the Table below:

	Tyrer-Cuzick score	BCSC score (or derived)
Initial model description /population	Tyrer and Cuzick, Stat Med 2004 Theoretical model, targets family history+++	Bralow 2006, Tice et al 2008 Parametric model developed on BCSC (1 M US screening cohort)
Validations	- UK screening cohort (c-statistic 0.57) - Family clinics (c-statistic > 0.7) - Several UK family –risk or other high risk populations (FH-risk, IBIS1, PROCAS) - Incorporation of mammographic breast density (cohort) and SNPs (case-control) - 2 cohort validations North America	- Mayo mammography health study - French screening population (350 000)(Ragusa et al) (c-statistic 0.60-0.65 according to inclusion of 40-50 and ethnicity)
Items	Age, menarche, age at first birth, previous biopsy, breast density, BMI, detailed family history+++	Age, short family history, breast density, previous breast biopsy, (ethnicity in USA)
Inclusion of SNPs	2 prospective cohorts, case control methodology (Brentnall et al, Evans et al), increase of AUC up to 0.65 LOE II	2 prospective cohorts, case control methodology, (Vachon et al, Shielh et al), increase AUC up to 0.69 Modeling studies LOE II
Proposed target population in MyPeBS	Best for participants with a family history of breast cancer	Best for general screening population

1.1.6 Genotyping allows breast cancer risk identification

Beside the previous clinical risk factors and their aggregation in scores, huge international efforts (Europe and North America), through advances in genome technology, have led to the identification of over a hundred and fifty common, validated single nucleotide polymorphisms (SNPs) associated with breast cancer risk (Pharoah 2002, Easton 2007, Ahmed 2009, Ghousaini 2012, Siddik 2012, Garcia Closas 2013, Kar 2016, Michailidou 2015, Michailidou 2017, Lewis 2017, Curtit 2017)

These SNPs predict either for invasive breast cancer in general for most of them and/or for risk of hormone-receptor negative, or risk of death from breast cancer. Most SNPs have a low effect, those described initially having the highest impact (OR 1.01-1.30 overall) (Hilbers et al 2013).

The latest publication (Michailidou 2017) identified 65 new independent loci that are associated with overall breast cancer risk at $P < 5 \times 10^{-8}$. The majority of credible risk single-nucleotide polymorphisms in these loci fall in distal regulatory elements, and by integrating in silico data to predict target genes in breast cells at each locus, they demonstrated a strong overlap between candidate target genes and somatic driver genes in breast tumors.

The complementarity of SNPs to predict cancer risk, with respect to other breast cancer risk factors, namely mammographic density, reproductive history, and lifestyle factors, is now demonstrated. Vachon et al found that Breast Imaging Reporting and Data Systems (BI-RADS) breast density and a polygenic risk score (PRS) composed of 76 SNPs are both important risk factors for breast cancer that can be incorporated into breast cancer risk models (BCSC model). If these models are used to estimate population risk, refining the high- and low-risk risk groups could result in more appropriate tailoring of screening and prevention interventions.

1.1.7 Genotyping techniques used in MyPeBS and their relevance

Genotyping to identify a dedicated SNP score for each individual in the risk-based arm of MyPeBS trial could be achieved either through the use of a dedicated chip, or through use of a large scale chip including specific

polymorphisms. We have chosen the second option that allow the identification of around 700,000 different polymorphisms in high quality highly reproducible manner.

Standard saliva kits will be used to harvest saliva from participating women allocated the risk-based arm. Kits will then be sent to a centralized platform in France (CEPH <http://www.cephb.fr/>). DNA will be extracted from saliva samples using standard protocols. Genotyping will be carried out (at a unique lab, at CNRGH <http://jacob.cea.fr/drf/ifrancoisjacob/Pages/Departements/CNRGH.aspx>) using a dedicated specifically engineered for MyPeBS trial, Illumina chip (Global Screening Array or equivalent), with over 700,000 variants. On top of the baseline variants present on the chip, we will add up to 1,000 additional variants selected for the purpose of back-up testing, quality controls, and BRCA1/2 founder Ashkenazi mutations identification (see below) in Israel. Briefly, this chip set includes one SNP variant every 4.2 kb, and captures greater than 94% of variants with a minor allele frequency greater than 1% in populations of European origin.

A polygenic risk score (312 polymorphisms) will be generated, while raw data of the whole chip results will be stored; the polygenic risk score will be returned to the risk stratification team for inclusion in risk estimation models.

Full stored raw data may be useful for two purposes: in case a new SNP of particular relevance is identified during the trial and present on the chip, it could be added to the SNP score for risk recalculation in all participants; we have organized towards this possibility. Furthermore, these raw data will be useful for long term additional research on the role of the genetic background in risk identification.

The genotyping activities will be conducted in a single lab and using a single chip and technology throughout the whole trial. This will ensure a high reproducibility and analytical validity. These analyses may however be subjected to batch effects.

We will therefore organize towards minimizing all potential batch effects and analytical problems. Potential SNP analyses failures will be anticipated by replacement SNPs present on the chip. Potential total technical failures linked to DNA amount or quality will lead to new sampling, as much as possible.

Quality controls of genotyping will be very careful and regular, with a predefined organized schedule of planned and unplanned controls.

1.1.8 Risk stratification models including SNPs

SNPs incorporated into known risk models allow a refinement of their discrimination potential with an increase of the c-statistics up to 0.69. They also allow for the identification of women at higher risk of specific breast cancers, such as triple-negative, an aggressive, fast-growing subtype. These latter, recently identified polymorphisms are potentially of great interest given the lower value of screening mammography among these subtypes.

Both the BCSC or Tyrer-Cuzick models combined with a polygenic score by simple multiplication allows much higher discrimination than the model alone, with clinically meaningful reassignments to both lower and higher risk categories. The addition of a polygenic risk score has been demonstrated to refine risk from the clinical models in women who are at an elevated risk of breast cancer and considering preventive therapy.

Of note, multiplicative models to integrate SNPs into clinical risk scores appear as the best models in several studies. Furthermore, analyses of SNP risk scores and environmental factors support independent multiplicative joint associations except potential very rare exceptions. Associations between known breast cancer risk loci and breast cancer is not significantly modified by environmental factors (Rudolph et al 2018).

- Shieh and al investigated the performance of the Breast Cancer Surveillance Consortium (BCSC) risk model in combination with a polygenic risk score (PRS) comprised of 83 single nucleotide polymorphisms identified from genome-wide association studies. They conducted a nested case-control study of 486 cases and 495 matched controls within a screening cohort. The PRS was calculated using a Bayesian approach. Increasing quartiles of the PRS were positively associated with breast cancer risk, with OR 2.54 (95 % CI

1.69–3.82) for breast cancer in the highest versus lowest quartile. In a multivariable model, the PRS, family history, and breast density remained strong risk factors. The AUROC of the PRS was 0.60 (95 % CI 0.57–0.64), and an Asian-specific PRS had AUROC 0.64 (95 % CI 0.53–0.74). A combined model including the BCSC risk factors and PRS had better discrimination than the BCSC model (AUROC 0.65 versus 0.62, $p = 0.01$). The BCSC-PRS model classified 18% of cases as high risk (5-year risk 3 %), compared with 7 % using the BCSC model. The PRS improved discrimination of the BCSC risk model and classified more cases as high-risk (Shieh et al 2016).

- Van Veen et al have described a prospective cohort study which enrolled 9363 women, aged 46 to 73 years, without a previous breast cancer diagnosis from the larger prospective cohort of the PROCAS study (Predicting Risk of Cancer at Screening) specifically to evaluate breast cancer risk-assessment methods. The predictive ability of a SNP score including 18 polymorphisms, SNP18, for breast cancer diagnosis (invasive and ductal carcinoma in situ) was assessed within this cohort. SNP18 added substantial information to risk assessment based on the Tyrer-Cuzick model and mammographic density. SNP18 was similarly predictive when unadjusted or adjusted for mammographic density and classic factors (odds ratios per interquartile range, 1.56; 95%CI, 1.38-1.77 and 1.53; 95% CI, 1.35-1.74, respectively), with observed risks being very close to expected (adjusted observed-to expected odds ratio, 0.98; 95%CI, 0.69-1.28). A combined risk assessment indicated 18% of the subcohort to be at 5% or greater 10-year risk, compared with 30% of all cancers, 35% of interval-detected cancers, and 42% of stage 2+ cancers. In contrast, 33% of the subcohort were at less than 2% risk but accounted for only 18%, 17%, and 15% of the total, interval, and stage 2+ breast cancers, respectively. They concluded that a combined risk is likely to aid risk-stratified screening and prevention strategies (van Veen et al 2018).
- Cuzick et al (Cuzick EBCC 2018) demonstrated that the addition of a SNP88 score to Tyrer Cuzick model version 8 could refine the risk classification in the IBIS1 cohort of women (women accrued were already classified at relatively high risk by classical criteria)
- Ziv et al (Ziv 2016) modeled the addition of 70 SNPs into the BCSC score. They concluded SNP testing is effective for reclassification of women for chemoprevention, but is unlikely to reclassify women with <1.5% 5-year risk. They proposed these results to be used to implement an efficient two-step testing approach to identify high-risk women who may benefit from chemoprevention.

1.1.9 Risk segmentation towards risk-based screening and prevention ^{19,162,177,179}

Several recent publications have attempted to segment individual breast cancer risk into meaningful categories, i.e. categories in which there is documentation of either a specific benefit, or on the opposite of an absence of benefit, of imaging screening.

Based on this literature, MyPeBS consortium has chosen meaningful categories of risk, in reference to already identified situations with demonstrated benefit.

The reference risk is a 5-year estimated risk of invasive breast cancer. This timeline appears relevant and meaningful since *i.*) predictions are considered accurate at 5- and 10-years but hardly beyond *ii.*) 2-year time frame is too short and not relevant for the present purpose, although there have been attempts to predict for such short term risk (Eriksson 2017) *iii.*) 5-year timeline appears as the most relevant in terms of individuals' awareness and concern regarding risk and dedicated prevention measures.

- Less than 1% risk is lower than the current average risk of a 45 years old woman in Europe. Such risk has never been associated with any benefit of mammographic screening, whereas harms are predicted to be very high in this population, with a negative risk-benefit ratio. Therefore, screening will be reduced in this category.
- A 5-year risk between 1.67 and 6% has previously been identified as relevant, with demonstrated benefits of several interventions such as more frequent mammographic screening or risk-reducing

strategies (SERMs and aromatase inhibitors). It is equivalent to the risk of women with a personal history of breast cancer or atypical breast lesion or in situ breast carcinomas.

- Finally, a 5-year risk beyond 6% is equivalent to that of very high-risk women, such as those bearing BRCA1 or BRCA2 germline mutations. It indicates in all participating countries, specific screening and prevention measures, which are all clearly demonstrated and documented in recommendations.

The Table Thresholds selected for the different risk categories (low, average, high and very high risk) in MyPeBS trial:

Risk level at 5-years	Low risk	Average risk	High risk	Very high risk
Numerical definition	Risk <1%	1 ≤ Risk <1.67%	1.67% ≤ Risk <6%	Risk ≥6%
Relevant similar situation	Average women less than 45 years old in Europe	Current women aged 50+	- Personal history of BC - Personal history of atypical hyperplasia - Women included in prevention trials	- Germline BRCA1/2 mutations or equivalent situations
Relevant benefit observed in similar situations	No demonstrated benefit of screening	Benefit of mammographic screening	- Benefit from prevention interventions in prevention trials - Benefit from more frequent mammographic screening in similar situations	- Benefit from annual MRI + mammographic screening - Benefit from prevention interventions

1.1.10 Effect of screening schedule and modalities on the efficacy of breast cancer screening

Holm et al (Holm 2015) described risk factors differentially associated with interval breast cancer relative to screen-detected breast cancer after adjusting for age and mammographic density. These risk factors were family history of breast cancer (OR, 1.32; 95% CI, 1.02 to 1.70), current use of hormone replacement therapy (HRT; OR, 1.84; 95% CI, 1.38 to 2.44), and body mass index more than 25 kg/m² (OR, 0.49; 95% CI, 0.29 to 0.82).

Observational data (Lauby-Secretan 2015, Kerlikowske JAMA Oncol 2015) and modeling studies (Shousboe Ann Int Med 2011) suggest that annual screening may be more effective than biennial screening for women at high risk due to dense breasts and other risk factors, and that triennial screening may retain most of the benefit of biennial screening but be less harmful and more cost-effective for women with low risk/low density.

Furthermore, the Cancer Intervention and Surveillance Modeling Network (CISNET) collaborated with the Breast Cancer Surveillance Consortium (BCSC) to evaluate varying screening intervals for digital mammography among subgroups of women based on age, risk, and breast density.

Trentham-Dietz and colleagues demonstrated that average-risk/low-breast density women undergoing triennial screening and higher-risk/high-breast density women receiving annual screening will maintain a similar or better balance of benefits and harms compared to biennial screening of average-risk women (Trentham-Dietz 2016).

Finally, a recent paper by Pashayan et al evaluated the benefit to harm ratio associated to risk-based screening. There again, it appeared clear that women who would undergo less screening in a low risk situation would derive a good benefit to harm ratio (Pashayan 2018).

For all these reasons, risk-based screening is expected to be non-inferior, and potentially superior to standard age-based screening since:

- In high risk individuals, although screening harms will not decrease and may even increase due to a higher screening frequency, such screening has large chances to be more efficient, as demonstrated in many publications
- In low risk individuals, benefit to harm ratio should be driven by much less harms in terms of false positive findings, overdiagnoses, radio-induced cancers, whereas efficacy should not be decreased if a lower frequency screening is used (but not no screening at all)

1.1.11 Choice of SNPs in MyPeBS

There are now more than 150 SNPs linked to breast cancer risk. Odd ratios of the initially described SNPs are, of course, much higher than the latter ones. Most SNPs identified to date have been more strongly associated with ER-positive disease, but more recent publications have focused on SNPs predicting for ER-negative breast cancer risk, as well as risk of aggressive or interval cancers.

Based on a full literature review, a final list of SNPs will be selected 3 months before trial launch; in order to incorporate the most recently described and validated polymorphisms. Selection criteria will be the level of evidence of the involvement of these SNPs based on GWAS data or additional data, the level of evidence of their usefulness as part of clinical risk scores, their independence of clinical variables, their potential coverage of non-Caucasian populations, their usefulness and complementarity to predict for aggressive cancers, and finally their expected or demonstrated calibration in the target populations.

Up to 90 SNPs have been evaluated as an integrative part of global risk scores in Tyrer-Cuzick and BCSC models. These are demonstrated to have a good calibration. For the most recently described SNPs, calibration is less certain and shall be ascertained during the initial part of the trial (among the initial 2,000 accrued individuals).

The process dedicated to the final SNP score definition has been clearly identified. The final polygenic risk score used during the trial has been decided by the steering committee of the trial 4 months prior to trial launch, after careful review of the recent literature including recent releases of validated SNPs and calibration data in the target population. This final score contains 312 validated polymorphisms (Pharoah, Easton et al, BCAC 2018). Its content may be subject to revision during the conduct of the trial, after annual reassessment of the literature by the Clinical Trial Steering Committee.

1.1.12 Breast cancer risk communication in MyPeBS

Refs: 3,13,14,40,55,90,130

A major issue is to make women better informed and more active in their screening decisions, as clearly acknowledged by several international studies. Indeed a key concern of national screening programs in all participating countries is to promote informed choices about decisions to attend screening, and any subsequent treatment options. Informed choices require good quality relevant information to be communicated to women, to allow them to make decisions consistent with their values.

This is in line with the ethical principle of autonomy, which requires that physicians and other healthcare professionals should allow women to participate to informed decision-making concerning their healthcare choices, especially for preventive care decisions. Furthermore, a balanced consideration of any screening

program should consider the harms of that program as well as benefits (beneficence and non-maleficence). Amongst the potential harms of risk-stratified screening are undue increases in general anxiety or distress related to cancer.

Communication of cancer risk estimations to individuals has been largely developed over the past 20 years for use in patients bearing a genetic high-risk predisposition to cancer. Communication of cancer risk as a way to target preventive interventions has recently been extended to the general population, with positive results. Tools are ready that allow effective communication of risk evaluations, together with prevention proposals, to individuals in the community (Lerman, Martinez-Alonso, O'Donnell, Fox, Morman, Johannsson, Wardle).

MyPeBS trial has the overall aim of assessing the impact of risk-stratified screening on women's understanding, awareness and emotional responses as compared to standard of care. Indeed, in the context of breast cancer screening, the psychological impact of risk communication needs to be further analyzed and all adverse reactions need to be anticipated. We will assess women's risk perception, anxiety, comprehension of the information provided, satisfaction, participation to the decision-making process, and quality of life in both arms, throughout the MyPeBS clinical trial.

It has been shown that attendance to the screening programs is related to individuals' socioeconomic profiles. Notably, underserved populations remain those where screening is lower and BC is discovered in more advanced stages with higher mortality. We will assess the attendance to MyPeBS clinical trial according to socio-economic variables. It will also be important to interpret results regarding understanding and anxiety with regards to these socioeconomic variables. The final recommendations to be produced upon MyPeBS results shall also address specific issues regarding equity of the program and access for underserved women.

Of note, the teams involved in MyPeBS have previous experience with breast cancer risk communication in the general population:

Manchester's team conducted the Predicting Risk Of Cancer At Screening (PROCAS NIHR Ref: RP-PG-0707-10031) study, which recruited over 58,000 women from the Greater Manchester NHS Breast Screening Program (NHSBSP), and showed that it is possible to accurately estimate a woman's individual risk of developing breast cancer through self-report questions and information on breast density derived from mammography. PROCAS has validated an algorithm to predict risk of breast cancer in individual women and has provided 10-year risk estimates to over 54,000 women in the NHSBSP. This is the first time that personalized breast cancer risk estimates have been made available to large numbers of women from the general breast screening population.

The PROCAS study found that at least 3% of women are high risk ($\geq 8\%$ 10-year risk) when all risk factors including mammographic density are assessed and a further 10% are at moderate (5-7.9% 10-year risk) risk.

In France, the RIVIERA study (Veron et al) aimed at evaluating the feasibility of risk information delivery and personalized breast cancer surveillance planning (PSP) by community practitioners (radiologists, GPs, gynecologists). 452 women were included, 448 were evaluable. 434 accepted the personalized prevention consultation (97% acceptance). 38% of women at baseline and 25% at 48H00 had no idea of their own breast cancer risk. Most women over-evaluated their risk. At 48H00, although the median estimated lifetime risk decreased from 40 [20-50] to 30% [10-50], self-evaluation of BC risk remained rather inaccurate. Though, women were satisfied with the clarity of the information delivered regarding risk and personalized programming. Anxiety levels were limited. The only predictive factor of state anxiety at H48 was trait anxiety ($p < .0001$). No factor independently predicted for inadequate risk evaluation at baseline, while perceived clarity of information received predicted for adequate risk self-evaluation at 48H00 ($p = 0.02$). Physician's category and state anxiety both predicted for patients' satisfaction ($p = 0.02$ and 0.008 respectively). In conclusion, risk assessment and PSP delivery is feasible in community practices with high acceptance rate. The use of a dedicated tool may catch underestimated high-risk situations in up to one third of the population. Most women estimate their own breast risk inadequately, even after a dedicated education consultation.

1.1.13 Breast cancer stage 2 and higher (2+) as a surrogate end-point of breast cancer specific survival and over

Tumor stage remains of high prognostic impact in patients with early breast cancer, both at short and long term. As an illustration, in the recent, very large, European breast cancer clinical trial Mindact (Cardoso et al 2016) in which four of the 5 MyPeBS countries participated, T stage remained one of the two major prognostic factors, with a hazard ratio (HR) of 1.92 for distant metastasis-free survival at 5-years (the other one being genomic risk assessment, HR 2.41). Tumor stage is of major impact at short term for ER-negative breast cancer (HR, in which metastatic risk is almost limited to the initial 5-6 years from diagnosis). Tumor stage is however, also associated with a major long-term prognostic impact in ER+ breast cancer patients. In the 20-year analysis of ER-positive breast cancer patients included in the major randomized trials (Pan et al 2017), T stage remains a major prognostic factor at long term: T1 tumors are associated with long-lasting annual risks around 1%, while it is around 1.5% for T2, and much higher for T3 and 4. Nodal status retains the most important prognostic impact. Overall, the HR of distant metastases for stage 1 as compared to T2N0 is 0.49 years 0-5 versus 0.70 years 5-20; but stages T1N1-3 to T2N4-9 (all stage 2 and higher) are associated with a HR of long-term relapse between 1.19 and 2.63 as compared to T2N0.

Higher tumor stage, because of its major prognostic impact, remains associated with higher benefits of adjuvant chemotherapy, larger radiation therapy indications and extended adjuvant endocrine therapies. All international and national recommendations currently use tumor stage to decide for therapeutic indications. Currently, stage 2 and higher breast cancers are therefore associated with much stronger treatments: increased indications of mastectomy versus breast conservation, increased indication for axillary clearance (although this is currently revisited), increased indication for chemotherapy, increased indication for radiation therapy including chest wall and lymph nodes, increased indications for extended endocrine therapy beyond 5 years (NCCN, ASCO, ESMO, Saint Gallen breast cancer treatment clinical guidelines). Recent data from the multicenter French Canto cohort illustrate the differential treatment load according to tumor stage at diagnosis (Arveux/André, personal communication). In Canto, women diagnosed with invasive breast cancers of stages II-IIIB versus stage I received 37 versus 14% mastectomies, 67 versus 17% axillary clearances, and 72 versus 35% prescriptions of adjuvant chemotherapy.

Finally, tumor stage has been proposed as a surrogate end-point for cancer-specific survival in different screening settings and especially in breast cancer screening trials, such as reported in the publication by Tabar et al in 2015.

1.1.14 Justification of the trial design and organization, potential biases and their prevention

Non-inferiority as primary objective

We have chosen non-inferiority as a primary objective since we wish primarily not to cause harm: it is essential, in a situation where mammographic screening as conducted in current screening programs, has demonstrated a 20% breast cancer specific mortality reduction, to make sure this aspect is preserved.

Non inferiority trials are currently largely used in case a given intervention is recognized as efficient but is associated with important toxicities, and one wants to demonstrated that a new alternative intervention is at least as efficient, but generally associated with a decrease of toxicities. Many such practice changes trials are published every year. This is the case in MyPeBS, where the current screening policy has proven to be efficient but is nowadays considered as associated with potential harms, such as false positive findings, overdiagnoses, overtreatments, radio-induced cancer. MyPeBS will de-escalate the current screening in part of the population, it is therefore crucial to demonstrate that this new screening method is primarily non-inferior to the current one.

Superiority as main secondary objective

MyPeBS will de-escalate screening in part of the population but escalate it in a large other part. There are major chances this risk-based policy may be superior to the current standard. Testing superiority of risk-based screening over standard screening is therefore the main secondary objective and MyPeBS has been designed to allow this key secondary comparison (only if non-inferiority is reached).

Stratification factors

We have carefully scrutinized all potential stratification factors, given the potential heterogeneity of the participants accrued according to the countries, as well as some heterogeneity in standard screening practices. We have finally identified 3 stratification factors that should allow an excellent balance between both arms: age (women aged <50 vs ≥ 50 , given this is the main criterion for entry into screening programs), prior mammogram (given the high rate of prevalent cancers on the first mammogram ever), and country. Stratification is not per region or center given the relative national homogeneity in practices together with the important number of centers.

Study entry mammograms

There will be no study entry mammograms. Upon enrolling in the trial and receiving a screening recommendation, each woman's next future mammogram will be scheduled. This will be dated from the date of her most recent mammogram in the two years prior to enrollment into the trial. For example, a woman who had a mammogram 3 months prior to study entry and received an annual screening recommendation would be invited to screen again 9 months after enrollment into the study. A woman who had a mammogram the year prior to study entry who receives a bi-annual screening recommendation would be invited to screen again one year after enrollment into the study.

Women who have not received a mammogram in the two years prior to enrollment may receive a mammogram at study entry if this is standard in their allocated arm and risk level (for risk-based arm).

For women assigned to the risk based screening arm who are less than 50 years of age and had no prior mammogram, the risk score will be evaluated based on the BIRADS density of D (Extremely Dense). If this assumption elevates her risk and results in a more intensive screening recommendation as compared with assuming the lowest BIRADS density, she will receive a study entry mammogram to accurately assess her risk and provide an appropriate screening recommendation. Otherwise, women who receive a screening recommendation of "No repeat screening until age 50", will not receive a study entry mammogram and will not be scheduled to receive a study mammogram until their exit mammogram unless their screening recommendation changes during the course of the study.

End of study mammogram

A study exit mammogram will be planned ONLY for the following women:

- Women in the risk-based screening arm who have been categorized as low risk (no planned mammogram during the course of the study);
- Women in the standard screening arm who had no screening mammogram during the 4-year study period given their age.

All these women will have a mandatory end-of-study mammogram at 4 years

For all the other women, the last mammography scheduled during the 4-year follow-up will be considered as the end-of-study mammography.

Organization within specific regions in the participating countries

This trial uses the existing national/regional screening structures for potential participants' information, accrual, data retrieval and follow-up. This is crucial for organizational reasons, in order not to disrupt existing pathways;

but also for future developments: risk-based screening, validated, would need to be organized within the existing structures.

Potential biases and their prevention

The identification of risk levels in the risk-based arm may induce different health behaviors that may by themselves influence the trial's result.

However, the impact of a change of health behavior on the risk of breast cancer at 4 years is expected to be null or very low. It might be impactful at a longer term. Therefore, the probability that it has an impact on the primary end point is very low but it may slightly influence some of the secondary endpoints.

Therefore, health prevention intervention will be displayed to all participants the same way.

As well a risk could be that low risk women are less breast aware. Breast awareness will therefore be displayed in all groups the same way. Regular reminders and annual risk reassessment will participate to sustain this. These measures shall contribute to both avoid study biases and risks for all participants.

1.1.15 MyPeBS population's anticipated age and risk structure

To make this trial feasible, the screening potential of each participating region/area has been carefully evaluated. Target accruals have been defined together. The recruitment will be competitive.

The realistic target age structure of women accrued in MyPeBS is: 25% aged 40-49, 45% aged 50-59, 30% aged 60-69. This age structure, as well as the risk structure in the risk-based arm, will be carefully and regularly scrutinized on order to allow potential recruitment adaptations. Monthly trial updates and steering committee meetings will be organized to allow this.

If the age and risk structure differs significantly from of initial plan, the study statistician, with the Clinical trial Steering Committee, together with the advice of the Ethics and data Monitoring Committee, will model these changes' effects on the initial statistical hypotheses and potentially propose an amendment of the study.

MyPeBS		women aged 40-49 (25%)	women aged 50-59 (45%)	women aged 60+ (30%)
risk level	average risk in level	Expected distribution	Expected distribution	Expected distribution
Low	0,8%	60%	28%	15%
average	1.4%	25%	33%	30%
high	2.3%	15%	40%	55%
TOTAL		10 625	19 125	12 750

1.1.16 Evaluation of potential screening harms in MyPeBS

Several secondary endpoints will carefully evaluate potential screening harms (safety endpoint) in MyPeBS: they include false positive recalls, negative impacts on patients reported outcomes, as well as an estimation of overdiagnosis. Finally, we will also attempt to evaluate radiation-associated risks in both arms.

Some of these evaluations will use the MISCAN model, which has been largely used for this purpose and in the context of the evaluation of large European screening programs beyond breast cancer (Van den Broek 2018; <https://www.ncbi.nlm.nih.gov/pubmed/?term=de+koning+miscan>). With the calibrated MISCAN model, the effects, risks and costs of a 30-years screening period are predicted. The main effect measures are the number of prevented breast cancer deaths and (quality adjusted) life-years gained by screening. We will also predict the number of screening examinations needed to prevent 1 breast cancer death and gain 1 life-year, and the reduction in advanced disease as a consequence of screening. Predicted risks are the number of over-diagnosed and over-treated breast cancers and the number of false-negative screening tests. False

positive screening tests will also be accounted for. Quality adjusted life years gained is calculated by applying a quality of life value to each phase of the disease. Such values have been calculated for screening attendance, the diagnostic phase, initial treatment, palliative treatment, the first year after treatment, the disease-free period >1 year after treatment, and terminal illness. By multiplying these values by the average duration of the different phases and the number of women to be expected in these phases, quality adjusted life-years are calculated. Quality adjusted life years *gained* are then calculated by comparing the predicted number of quality adjusted life years in a screening situation with the predicted number of quality adjusted life years in a no-screening situation. In this project, we intend to also use empirical data from the trial itself, by adding 5Q-ED.

Number of over-diagnosed and over-treated breast cancers: The predicted number of over-diagnosed breast cancers is calculated as the number of breast cancers that are diagnosed during the lifespan of the simulated population in a screening situation minus the numbers of breast cancers that are diagnosed during the lifespan of the population in a no-screening situation. Over-treatment is the treatment of over-diagnosed breast cancer. It is calculated as the number of over-diagnosed tumors multiplied by the probability that a certain treatment is used for that tumor. A distinction is made between tumor stages. The probabilities that a specific treatment is used for a certain screen-detected tumour stage are based on earlier estimates, and the empirical data from the trial.

Radiation risk: We estimate radiation-induced breast cancer incidence by using the excess absolute risk model from pooled analysis of 4 cohorts by Preston and colleagues, the preferred model for estimating radiation induced breast cancer incidence. This model assumes that excess risk for radiation-induced breast cancer increases linearly with increasing radiation dose within the exposure ranges from mammography. In addition, risk decreases with increasing age at exposure, especially after 50 years old (a surrogate for menopause), and increases with attained age; the highest incidence of radiation-induced breast cancer occurs late in life. We have earlier modeled the latency period for developing radiation-induced breast cancer by using a logistic function that phases in increased breast cancer risk between 4 and 11 years after exposure. We estimated radiation-induced breast cancer mortality by multiplying radiation-induced breast cancer incidence by the age-specific case–fatality rates of non–radiation induced breast cancer derived from MISCAN-Fadia and assuming 100% adherence to screening and available treatment. We assume that breast cancer induced by radiation is screen-detected at the same rate as non-induced cancer (Miglioretti, 2016).

1.1.17 Imaging techniques in MyPeBS

Breast cancer screening is based on imaging. To date, 2D mammography, either film screen or digital, has been the only available test for women at population risk. In the last five years several studies have shown that digital Breast Tomosynthesis (DBT), a 3D imaging technique, is more sensitive than full field digital mammography (FFDM) and more specific but whether or not this will result in earlier diagnosis and better prognosis is still unclear. Nevertheless, DBT used in addition to FFDM or with a synthetic 2D reconstruction from the tomo planes, received Food and Drug Administration (FDA) approval for primary screening.

Ultrasonography (US) is used as a supplement to FFDM for women with Breast density C and D according to BI-RADS classification in some countries (for example in France and Belgium in MyPeBS) and in an opportunistic manner for screening in many European countries. For women with established familial risk many guidelines (eg NICE) recommend the use of magnetic resonance (MRI) for women under 60 years.

The imminent adoption of new screening imaging technologies such as DBT and supplementary US has been carefully considered in the MyPeBS trial design. DBT is likely to be included in future screening guidelines for all or for some groups of women. Including DBT as part of the intervention, i.e. offered only to some risk groups, would make the intervention obsolete if DBT becomes standard practice. Furthermore, it would be impossible to disentangle the effect of personalizing screening and the effect of tomosynthesis improved sensitivity in the experimental arm. However it is important to show if the effect of personalized screening is similar with FFDM and DBT. Some participating centers are already using DBT with FFDM in population-based pragmatic trials or demonstration projects, thus it will be possible to have some women recruited in the MyPeBS screened with

DBT in both arms. The analysis of the trial results will be then stratified by use of DBT, and if there is no interaction, the conclusions about the effect of tailoring would be applicable to screening with FFDM and also DBT.

A specific secondary objective is therefore dedicated to evaluating the impact of DBT in MyPeBS.

The second important point in the trial design is the use of supplementary whole breast US (hand held HH or Automated Breast AB) with FFDM in women with dense breasts. In some countries screening is already modified according to breast density. Besides increasing the risk of cancer, breast density reduces mammographic sensitivity and can delay diagnosis. However pragmatically US (HHUS or ABUS) in all dense breasts would be unsustainable for most organized screenings of the participating countries.

Therefore the trial design takes into account the following constraints: 1) maintaining the control arm as the “standard of care in each country”; 2) harmonizing the experimental arm imaging procedures among countries as much as possible; 3) proposing, for high-risk women, an intervention that improves sensitivity in dense breasts; 4) proposing a sustainable protocol for personalized screening. In those centers where US is not routinely used in dense breasts, US will be added in the experimental arm only, for women who have BIRADS C/D dense breast (or equivalent with density assessment tools) and are in risk group 2/3. Optimization of the threshold for use of US will be possible according to the results of the ongoing studies, in particular the ASSURE study (conducted by centers that are included in MyPeBS) and the Wisdom trial, the USA companion study of MyPeBS.

1.1.18 Use of Digital 3D tomosynthesis in MyPeBS

Digital mammography's overall sensitivity is limited by the presence of dense fibroglandular breast tissue, which can obscure an underlying cancer (Kolb 2002; Mandelson 2000). Likewise, specificity is also reduced by the presence of overlapping fibroglandular tissue, which can mimic the appearance of cancer.

In the early 2000s, the conversion from analog film-screen mammography to FFDM improved diagnostic performance, particularly in women with dense breast tissue. Digital breast tomosynthesis (DBT) represents yet another significant advance in mammography technology, enabling multiple tomographic images to be obtained in any conventional mammographic view, creating a “semi-3D” mammogram. This enables visualization of a sequential stack of thin image “slices” of the breast, minimizing the masking effect of overlying tissue and enabling improved cancer detection while simultaneously reducing false-positive findings. The FDA approved DBT in 2011, and multiple studies have shown that DBT is effective in both screening and diagnostic settings (Pisano 2005; Svahn 2015; Shin 2015; Vedantham 2015; Hooley 2017).

Studies have shown that the use of DBT in combination with digital mammography in breast cancer screening programs increases cancer detection rate compared with DM alone, while results for false positive recalls have been somewhat conflicting (Skaane 2013; Lang 2016; Bernardi 2012; Friedewald 2014; Greenberg 2014; Rose 2013; Yun 2017; IARC 2016; Hodgson 2016; Houssami 2016, Gilbert 2016). However, this comes with an increase of the radiation dose, to an extent that is variable depending onto the manufacturers and type of use. In addition, it is unknown if the additional cancers detected represent clinically meaningful cancers or if they are dormant or slow growing tumors that never would have become clinically important within the woman's lifetime; the latter are usually referred to as overdiagnosis.

DBT seems of particular interest in (but not limited to) dense breasts and young women.

European recommendations are expected to clarify the position of DBT in breast cancer screening. Meanwhile, some countries and/or regions or centers, are on the process of making DBT a potential/obligate technique of breast cancer screening. DBT's position will be evolving throughout the conduct of MyPeBS trial. For these reasons, our trial allows DBT; it will very carefully assess and watch DBT use, will organize towards evaluating DBT's efficiency within the trial; but randomization will not include the use of DBT as a stratification factor.

1.1.19 Assessment of Breast Mammographic Density towards breast cancer risk evaluation

High mammographic density is associated with both risk of cancers being missed at mammography, and increased risk of developing breast cancer (114,140,161,162,177,179,181,184,193). Stratification of breast cancer prevention and screening requires mammographic density measures predictive of cancer (4,15,16,162,177,179).

The relationship of density with risk was established using expert visual assessment of film mammograms (Boyd 1995) with computer-assisted methods providing a little bit less powerful but potentially more reproducible estimates. With increasing uptake of full-field digital mammography (FFDM), the association between automated density assessment methods and cancer risk is under investigation (Eng 2014, Astley 2018). The most widely used method of assessing mammographic density in the USA and Europe is the BI-RADS categorization, where experts assign mammograms to one of four classes, the upper two being considered “dense”. The higher Bi-RADS category is associated with a 3 to 4-fold higher breast cancer risk than the lower one. Visual assessment of percentage density may be recorded on visual analogue scales (VAS), also providing a continuous measure. This yielded a strong relationship with breast cancer risk for film mammograms, with an odds ratio (OR) of approximately 7 for 76–100% density relative to 0–25% (Duffy 2008). Several softwares have been developed that allow the automatic evaluation of breast mammographic density by different techniques or approaches.

A recent case-control study (Astley 2018) conducted on the PROCAS cohort compared mammographic density assessed by VAS, thresholding (Cumulus) and fully-automated methods (Densitas, Quantra, Volpara) in contralateral breasts of 366 women with unilateral breast cancer (cases) detected at screening on entry to the study (Cumulus 311/366) and in 338 women with cancer detected subsequently. Visual density assessment demonstrated a strong relationship with cancer, despite known inter-observer variability. Percentage density measured by Volpara and Densitas also had a strong association with breast cancer risk, amongst the automated measures evaluated, providing practical automated methods for risk stratification.

In MyPeBS, centers will be provided as much as possible, with a common automated system dedicated to density evaluation for digital mammography, as well as DBT (two different softwares are planned).

We will define and validate the thresholds equivalent to BiRADS A, B, C and D. Validation of thresholds will include systematic review of the literature and data analysis of the participants’ databases to compare subjective BiRADS classification and automatic evaluation.

1.1.20 Double reading of screening mammograms

Double reading of mammograms has been shown to increase screening sensitivity, with an average around 6-8% of all cancers identified by second reading in screening programs. The effect of second reading might however be less important when tomosynthesis is used.

In the present trial, double reading is mandatory in all participating countries but Israel. Double reading will be performed as usual for all women accrued outside Israel, in both arms and for all mammograms.

Randomization is stratified per country, which will allow taking into account this factor of heterogeneity between countries.

1.1.21 Imaging quality assessments in MyPeBS

In the MyPeBS trial some 300 radiologists will report breast screening cases across five countries, therefore it is important to monitor their performance and ensure that there is an established standard of performance and equivalence of skill levels in identifying any breast abnormalities. Radiological reporting performance is inherently variable, both due to differences between radiologists in their skill and also due to underlying

perceptual and cognitive factors related to the process of visual inspection of medical images. The radiological reporting process has been appropriately modelled. Built upon this theoretical model the PERFORMS scheme has been developed in breast screening and has been used in the UK for 30 years to provide quality assessment and to ensure that radiologists are reporting breast screening cases at a suitable level of screening accuracy. The scheme has also been successfully used internationally to assess reporting skill levels.

Women in both arms of the trial will be screened in years 1 and 2 at several breast-screening centers in each of the five participating countries and according to prevailing national screening guidelines. At each center a number of radiologists will inspect and interpret the screening mammograms. The projected numbers of radiologists taking part per country are: Belgium 50-60; Italy 25-30; UK 20-30; Israel 8, and France 200. In order to monitor reporting quality practices, each radiologist will detail information regarding their reporting mammographic workstation and relevant reporting room information characteristics. Additionally, to ensure that all radiologists meet a minimum standard of reporting accuracy they will report PERFORMS test sets of known challenging cases every six months in the first two years. The results of these tests will be fed back to the participants and reported to the MyPeBS coordinators.

PERFORMS is a web based self-assessment scheme in which radiologists are given access to sets of carefully selected multi-vendor challenging cases which they view on their workstations using their usual clinical viewing software. For each case examined radiologists report the possible presence of key mammographic features into the App. For each test case they will determine whether they consider the case as normal, benign or malignant and they will also identify the location and type of any potential abnormal appearance. Once all the test cases are completed then immediate feedback is given by the App to the radiologist on their performance. Additionally their performance will be logged on the PERFORMS system and analysed using ROC and JAFROC analyses. Reading the test sets will ensure that their performance in identifying potential abnormal mammographic appearances is satisfactory and is also compatible with the performances of their trial peers.

It is important that all the radiologists in the trial across the five countries are all able to identify early signs of cancer with equivalent skill. To ensure that all participating radiologists meet a minimum standard of reporting accuracy, during the first two years of the trial, when women are being recruited, all radiologists will also regularly read PERFORMS test sets of known difficult mammographic cases and report these using the PERFORMS App. For centres using tomosynthesis then PERFORMS tomosynthesis test sets will also be used.

1.1.22 Germline genetic testing for high penetrance genes in MyPeBS

While germline deleterious genetic variants of high penetrance genes (BRCA1, BRCA2, TP53, PALB2, PTEN, CDH1, RAD51c, and so on) are rare in general western populations (at most 1 in 500 individuals), three founder mutations of BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT) genes are frequent in the Jewish Ashkenazi population (3% of the population).

Previously identified germline mutation carriers of high-penetrance breast cancer susceptibility gene mutations will not be allowed to enter MyPeBS, given their need of specific screening programs.

Germline mutations of high penetrance susceptibility genes will not be searched systematically in MyPeBS, given their rarity, the complexity of such search and the important risks of harms this would be associated to (high risk of psychological harm given the high frequency of unknown variants, for instance).

However, two situations must be highlighted:

- in MyPeBS, participants for whom a family history compatible with the presence of a high penetrance gene is identified, will be advised a genetic counselling within the national oncogenetic network of each country. In the advent of the identification of a mutation in a high-risk gene, the screening program will be modified accordingly to include yearly mammogram and MRI screening (up to age 60), as recommended in all participating countries.

- in Israeli women, given the prevalence of the three founder mutations of BRCA1 and BRCA2, it appears necessary to propose a pre-identification of these genetic alterations. We will therefore incorporate SNPs dedicated to the identification of these three founder mutations.

However:

- The results of these SNPs will be only provided to women accrued in Israel and who have signed a dedicated specific consent allowing for this identification, after adequate information
- The results of these SNPs will not have any medico-legal value and will only indicate the need for a dedicated genetic counselling and genetic test including proper DNA sequencing towards identification of such germline mutations, if finally present.

In the advent of the identification of one such confirmed mutation, the screening program of the concerned woman (risk-based arm only) will be modified accordingly to include yearly mammogram and MRI screening (up to age 60), as recommended in all participating countries.

1.1.23 Risk reduction measures in MyPeBS

Participants of MyPeBS in both arms will receive general information on breast cancer risk reduction strategies, mostly based on lifestyle habit changes and avoidance of certain environmental or hormonal exposures. This information will be provided essentially on the participants' portal.

Women in the risk-based arm will be further informed on potential risk-reducing strategies associated with their individual breast cancer risk level and individual risk factors. Upon risk calculation, they will receive a printed + online document summarizing all their personal information, risk category assignment, proposed screening strategy, but also suggested personalized risk-reduction measures (such as avoidance of certain endocrine therapies, dietary and exercise recommendations, etc). These measures will be predefined by the trial steering committee and detailed in the full study protocol. They will be able to retrieve all their personal information in their personal account on the trial's web platform. They also will be able to gather more general information on the project's website.

It is likely that, if aware of their risks, a sizeable proportion of women at high/moderate-risk would opt for lifestyle prevention (extra physical activity, diet/healthy weight maintenance or loss of excess weight, alcohol restriction) to reduce cancer risk. Such changes will be captured, although no direct intervention beyond information is planned within the trial. Of note, UK is the only country proposing risk-reducing therapies (Tamoxifen, raloxifen or aromatase inhibitors, based on NICE recommendations) in women at high risk.

In general, communicating increased risk has small but significant effects on increasing healthy lifestyle behaviors, but the best evidence suggests that communicating lower than average risk does not lead to unhealthy lifestyle behaviors. If even small effects on these behaviors are achieved by communicating personalized risk information, then large population reductions in these unhealthy behaviors should follow. The overall net effect of chemoprevention, additional screening and changes in lifestyle behavior is likely to be patient benefits from a reduction in breast cancer incidence and mortality but is very unlikely to influence the trial results, given the 4 years endpoint.

Breast cancer awareness remains a major cornerstone of reduction of the risk of advanced breast cancer: women must be advised of both symptoms leading to see a doctor and eventually to have a diagnostic mammogram and health behaviors leading to reduced risks of breast cancer (203-206). Participants will be yearly reminded of the fact that even a low risk does not mean an absence of risk and that even yearly mammograms can miss some cancers and that, therefore, seeing a doctor in case of a symptom remains crucial.

Self-palpation will not be specifically encouraged in the absence of proof of any benefit on breast cancer specific survival or other outcomes, but can be taught to women who wish so (200-202)

1.1.24 Rationale for evaluation of PROs in MyPeBS

Refs: Lerman, Hersch, Martinez-Alonso, O'Donnel, Fox, Morman, Johansson, Wardle

As mentioned previously, there are number of potential human costs to implement the communication of risk information on such a scale as in MyPeBS trial. This includes possible undue worry and anxiety for women at high-risk, a lack of informed decision making regarding treatment options, reduction in mammography attendance, false reassurance in those at low-risk, resulting in subsequent nonattendance at screening and lack of attendance to health-related behaviors that place women at increased risk. The existing literature suggests that many of these harms are not likely, but evidence is not compelling.

The very careful evaluation of participants' related outcomes (PROs) is therefore a key component of MyPeBS trial.

The overall methodology of participants' reported outcomes measures (PROs) in the present trial is based on online questionnaires (exceptionally paper questionnaires). In MyPeBS, we use validated well-known questionnaires, except for very specific purposes (e.g., comprehension or satisfaction with specific documents...), for which dedicated questionnaires have been developed and validated with a group of patient's advocates, healthcare professionals and researchers.

Comprehension of information provided

Based on the information tools used, we have developed a comprehension questionnaire containing true/false questions divided into three categories of information provided:

- (1) General information on breast cancer;
- (2) Information on breast cancer risk;
- (3) Information on benefits and risks of breast cancer screening.

The main reasons for using this type of questionnaire are:

- Data obtained using true/false questions are easy to analyze as compared to questionnaires containing open-ended questions
- This type of questionnaire provides a better comprehension assessment of the information provided as compared to a questionnaire based only on the comprehension feeling

Concerning the evaluation of comprehension at 4 years, we will administer the same questionnaire to women and add questions about their information seeking-behaviors related to breast cancer screening in general and related to risk stratified breast cancer screening issues as well. We will ask for instance whether women searched for information on the internet, in the media, or asked questions to healthcare professionals. One particular aim will be to test whether or not there is a correlation between information seeking-behaviors, comprehension level, and women's characteristics (mainly socio-economics and socio-demographics).

Participants' risk perception

It is essential that all decisions made as part of screening are informed, and based on sound understanding of good quality information provided. In addition to the assessment of comprehension, a key element of understanding is how accurately women perceive their own risk of breast cancer following risk-stratified screening, and whether this has been improved, relative to standard screening.

Uptake of options that may reduce future risk of breast cancer such as increased mammography in women at high risk, or increases in healthy eating or physical activity is linked to perceptions of the risk of disease and benefits of these behaviors in reducing risk. By contrast, a potential harm of risk-stratified screening is that those who are told they are low risk may increase their unhealthy behaviors through being falsely reassured, i.e. a « certificate of health effect ».

For these reasons, we will assess perception of risk of breast cancer, and perceptions of efficacy and risks of these prevention options (Evans 2016; Weinstein 1999). We will also assess intentions to attend future

screening and intentions to change lifestyle behaviors and healthy eating. We will assess how perceptions of risks and benefits predict these intentions, and also whether they predict subsequent uptake of mammography.

Psycho-social impact of both screening methods

Amongst the potential harms of risk-stratified screening are undue increases in general anxiety or distress related to cancer. The results from PROCAS1 and RIVIERA studies found little evidence for elevated distress, although distress was higher in women who received higher risk results (Evans et al 2016, Veron et al 2018). To assess if increased distress is a harm of risk-stratified screening, we will compare the levels of general anxiety and cancer-specific worry between women who receive risk-stratified screening and women who receive standard screening. It is generally found that cancer-specific worry measures are more sensitive to the effects of receiving risk information than more general measures of anxiety (Bond 2013; Nelson 2016). In contrast, there is better evidence that more general measures of anxiety are better linked to diagnoses of psychological disorders (Spiegelhalter, 1983). For this reason we will assess both indices of psychological distress. We will assess both variables using standardized measures: the STAI short form to assess general state anxiety (1992) and the Lerman cancer-worry scale (1991).

There is also evidence that both general anxiety and cancer-related worry peak shortly after receiving information on cancer risk (Bond 2013; Nelson 2016) and then gradually decline. For this reason, we will assess these variables over time across five countries, to examine whether there are short-term increases as well as any longer-term effects.

In addition, it is important to understand the reasons for any increases in distress in the risk-stratified screening groups, as it may be an intrinsic result of receiving risk feedback, or it may be more modifiable effects of the healthcare system. For this reason, we will conduct - in England and France only - a qualitative assessment with up to 24 women who undergo risk-stratified screening. They will be interviewed three months after receiving their risk estimation results. They will be purposively sampled to ensure variation in risk results received, and variation in socio-economic status. They will be asked about how acceptable they found the process, what they understood was the purpose of each element of the screening process, if they would recommend the process to their friends, and how the process could be improved. A matched sample of 16 women in the same countries who declined to participate to the trial will be interviewed to assess their views of this form of screening, and what they found to be not acceptable about it. Data analysis will use a manifest level approach to thematic analysis.

Participants' satisfaction

We will use a questionnaire assessing decisional satisfaction and regret regarding trial participation using the satisfaction with decision scale (SWD) and the decisional regret scale (DRS), respectively. The 6-item SWD scale has good reliability and discriminant validity (Holmes-Rovner et al, 1996). The DRS is a widely used 5-item scale with good internal consistency (Brehaut et al, 2003).

In terms of trial-related behavior, intention to participate in the trial will be assessed after the trial participation decision had been made at 1 year and that actual enrolment and subsequent dropout were recorded at the end of their participation at 4 year. We will assess the differences between both arms using equality of proportion and chi-square tests.

Furthermore, we will assess participants' satisfaction regarding care received during the trial, in both arms. For this purpose, we will adapt the Sat-35 questionnaire by using only appropriate items, as previously described.

To be as close as possible to women concerns, this work will be developed and conducted in close collaboration with patients' associations and advocates, particularly ICPV and the European Cancer leagues.

Impact of socio-economic status

We will verify whether MyPeBS participants' characteristics are representative of the social heterogeneity of the participating countries, and how much social characteristics influence screening perception and behavior (such as compliance with the proposed program).

We will analyze women's socio- demographics, i.e. age, education level, income level, marital status, profession, geographic area, number of children. We will compare the characteristics of invited women versus participant women in terms of socio- demographics, age, and geographic location.

We will focus our attention on social economic and social inequalities using either the European Deprivation Index (EDI), an aggregated measure of deprivation validated in many European countries that has already been used to assess inequalities in cancer screening access, or using the EPICES score, an individual index taking into account the "social health" of individuals that is a potential predictor of screening participation. In parallel, we will use the ISCED score of education, which has as well been largely validated. Our deprivation assessment will therefore be aggregated from EDI/EPICES and ISCED evaluations.

We will analyze the impact of socio-demographics and deprivation level on women's participation to risk stratified breast cancer screening as well as to breast cancer screening in general using multivariable logistic regression analyses.

Quality of life

Concerning quality of life, we will use the Euroqol 5D questionnaire (EQ-5D) - a standardized instrument for use as a measure of health outcome - that has already been translated in several languages. This questionnaire comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems.

All questionnaires of this task will be administered to women at baseline and at 4 years.

Quality of life (QoL) among different socio-economic groups will be compared using both an aggregated and un-aggregated (i.e. considering the five dimensions of the EQ-5D separately) measure of QoL based on the responses to the EQ-5D questionnaire.

1.1.25 Modelling MyPeBS to quantify the long-term benefits, harms, and cost-effectiveness of risk-based screening scenarios

To date, the additional harms (false positive mammograms, possibly over diagnosed cases, in retrospect unnecessary biopsies, false negative mammograms) and additional benefits (breast cancer deaths averted, quality-adjusted life years saved, breast cancer mortality reduction) of using polygenic risk information to tailor screening strategies remain untested and unknown. The goal of this study is to personalize routine breast cancer screening based on women's individual risk profile, including age, breast density, family history and polygenic risk score. Although the trial will result in short-term estimates of some, modeling is indispensable to quantify long-term harms and benefits. The main objective of WP4 is to evaluate the effects, costs, and cost-effectiveness of risk-based screening scenarios and to estimate these long-term (lifelong) benefits and harms of these strategies compared to current practice. In order to extrapolate the (relatively) short-term findings of the trial (such as incidence of advanced BC and the number of biopsies) to their expected long-term health outcomes (such as BC mortality reduction and quality-adjusted life-years gained) a model of the natural history of BC and BCS is needed.

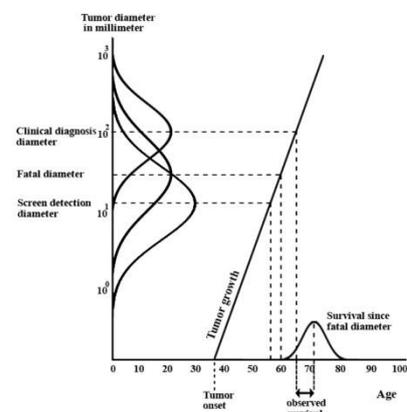
Erasmus University developed and extensively validated the MISCAN microsimulation natural history model for the evaluation of BCS. The model has previously been applied to inform the Dutch cancer screening programmes, has been extensively used in other European countries and has been used to inform the US Preventive Services Task Force. A simulation model is needed that can translate the trial findings to life time estimates. The micro-simulation analysis model 'MISCAN' is used for this purpose, because it includes research-based assumptions about the natural history of breast cancer and breast cancer survival, and screening-related survival benefits that have been initially derived from the breast cancer screening trials, and more recent based on IARC overview. We will adapt the existing MISCAN-breast model to represent a country-specific situation by including national country-specific data on e.g. demographics, health care system, screening and treatment situation, and costs, and will then use the country-specific models to evaluate the cost-effectiveness and harm-benefit ratios of the risk-based screening strategies in MyPeBS, compare those

to current (country-specific) practice (i.e. control arm), and, finally, compare the results across countries. The costs, effects, and cost-effectiveness will be estimated for the risk groups, and using data on the size of each group, the results can be combined to provide an estimate for the total population. The MISCAN model has also the flexibility to take into account promising future developments. The model already includes different risk factors, such as breast density, as well as different molecular subtypes of BC (by ER/HER2), and other screening modalities (e.g. ultrasound). These features give the possibility to also model alternative risk-based screening scenarios to be able to see whether a different stratification, e.g. using other cut-off levels for risk, and/or the use of different screening modalities, could potentially even further increase the cost-effectiveness of risk based screening. In addition, both arms of the WISDOM trial will be simulated and compared to those estimated for the European risk-based screening strategies.

Modelling effectiveness (and cost) of risk-based breast cancer screening compared to standard existing routine screens

The cost-effectiveness of mammography screening is calculated by comparing estimated life-years and costs of breast cancer in a risk-based screening situation, with life-years and costs in a situation without such a screening approach. We will assume that the current screening programme will be continued for a period of 30 years. The simulated cohort will have the same age distribution as observed in the trial. To account for all potential screening effects and costs, outcomes will be measured during the remaining lifespan of the simulated trial population.

A detailed description of MISCAN is presented below. The MISCAN-Fadia model, acronym for MISCAN Simulation ANalyses - Fatal Diameter, consists of four main components: demography, natural history of breast cancer, screening, and treatment. Since tumor size is measurable at diagnosis and tumor growth is continuous, these properties form the biological approach to simulate breast cancer natural history. The “fatal diameter” concept implies that the best available treatment will only cure tumors that are diagnosed at a smaller diameter than the tumor’s fatal diameter which reflects distant metastases of the disease. The model simulates individual life histories from birth to death, with and without breast cancer, in the presence and in the absence of screening and treatment. Life histories are simulated according to discrete events such as birth, tumor inception, the tumor’s clinical diagnosis diameter in the absence of screening, and death from breast cancer or death from other causes.



When a breast tumor is initiated in a simulated woman, values of six tumor characteristics are generated: growth rate of the tumor, the tumor’s fatal diameter that represents distant metastases, survival time after reaching the fatal diameter, screen detectability diameter (threshold), and the clinical diagnosis diameter. The distribution curves on the y-axis demonstrate the probabilistic nature of the simulations and the variation between the screen-detection, fatal and clinical diagnosis diameter of tumors. The growth rate of the tumor determines the times since its initiation at which the tumor reaches the screen detectability diameter, the clinical diagnosis diameter, and the fatal diameter. If in the absence of screening the clinical diagnosis diameter is larger than the fatal diameter, the woman will die of breast cancer and the observed survival time is given (example depicted in Figure). A woman will be cured if the breast cancer is detected, either clinically or through screening, before the fatal diameter is reached. Treatment (not shown) is modeled as a shift in fatal diameter and may affect survival and in the best scenario cause of death.

Calibration of the MISCAN breast cancer model

To predict the cost-effectiveness of the separate screening strategies, MISCAN is first calibrated with country-specific demographic, epidemiologic and screening characteristics. In the model, these characteristics are governed by a number of parameters. We estimate the values of these parameters by numerical minimization of the deviance between predicted and observed outcomes in the trial. A Chi-square test applied to the deviance between predicted and observed outcomes is used as a measure of goodness-of-fit. The probability

of dying of other causes than breast cancer will be included in the model by using a recent life-table of the (country-specific) female population, corrected for breast cancer death. A 'dynamic' population that mirrors the age distribution of women in the trial during a certain time period is thus constituted.

Subsequently, the characteristics of the screening programme (or arm) are modelled. To do so, we use the number of screening invitations and examinations, the average time interval between two screening examinations, the attendance rates after an invitation for a first/ subsequent screening round, attendance rates if a woman has previously attended screening and the attendance rates if a woman has not previously been screened. If data are available, opportunistic (unscheduled) screening can be incorporated.

The model parameters that underlie mean pre-clinical stage durations and transition probabilities between pre-clinical disease stages were originally based on pilot studies before the implementation of nation-wide screening in Nijmegen and Utrecht and since then the outcomes of the Dutch nation-wide breast cancer screening programme. The parameters have been used with modification to model various screening situations; we therefore assume that they will be suitable as first step to model the trial situation as well. The model-predicted age- and stage- specific incidence in pre-screening years, the rates of screen-detected and interval cancer by screening round and interval length, and the incidence of clinically diagnosed cancers after screening implementation are fitted to the corresponding observed data. If necessary, the parameter values for transition probabilities between the various tumour stages, the mean durations of the various preclinical screen-detectable stages, and the sensitivity of mammography will be adjusted, by minimizing the deviance between observed and predicted outcomes. Observed data can often be explained by several different combinations of parameter values (e.g. a slightly higher test sensitivity with a slightly shorter duration could result in a similar fit between predicted and observed data). By including different age groups and using data from several screening rounds, best parameters often fall into a smaller range. Age- and stage dependent survival after clinical diagnosis or screen-detection in MISCAN is modelled using several international sources. These survival assumptions have been used to model breast cancer mortality in various different screening situations; we therefore expect the parameters values to be valid for the trial as well. The screening-related breast cancer mortality reduction is then calculated, by comparing the predicted breast cancer mortality in the risk-based screening situation, with the predicted breast cancer mortality if screening would have taken place according to the control arm.

Effects and risks of mammography screening

With the calibrated MISCAN model, the effects, risks and costs of a 30-years screening period are predicted. The main effect measures are the number of prevented breast cancer deaths and (quality adjusted) life-years gained by screening. We will also predict the number of screening examinations needed to prevent 1 breast cancer death and gain 1 life-year, and the reduction in advanced disease as a consequence of screening. Predicted risks are the number of over-diagnosed and over-treated breast cancers and the number of false-negative screening tests. False positive screening tests will also be accounted for. Quality adjusted life-years gained is calculated by applying a quality of life value to each phase of the disease. Such values have been calculated for screening attendance, the diagnostic phase, initial treatment, palliative treatment, the first-year after treatment, the disease-free period >1 year after treatment, and terminal illness. By multiplying these values by the average duration of the different phases and the number of women to be expected in these phases, quality adjusted life-years are calculated. Quality adjusted life-years gained are then calculated by comparing the predicted number of quality adjusted life-years in a screening situation with the predicted number of quality adjusted life-years in a no-screening situation. In this project, we intend to also use empirical data from the trial itself, by adding 5Q-ED.

Number of over-diagnosed and over-treated breast cancers: The predicted number of over-diagnosed breast cancers is calculated as the number of breast cancers that are diagnosed during the lifespan of the simulated population in a screening situation minus the numbers of breast cancers that are diagnosed during the lifespan of the population in a no-screening situation. Over-treatment is the treatment of over-diagnosed breast cancer.

Radiation risk: We will estimate radiation-induced breast cancer incidence by using the excess absolute risk model from pooled analysis of 4 cohorts by Preston and colleagues, the preferred model for estimating radiation induced breast cancer incidence.

Costs

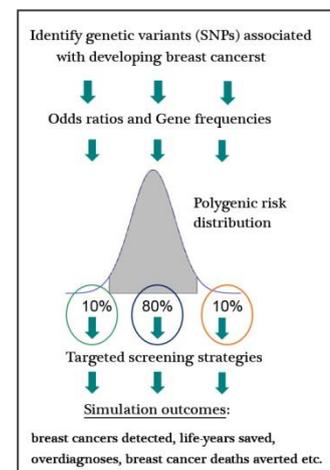
In general, we will follow the recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses, as put forward by the 2nd panel on cost-effectiveness in health and medicine. The costs of screening are all expenses directly and indirectly related to the screening programme, breast cancer diagnostics, treatment and follow-up that would not have been made if no screening had taken place. Costs that are involved with over-diagnosis, over-treatment and false-positive outcomes are included. Short- and long term direct and indirect costs are accounted for. Costs are calculated as the costs per unit multiplied by the resource use. Unit costs will be assessed in co-operation with participating countries. ‘Costs’, in terms of the impact on quality of life, are incorporated by multiplying the predicted gained life-years by a utility estimate. To account for time preference, all costs are 3% discounted. The costs of the screening programme include the costs of inviting women to participate in the screening programme and the costs of a mammogram and/or genetic testing. Indirect costs will be taken into account.

The costs of diagnostics are calculated as the costs per diagnostic examination multiplied by the number of examinations that is needed to diagnose 1 tumour. This includes the costs of clinical breast examinations, opportunistic mammography (outside the screening programme), diagnostic mammography, imaging diagnostics, minimal invasive diagnostics and pathological examinations. A distinction is made between the diagnostics that are needed for 1 screen-detected tumour, and the examinations that are needed for the clinical diagnosis of a tumour outside or without a screening programme. We use data on the diagnostic work-up of a positive screen-mammogram and data on all diagnostics needed to clinically diagnose a tumour, including false positive tests. The number of diagnostic examinations that are needed and the costs per unit will be calculated based on the trial data.

The costs of treatment are calculated as the unit costs of a specific treatment, multiplied by the frequency with which that treatment is used. A distinction is made between the treatment use for a screen-detected tumour and the treatment use for a clinically diagnosed tumour outside or without a screening programme. We include over-treatment, i.e. treatment of tumours that would not have been clinically diagnosed if there were no screening programme. Direct and indirect short- and long-term treatment costs are incorporated. To account for stage shifting due to screening and its consequences on the treatment costs, specific treatment probabilities for each separate tumour stage are needed. Treatment use is further specified for the age groups.

Analyses by risk (stratification)

Multiple single nucleotide polymorphisms combined together are translated into a polygenic risk score to stratify women based on their polygenic risk. In this figure, a simplified analysis of using polygenic risk to inform screening strategies is demonstrated by dividing the population into three (low, median, and high) risk groups with varying risk and prevalence. In this example 10% of the population is classified as low risk, 80% is classified as average risk, and 10% as high risk. Compared to the average risk group, more frequent screening could be offered to the high risk group and less frequent screening could be offered to the low risk group. With more risk groups, or even a continuous risk distribution we can “optimize” the tailoring of screening strategies based on polygenic risk. This would lead to a re-distribution of the benefits and harms of routine screening compared to the current “one size fits all” mammography screening approach that is merely based on a woman’s age.



Preliminary modeling indicates that targeted screening based on (so far published) genetic risk profiles only, led to more benefits than untargeted screening for the same number of screens. A screening strategy with an earlier starting age (40y) for the 10% at highest risk and a later starting age (60y) for the 10% at lowest risk

led to substantial benefits in the high risk group (an increase in deaths averted of 19.8%), and translated into an increase in life-years gained of 3.6% (figure). For this proposal, we will however also include our density stratification, and extended model by ER/HER-status, being able to make more precise predictions across a broader spectrum of ages. The models can incorporate co-morbidity, if substantial high quality data can be gathered in the project. At age 40 years, women in the simulated model cohorts are assigned an initial breast density on the basis of the distribution of BI-RADS density categories for premenopausal women in the Breast Cancer Surveillance Consortium (BCSC) women. At age 50 years, women are assigned to the same breast density category or the next lower category so the prevalence of breast density categories matched the BCSC observed prevalence for postmenopausal women. Sensitivity and specificity of digital mammography are determined as a function of age, breast density, and screening interval. The current model incorporates modeling of molecular tumor subtypes and evaluates benefits under screening and adjuvant treatment regimens by molecular subtypes (Munoz et al).

Special attention will be given to the different recruitment strategies in the European countries involved, and possible future other recruitment strategies considered. Also, the substantial differences in health care systems and cultural differences across countries will be considered, possibly in different country-specific models and costing. For Israel, we will add a specific high risk group (and possibly different natural history model) for Ashkenazi Jews. Finally, sensitivity analyses will be performed, e.g., on expected risk levels, different cut-offs for screening strategies, sensitivity and specificity for subgroups (if limited data), participation rates, and opportunistic screening, treatment effect, cost and screening effect.

1.1.26 Long-term follow-up in MyPeBS

Although the intervention in MyPeBS will only last for 4 years, part of its consequences could last longer, especially in so-identified high risk women, who may continue both the more intense screening they have been proposed, as well as risk-reducing strategies they were advised on. It is therefore crucial we can have access to long-term stage II and higher breast cancer incidence, as well as long-term breast cancer specific mortality.

We intend to retrieve such data at 10- and 15-years from study entry.

This will allow first to identify the long-term effect of risk-based screening program as compared to standard screening, but also to refine long-term risk assessment and risk scores, in this very carefully annotated cohort.

To this end, we will not be able to retrieve data from participants nor investigators, who will not be asked any more participation after 4 years. We have therefore organised towards being able to cross our database with national health system databases and national security insurance systems databases, in each country.

1.1.27 Long-term additional research developments based on MyPeBS' database, rationale for collection of images and saliva DNA

Finally if risk-based screening is demonstrated as more efficient and more acceptable for women than standard screening, it will become crucial that risk identification can be further refined in the future.

This refinement would also dramatically serve prevention programs in the future.

It is highly likely that germline DNA can contribute to such risk identification refinement in the future, not only through the discovery of new SNPs, but also to avenues open by the potential of whole genome sequencing, and epigenetic assessments, for example.

Beside this, mammographic and other images also are of great promise for the purpose of risk identification.

For these reasons, we have organised towards storing saliva DNA of women who will consent to, for the purpose of additional research as described. We also wish to collect and store mammographic images of a maximum of participants, provided they have given their consent for this, as well. The informed consent form has been written accordingly.

1.2 Benefit-risk assessment

As demonstrated above, risk-based breast cancer screening is highly promising, given its potential ability to allow more screening efficacy in those who derive any benefit of such screening because of a higher breast cancer risk, together with decreasing harm in women who might not derive benefit from mammogram given their low personal breast cancer risk.

However, risk zero does not exist, and it is important to verify that a positive benefit-harm ratio is maintained for all participants throughout the trial.

The individual potential benefits and harms will be carefully explained to participants throughout the trial. They are explained in the informed consent, to allow women to make their own decision regarding not only participation to MyPeBS trial, but somehow also to screening in general.

Risk reduction measures will be maintained throughout the trial:

Trial-level risk reducing measures will always be applied to maximise the benefit-harm ratio for all (yearly reassessment of risk, reminders, 4-year mammogram for all, careful surveillance of the trial by the Ethics and Data Monitoring Committee, ...). Breast cancer awareness will be repeatedly stimulated for all participants throughout the trial. This is will even more pronounced for women in the low-risk group of the risk-based arm, who will have their next mammogram after 4 years.

1.2.1 *Effects and risks of mammography screening in the standard arm*

The benefits and harms/risks from standard mammographic screening have been extensively described in 1.1.2. We summarize them below:

- Mammographic screening has been associated with an average 20% reduction in breast cancer-specific mortality in average risk-women: The available evidence is derived from 11 randomized trials and their meta-analysis with 13 years of follow-up: The benefit is demonstrated for women over 50, while 2 studies demonstrated benefit for women aged 40-49, and others were negative, leading to divergent interpretation and recommendations throughout countries. Of note, the relative reduction in breast cancer specific mortality appears higher for women actually attending screening. Trials indicated no statistically significant reductions in all-cause mortality with screening. Risk for higher-stage breast cancer was reduced for age 50 years and older (RR 0.62 [95% CI, 0.46 to 0.83]; 3 trials), but not for age 39 to 49 years old (RR 0.98 [95% CI, 0.74 to 1.37]; 4 trials).
- As stated before (1.1.2), this is not without potential harms. Screening can lead to false-positive recalls, estimated to occur in more than half of the women after 10 years of annual screening; and many unnecessary biopsies: Another risk is overdiagnosis, which is currently estimated to occur in about 10% of breast cancers diagnosed through screening, although estimates range from 1% to 30%, depending on the population and estimation methods. Finally, mammographic screening is also associated with a small lifetime risk of radiation-induced cancer.

Tomosynthesis with mammography reduces recalls (16/1,000), but increases biopsies (1.3/1,000) and cancer detection (1.2/1,000): Even if concern exists regarding radiation doses administered; tomosynthesis remains therefore an option, but not a standard of mammographic screening.

1.2.2 Effects and risks of mammography screening in the risk-based arm

We will describe here the potential benefits and risks to be derived by participants randomized to the risk-based arm.

1.2.2.1 Potential benefits

As previously demonstrated, increased mammographic screening intensity (up to yearly mammogram) has been clearly demonstrated as to increase screening sensitivity. It is currently used in high-risk situations, such in women previously treated for breast cancer, atypical lesions, or previous chest wall irradiation, as well as high risk genetic conditions, together with MRI. Such MRIs have been demonstrated as highly efficient for reducing the risk of advanced breast cancer among high-risk individuals.

Decrease in the incidence of advanced breast cancers

We expect a decrease in the incidence of stage 2 and higher breast cancers, which will concern women identified at average risk and aged 40-50, or at high-risk.

According to our assumptions (Table below - based on “no screening” before 50 and mammogram every 2 years), among 530 women overall expected to develop breast cancer at 4 years in one arm (among 42,500 participants), a risk-based strategy will increase the screening intensity in 329 of the women who are expected to develop breast cancer (light green).

We should therefore avoid 50 stages 2 or higher breast cancers in women who will get more screening than they would have in the standard arm.

MyPeBS		women aged 40-49 (25%)		women aged 50-59 (45%)		women aged 60+ (30%)	
risk level	average risk in level	Expected distribution	Expected cancers at 4y	Expected distribution	Expected cancers at 4y	Expected distribution	Expected cancers at 4y
Low	0,8%	60%	41	28%	34	15%	12
Average	1.4%	25%	30	33%	71	30%	43
High	2.3%	15%	29	40%	141	55%	129
TOTAL		10 625	100	19 125	246	12 750	184

Decrease of the incidence of false positive recalls and overdiagnosis among women classified as low-risk

In women identified as having a low risk, we expect to reduce the risk of false positives findings (around 300), as well as overdiagnosis (around 5), together with the levels of the stress/anxiety induced by regular mammograms. No impact is expected on radio-induced cancers in such short term but this theoretical benefit exists.

Decrease in breast cancer risk through risk reduction measures in women identified at high-risk

Although this will not be a directly measurable effect, we can expect that women identified at high risk will consider risk-reduction measures, which may contribute in a long-term breast cancer risk reduction.

1.2.3 Potential risks from the participation in the risk-based arm

Small increase in stage 2 or higher breast cancers in women identified at low-risk

Such women are at low but not null breast cancer risk. 87 breast cancers are expected in women for whom only 4-yearly mammogram will be planned (low-risk), but for 41 of these women, the standard is an absence of mammogram since they are aged 50 or less. Only 46 cancers are expected in low risk women for whom the current standard would be to do bi-yearly mammogram, and who will get 4-yearly mammogram instead (light orange in the table above). According to the most pessimistic estimation an excess of 5 stage 2 or higher breast cancers may therefore be observed in these low-risk women.

This potential increase must be prevented by specific dedicated measures including information of participants in this group, repeated and careful breast awareness and annual reassessment of risk.

Increase in false positive recalls and overdiagnosis in high-risk women and in women less than 50 undergoing end of study mammogram

Overall, we should observe an increase in false positive recalls among these patients. The rate of such events is hardly evaluable, since such recalls are proportionally less frequent in women undergoing yearly mammograms than those getting bi-annual screening. It could be around 500 additional false positive findings. As well, there should be an increase in potentially overdiagnosed breast cancers, although such events appear rarer among high-risk individuals.

Increase in anxiety from risk identification and from additional screening images in the high risk women

It might happen, but is not certain, that the identification of a high-risk situation can cause anxiety or distress. From previous studies, it seems this anxiety is transient and low. This will be carefully scrutinized throughout the study with interim analyses of psychological safety.

1.3 Study population

This study addresses women from the general population aged from 40 to 70 years old, who will be invited by the standard screening program to perform a breast cancer screening (potential participants' information on the trial by participating regional screening structures: 3 in Belgium, 3 in UK, 4-6 in Italy, 11 in Israel, 40 in France) or self-referral in a participating region.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to show non-inferiority of the risk-stratified screening strategy in terms of incidence rate of breast cancer of stage 2 and higher (2+), compared to standard screening.

2.2 Secondary objective(s)

(ALL AT 4 YEARS/DURING INTERVENTION PERIOD UNLESS OTHERWISE INDICATED)

1. The key secondary objective, if non-inferiority is shown, is **to demonstrate superiority** of the risk-based screening arm to reduce the incidence rate of stage 2+ breast cancer, compared to standard screening.

2. To compare the rate of morbidity between the two arms, in terms of false positive imaging findings and benign biopsies
3. To describe the psycho-social characteristics of the population accrued and evaluate the psycho-social impact of each strategy (acceptance, observance, anxiety, distress, satisfaction, decisional regret, etc.)
4. To evaluate the costs and cost-effectiveness of each strategy
5. To evaluate the stage-specific incidence of breast cancer of any stage in each arm
6. To estimate overdiagnosis and overtreatment rates in risk-based screening and standard screening arms
7. To compare the rate of false negative mammograms and interval cancers between arms
8. To evaluate superiority of risk-based screening in terms of breast cancer-specific mortality at 10-years and 15-years in MyPeBS and in a combined analysis of the Wisdom and MyPeBS studies
9. To evaluate the added value of tomosynthesis (TS) in the detection of stage 2+ breast cancers
10. To evaluate the incidence of all stage and stage 2+ breast cancers at 10- and 15-year follow-up
11. To evaluate the incidence of stage 2+ breast cancer in risk-based screening in women aged 40-50 years old as compared to standard screening
12. To evaluate the rate of breast cancers discovered at second reading in each arm
13. To evaluate false positive imaging findings and benign breast biopsy rates in women classified in the low risk category in risk-based arm

EXPLORATORY OBJECTIVES (ALL AT 4 YEARS/DURING INTERVENTION PERIOD UNLESS OTHERWISE INDICATED):

1. To evaluate the added value of ultra-sound in the detection of stage 2+ breast cancers in each arm
2. To describe and compare between the arms, the rates of breast cancer predicted at 10- and 15-year, metastatic risk >10% using validated clinical-pathological predictors and the rates of cancers requiring chemotherapy
3. To explore the efficacy and morbidity of risk-based screening versus standard screening in subgroups (including country, risk and age categories)
4. To refine long-term breast cancer risk prediction scores through improvement of existing scores and/or description of new risk scores including clinical, imaging and/or genotyping characteristics and prediction of different breast cancer subtypes
5. To refine the breast cancer risk prediction value of mammographic and other images
6. To evaluate our ability to predict for poor psycho-social impact and low compliance to screening
7. To evaluate the accuracy (sensitivity and specificity) of SNPs to predict for the presence of a founder mutation of BRCA1 or BRCA2 ((BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT))

3. STUDY DESIGN AND ENDPOINTS

3.1 Description of the Study Design

MyPeBS is a European randomized open-label, multicentric, study assessing the effectiveness of a risk-based breast cancer screening strategy (using clinical risk score and polymorphisms) compared to the standard of care in terms of detection of high-risk cancers (**according to current national guidelines in each country**), in detecting stage 2 + breast cancers.

Our overall objective is to compare the effectiveness of two Breast Cancer Screening strategies:

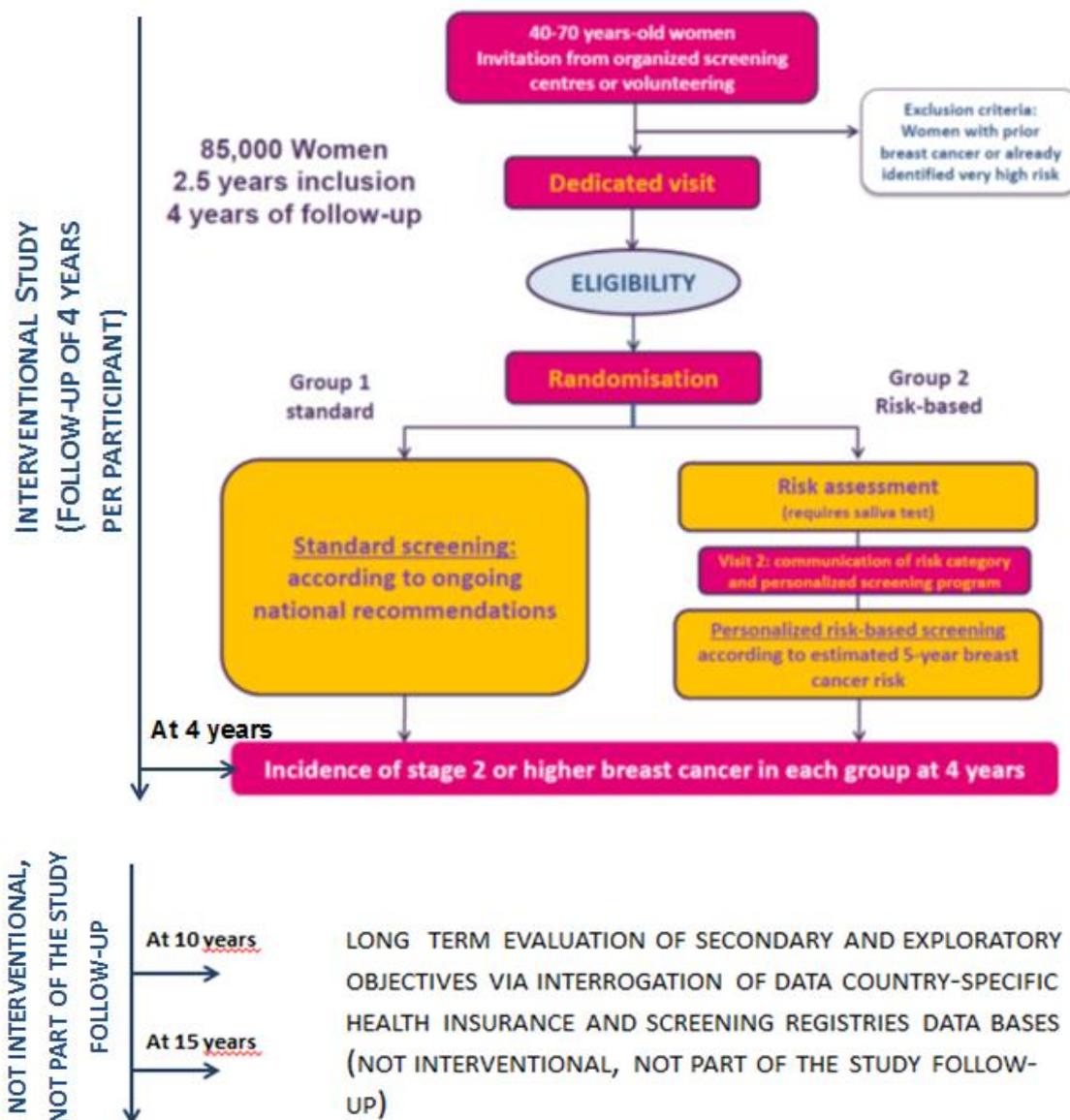
- **Standard strategy:** Current standard of care in participating countries where women are invited to a common schedule of screening mammograms performed once every 2-3 years starting from ages 40-50 up to ages 69-70, while the already identified very high risks individuals (at most 5%) have more intense personalized follow-up;

- **Risk-based strategy:** Extension of the personalized screening strategy, in which women are invited to radiological examinations scheduled according to their risk of developing breast cancer and to an individually-defined plan, for the whole population.

Our primary hypothesis is that risk-based screening will be **non-inferior** in terms of overall stage 2+ breast cancer incidence. We hypothesize it should also be **superior (decreased incidence of stage 2+ breast cancer); equally or more cost-effective;** but more acceptable (resulting in a wider coverage and a better compliance) **than standard screening.**

Women will be differentially screened for 4 years and then, after an end-of-study mammogram, they will return to the routine screening practice. The main endpoint is measured at the end of the four years of intervention. Furthermore follow-up data will be collected for 15 years from study entry of long-term cumulative breast cancer incidence and breast cancer specific survival.

General design



3.1.1 Selection

Women meeting inclusion criteria in a region participating in the study will be informed of the trial by the regional referral screening organization. Some women may self-refer to an including center or will be proposed the study while consulting for a pre-planned screening event or for a regular clinical visit to a GP or radiologist.

Women will only be able to enter the study if they live in a participating region/area from a participating country, due to organization constraints.

3.1.2 Accrual visit

Women interested in participating in the study will have a dedicated visit with an investigator in a participating center. During this visit, women will get all necessary oral and written information regarding current breast cancer screening (benefits and disadvantages), and regarding breast cancer risk, as well as the motivations, objectives, methodology, organization and logistics of the MyPeBS clinical study. They will be provided written information regarding both breast cancer screening and MyPeBS study.

Women will have a reflection time interval of 2 weeks before signing the informed consent, if they wish so.

Women who meet the inclusion criteria and are willing to participate will:

- Be created a dedicated portal entry by their accruing physician
- Be personally delivered the information on the trial by the investigator
- Be able to read the informed sheet and sign the informed consent form online on their personal portal in the study
- Sign a written online informed consent form.
- Be asked to fill-in online baseline questionnaires (see Table 1 and I, schedule of activities), before the result of the randomization.

3.1.3 Randomization

Women who have signed the informed consent and fulfill all eligibility criteria will be randomized directly online by the investigator (see 3.4.2)

The results of the randomization will be immediately provided to both the investigator and the woman.

- Women randomized to the standard arm will immediately receive their personal "standard" screening schedule for the next 4 years. No other study visit with the investigator is formally planned.
- Women randomized to the risk-based arm will be asked to provide a saliva sample (see below). Their breast density will be evaluated. They will be scheduled for a second visit (physical or by telephone interview according to national/local regulations), during which they will be communicated their risk estimation and their personalized, risk-based, screening schedule/plan for the next 4 years.

3.1.4 Follow-up

Women participating in the study will be asked to comply with the protocol for 4 years from randomization, according to their schedule of screening examinations defined at study entry (standard-of care or risk-based).

A mandatory end of study mammogram is planned at 4 years

A study exit mammogram will be planned ONLY for the following women:

- women in the risk-based screening arm who have been categorized as low risk (no planned mammogram during the course of the study);

- women in the standard screening arm who had no screening mammogram during the 4-year study period given their age

These women will all have a mandatory end-of-study mammogram at 4 years

For all the other women, the last mammography scheduled during the 4-year follow-up will be considered as the end-of-study mammography.

During their 4-years participation in the study, women will be screened according to their assigned screening scheme in either arm:

BREAST CANCER SCREENING SCHEME IN THE STANDARD ARM

Standard arm (either no mammogram or mammogram(s)/1-2-3 years according to age and country – will be defined individually at entry)				
Population	40-49 (France, Belgium, UK and Israel) 40-44 (All women of Italy) 45-49 (for some women depending the region of Italy)	50-70 (UK)	50-70 (France, Belgium, Italy and Israel)	45-49 (Some regions of Italy)
Planned images	No mammogram	Mammogram* every 3 years	Mammogram* every 2 years	Mammogram* every year

RISK THRESHOLDS IN MYPEBS AND BREAST CANCER SCREENING SCHEME IN THE RISK-BASED ARM

Risk-based arm				
Risk level	Low risk	Average risk	High risk	Very high risk
Numerical definition (invasive breast cancer risk at 5-years)	< 1%	1-1.66%	$\geq 1.67\%$ and < 6%	$\geq 6\%$ at 5 years
Mammogram*	1 at end of study	Every 2 years	Yearly	Yearly
Additional	Yearly breast cancer awareness reminder	High density: US or ABUS/ 2 years	High density: US or ABUS/ year	Annual MRI until age 60

* Or Tomosynthesis + synthetic 2D if applicable in the country/center
The use of ultrasound will be conducted as in the previous table

3.2 Study Endpoints

3.2.1 Primary endpoint

The primary endpoint is the incidence rate of stage 2 + breast cancers at 4 years (UICC 2010)

3.2.2 Secondary endpoint(s)

SECONDARY ENDPOINT(S): (All at 4 years/during intervention period unless otherwise indicated):

1. Rates of false positive imaging findings and benign biopsies in each study arm
 - False positive imaging findings include BI-RADS-ACR 3, 4 and 5 (or equivalent) lesions identified on screening images and leading to the need of additional images (US, MRI...), later control or breast biopsy
 - Benign biopsies include any percutaneous or surgical breast diagnostic procedure aimed at identifying the nature of a breast image
2. Socio-psychological assessments at baseline, and then at 1 and 4 years including evaluation of: comprehension of information, acceptance of proposed screening strategy, observance, persistence, anxiety, distress, satisfaction, decisional regret (see questionnaires in table 1)
3. Crude costs, comparison of cost-effectiveness, and budget impact of each strategy
 - Crude costs are defined as full real costs per stage 2 cancer diagnosis in each arm
 - The cost-effectiveness of mammographic screening will be calculated by comparing estimated life-years and costs of breast cancer in each arm
4. Incidence of stage-specific breast cancer in each arm (including DCIS)
5. Estimates of overdiagnosis and overtreatment rates in each study arm
 - Overdiagnosed breast cancer cases are defined as cancers that would never have been diagnosed, if women had not been screened. Differential overdiagnosis can be measured comparing the cumulative incidence of breast cancer from recruitment to a reasonably long period after the end of the study intervention, i.e. longer than the expected sejour time of screen-detected cancers. Breast cancer incidence rates in each arm will be determined approximately 10 - 15 years after the end of the interventional period of the study via interrogation of databases from national health insurances and/or organized breast screening structures.
6. Rate of false negative images and interval cancers in each arm
 - False negative images: in case of diagnosis of breast cancer in women whose last screening images (including mammogram +/- US and MRI) were considered as Breast Imaging- Reporting and Data System 1 or 2 (BI-RADS 1 or 2) at 6 months maximum before diagnosis
 - Interval cancers are defined as a breast cancers diagnosed between a negative screening episode - [mammogram classified as normal (BI-RADS ACR 1 or 2 or equivalent) or abnormal mammogram but negative assessment] and the next planned mammogram
7. 10- and 15-year breast cancer specific survival in MyPeBS and in a combined analysis of the Wisdom and MyPeBS studies
8. Detection rate of stage 2+ breast cancer in women who had screening tomosynthesis (where and when available) and the rate without tomosynthesis
9. Incidence of all stage and stage 2 + breast cancers at 10- and 15-year follow-up
10. Incidence of stage 2 + breast cancer in each arm, in women aged 40-49 at inclusion
11. Rate of breast cancers identified at second reading in each arm
12. Rate of false positive imaging findings and benign breast biopsies in women classified at low risk in risk-based arm

3.2.3 Exploratory endpoints (all at 4 years/during intervention period unless otherwise indicated):

1. Percentage of breast cancers and stage 2 + cancers that were detected solely by ultrasound in each arm

2. Rate of high metastatic risk breast cancers in each arm using a validated clinical predictor
3. Subgroups analyses of incidence of stage 2 + breast cancers and any stage breast cancer, as well as false positive findings and benign biopsies in each arm (including country, risk and age groups)
4. Updated/new breast cancer risk prediction scores including clinical variables, imaging parameters and genotyping
5. Identification of updated/new imaging parameters to predict breast cancer risk
6. Identification of predictors of poor psycho-social impact and/or compliance to screening
7. Accuracy (sensitivity and specificity) of SNPs to predict for the presence of a founder mutation of BRCA1 or BRCA2 (BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT))

3.3 Inclusion and randomization procedure

3.3.1 Informed consent

Informed consent form (ICF) may be obtained greater than 30 days before randomization; however, it must be obtained prior to any protocol required assessment (i.e., Screening).

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization.

The process required for electronic online informed consent has been described previously in 3.1.2.

Signed and dated ICFs for enrolled patients will be maintained online.

3.3.2 Baseline data collection

Women and/or their accruing investigator will be responsible for entering baseline demographic and medical history data into the participant's file.

These data will be used for risk assessment but are crucial for both arms.

Physical examination data and the eventual results of the most recent mammogram will be entered as well.

3.3.3 Randomization

After written informed consent has been obtained, the study site will obtain a unique patient number or unique patient identifier which will stay the same throughout the entire study covering all study periods (as described in section 12). At this time point the patient is enrolled into the study.

Women who have signed the informed consent and fulfill all eligibility criteria will be randomized directly online by the investigator, 1:1 to either standard-of-care screening or a risk-based screening strategy.

Women will be randomized for either arm immediately during the accrual visit through the use of the online real-time randomization module of the study.

The results of the randomization will be immediately provided. See study scheme.

- Women randomized to the standard arm will immediately receive their personal "standard" screening schedule for the next 4 years. No other visit with the investigator is formally planned.
- Women randomized to the risk-based arm will be asked to provide a saliva sample (see below). Their breast density will be evaluated. They will be scheduled for a second visit (physical or by telephone interview according to national/local regulations), during which they will be communicated their risk estimation and their personalized, risk-based, screening schedule/plan for the next 4 years.

The randomization will use permuted block lists (with a random block size) and will be stratified by:

- Country
- Age (women aged <50 vs ≥ 50)
- Prior mammogram (yes or no)

3.4 Premature Study Termination and Suspension

The study can be suspended or stopped by the sponsor after meeting with the international coordinating investigator, following a recommendation by an oversight committee (Clinical Study Steering Committee, which is supervised by the Executive Committee and advised by the Ethics And Data Monitoring Committee) or following recommendation by the regulatory authority and/or the responsible Ethics Committee for the following reasons:

- Insufficient woman enrolment
- Lack of significant results («futility»)
- Insufficient quality of data collection
- High frequency and/or unexpected harms

3.5 Participants' withdrawal of study

Participants' withdrawal concerns women who choose to stop study participation and all other protocol-defined procedures. This can occur under the following circumstances:

- Participant withdraws her consent to participate in the study a: the woman will inform her investigator directly of her choice to withdraw. Her investigator is responsible to note this withdrawal in the woman's medical file. Furthermore, the investigator **has to declare this withdrawal on the web-platform**. The reason of such withdrawal will also be collected, if available.
 - Further data collection for the study will be stopped
 - Women may additionally decide that want to have all data removed from the database or have her samples destroyed. in this instance, the investigator shall contact the sponsor in order to discuss the adequate course of action.
- An investigator may decide to terminate a woman's participation in the study, if this is in the interest of the woman (**this termination has to be declared in the web-platform**). The reason of such termination will be filled in by the investigator.

Investigators duties in this situation:

Participants may withdraw their consent at any time without justification, irrespective of the reason(s). In the case of study withdrawal the investigator should attempt to obtain as much information as possible. This information should be noted in the woman's medical file and it has to be declared on the web-platform. The woman's withdrawal of consent does not impact the woman's right to keep on routine screening program.

4. PARTICIPANTS' SELECTION

4.1 Inclusion criteria

Women from the general population (**only if they are invited by the national screening program or self-referred in a participating region of one of the participating countries**) will be eligible for the study if they fulfill all the following criteria (verified during the baseline phase and before randomization):

1. Female (whether born female or not)
2. Aged 40 to 70 years old (inclusive)
3. Willing and able to comply with scheduled visits, laboratory tests, and other trial procedures
4. Able to provide written informed consent obtained prior to performing any protocol-related procedures
5. Sufficient understanding of any of the languages used in the study
6. Affiliated to a social security/national healthcare system

4.2 Non-inclusion criteria

Women are not eligible to participate in the study if they meet any of the following criteria:

1. Personal history of breast carcinoma, either invasive or ductal carcinoma in situ (DCIS)
2. Prior history of atypical breast lesion, lobular carcinoma in situ or chest wall irradiation
3. Known condition or suspicion of a very high risk predisposition to breast cancer: germline mutation of BRCA1/2, PALB2, TP53 or equivalent
4. History of bilateral mastectomy
5. Recent abnormal breast finding under work-up (clinically suspect lesion or BI-RADS 4 or 5 image)
6. Psychiatric or other disorders that are not compatible with compliance to the protocol requirements and follow-up
7. Women who do not intend to be followed-up for 4 years

Of note, efforts will be made towards including women largely representative of the Western European population and Israel, through the coverage of different regions within Europe and within each country, through the representation of diverse ages, lifestyles, socio-economical and cultural categories.

5. INTERVENTIONS

5.1 Trial conduct if the standard arm

In the standard arm of MyPeBS, women are screened for breast cancer according to the current national guidelines and procedures:

- Bi-yearly or tri-yearly mammogram and/or tomosynthesis starting at age 40-50, up to age 69-70 according to countries, with or without Ultrasound (US) according to breast mammographic density and ongoing guidelines.
- The current national/regional guidelines in use in the including center may be subjected to change during the trial. Guidelines and procedures in the standard arm will be updated accordingly. Current per country and per age guidelines applicable to standard arm are described in table 2.

Breast cancer risk reduction measures:

Participants in the standard arm will be informed of potential risk-reducing strategies. They will be provided written and on-line information material and encouraged to follow these predefined measures.

Participating women will receive standardized self-awareness recommendations, although they will remain free to comply with them or not.

BREAST CANCER SCREENING SCHEME IN THE **STANDARD** ARM

Standard arm (either no mammogram or mammogram(s)/1-2-3 years according to age and country – will be defined individually at entry)				
Population	40-49 (France, Belgium, UK and Israel) 40-44 (All women of Italy) 45-49 (for some women depending the region of Italy)	50-70 (UK)	50-70 (France, Belgium, Italy and Israel)	45-49 (Some regions of Italy)
Planned images	No mammogram	Mammogram* every 3 years	Mammogram* every 2 years	Mammogram* every year

* Or Tomosynthesis + synthetic 2D if applicable in the country/center

As stated, all participating countries have specific guidelines for:

- High-risk women defined as having had a previous breast cancer or high-risk situations including radiation therapy for Hodgkin's disease or atypical hyperplasia. These women will not be eligible for MyPeBS
- Very high-risk women defined as having a germline mutation of either BRCA1 or BRCA2 genes or an equivalent situation. The women already identified as such will not be included in MyPeBS

A summary of ongoing guidelines in the participating countries at the time of the final design the present protocol is shown below:

Country	Region	Age eligibility in OS	Mammographic screening frequency	2 nd reading	Ultrasound policy	Tomosynthesis policy	Other
Belgium	Brussels	50-69	2 years	Yes	Not included in program	Outside OS	No CBE
	Leuven					Within OS	
Italy	4-6 regions	45-49 (some regions)	1 year	Yes	Not included in program	Outside OS (ongoing clinical trials)	No CBE
		50-69	2 years				
		70-74 (some regions)	2 years				
UK	Cambridge Manchester Leeds	50-73	3 years	Yes	Not included in program	Not included in program	No CBE
Israel	National-basis	50-74	2 years	No	Based on the radiologists' decision (dense breasts)	Sometimes, not mandatory	No CBE
France	National-basis	50-74	2 years	Yes	In all women with dense breasts	Outside OS	+ CBE

OS: organized screening, CBE: clinical Breast examination consisting in echography of breast

Use of ultrasound and tomosynthesis: will be done in this arm according to current national/regional guidelines in each country

BREAST CANCER AWARENESS

Breast cancer awareness remains a major cornerstone of the reduction of the risk of advanced breast cancer: women must be advised of both symptoms leading to see a doctor and eventually to have a diagnostic mammogram and health behaviors leading to reduced risks of breast cancer (see below)

- Participants with a low risk estimation will be specifically sensitized by investigators to the fact that low risk is not an absence of risk. They will be yearly reminded of this point.
- All participants will be taught which breast symptoms must lead to see a doctor.
- All participants will be yearly reminded that mammograms can miss some cancers and that, therefore, seeing a doctor in case of a symptom remains crucial.
- Breast self-palpation will be taught to women who ask for it only

5.2 Trial conduct in risk based arm

Women in risk-based arm will provide a saliva sample during visit 0 (baseline). This sample will be sent out for centralized genotyping.

During a second dedicated visit (8-12 weeks after the initial visit) risk-estimation will be delivered and explained

to women. This is the moment when they will be proposed their personal screening program. This visit may be physical or by telephone interview according to countries.

5.2.1 Saliva sample

This sample will be provided by the participants randomized to the risk-based arm, at day 0 (randomization).

- A dedicated kit will be available at the investigator's office.
- The investigator will scan the bar code of the tube and kit into the participant file, to allow identification of the sample, which will not have any other identification mean but this bar code.
- The investigator will fill the online data regarding saliva harvest
- The woman is required to spit her saliva into the device. A minimal amount of 2 mL of saliva is required. If the woman thinks she cannot provide that amount, it might be possible that she/the investigator does a chick massage, to stimulate saliva production, and/or uses a dedicated single-use pipette provided, to harvest saliva inside the mouth. It is important the saliva is pure and the absence of contamination of other personal fluids or food, or other contaminants, must be ensured.
- Once the sample is ready, the investigator will close the tube, put it into the shipping box and bag together with the proper related document
- The sample must be shipped within the next 5 days at most

5.2.2 DNA extraction and genotyping

Saliva DNA will be extracted from saliva samples using standard protocols, at a central laboratory (CEPH, Paris, France, <http://www.cephb.fr/>). Aliquots will be made and 1 aliquot tube dedicated to genotyping will be sent out to CNRGH. Leftovers of DNA will be stored at CEPH.

Samples will be identified by bar code throughout their process in the two labs.

Genotyping will be carried out at a unique centralized lab, at CNRGH, France (<http://jacob.cea.fr/drf/ifrancoisjacob/Pages/Departements/CNRGH.aspx>) using a dedicated specifically engineered for MyPeBS trial, Illumina chip (Global Screening Array or equivalent), with over 700,000 variants. On top of the baseline variants present on the chip, we will add up to 1000 additional variants selected for the purpose of back-up testing, quality controls, and BRCA1/2 founder Ashkenazi mutations identification (see below) for Israeli women. Briefly, this chip set includes one SNP variant every 4.2 kb, and captures greater than 94% of variants with a minor allele frequency greater than 1% in populations of European origin.

A polygenic risk score will be generated, while raw data of the whole chip results will be stored; the polygenic risk score will be returned to the risk stratification team for inclusion in risk estimation models.

SNP score definition

The full SNP profile will be defined by the clinical trial steering committee 4 months ahead of the start of accrual, so that the MyPeBS specific chip is engineered and tested before trial launch.

SNP calibration

The proper calibration of each SNP in the accrual population will be assessed after 2,000 women have been included in the risk-based arm.

In case major new variants become available during the conduct of the trial, they will be implemented in the SNP score; and individual risk reassessed. The likelihood of such event will be minored by the proper initial selection of SNP score.

Jewish Ashkenazi founder mutation-linked polymorphisms

For participants in Israel who have signed a specific additional consent, the results of SNPs linked to the three germline founder mutations of BRCA1 (185delAG and 5382insC), and BRCA2 (6174delT) will be transmitted together with the SNP score and integrated in the risk calculation.

- The results of these SNPs will be only provided to women accrued in Israel and who have signed a dedicated specific consent allowing for this identification, after adequate information
- The results of these SNPs will either indicate: YES, a founder mutation is probably present or NO, no such mutation is likely
- The results of these SNPs will not have any medico-legal value and will only indicate the need for a dedicated genetic counselling if positive. This will indicate genetic testing including proper DNA sequencing towards identification of such germline mutations, if finally present. The women will be classified at very high risk until they have a confirmed result based on sequencing
- Negative results will neither have a medico-legal value, since this technique is not a proper validated assessment of the presence of such mutations and may have a sensitivity a little lower than 100%.

5.2.3 Evaluation of 5-year breast cancer risk for women randomized in the Risk based arm / risk stratification

Women in the risk-based arm will have their 5-year risk automatically evaluated by the risk module, upon availability of all data. The results will be available for communication to the participant during her second visit.

This risk evaluation uses dedicated risk scores including mammographic density (if available) and SNPs (BCSC score adapted to national incidence + Tyrer-Cuzick in case of family history >1).

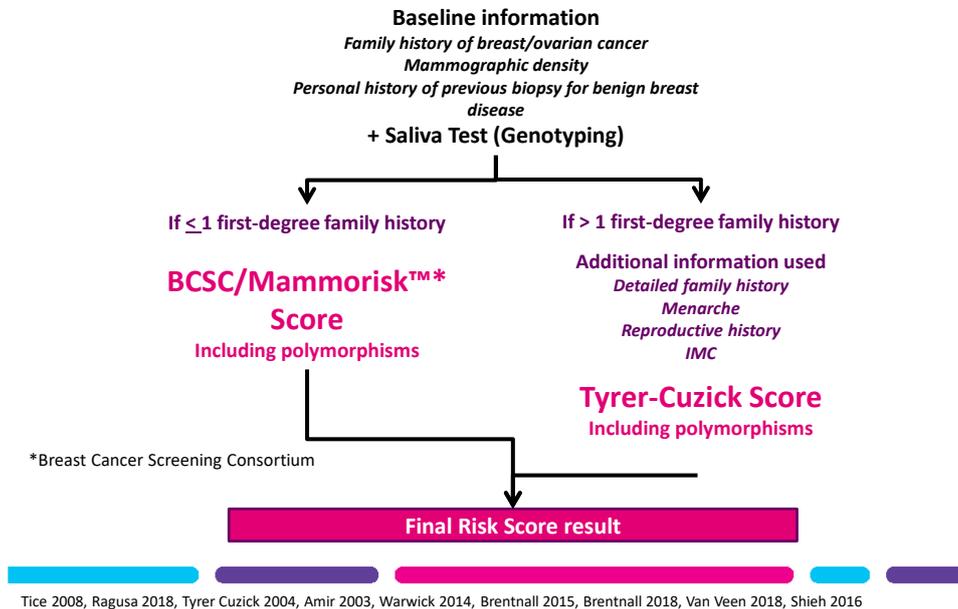
This risk evaluation will be conducted centrally using a dedicated external module of the web-platform (12.1.1) by Statlife, upon receipt of all necessary data (see below).

Risk score used

As shown in Fig 1, for women with at most 1 first degree family history of breast or ovarian cancer, risk assessment will be conducted using Mammorisk™ with the implementation of the polygenic risk score results. Mammorisk™ uses age, family history, history of a previous benign biopsy, mammographic density. It evaluates 5-year invasive breast cancer risk using a k nearest neighbor's method. It has been derived from and validated on the Breast cancer Screening Consortium cohort and validated on French screening cohorts. It has previously been used for risk stratification in a national prospective trial. The risk assessment requires adjustment for national breast cancer incidence. Each woman's genotyping results (SNP score) will be implemented into the risk calculation as previously described, for a final risk calculation including SNPs results. As shown in Fig 1, women with more than one first-line first degree relative with breast cancer will have their risk estimated using the Tyrer-Cuzick™ risk score implemented with each person's polygenic risk score as previously described.



Risk evaluation – risk-based arm



Data required for risk assessment

- Clinical and epidemiological characteristics needed for risk stratification will be retrieved from baseline questionnaires filled by participants and their investigator at study entry: age, family history of breast cancer (1st and 2nd degree relatives), personal hormonal and reproductive history, personal history of benign breast disease (with either breast biopsy/FNA and/or surgery), BMI...
- Breast mammographic density evaluation is part of both risk assessment scores.
 - Baseline mammographic density will be that of the most recent mammogram available for the woman
 - Baseline breast mammographic density will be evaluated using a standard procedure as often as possible, i.e. unique validated software provided to MyPeBS' radiologists. If this unique software is not available, radiologists' BI-RADS visual assessment will be used. If no baseline breast mammography is available (women under 50y), the maximum risk will be applied.
- **Genotyping results** will be transmitted by the genotyping lab (CNRGH) to Statlife in a pseudonymized format (tube ID will be the only identifier between these structures)

Risk score assessment

The individual breast cancer risk will be estimated using the modified Mammorisk™ (by inclusion of SNPs) or, if more than one first degree family history of breast/ovarian cancer, using the modified Tyrer Cuzick™ score, both including polymorphism risk score.

Breast cancer risk levels will to be classified into 4 meaningful categories, which have been defined by the clinical trial steering committee, according to available guidelines and published literature (see 1.1.9).

Statlife is in charge of the centralized and automated software dedicated to risk evaluation. Their module will automatically extract all necessary variables from the central database and incorporate the polygenic score once available, as well as mammographic density.

Statlife will transfer the final risk score of each participant upon availability, to the investigator, who will be in charge of transmitting the result to the participant. The bases of risk calculation will be available on the result

sheet for each participant. The result of the polygenic risk score will also be available and transmitted. Results will be transparently transmitted to allow for awareness and empowerment of participants.

The risk categories estimated using the risk models or identified in other situations, are listed in the Table below.

What if some data is missing?

- If genotyping is not available (failure of technique, participant's refusal), the personal risk will be estimated by the risk score alone (clinical variables + mammographic density)
- If mammographic density is not available:
 - If the participant is 50 years old or more, a baseline mammogram will be mandatory, that will allow density evaluation
 - If the participant is 40-49 years old, the maximum density-linked risk will be applied (BI-RADS class D)
 - If one or two clinical data are not available: risk should be estimated without this information

Risk recalculations

Of note, risk recalculation may occur during the 4-years follow-up of each patient and will be conducted the same way. This may occur if:

- Participant/investigator declares a significant event that may change the participant's risk level (breast biopsy with benign diagnosis, diagnosis of atypical lesion, identification of the participant as a carrier of a germline mutation of a high penetrance gene)

- Identification of a new, major risk polymorphism that would be incorporated in the polygenic risk score

Risk level	Low risk	Average risk	High risk	Very high risk
Risk model numerical definition (risk score, invasive breast cancer risk at 5 years)	< 1%	1-1.66%	$\geq 1.67\%$ and < 6%	$\geq 6\%$ at 5 years
Other situations	-	-	<ul style="list-style-type: none"> • Any woman diagnosed with an invasive breast cancer during the trial • Any woman diagnosed with an atypical breast lesion or in situ breast carcinoma during the conduct of the study (outside of baseline) 	<ul style="list-style-type: none"> • Israeli women identified as probably bearing a founder gBRCA mutation by SNP assessment • Any woman who appears to be a carrier of a high penetrance susceptibility gene mutation, at any moment during the study (outside of baseline)

5.2.4 Risk communication to participants in the risk-based arm

Risk will be communicated to the participants directly by their accruing investigator.

Personal breast cancer risk estimation will be communicated by three supports:

1. Oral communication, assorted with all necessary information on how risk was assessed and what are the consequences of the risk level identified
2. Written result sheet: a written report will be available and proposed to all participants at the time of risk communication. It can be printed. It will include:
 - Identification number of the participant (tube ID)
 - Risk assessment as a category (low/average/high/very high)
 - How the participant's risk was assessed (based on which factors and measures)
 - If indicated (Israeli participants who gave their informed consent) and only if positive, the results of the search of the three founder gBRCA mutations-linked polymorphism
 - The proposed screening program and schedule
 - Additional recommendations regarding the potential indication of genetic counseling
 - Risk-reduction measures
 - General breast awareness
 - Links to more information and answers to potential questions
3. Online communication: the full results described previously will also be available on the patients personal MyPeBS' portal. Additional information on risk factors, as well as on breast cancer screening and risk reduction measures will be available to all participants on the portal.

Personal breast cancer risk will be verbalized, explained and communicated to the participants as a risk category compared to women of the same age. The risk categories will be: low, average, high or very high.

Participants who wish can be communicated their precise risk estimation as a 5-year risk percentage or as "one women in xx with the same characteristics as yours may develop breast cancer within 5 years". Such communication will not be mandatory.

5.2.5 Breast Cancer Screening in the risk-based arm

In the risk-based arm, women are screened in a risk-based fashion:

Screening recommendations in each risk category are as described in the Table below.

- Women identified at low risk will not have any mammogram until an end of study mammogram at 4 years.
- Women at average risk will have a mammogram every 2 years
- Women at high risk will have a yearly mammogram
- Women at very high risk will have a yearly mammogram + yearly MRI until age 60. Both shall be performed at the same time period, MRI being performed before mammogram.
- Breast US is proposed in women with dense breasts, according to national guidelines

2D digital mammogram may be replaced by tomosynthesis according to the country's, regions' and centers' policy.

Definition of risk thresholds and breast cancer screening scheme in the **risk-based** arm are summarized below:

Risk-based arm				
Risk level	Low risk	Average risk	High risk	Very high risk
Numerical definition (invasive breast cancer risk at 5 years)	< 1%	1-1.66%	$\geq 1.67\%$ and < 6%	$\geq 6\%$ at 5 years
Mammogram*	1 at end of study	Every 2 years	Yearly	Yearly
Additional	Yearly breast cancer awareness reminder	High density: US or ABUS every 2 years	High density: US or ABUS every year	Annual MRI until age 60

* Or Tomosynthesis + synthetic 2D if applicable in the country/center

The participants' screening schedules will be organized according to the date of their last previous

mammogram, as described in the Table below:

		Planned initial Mammogram/ DBT schedule		
		Every 2 years	Yearly	Yearly
Schedule of first screening mammo/DBT according to previous mammogram	No previous mammogram	immediately	immediately	immediately
	Previous mammogram < 1 year	2 years from previous one	1 year from previous one	1 year from previous one
	Previous mammogram between 1 and 2 years	2 years from previous one	immediately	immediately
	Previous mammogram > 2 years	immediately	immediately	immediately

5.2.6 Breast cancer awareness in risk-based arm

Breast cancer awareness remains a major cornerstone of the reduction of the risk of advanced breast cancer: women must be advised of both symptoms leading to see a doctor and eventually to have a diagnostic mammogram and health behaviors leading to reduced risks of breast cancer (see below)

- Participants with a low risk estimation will be specifically sensitized by investigators to the fact that low risk is not an absence of risk. They will be yearly reminded of this point.
- All participants will be taught which breast symptoms must lead to see a doctor.
- All participants will be yearly reminded that mammograms can miss some cancers and that, therefore, seeing a doctor in case of a symptom remains crucial.
- Breast self-palpation will be taught to women who ask for it only

5.2.7 Risk level assignment modification in risk-based arm

These risk-based screening recommendations might be subject to evolution during the trial, both at a personal participant level and at a general trial level

- At a personal level, a web-based yearly update will be organized for all women in the risk-based arm to better adapt their risk profile if required (only if change of family history, if personal benign breast biopsy, if identification of atypical lesions or if identification of a germline high risk mutation; as described before). See section 5.5
- At the trial level, the re-evaluation will take into account published evidence-based knowledge notably based on SNPs

Other measures associated with risk level:

GERMLINE GENETIC TESTING

Of note, for the women identified as having a high-risk family-history, genetic counselling might be advised, according to national and international guidelines. This advice will be part of the recommendations produced by the risk assessment tool. This genetic counselling will be performed in the standard genetic network of the country, and genetic testing for the search of germline BRCA1/2 mutations (or panel testing) usually performed in a cancer-affected relative rather than in the healthy consultant. Such women will of course remain within the trial, and be assigned high or very high-risk categories, with the adequate proposed follow-up.

In Israel specifically, it has been planned that women who have signed a dedicated informed consent (proposed to all participants at trial entry) will have an additional evaluation of polymorphisms together with their SNP score, aiming at identifying the presence of one of the three Ashkenazi founder mutations. Such finding will prompt genetic testing for confirmation, as described previously.

BREAST CANCER RISK REDUCTION MEASURES

Participating women will receive standardized self-awareness recommendations, although they will remain free to comply with them. They will be informed on potential risk-reducing strategies associated with their individual breast cancer risk level and individual risk factors. Upon risk calculation, they will receive a printed + online document summarizing all their personal information, risk category assignment, proposed screening strategy, but also suggested personalized risk-reduction measures (such as avoidance of certain endocrine therapies, dietary and exercise recommendations, etc...). These measures have been predefined by the trial steering committee.

Participants will be able to retrieve all their personal information from their personal account on the trial's web platform. They also will be able to gather more general information on the project's website

5.3 Imaging protocols and techniques used in both arms

It is crucial that imaging quality is high in the present study. Monitoring of the imaging quality and dose administered will be implemented through continuous data collection and audits will be conducted.

The participation screening centres will be asked to adhere a simple quality chart derived from ASSURE and European guidelines (ECIBC), derived from/in line with the previous experience of several members of the consortium in such projects as ASSURE and in the construction of European QA guidelines (ECIBC). This QA chart will indeed be inspired by ECIBC guidelines platform for all breast cancer processes and quality assessments

(<http://ecibc.jrc.ec.europa.eu/-/the-ecibc-guidelines-platform-for-all-breast-care-processes>
<http://ecibc.jrc.ec.europa.eu/documents/20181/22500/EC+Initiative+on+Breast+Cancer.pdf/a586dfb5-83d2-4ee3-a345-9ddf72363fa8>).

Radiologists will be asked follow the best standard procedures and the on-going national and European recommendations regarding all imaging procedures throughout the study, whatever the arm participants are randomized to.

5.4 Women's discontinuations of assessment/follow-up

Women can discontinue the study MyPeBS for the following reasons:

- End of study: all women will discontinue from the study and go back to routine screening at 4 years from randomization
- Women decline further assessment but accept to continue with answering questionnaires
- Personal reasons such as moving to an area where the study is not available
- Investigator's decision
- Death

Women who discontinue assessment/follow-up will continue with the study and the protocol-defined procedures, unless they specifically withdraw their consent and indicate that they do not want to perform any further study-related visits or assessments (for woman withdrawals see Section 5.).

5.5 Change of ongoing schedule

Women in the following conditions will remain on study unless they do not wish to, but their schedule might be altered/modified:

- Women who are diagnosed a benign lesion and had to undergo a mammographic control
 - o The participant's schedule may be reorganised to fit with the new schedule of mammograms. Risk must be reassessed with this new information
- Women who are diagnosed with an atypical breast lesion or in situ carcinoma of the breast.
 - o The participant's schedule may as well be reorganised to fit with the new schedule of mammograms. Risk must be reassessed with this new information
- Women who are diagnosed an invasive breast adenocarcinoma or another breast cancer during the trial
 - o They can remain on trial but their risk will be reclassified as high risk and their further schedule adapted accordingly
- Women who had their risk recalculated based on other personal or familial events which have changed their risk level
 - o A new schedule will be provided upon risk recalculation
- Pregnant women
 - o A new schedule will be provided based on participant's availability
- Women who require a modification in their schedule for the advent of a medical condition that is no longer compatible with the scheduled examinations
 - o Women will remain on trial and their schedule adapted accordingly
- Women who require a modification in their schedule for other personal reasons
 - o This must absolutely be limited but may be punctually acceptable

6. EVALUATION OF EFFICACY

6.1 Efficacy evaluation

The primary evaluation endpoint is the incidence rate of stage 2 + breast carcinoma after 4-years of follow-up from the randomization.

6.2 Safety evaluation

6.2.1 Specific screening-linked safety

In this trial, safety assessments concern some of the secondary endpoints which measure parameters considered as "safety evaluations" since they are linked to screening-related harms:

1. False positive recalls have been defined in the end points and will be carefully scrutinized
2. Overdiagnosis will be estimated
3. The theoretical radiation exposure and potential associated radiation-induced cancer risk will be estimated

6.2.2 **Classical safety:**

Beside these specific screening-linked safety evaluations, no other safety evaluations linked to daily assessments and imaging are planned: as the present clinical trial is totally based on current practices, there is no obligation for any specific AE reporting within MyPeBS.

However, we will take some risk reduction measures for this trial:

- **Breast cancer risk reduction measures in the standard arm**

Participants in the standard arm will be informed on potential risk-reducing strategies. They will be provided written and on-line information material and encouraged on these predefined measures.

Participants will be taught breast self-palpation if they wish so, but this will not be mandatory within the trial.

- **Germline genetic testing**

Of note, for the women identified as having a high family-history, genetic counselling will be advised, according to national and international guidelines. This advice will be part of the recommendations produced by the risk assessment tool. This genetic counselling will be performed in the standard genetic network of the country, and genetic testing for the search of germline BRCA1/2 mutations (or panel testing) usually performed in a cancer-affected relative rather than in the healthy consultant. Such women will of course remain within the trial, and be assigned high or very high risk categories, with the adequate proposed follow-up.

Specifically in Israel, women who have signed a dedicated informed consent will have an additional evaluation of polymorphisms together with their SNP score, aiming at identifying the presence of one of the three Ashkenazi founder mutations. Such finding will prompt genetic testing for confirmation, as described previously.

- **Breast cancer risk reduction measures in risk-based arm**

Participants will be informed on potential risk-reducing strategies associated with their individual breast cancer risk level and individual risk factors. Upon risk calculation, they will receive a printed + online document summarizing all their personal information, risk category assignment, proposed screening strategy, but also suggested personalized risk-reduction measures (such as avoidance of certain endocrine therapies, dietary and exercise recommendations, etc). These measures have been predefined by the trial steering committee.

Participants will be able to retrieve all their personal information in their personal account on the trial's web platform. They also will be able to gather more general information on the project's website.

7. DESCRIPTION OF VISITS AND INVESTIGATIONS

In this trial, organized Breast screening structures (OBSS) will be involved to coordinate women's information on the trial and data retrieval.

The nature of recruiting centers will be different depending on the country: in most countries, centralized screening centers will be the recruiting centers, whereas in France, recruiting centers will be a defined list of community GPs, Radiologists and gynecologists in participating areas.

In all countries, coordination centers will centralize data retrieval and pseudonymization for transmission to the database. The number of coordinating centers will vary country by country (3 in Belgium, 3 in UK, 4-6 in Italy, 11 in Israel, 40 in France).

7.1 Clinical centers

To select the participating sites, we will have different approaches according the strategy of the screening organization of each country.

In UK, Italy, Israel and Belgium, the screening program is organized with limited centralized screening centers and we have already identified them and obtained the involvement for most of them (3 for Belgium, 4-6 regions for Italy, 2-3 areas in UK and 11 centers for Israel). They will be the recruiting centers.

In France, the process of site selection is different. The recruiting centers will be either community of general practitioners, radiologists and gynecologists in the 15 participating areas.

- Women aged from 40 to 70 years will be informed of MyPeBS trial by the screening structures of their area
- They will be included by one of the participating physician in the area (either a GP, or radiologist, or gynecologist)
- Data collection of exams and follow-up will be coordinated by the screening structures

For further information, see the appendix

7.2 Information of potential participants

In each country (but only in the area participating in this trial), women of general population aged 40-70 years old will be informed of MyPeBS trial by the coordinating physician of their regional national screening program. In the framework of this trial, public web-platform containing information about this trial and the patient informed consent will be available to inform women in parallel of this personal information.

7.3 Baseline visit (V0)

Women eligible for the study and having signed the informed consent form will perform a baseline visit. Women can be provided with the informed consent sheet and have a 2 weeks reflection time potential interval before trial accrual.

Upon signature of the informed consent, women can be immediately randomized either in standard screening arm or in risk-based arm.

During this visit, the investigator has to create the profile of the woman into the web-platform and to interview the woman for retrieving medical history and medical data.

Women have to answer the following questionnaires (via a touchpad, a phone or via their own profile on web-platform):

- Socio-demographic and economical status questionnaire
- Comprehension questionnaire
- State anxiety
- Quality of life (EQ-D)

After written informed consent has been obtained, the study site will obtain a unique patient number or unique patient identifier which will stay the same throughout the entire study covering all study periods (as described in section 12). At this time point the patient is enrolled into the study.

Women who have signed the informed consent and fulfill all eligibility criteria will be randomized directly online by the investigator, 1:1 to either standard-of-care screening or a risk-based screening strategy.

Women will be randomized for either arm immediately during the accrual visit through the use of the online real-time randomization module of the trial.

The results of the randomization will be immediately provided. See study scheme.

- Women randomized to the standard arm will immediately receive their personal "standard" screening schedule for the next 4 years. No other visit with the investigator is formally planned.
- Women randomized to the risk-based arm will be asked to provide a saliva sample. Their breast density will be evaluated. They will be scheduled for a second visit (physical or by telephone interview according to national/local regulations), during which they will be communicated their risk estimation and their personalized, risk-based, screening schedule/plan for the next 4 years. The saliva sample will be sent to the central lab for DNA extractions and genotyping.

7.4 Visit 1 or phone call (more and less 8 - 12 weeks after the randomization date - V0) only for women randomized in risk-based screening program

These women will come back for a second dedicated visit (physical visit in France and Belgium) or be reached by their investigator through a dedicated phone call (for the other countries) to inform them regarding their personal risk evaluation result and proposed screening program.

The investigator has to record the score result into the website and to give the woman her schedule screening program personalized on her risk. The risk results will be communicated orally as well as through written documents available on the participant's personal portal.

The women's follow-up schedule will be organized from that time (automatic planning based on previous mammogram)

7.5 Imaging examinations (follow-up during 4 years from randomization)

Women have to perform imaging exams according the scheduled screening program given to her. All women must perform a final imaging exam at the end of the 4-years follow-up.

7.6 End of study visit and mammogram

- No end of study visit will be performed.
- Women will follow their current screening schedule until 4 years from randomization
- Women in the risk-based arm who were evaluated at low risk and did not get mammogram during 4 years, will have an end of study mammogram (specific invitation)
- After 4 years, the women' later screening schedule outside of study will be determined with her usual treating physician

7.7 Update of participants' data on the web-platform

During the trial, there will be different levels of data updates on the web-platform:

- **direct updates by woman:** they will be required to update yearly on their personal portal the date and type of imaging exams potentially performed according to their own screening program; the questionnaires at months 3, 12, and 48 (for more details for the questionnaires, please refer to schedule of activities page 13-14 and appendix 04). Women will be asked to report all relevant new data that might affect risk evaluation or screening schedule
- **updates from the organized breast screening structures and/or investigators according to countries:** results of screening examinations or events
- **cross-over with database of national insurance system** at the end of the study (at the end of the study).

7.8 Provisions in case of assessment or study interruption

If the study assessment is discontinued by a woman, further follow-up and assessment will be at the investigator's discretion as per screening standard. If the woman developed a breast cancer, she will take care as usual practice by her general practitioner, who will address her to a specialized center.

7.9 Participation of women in other clinical trials

Participants in MyPeBS can eventually participate in other clinical trials, whatever the field. It is however asked that they inform their investigator if they consider such participation, who in turn will ask the sponsor. The sponsor will check whether the safety of the participant and the integrity of MyPeBS trial is preserved, in case of such participation.

The sponsor may ask the woman not to participate to another trial in specific situations where both participants safety and trial's integrity cannot be preserved. Alternatively, the woman may discontinue her participation in MyPeBS.

8. DESCRIPTION OF STATISTICAL METHODS

An initial statistical analysis plan (SAP) will be produced by the statistician before the inclusion of the first woman (version n°1). This document will be validated by the Steering Committee. The SAP may be revised during the course of the study in case of substantial modification of the protocol or following recommendations of the Independent Data Monitoring Committee. Any revision of the SAP will be validated by the Steering Committee.

8.1 Statistical hypothesis and sample size determination

Randomization

Women who have signed the informed consent will be assigned a unique participant identifier and will be randomized 1:1 to either standard screening or the risk-based screening strategy. Randomization will be performed through an automated real-time online system (permutation blocks).

Stratification

Randomization will be stratified by country, age (women aged <50 vs ≥ 50), and prior mammogram (yes or no). This will ensure to balance screening modalities, global population risks, and the rate of prevalent breast cancers at entry.

Required number of women to be included

The incidence rate of stage 2 + breast cancer in the MyPeBS standard arm is expected to be around 120 cases/100,000/year. This number is derived from what is observed in the screened populations of European countries and including women aged 40 to 50 years for whom the incidence rate is lower:

- Incidence in women aged 50-74 years old is 140 cases/100,000 women/year on average in screened populations taking into account interval cancers and cancers not detected in women who are not screened
- We expect to include 25% of women aged between 40-49 years old
- Incidence in women aged 40-49 years old is half than older women
- Expected incidence of stage 2+ breast cancers for 100,000 women followed up for 1-year in the standard arm of MyPeBS is therefore: $(140 \times 0.75) + (0.25 \times 0.5 \times 140) = 105 + 17.5 = 122$. A slightly conservative estimate is therefore 120.

We anticipate a drop-out rate lower than 5% in both arms, and non-compliance rates of 10% in the risk-based screening arm and of 30% in the standard arm. These women will not be included in the per-protocol analysis due to non-compliance, in the 4-year period after inclusion.

The primary hypothesis is that the risk-based screening arm will be non-inferior to the standard screening arm in terms of cumulative hazard rate in the per-protocol population. The cumulative hazard functions of cancers of stage 2 + will be compared between the 2 study arms.

Further assumptions are a non-inferiority margin of a 25% relative increase in the risk-based arm (null hypothesis $H_0: \lambda_e/\lambda_c \geq 1.25$ with t and c standing for experimental and standard arm, respectively; it corresponds to an absolute increase in the cumulative hazard rate of stage 2 cancer or higher after 4 years up to 120/100000 stage 2 cancers the risk-based arm under H_0), 80% power, 2.5% significance level, 1-sided test. If we assume that under the alternative hypothesis a 10% relative improvement can be expected by the experimental risk-based-stratified screening arm (i.e. $\lambda_e/\lambda_c = 0.9$) due to our anticipated increase in the average numbers of mammograms in the experimental arm, a total of 298 stage 2 breast cancers are required for the non-inferiority assessment using a logrank test. We assume a total of 85,000 participants, 42,500 in each arm, to be included over 2.5 years.

For the primary and key secondary endpoint analysis, each subject will be followed for four years, to be able to compare cycles of mammograms between the 2 screening arms. Later updates of the trial analyses will be performed using longer follow-up.

8.2 Planned statistical analysis

8.2.1 Statistical analysis plan

A statistical analysis plan (SAP) describing in detail all statistical analyses performed will be elaborated. An intermediate progress report will be made after 1 year of inclusion to evaluate the robustness of the study with regards to estimated initial inclusion rates, expected age categories, risk predictions, and compliance to screening recommendations, on the overall population and at the country level to recommend potential changes to the protocol and/or study management. Indeed if the age and risk structure of the population appeared significantly different from those expected, with potential important influence on the study's power or ability to conclude, amendments may be proposed by the Clinical Trial Steering Committee, upon advice of the Ethics and data Monitoring Committee.

This progress report will be updated after 2 years of inclusion and during the follow-up period after the last woman randomization.

Beside this, the spread of SNPs chosen and harmonious population repartition will be verified after 5,000 women are included.

All the analyses for the progress reports will be conducted blinded from the efficacy outcomes of the study (breast cancer incidence). Once all the participants have been followed for 4 years, the cleaned database will be locked and a final statistical report prepared.

The primary analysis will compare the cumulative hazard functions of cancers of stage 2 + between the two randomized groups of women using a logrank test. The rate of cancers of stage 2 + cancers for each arm will be estimated as the number of cancers of stage 2 + detected either clinically or by screening out of the total person-years of follow-up.

The primary non-inferiority analysis will be performed on the per-protocol (PP) population, which will include all randomized and eligible women in the arm they were randomized to, who complied with their screening recommendation in terms of number of mammograms. The analyses will be repeated in the Intention-To-Treat (ITT) population for sensitivity. An additional sensitivity analysis, we will be performed using causal inference methods to estimate the average effect of the risk-based screening versus standard screening on stage 2 incidence as if all participants will have complied with the protocol.

If non-inferiority of the risk-stratified screening arm relative to the control arm is concluded for the primary endpoint, then superiority of the risk screening arm will be tested against the standard arm (closed testing procedure). The inferential superiority analysis will be performed in the ITT population, with the PP and causal inference analysis for sensitivity. We estimate that for the superiority analysis we will have at least 80% power to detect a 30% relative decrease in the risk-based arm.

In another additional sensitivity analysis, we will exclude all prevalent cases (cancer detected 2 months after the first mammography) from the analysis and focus on women with no cancer at study entry in order to re-evaluate the benefit of risk-adapted screening thereafter.

Standard statistical methods as Kaplan-Meier analyses, Cox proportional cause-specific hazards regression will be used to compare the time-to-event variables between the 2 study arms and estimate hazard ratios adjusted for the stratification factors at a one-sided 0.025 significance level.

A multivariable model will also be constructed using relevant key risk factors of breast cancer on the different time-to-event endpoints. A competing risk cumulative incidence approach will also be applied.

The overall excess overdiagnosis with risk-stratified screening compared to standard screening will be estimated from the study. Different lead time models will be applied to obtain a range of mode-based estimates of overdiagnosis; a microsimulation model will be calibrated to the study population for overdiagnosis estimates, and cost and cost-effectiveness evaluations.

8.2.2 Final analyses decision rules

Final analyses will be conducted once all participants accrued and who have remained on study have reached 4 years from randomization.

8.2.3 Accrual rates and accrual duration

Accrual duration is 2.5 years (1st patient in until last patient in)

Accrual will be competitive throughout the trial

Accrual rates will be carefully monitored and reported

8.3 Study populations to be analysed

8.3.1 Definition of per-protocol population for the primary endpoint analysis

The per-protocol (PP) population will include all randomized and eligible women in the arm they were randomized to who complied with their screening recommendation.

Per-protocol definition of compliance (the study entry mammogram, if any, will not be considered) will be used for the primary analysis of the trial and is described below, according to randomization arm:

Per-protocol definition for standard arm:

Standard arm				
(either no mammogram or mammogram(s)/1-2-3 years according to age and country – will be defined individually at entry)				
Population	40-49 (France, Belgium, UK and Israel) 40-44 (All women of Italy) 45-49 (for some women depending the region of Italy)	50-70 (UK)	50-70 (France, Belgium, Italy and Israel)	45-49 (Some region of Italy)
Planned images	No mammogram	Mammogram every 3 years	Mammogram every 2 years	Mammogram every year
Per-protocol definition	≤ 1 mammogram over 4 years	≥ 1 mammogram over 4 years AND < 4 mammograms over 4 years (excluding diagnostic mammograms)	≥ 1 mammograms over 4 years AND < 4 mammograms over 4 years (excluding diagnostic mammograms)	≥ 2 mammograms over 4 years

Per-protocol definition for risk-based arm:

Risk-based arm				
	Low risk	Average risk	High risk	Very high risk
Planned images	Mammogram every 4 years +/- US if dense breast	Mammogram every 2 years +/- US if dense breast	Mammogram every year +/- US if dense breast	Mammogram + MRI every year for women < 60
Per-protocol definition (outside of baseline and end of study mammo)	≤ 1 mammograms over the 4 years	≥ 1 mammograms over 4 years AND < 4 mammograms over 4 years (excluding diagnostic mammograms)	≥ 2 mammogram over 4 years	≥ 3 mammograms over 4 years ≥ 3 MRIs over 4 years

8.3.2 Definition of intent to treat population for the main secondary endpoint analysis

Intent to treat population comprises all women randomized to either study arm and evaluable for the main secondary endpoint analysis, whatever was their compliance with the screening schedule they were assigned to.

8.4 Interim analyses

No interim analyses of the primary endpoint are planned.

Intermediate analysis of the secondary socio-psychological endpoints will be performed at year 1 and then on a yearly basis to verify that there is not detrimental psychological impact of the risk assessment and/or participation in the protocol. The results of these yearly evaluations will be examined by the trial steering committee as well as the Ethics and Data Monitoring Committee.

8.5 Definition of events for final analysis

Events considered for incidence rate of stage 2 + breast cancers are:

- **Stage 2, 3 or 4 invasive primary breast adenocarcinoma** occurring from the day of randomization until 4 years from this day (defined from UICC 2010 classification, which means including all T2, T3 and T4 adenocarcinomas carcinomas, and/or carcinomas with lymph node involvement > pN1a)
- Death related to breast cancer that occurred without a prior breast cancer diagnosis

The following lesions are NOT considered as events:

- Adenocarcinomas of stage 0 or 1 (of note, T1pN0i+ and pN1mi lesions are classified as stage 1)
- In situ adenocarcinomas
- Non primary breast adenocarcinomas (of metastatic origin)
- Breast tumours that are not adenocarcinomas including lymphomas or sarcomas
- Deaths not related to breast cancer

8.6 Definition of secondary endpoints

Secondary endpoints are defined in 3.2

8.6.1 Definition of Overdiagnosis

Overdiagnosed breast cancer cases are defined as cancers that would never have been diagnosed, if women had not been screened. Differential overdiagnosis can be measured comparing the cumulative incidence of breast cancer from recruitment to a reasonably long period after the end of the intervention, i.e. longer than the expected sejour time of screen-detected cancers. In this study the two groups will be monitored for breast cancer incidence for 10- and 15-years after the end of the intervention.

The overall excess overdiagnosis with risk-based screening compared to standard protocol will be estimated from the trial. Different lead time models will be applied to obtain a range of model-based estimates of overdiagnosis. A microsimulation model will be calibrated to the trial population for overdiagnosis estimates and cost and cost-effectiveness evaluation.

8.6.2 Definition and methods for other secondary end points

- False positive recalls and rates of benign biopsies will be measured as stipulated by the European Guidelines for Breast cancer screening (<http://www.euref.org/european-guidelines>, and <http://ecibc.jrc.ec.europa.eu/-/european-guidelines-for-breast-cancer-screening-and-diagnosis-the-european-breast-guidelines>)
- Socio-psychological impact of risk-based screening as compared to standard, will be evaluated using validated questionnaires, as largely described in WP5 of the whole project
- Costs and cost-effectiveness will be evaluated as largely described in WP4 of the whole project H2020 (refer to section 1.1.25)
- Underserved women will be defined using both the European Deprivation Index (EDI) and the International Standard Classification of Education (ISCED) scales, both being validated at a European level
- Interval cancer will be defined following the European Commission's definition, as a primary breast cancer, which is diagnosed in a woman who had a screening, test, with/without further assessment, which was negative for malignancy, either:

- before the next invitation to screening, or
 - within a time period equal to a screening interval for a woman who has reached the upper age limit for screening.
- Breast cancer specific survival will be defined according to the DATECAN definition (Gourgou et al)

As planned in the secondary end-points, we will perform joint analyses of MyPeBS with the WISDOM personalized breast cancer screening trial performed in California and the Midwest (PI Laura Esserman, UCSF). These analyses will be performed after the primary analysis of MyPeBS (scheduled for 2025) and WISDOM (scheduled for 2020). The joint analyses will address two different objectives:

- Estimate the differential effect of stratified screening in terms of decreasing stage 2+ cancers across the two trials
- Joint analysis for long-term disease specific mortality (this will require at least 10- and 15-years of follow-up)

A joint steering committee will be set-up and a statistical analyses plan for the joint analysis using meta-analysis techniques.

9. OVERSIGHT COMMITTEES

MyPeBS project is conducted by a European consortium regrouping 50 major physicians, scientists, healthcare providers and patients' advocates in the field, from 6 countries.

The sponsor of the clinical trial is UNICANCER.

9.1 Clinical trial Steering Committee

In the framework of this clinical study, a Clinical trial Steering Committee (CTSC) will be constituted to oversee all questions regarding the clinical trial as well as the exploitation of the common database (ancillary studies and industrial partnerships).

The clinical trial Steering executive committee will meet physically twice a year (or at least through a teleconference) every months during the set-up and the beginning of the accrual phase to ensure an effective and timely start of the clinical trial. Additional meetings may be organised, as required.

- This committee will be constituted of the coordinator, a representative of the sponsor, the PI of the five countries participating in the trial, 2 representatives of patients, and the task leaders of work package of European project (Methodology, Statistical analysis, genotyping, imaging, quality insurance, risk evaluation)
- The Steering Committee is composed of and working according to the study related CTSC Charter, which will be written, approved and signed by all members before any activity.
- All CTSC members will have to fill and update yearly a conflict of interest statement form, throughout their participation as members of the CTSC.
- The SC is responsible for top-level trial design and management decisions, also in consideration of any DMC recommendations
- The Steering committee will also follow the conduct of this study, assist the sponsor (UNICANCER) in resolving issues and/or questions encountered during the conduct of the trial and will consider, with the sponsor, changes to the protocol as necessary.
- The steering committee will be scientifically responsible for the proper conduct of this study and the interpretation and publication of its results.

- The SC will be responsible for writing the publication plan, revising and authorizing all publications issued from the trial, organization publication agenda.
- It will meet by phone conference every month during the set-up and the beginning of the accrual phase to ensure a effective and timely start of the clinical trial. Meeting schedule will be reduced once accrual is going as planned and during the follow-up phase.
- Two-yearly physical meetings of the SC will be planned throughout the conduct of the study.
- Additional representatives and investigators might be invited to address specific questions as necessary.

9.2 Ethics and Data Monitoring Committee

The Ethics and Data Monitoring Committee, which is independent of the trial team, will oversee the progress of the study, safety of the participants, and ethical issues, including any that arise from new information from other sources. It will confer no less than about once a year, and can request extra meetings at any times it considers appropriate. Progress reports and data will be provided when it confers, and it can demand any analyses or information it considers appropriate to inform its decisions. The terms of reference of the data monitoring committee are to:

- Advise the trial management group on any ethical issues that arise;
- Respond to any ethical concerns that are raised about the trial (although such concerns should generally be communicated first to the trial coordinator, they can be communicated directly to the chair of the committee);
- Advise the trial management group if, in the opinion of the committee, there is at any stage proof beyond any reasonable doubt that the screening modalities proposed to women in either arm, whether in the global population or subgroups, should be changed;
- Independently review the contents of the progress analyses reports
- Review the reports relevant to study conduct and assumptions, outcomes, and make recommendations regarding changes or adjustments that may be required to ensure woman safety and preserve Study integrity;
- Make recommendations at the end of each closed meeting suggesting either to:
 - continue the study according to the protocol and any relevant amendments;
 - discontinue the Study (with provisions for orderly discontinuation in accordance with Good Clinical Practice);
 - modify the study protocol, which may include, but are not limited to: changes in inclusion/exclusion criteria, alterations in Study procedures or Study conduct, increase the number of events at final analysis and/or number of participants enrolled according to the protocol and Statistical Analysis plan and any relevant amendment;

The data monitoring and ethics committee will include an independent group of 5 individuals who have experience and expertise in ethics, in the management of women in the intended study population, experience in statistical methods (through the participation of at least one statistician), experience in monitoring the safety of randomized clinical trials, and who are not participating in the Study, neither have any conflict of interest with the study or any related topic. All DMC members will have to fill and update yearly a conflict of interest statement form, throughout their participation as members of the DMC.

10. ACCESS TO DATA

It is the responsibility of the sponsor to obtain the agreement from all parties involved in the research in order to guarantee that the sponsor has direct access to all investigator sites, original records, source data/document and reports to allow quality control and auditing by the sponsor or on behalf of the sponsor.

Access to data aggregated for the study will be carefully regulated by the clinical trial steering committee and the sponsor.

11. QUALITY ASSURANCE

11.1 Data collection

The study management will be performed by UNICANCER in concertation with screening structures and/or coordinating centers.

11.1.1 Structure and protection of central website and database

The web platform/interface for MyPeBS will allow many crucial functions linked to accrual, follow-up, information and communication activities.

It will be developed by a partner of the project (Eonix) and hosted by Eonix for the database and by a trusted third party for the personal data of the participant (private portal of the participant). This web-interface is under the supervision and coordination of UNICANCER. The data management will be managed by Center Georges François Leclerc at Dijon:

This web-platform/interface addresses the following needs and specifications:

- E-consent signature and e signature for the contract agreement with sites (if applicable)
- Entry of all data necessary for the database
- Filling of all online questionnaires by participants
- Entry of all follow-up data
- Randomization
- Transmission to the investigator and participant in their portal of the estimation of personal risk in risk-based arm, using BCSC risk model or Tyrer-Cuzick risk model including customized component using PRS
- Automated updates of risk status if additional SNPs or change in clinical variables
- Interactive Participant Portal with secure authentication
- Designed cases/service desk to capture bugs, requests from participants, etc.
- Outside mammography workflow to capture mammography results from participants and/or screening centers
- Series of workflow rules and triggers based on enrollment and study status
- Transmission of participants' personalized programs and invitation dates to screening centers
- Sensitive data such as genotyping analyses must not be linked to the participants
- Participants identifications (IDs) must be only available for the participants themselves in a protected area on server participant portal (hosted by a trusted third party), any data leaving this area must be encrypted and pseudonymized.

Additional items may be relevant according to countries and centers possibilities:

- Direct collection of breast density assessment upon possibility of link with density software
- If possible, direct collection of mammographic images in some centers as a sub-study according to local possibilities (crucial potential research impact)
- Communication and cross-talk with social security insurance to cross data, in certain countries, to be specified (probably not directly possible for most – would require to be done at the center level, since data will then be anonymous)

The web interface for MyPeBS will contain several interconnected modules.

1. Module of e-signature

The contract agreement between sites and UNICANCER and/or national coordinator center can be signed electronically only if this process is applicable and acceptable in the different countries.

The e-signature will be used to sign the consent form between the investigator and the participant. The signed consent form will be archived in a secure place.

2. Module for the CRF database

It will be based on a specific server hosted by Eonix. It will host all CRF data. All data available will be totally anonymous, participants being identified by a unique code number.

3. The randomization module is integrated directly into the web-platform.

4. Risk assessment portal is the risk assessment model.

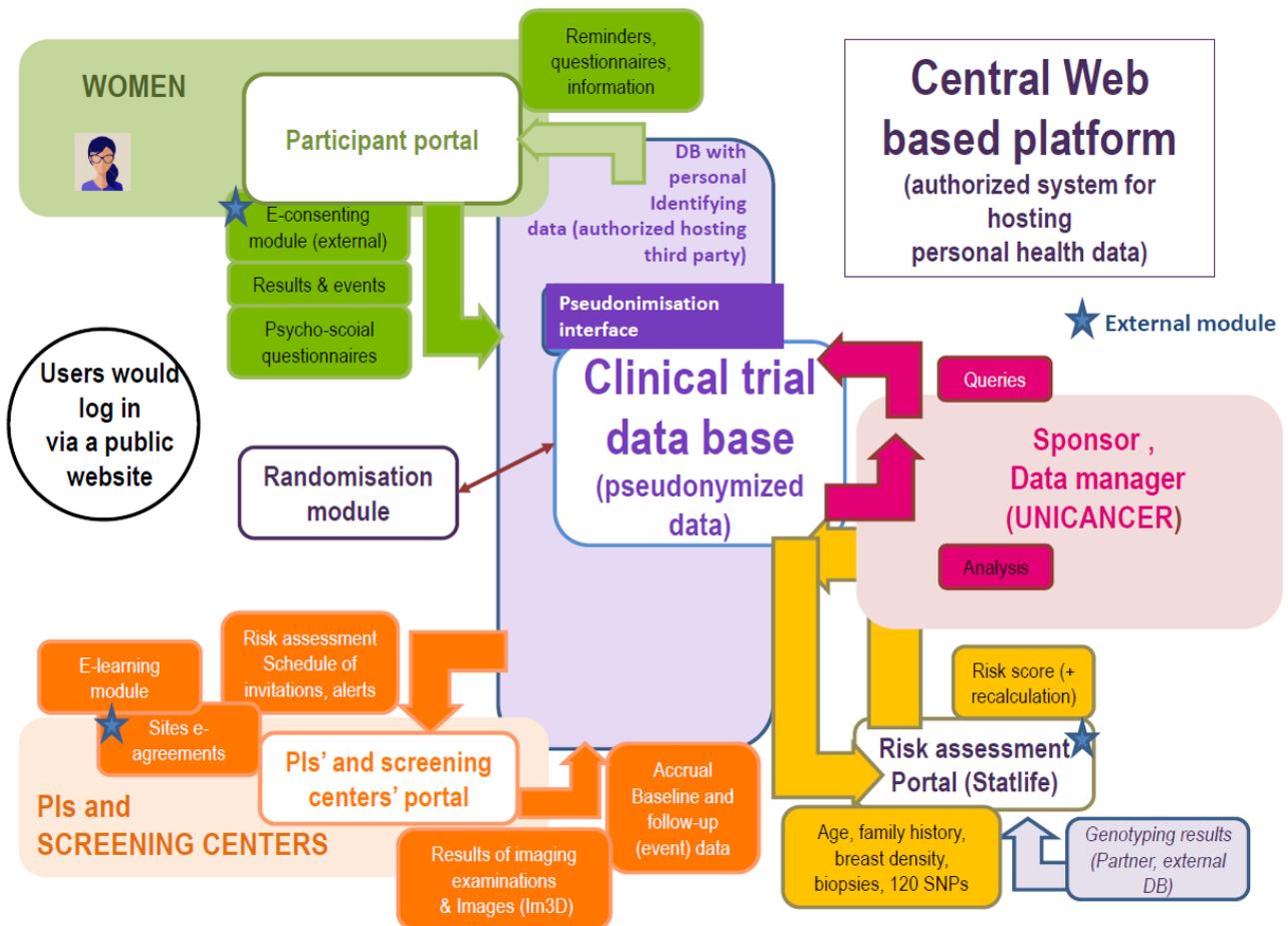
It will be developed and hosted by Statlife. It will be able to integrate genotyping data limited to the relevant results of the target 120-150 polymorphisms. All data will be totally anonymous. This module will export risk information to the central base data (CRF). This module will allow automated recalculations of risk in case of new validated SNPs or new relevant clinical data.

5. Participant portal is the integrated portal for participants with secure authentication.

It is dedicated to participants' secured access to their private account on MyPeBS. It will be developed and hosted by Eonix. A trusted third party will be responsible for keeping all personal data (name, surname, address, e-mail, phone number,...) of the participant. This will be the only place participants' names and email addresses are entered, and these data will be totally anonymized and encrypted for externalization outside of this module. This interface will allow participants to fill and change their personal data, fill questionnaires, and receive invitations or reminders for their personal surveillance program. They also will be able to enter data on their screening exams or results, as well as events.

6. Pls' and screening centers portal is the integrated portal for screening structures and investigators.

It will be dedicated to the interface with the screening centers. It will be partially country-specific. It will be developed and hosted by Eonix. It will allow direct entry of data (results, events...) and images from the screening centers, as well as inverse communication with the screening centers on randomization allocation for a given participant, surveillance program, dates of invitations, reminders, etc.



11.1.2 Overall Data collection rules

Regarding the data collection, the general principles are described in the Table below:

- A minimal information is entered by the investigator and women at the baseline
- A web-based yearly update of personal data will be self-entered in the system by all participating women upon yearly invitation (email, SMS, other)
- Results of images will be both self-declared and retrieved through the screening coordination centers for the purpose of the main end point. For secondary end-point (economical analysis) additional data will be collected from national insurance system.
- An out-of-study mammogram will be mandatory at 4 years for all women included

Type of data	Mode of collection	Comment
Baseline data	Web-platform site	Filled by investigator and women
Randomization	Web-platform site	
Initial risk assessment	Web-platform site	Filled by investigator and/or women for some country
Questionnaires	Web-platform site	Filled by participants
Update of personal participants data	Web-platform site	Filled by participants

Results of all imaging examinations	Web-platform site	Filled by women and screening centers
Results of biopsies or surgeries (benign)	Web-platform site	Filled by women and screening centers
Cancer events	Web-platform site	Filled by women, investigators, filled /imported from screening centers and imported from national security insurance database

All women will be followed for 4 years from randomization for the inferential analysis of the trial.

Long-term breast cancer specific mortality data will be retrieved in each country through regularly (if possible) and otherwise at the end of the trial crossing with national databases (national health insurance databases and national epidemiological and statistical databases) in concerted, pre-planned, anonymous fashion.

A long term data collection for the evaluation of incidence and breast cancer specific mortality via interrogation of data country-specific health insurance and screening structures data bases will be performed up to 15 years from study entry of the participants.

11.1.3 Data management

Data Management will be undertaken by the data management team of Centre Georges François Leclerc at Dijon and UNICANCER. The Database is under the responsibility of UNICANCER. A specific database will be created, tested and validated before the start of data capture. Database management will be provided through the database included into the web-platform. A data validation plan will be developed and will describe in detail the checks to be performed for each significant variable and a list of obvious authorized corrections. The essential data necessary for monitoring the primary and secondary endpoints will be identified and managed at regular intervals throughout this work in collaboration with the coordinator and the clinical trial project management. The data entry into this database will be filled in by investigator site, by participant and/or by screening centers. The data will be controlled and cleaned by the team responsible for data management. The database will be frozen after final quality control, and then exported for the statistical analysis of the primary and secondary objectives.

This centralized clinical database will need to have interrelation with the screening structures and national security insurance. A web-platform will be developed to propose services to allow the screening centers and the national security insurance to connect their own systems.

For the purpose of long term follow-up and economical analyses respectively, individual records will be linked to national health security systems in the different countries (e.g. SNIIRAM, NHS Digital and PHE datasets) using an trusted third party according to national guidelines, so that the centralized clinical trial database stays pseudonymized. The trial will be conducted in accordance with all relevant aspects of the Data Protection Act and the Health Research Authority Confidentiality Advisory Group (and previously, the National Information Governance Board) requirements. The data will be treated with appropriate confidentiality, and used only for medical research.

11.1.4 Quality controls, mechanisms to ensure security of data collected

Woman will be identified by a numeric code.

All women will receive a unique woman identification number when signing the informed consent form and before any trial procedure is performed. This number will be used to identify the woman throughout the trial and will be used on all trial documentation related to this woman. The woman identification number will remain constant throughout the entire trial.

All data necessary to the research will be entered timeliness into the trial database.

In this trial, a minimal data will be collected:

- Baseline data including identification of the woman, date of birth, age, personal medical history of the woman and familial history
- Initial risk assessment
- randomization
- Questionnaires
- Results of all imaging examinations
- Results of biopsies or surgeries (benign)
- Cancer events
- Death

The data base will be considered as the source document for the data indicated above

During the trial, notification to the women may be sent via the web-platform for data consistency validation by data manager of UNICANCER (Centre Georges François Leclerc, Dijon).

When using database, traceability of access and changes is traced by the software (audit trial).

The access code (login) and passwords to access the web-platform will be sent directly to each users personal (woman, investigator and organized structure) email account. The logins and personal passwords for investigators and organized structure to connect to the data base, via the website- <https://www.MyPeBS.eu/>, will be generated by data manager. Instead of the logins and personal passwords for woman will automatically be generated by the web-platform.

A password non-disclosure certificate will be signed by the principal investigator of each centre engaging his/her responsibility regarding the confidentiality of the access codes for all users of the data base at their centre.

11.1.5 Study monitoring plan

The monitoring within MyPeBS will be mostly automated through the common database and the central website.

However, the following measures will be set-up

- Initiation visits (in area zones and/or remote via web and phone conference) to provide all investigators with the necessary information and train them to the specificities of MyPeBS-CT protocol. Furthermore in the web-platform the investigators will have access to an e-learning with a qualifying certificate.
- a limited remote monitoring to ensure the authenticity and credibility of data in accordance with the principles of Good Clinical practice, including:
 - verifying the informed consent (confirmation will be asked to each women in the data base of the signature the informed consent and when)
 - verifying that the CRF data is consistent and in agreement with the source documents via the cross-over of the data filled by the participant and the information available in the organized structure.
- If necessary (too many inconsistencies), an audit of the participating investigational centers

11.1.6 Site Enrolment Requirements

Following regulatory and ethical approval for each participating site, it is the responsibilities of the Sponsor to formally activate sites according to local obligations. Sites will only be able to enrol patients once formal site activation has been performed by the Sponsor.

11.2 Audits and inspections

As part of UNICANCER's audit program, the sponsor may audit some investigational centers. The center and the investigator agree that audits be carried out by Sponsor or any person duly authorized during the study and for at least 15 years after the study.

The investigational centre and the investigator agree to devote the time necessary for the audit procedures, allow the control of the study documentation, and provide additional information requested by the sponsor.

A Competent Authority may also request a study inspection (during the study or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately of this request. The investigator must allow the inspectors direct access to the study documents and source documents.

The investigational centre and the investigator agrees to devote the time necessary for inspections procedures, allow the control of the study documentation, and provide additional information requested by the inspectors of the concerned Competent Authority.

12. MANAGEMENT OF THE SAFETY OF PARTICIPANTS

12.1 Adverse events

In this study, no treatment or medical device is tested,, the aim of this study is to show the non-inferiority of the risk-stratified screening strategy in terms of incidence of breast cancer of stage 2 +, compared to standard screening. The methods used in this study, for the cancer detection, including mammogram, Breast ultrasound or MRI are done according to the standard practice. As a consequence, no adverse event specifically related to the study is expected. In case of adverse event that meets the definition of serious adverse event (results in death, is life-threatening, requires participant's hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, induces a congenital anomaly or birth defect, or is medically relevant in the context of the study), the study site must declare the event according to the standard practice of the country where the event occurred.

12.2 Events of special interest

Events of specific interest listed in this paragraph will be collected during the study.

Some events could have an impact on the medical care of participants. Two cases were identified:

- Pregnancy because the radiological exam must be interrupted temporally
- Discovering of breast cancer (except during the screening)

In these cases, it will be asked to the participants to inform their doctor. This information is present in the information letter. They also have to declare the event on the participant web-platform. **The Sponsor will inform, immediately after awareness, French competent authority of all cases of pregnancy and breast cancer occurred with women of low risk group.** These cases will be presented during the EDMC.

In this trial, safety assessments concern some of the secondary endpoints which measure parameters considered as "safety evaluations" since they are linked to screening-related harms:

- False negatives and breast cancers that occurred between two mammograms considered as normal
- Detection of false positives in imaging (images considered suspicious, requiring biopsy and at final the diagnosis is benign);

- The estimation of overdiagnosis cases (which can only be a comparative estimate between the two treatment arms);
- The estimation of the theoretical risk of radio-induced cancers (which also can only be an estimation);
- All causes of deaths.

These data will be estimated from the study at the end of the study.

12.3 Security of participants

Participants classified into the “low risk” category (and above the onset age for standard breast screening in their country) will have less frequent breast imaging comparatively to standard practices; for these participants, the detection of potential cancer could be delayed of a maximum of 2 years as compared to the standard screening frequency (also see section 1.2.3. of the protocol).

Therefore, specific risk reduction measures will be put in place in this subgroup of patients:

- Breast cancer awareness remains a major cornerstone of the reduction of the risk of advanced breast cancer: women must be advised of both symptoms leading to see a doctor and eventually to have a diagnostic mammogram and health behaviors leading to reduced risks of breast cancer (see below)
- Participants with a low risk estimation will be specifically sensitized by investigators to the fact that low risk is not an absence of risk. They will be yearly reminded of this point.
- All participants will be taught which breast symptoms must lead to see a doctor.
- All participants will be yearly reminded that mammograms can miss some cancers and that, therefore, seeing a doctor in case of a symptom remains crucial.
- Breast self-palpation will be taught to women who ask for it only

All cancers detected in this risk-based group will be reviewed at EDMC meeting (Ethics and Data Monitoring Committee, which shall meet at least once a year during the whole study duration and shall review the events of special interest collected throughout the study) with the objective of continuously evaluating whether this subgroup of participants is not too much disadvantaged by their participating to the study.

12.4 Annual safety report.

Events of special interest will be discussed during the EDMC, the minutes of this meeting will specify the number and frequency of breast cancers occurred in the overall included population and in the considered “low risk” subgroup as well as the stage of the cancer and evaluate if these participants are disadvantaged or not.

The annual safety report will include all available safety information and minutes of EDMC. This report will be sent to the competent authority and to the Ethics Committee of each country, according to local regulations.

12.5 Sample management

Saliva samples will be sent to the central laboratory for DNA extractions and genotyping. DNA extracted from saliva samples will be analyzed and the leftover of DNA will be stored anonymously in a specific dedicated biobank (if the related consent form is signed by the participant). Furthermore, we will be able to re-evaluate risk as new variants could be identified by re-analyzing the mature trial data, as opposed to carrying out additional genotyping.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 General requirements

The clinical must be conducted in accordance with:

- The principles of ethics as stated in the last version of the Declaration of Helsinki,
- The relevant provisions of Good Clinical Practices defined by the International Conference on Harmonisation (ICH–E6 R2, December 2016),
- According to the country specific laws and regulations

13.2 Clinical Study Authorisation

Prior to the start of the study, the sponsor or the investigator will submit the study protocol, patient information sheet(s), informed consent form(s), and other study-related documents as required by local regulations, to the respective regulatory authorities for their authorisations and to the responsible Independent Ethic Committee (IEC)/Institutional Review Board (IRB) for their written approval.

The sponsor or the investigator will inform the IEC/IRB and regulatory authorities, according to local regulatory requirements, about protocol amendments including any new information that require an ethical/regulatory reconsideration of the study protocol.

13.3 Identification of women in the trial

A woman, participating in the trial, will be identified by a code.

All women will receive a unique identification number when they sign the informed consent form. This number will be used to identify the woman throughout the study and must be used on all study documentation related to this woman. The woman identification number must remain constant throughout the study.

13.4 Woman information and consent

The patient information sheet and informed consent form must be written in accordance with the ICH Harmonised Tripartite Guideline for Good Practical Practice (see Appendix 2) and applicable local regulations.

The English versions of the patient information sheet (PIS) and informed consent form (ICF) will be considered as the templates that will be translated and adapted to the appropriate national and local regulations. The changes made and the reason for the changes must be provided to UNICANCER. The adapted documents must be validated by UNICANCER before being implemented in the specific country.

Prior to the participation of a woman in the study, this woman will be informed both verbally and in writing about the objectives of the study, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items must be explained by the investigator in a language and in terms that are easy to understand by the woman. The women must be given enough time to consider their participation and decide whether they wish to participate or not in the study. They can have a 2 weeks reflection time before deciding whether or not to participate. Women will also be informed that their participation is voluntary and that they have the right to withdraw from the study at any time without giving the reasons and without this impacting their subsequent medical care.

The patient information sheet and the informed consent form must be associated within the same document to ensure that all information regarding the study is provided to the woman. Women will confirm their consent in writing prior to starting the study and before undergoing any study-related procedure. The informed consent forms must be personally dated and signed electronically by the women and the investigator. The informed consent form is archived in the web-platform. In the event that the woman decides to withdraw from the study, the woman is not obliged to give reason(s) for withdrawing. However, the investigator should make a reasonable effort to obtain the reason(s) while fully respecting the woman's rights.

If any changes in the written patient information or informed consent form occur during the study, the investigator will ensure that all women impacted by the changes and still participating in the study receive the updated patient information in a timely manner and are asked for written consent for the changes made.

13.5 Changes to protocol

The study will be conducted in strict compliance with this protocol. Changes will be included in an amended version of the study protocol. The list and tracking of modifications and rationales will be provided in the amended version of the study protocol.

Amended study protocols will be submitted to the IECs/IRBs concerned and to the regulatory authorities by the sponsor or physician-investigator according to international and local requirements. If an IEC/IRB requires modifications to the amended study protocol, the patient information sheet, and/or the informed consent form already approved by other IECs/IRBs, the sponsor will decide in each case whether these changes will be adopted only for the investigational centre(s)/country concerned, or for all participating centres/countries. Amendments will only be implemented after authorisation/approval from the Competent Authority/Ethics Committee has been obtained.

13.6 Sponsor responsibilities

UNICANCER, the sponsor of the study, has initiated this study and is therefore accountable for the study management and for verifying that the financing schedule covers the anticipated expenses.

The main sponsor responsibilities are:

- The protocol writing and amendments, as well as study-related documents;
- The subscription of a civil-responsibility insurance;
- The obtaining of an EudraCT (European Drug Regulatory Authorities Clinical Trials database) identification number;
- The request according to local regulatory requirements the opinion of the responsible IEC/IRB, and authorisation from the respective regulatory authorities for the initial protocol and subsequent amendments (if applicable);
- To inform investigational centres institutions and investigators, according to local regulatory requirements about the study;
- The notification to the respective regulatory authorities and to the IEC/IRB of new event which may modify the risk/benefit profile of the study, and the measures taken, according to the local requirements;
- The recording of the study in a publicly accessible database(s) before recruitment of the first woman, at least “clinicaltrial.gov” and EudraCT.
- The permanent assessment of ongoing safety of the investigational drug/therapy and consequently the women’s safety;
- The notification of the start and the end of the study to the respective competent authorities and to the responsible IEC/IRB, according to the local regulatory requirements;
- The final report writing on the study and its communication, according to local regulatory requirements, to the respective competent authorities;
- The information on the study’s results, according to local regulatory requirements, to the respective competent authorities, to the responsible IEC/IRB. The study’s results may also be communicated to the research participant, at their request, by the investigator;

The archiving of the study’s essential documents for a minimal duration of 25 years after the research has ended

13.7 Insurance compensation

UNICANCER, the sponsor of the study certifies that it has taken out a civil liability insurance policy covering its civil liability for this clinical study under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not exempt the investigator and its team from maintaining their own liability insurance policy.

13.8 Investigator responsibilities

The principal investigator of each investigational centre participating in the study commits to conduct the study as specified in this protocol and in accordance with the current Declaration of Helsinki (see Appendix 1) as well as the current ICH Harmonised Tripartite Guideline for Good Clinical Practice (see Appendix 2).

It is the responsibility of the principal investigator to:

- Provide to the sponsor with their curriculum vitae (CV) and those of their collaborators, and evidence that the centre will be able to conduct the study. The CV must be current (no older than 1 year), dated and signed;
- Start recruiting women only after receiving approval from the sponsor;

- Be available for audits, and investigator meetings (if applicable).

It is the responsibility of each principal investigator and each investigator team member to:

- Ensure the confidentiality of all data recorded during the study;
- Collect the informed consent, written, dated, and signed personally by each individual research participant before any specific selection procedure for the study;
- Regularly complete the case report form (CRF) for each women included in the study;
- Declare to the sponsor as soon as being aware of, any serious adverse event occurring during the study according to provisions of this protocol;
- Accept visits by possibly those of auditors mandated by the sponsor or the inspectors of the respective regulatory authorities;
- Date, correct, and sign the corrections made in the CRF and the requests of the data correction forms (DCF) for each woman included in the study;
- Sent regularly (in minima once per week) to the dedicated platform the Saliva kit.

13.9 Federation of the Patient Committees for Clinical Research in Cancerology

This committee reviews clinical documents provided to patients in oncology clinical studies. The French patient committees' federation is coordinated by the "Ligue Nationale Contre le Cancer" and the French NCI (INCa). The committee reviews the study documents, and makes suggestions for improving these, in terms of the quality of information given to women, to maximise the convenience and comfort of study women.

13.10 Human biological samples collection

In the framework of this study, a saliva sample is collected only for the women randomized in the risk-based screening arm.

This biological sample is necessary to perform DNA analysis (genotyping for obtaining a polymorphism risk score, which is integrated with clinical data for obtaining a risk score per participant). The patient will be informed via a patient information sheet and, in the absence of opposition of her part, biological samples for research will be prepared, stored and used for this purpose.

Further use of the leftover of these biological samples (DNA) for the purpose of scientific research is subject to written consent from the patient. This consent is revocable at any time during the study. Similarly, at any time during the research, the patient has the possibility to request the destruction of their samples.

Furthermore, it must be noted that the results of biological studies may be published only if all data relative to the patients are made anonymous.

14. DATA PROCESSING AND CONSERVATION OF DOCUMENTS AND DATA OF THE RESEARCH

14.1 Data processing

14.1.1 *Under the responsibility of the sponsor*

The statistical data will be transferred to the study statistician for analysis. The study data remain the property of UNICANCER, the research sponsor.

The software provided by EONIX will be used for data entry, management, and archiving of data. The statistical analysis will be performed using the SAS software.

14.1.2 *In the investigational centre, when computerised medical records are used*

If computerised woman records are used in a participating centre to process or store study data, the centre must:

- Verify and document that the computer system used to process the data conforms with the requirements concerning data completeness, accuracy, and reliability with respect to expected performances (quality validation)
- Define and follow the standardised procedures related to these systems
- Ensure that these systems allow modifications of collected data, that each modification is automatically authenticated, and that the data cannot be removed (i.e. any change or modification of the data must be traceable)
- Set up and maintain a security control to prevent unauthorised access to the data
- Establish and regularly update the list of persons authorised to have access and modify the data
- Carry out appropriate backups of the data
- Ensure confidentiality, whenever it is applicable (e.g. during data input)
- Ensure that the individual computerised woman data are processed according to local regulations

If data are transformed while being processed, it should always be possible to compare them with the original observations/records.

The computerised system used to identify study women must not be ambiguous and must allow the identification of all data collected for each woman while maintaining confidentiality in accordance with the national legal requirements.

14.2 Retention of documents by investigator sites

The investigator must maintain source documents for each study woman.

All information in case report forms must be traceable and consistent with source documents, which are generally maintained in the woman's file. The source documents should contain all demographic and medical information, laboratory data, radiology, electrocardiograms, etc., including the original copy of the signed patient information sheet and informed consent form.

The investigator must retain essential documents as described below. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- Approvals from the responsible IEC/IRB for the study protocol and all amendments

- Authorisations from respective regulatory authorities for the study protocol and all amendments
- All source documents and laboratory records;
- CRF copies;
- Patients' informed consent forms;
- Investigator master file (IMF);
- Any other pertinent study document.

All original study documents must be kept in a locked and secured place and be considered as confidential and all study document included into the IMF will be available into the web-platform.

Data will be archived under the responsibility of the principal investigator of each participating centre according to the national regulatory requirements. The study documents, including a list of the women's identifications must be archived for a minimum period of 25 years after the end of the study. UNICANCER will inform the investigational centres when the study-related records are no longer required.

The investigational centre may destroy the data only after written authorisation from the sponsor.

15. DATA OWNERSHIP AND CONFIDENTIALITY

By signing the protocol, the investigator agrees to keep all information provided by UNICANCER strictly confidential and to ensure similar confidentiality from their staff. This obligation does not cover information provided to the women and information already publically available.

Study documents provided by UNICANCER (protocols, CRFs, and other material) will be dematerialized and stored appropriately to ensure their confidentiality into the web-platform in the investigator portal. The information provided by UNICANCER to the physician-investigator may not be disclosed to others without direct written authorisation from UNICANCER.

The physician-investigator commits to not publish, spread or use in any manner, directly or indirectly, the scientific and technical information and results related to the study.

16. PUBLICATION RULES

Publications and presentations resulting from the MyPeBS study will comply with recognized ethical standards concerning publications and authorship, including Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors.

Furthermore, publications and any kind of presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for this study. It is expressly understood that publication of MyPeBS primary endpoint Results shall be made whether the Results are positive or negative, in accordance with accepted scientific practice and in particular with ICMJE recommendations

The detailed "Publication and Presentation Policy" shall be approved by the Clinical trial Steering Committee and made available to all investigators, sites and groups participating in the study.

All information resulting from this study is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the study.

Any publication, abstract or oral presentations including results of the study must be submitted to the sponsor (UNICANCER) for approval.

Additionally, all communications, manuscripts or oral presentations must include a section mentioning UNICANCER as well as any institution, physician-investigators, collaborative research group, scientific society that has contributed to the study, including organizations that have provided financial support.

The first author and writer of the main publication will be the principal investigator. The principal investigator may however designate another person to (co-) write the publication.

As for the main publication authors are listed in the following order:

- the study coordinator (first or last author)
- the leads of each project's workpackage
- the PI of each country
- the members of the executive committee
- the other investigators will appear in the list of co-authors in decreasing order, according to the number of recruited women regardless of their affiliation to a cooperative group
- the statistician (The statistician's position is among the first three authors or the last author of the publication)
- a R&D UNICANCER representative

Similarly, publication of the sub-studies (e.g. biological/ancillary studies) will include persons who have carried out the sub-studies as well as the names of all individuals who have contributed to these sub-studies and a sponsor representative.

It is desirable to include the contributors from weakly recruiting centres who have not been mentioned in the first article in the later publications.

Any conflict regarding publication authorship will initially be submitted to the study EDMC and then to the CSR (Comité Stratégique Recherche [Strategic Research Committee]) for resolution in case of major disagreement.

UNICANCER will arbitrate and rule any dispute that may arise.

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18. APPENDICES

- Appendix 1: World Medical Association – Declaration of Helsinki
- Appendix 2: ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP)
- Appendix 3: Ancillary/translational studies
- Appendix 4: Fluxogram
- Appendix 5: Women questionnaires

Appendix 1: World Medical Association - Declaration of Helsinki

The current Declaration of Helsinki can be found on the World Medical Association web page via the link provided below:

<http://www.wma.net/>

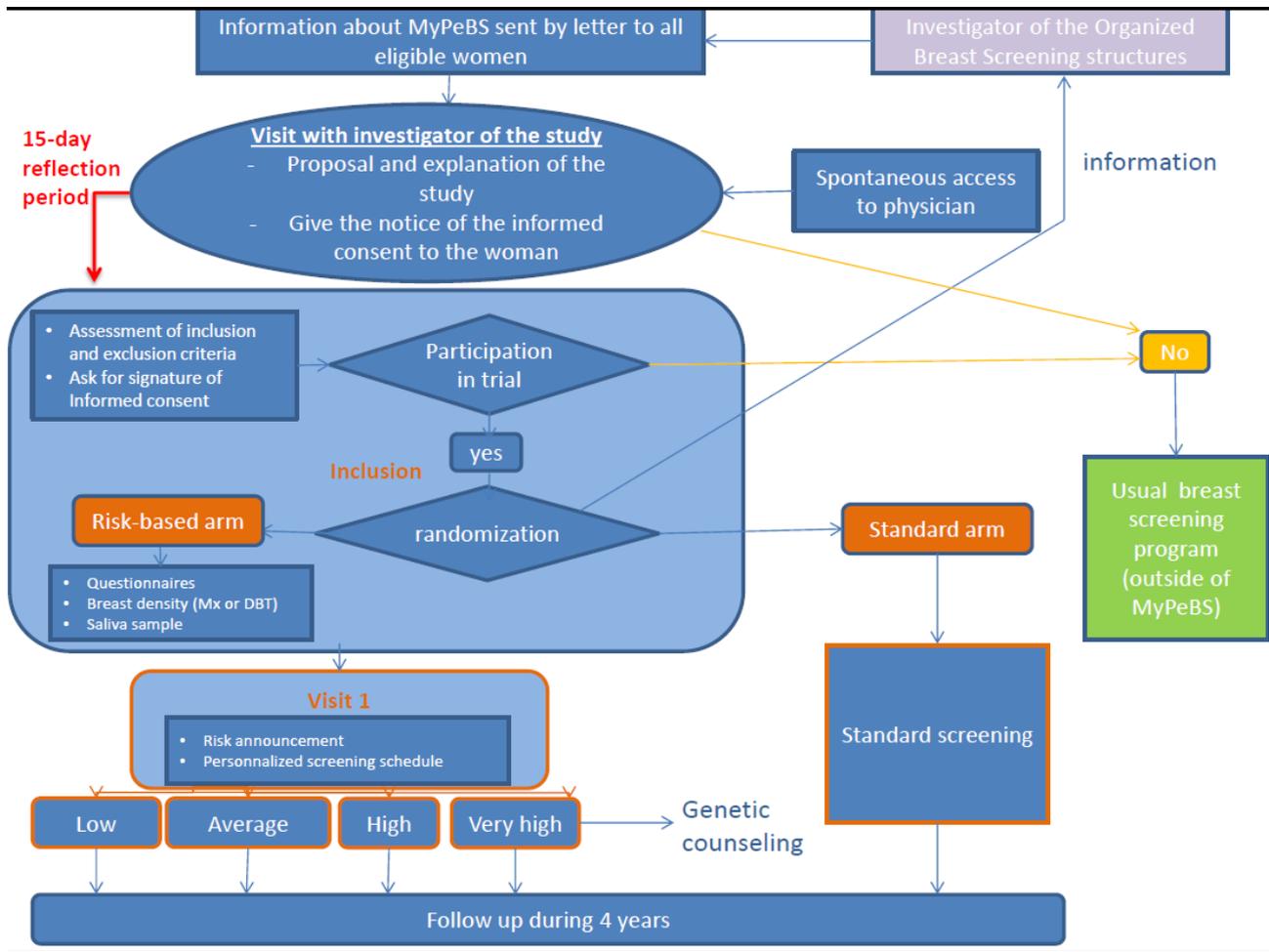
Appendix 2: ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP)

The current ICH-GCP can be found on the European Medicine Agency web page via the link provided below:

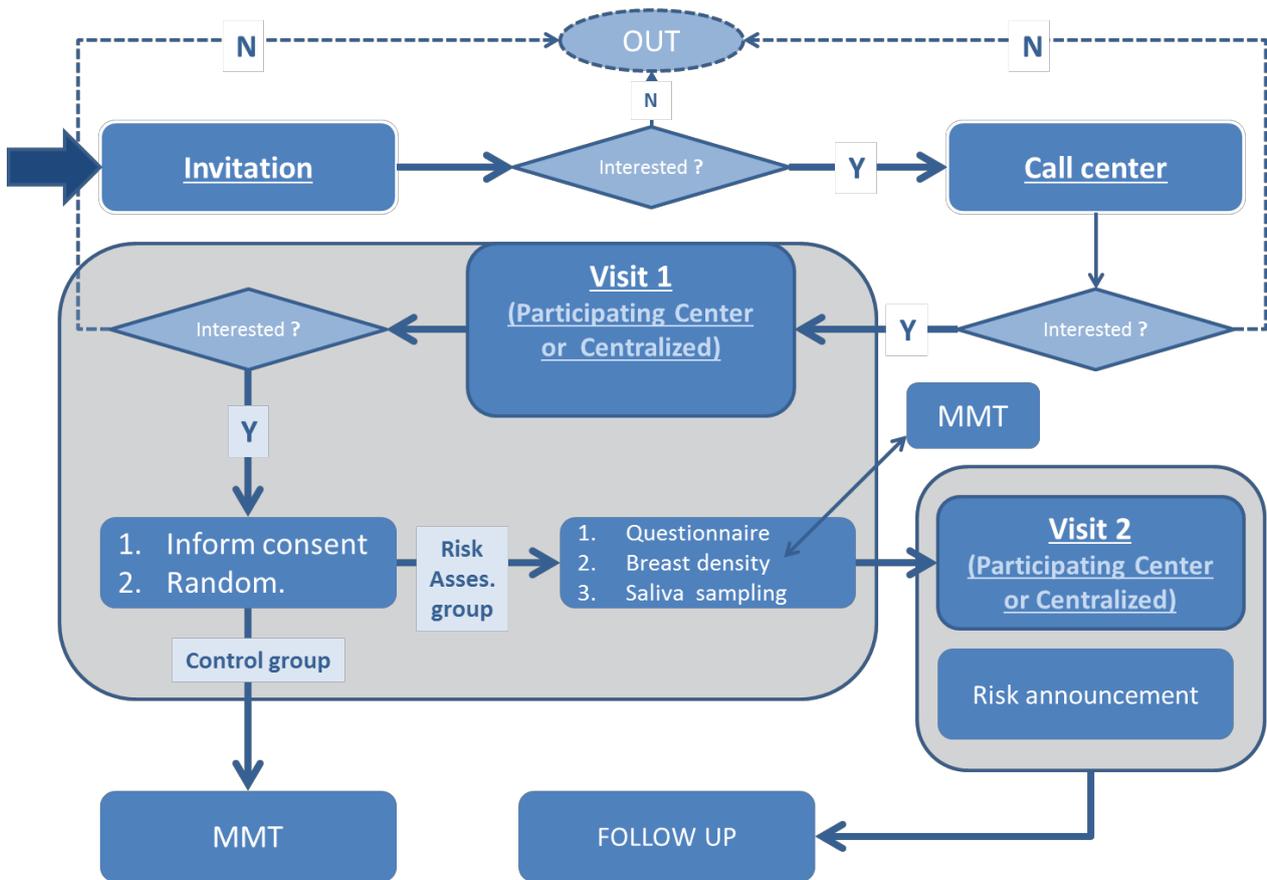
<http://www.ema.europa.eu/>

Appendix 3: Fluxograms

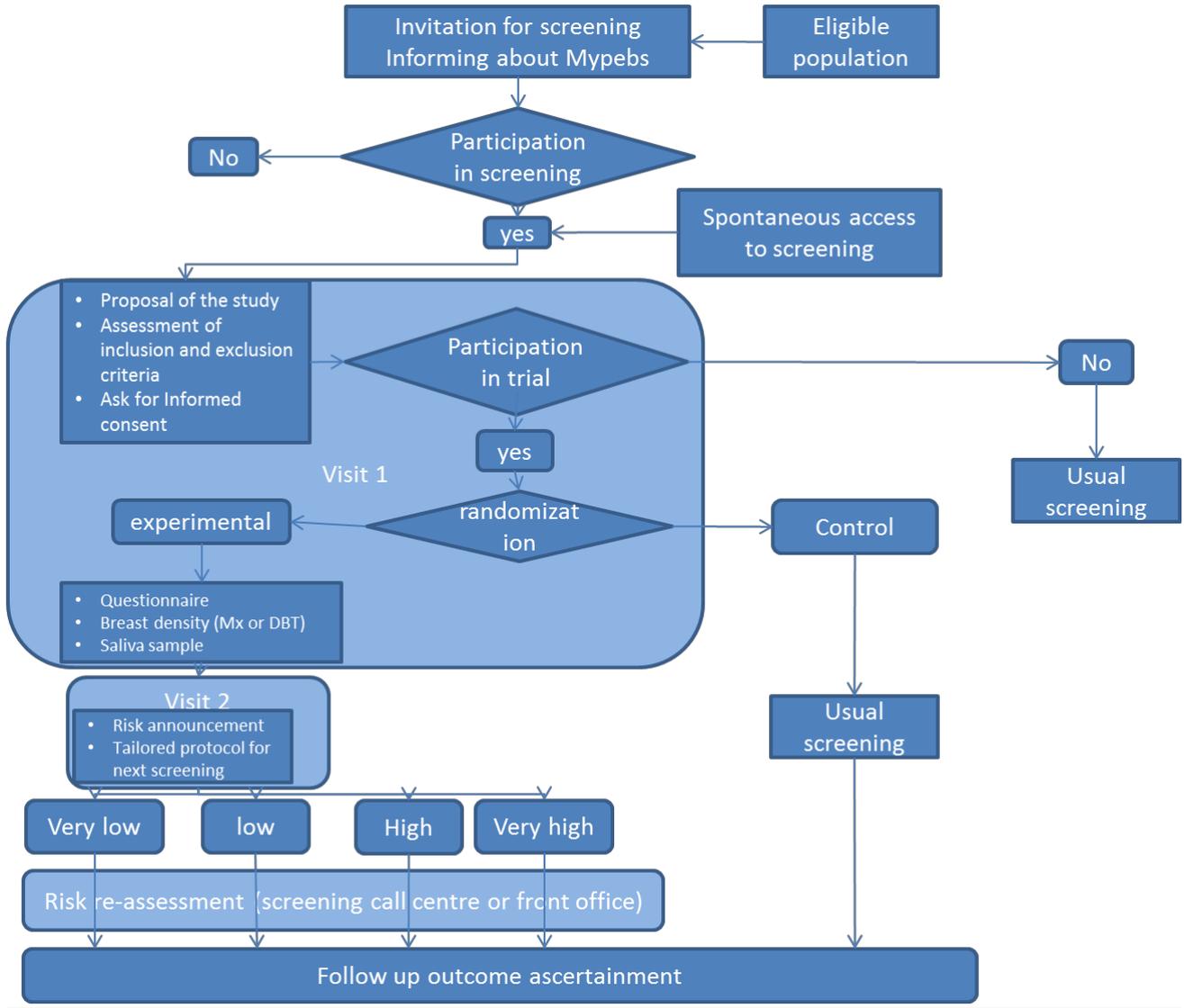
In France



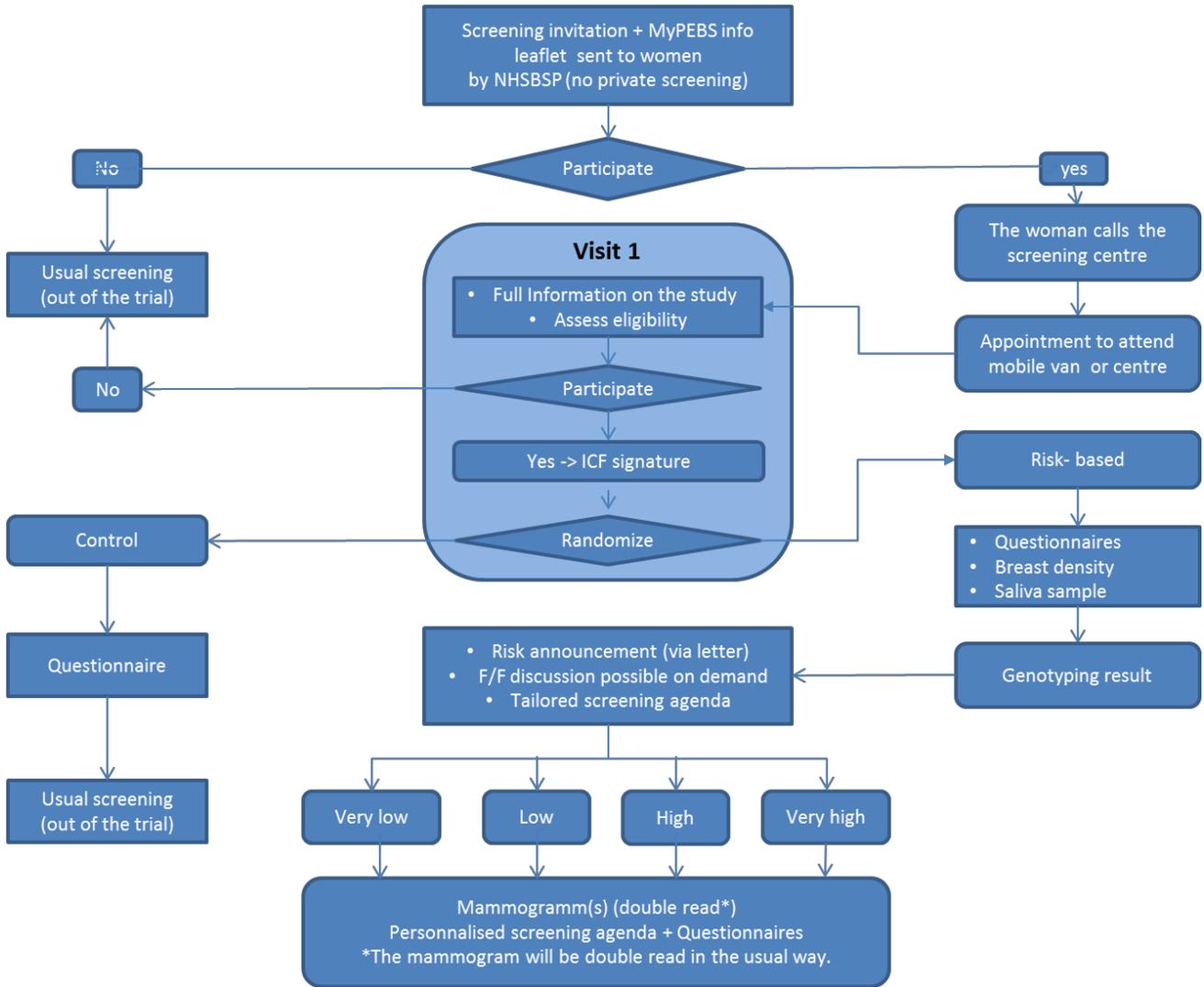
In Belgium



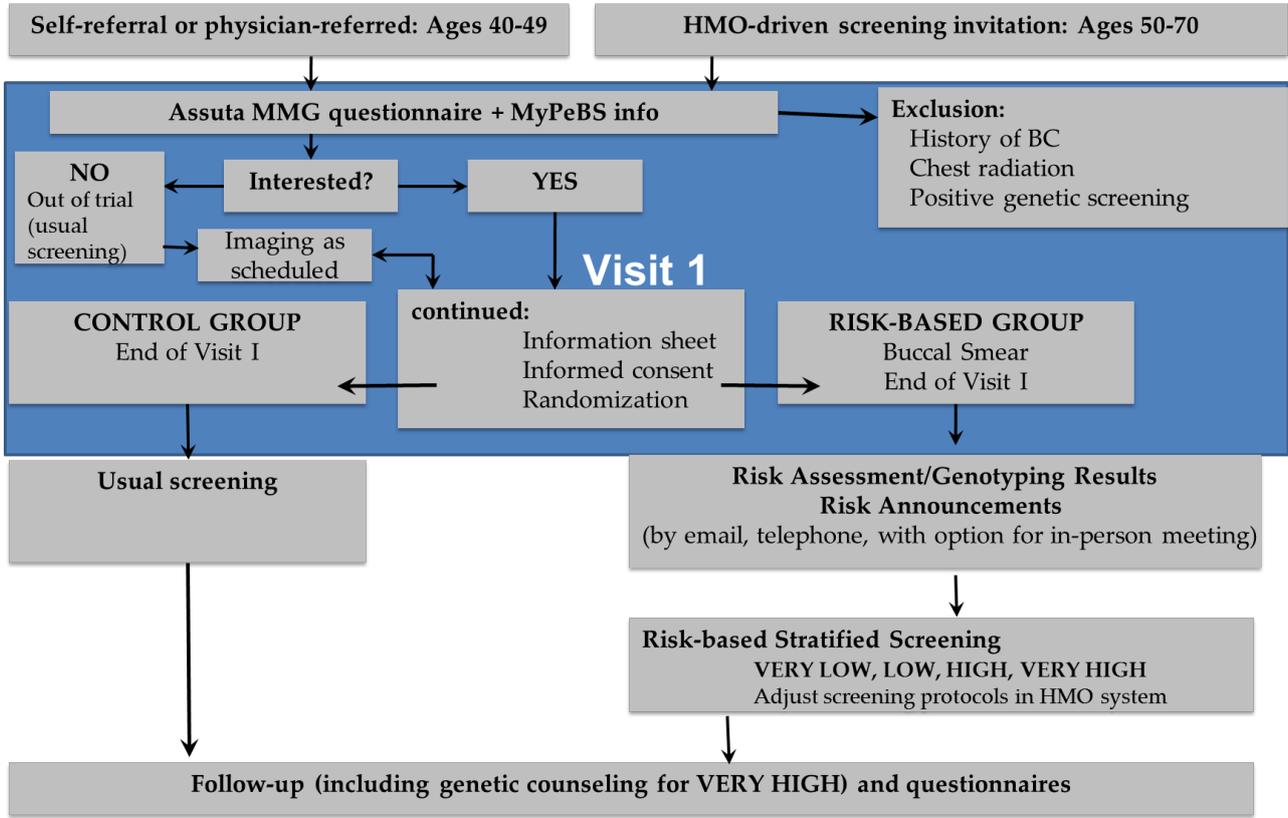
In Italy



In UK



In Israel



Appendix 4: Participants' questionnaires

The following questionnaires will be used in this study:

- Socio-demographic and economical status questionnaire
- Comprehension questionnaire
- STAI short form (state anxiety)
- Quality of life (EQ-D)

TABLE 1 – SOCIO-PSYCHOLOGICAL QUESTIONNAIRES

VISITS	Baseline	Risk-based screening arm	Follow-up	
Visits n°	Visit (V0)	V1	NA	NA
Visit Dates	D0	V0 + 8-12 weeks	M12 +/- 6 months	M48 +/- 6 months
Type of visit	physical	physical or telephone call	On-line	On-line
QUESTIONNAIRE				
1. STAI short form (state anxiety)	X	X	X	X
2. Comprehension questionnaire	X	X		X
3. Information seeking-behavior questionnaire		X		X
4. Quality of life (EQ-5D)	X			X
5. Satisfaction			X	X
6. Socio-demographic and economical status questionnaire	X			X

STAI short form

A number of statements which people have used to describe how they feel are given below. Please read each statement and then circle the most appropriate number to the right of the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately	Very much
1. I feel calm	1	2	3	4
2. I am tense	1	2	3	4
3. I feel upset	1	2	3	4
4. I am relaxed	1	2	3	4
5. I feel content	1	2	3	4
6. I am worried	1	2	3	4

Comprehension & Information seeking-behaviour questionnaire

Comprehension

Frequency : Baseline, +3/5m, +4y

Below are some questions about breast cancer screenings. Some sentences are true, others are false. Take your time, and for each question, please circle the answer that you think is correct.

Circle only one answer

TRUE

FALSE

BREAST CANCER

1. Breast cancer is the most common cancer for women in occidental country
2. We can always cure breast cancer

BREAST CANCER SCREENINGS

3. Screening makes it possible to detect cancer as early as possible before it gives symptoms
4. The sooner you detect breast cancer, the easier it is to heal it
5. Mammography screening consists of making a breast x-ray on a regular basis
6. Stratified screening relies on a saliva sample to analyse DNA
7. Calculating individual risk include information on age, family history of cancer, biopsy history, breast density

BREAST CANCER SCREENINGS' BENEFITS AND RISKS

1. Mammography can be painful.
2. Breast cancer screening reduces breast cancer mortality by an average of 20%. In other words, it avoids 1 out of 5 deaths.
3. Sometimes, breast cancer screening can detect a non cancerous tumor that leads to exams, such as a biopsy to know whether

the tumor is cancerous or not.

4. Sometimes, breast cancer screening can lead to over-diagnosis, that is it detects a tumor that that does not progress to cancer and thus lead to unnecessary treatments (surgery, chemotherapy, radiotherapy).
5. Stratified screening allows the adaptation of the frequency of screening tests according to the individual risk of each woman
6. Stratified screening allows women at higher risk of breast cancer to benefit from more intensive exams with different techniques
7. Stratified screening allows women at low risk of breast cancer to do screening less often

Information seeking-behaviour questionnaire

Frequency : +3/5m, +4y

1. Did you search for information on breast cancer screening (please check on box)
Yes
No
2. If yes, did you search in/on :
 - Internet :
 - o Cancer websites (NCI, comprehensive cancer centers)
 - o General websites (Google, Bing, Yahoo etc.)
 - Libraries
 - Medical articles
 - Mass media
 - Ask questions to healthcare professionals (GP etc.)
 - Ask questions to family and friends
 - Others please specify :
3. If yes, did you search for information focused on stratified breast cancer screening?
Yes
No
4. If no,
 - a. Did you search for information on organized breast cancer screening?
 - b. Did you search for information on breast cancer ?
 - c. You did not search for information at all

Quality of life

EQ-5D questionnaire.

Frequency : Baseline, +4y

Q1. Mobility

1. I have no problems in walking about
2. I have slight problems in walking about
3. I have moderate problems in walking about
4. I have severe problems in walking about
5. I am unable to walk about

Q2. Self-care

1. I have no problems washing or dressing myself
2. I have slight problems washing or dressing myself
3. I have moderate problems washing or dressing myself
4. I have severe problems washing or dressing myself
5. I am unable to wash or dress myself

Q3. Usual activities (e.g. work, study, housework, family or leisure activities)

1. I have no problems doing my usual activities
2. I have slight problems doing my usual activities
3. I have moderate problems doing my usual activities
4. I have severe problems doing my usual activities
5. I am unable to do my usual activities

Q4. Pain/discomfort

1. I have no pain or discomfort
2. I have slight pain or discomfort
3. I have moderate pain or discomfort
4. I have severe pain or discomfort
5. I have extreme pain or discomfort

Q5. Anxiety/depression

1. I am not anxious or depressed
2. I am slightly anxious or depressed
3. I am moderately anxious or depressed
4. I am very anxious or depressed
5. I am extremely anxious or depressed

Trial Program Satisfaction

This questionnaire will include an evaluation of the overall satisfaction of women to participate to the study with the two screening strategies (information, communication tools, organization of the screening). The intention to participate in the study will be assessed after the study participation decision had been made at 1 year and that actual enrolment and subsequent dropout were recorded at the end of their participation at 4 year. We will assess the differences between both arms using equality of proportion and chi-square tests.

We have selected and modified questions of a satisfaction questionnaire on organization of the screening process and the information received validated by Bairati & al (2014) and use actually in Canada (<https://www.ncbi.nlm.nih.gov/gate2.inist.fr/pmc/articles/PMC3893508/>)

Frequency : 1y, +4y

7 questions with answer according a 5 points scale

You are involved in MyPeBS a breast cancer screening clinical study. Could you please answer the following questions about your satisfaction. Please indicate for each statement to what extent you agree or disagree now.

Use the following scale to answer the questions.

1 = strongly disagree

2 = disagree

3 = neither agree nor disagree

4 = agree

5 = strongly agree

1. The decision to participate to My PeBS clinical study was a good decision for me.
2. I regret to participate (or to have participated) in MyPeBS study because the medical follow-up does not correspond to what I expected.
3. I regret to participate (or to have participated) to MyPeBS study because the anxiety generated is greater than I expected.
4. I am satisfied with the information I received in the documents on the pros and cons of participating in MyPeBS study.
5. I am satisfied by the clarity of the information given in MyPeBS documents to present the study (informed consent and information sheets).
6. I am satisfied with the explanations given by health professionals about what happens for me at each stage of MyPeBS study (different exams and their rhythm)
7. I am satisfied by the personal information offered by the web-platform dedicated to MyPeBS study.

Socio-demographic and economical status questionnaire

Our objectives are to verify whether MyPeBS participants' characteristics are representative of the social heterogeneity of the participating countries, and how much social characteristics influence screening perception and behaviour (such as compliance with the proposed programme).

We will analyse women's socio- demographics, i.e. age, education level, income level, marital status, profession, geographic area, number of children. We will compare the characteristics of invited women versus participant women in terms of socio- demographics, age, and geographic location.

We will focus our attention on social economic and social inequalities using either the Material Deprivation Index (MDI) developed by Eurostat based on a European survey (EU-SILC).

Justifications for using the Material Deprivation Index (MDI)

The set of items is extracted from « What can be learned from deprivation indicators in Europe » (Guio, 2009). Cited 139 times.

Rationale:

(1) items based on a European survey (EU-SILC) from the European Commission / Eurostat (it is the same survey from which the European Deprivation Index (EDI) has been validated);

(2) the multi-dimensionality of the index has been validated from a CFA;

(3) the number of items is manageable (7 or 9 items) ;

(4) the material deprivation index (MDIs) is theoretically justified¹;

(5) it is used as a formal measure to monitor the EU poverty target (http://ec.europa.eu/eurostat/statistics-explained/index.php/Material_deprivation_statistics_-_early_results) ;

(6) threshold values are derived to classify individuals into "material deprivation" or "severe material deprivation";

(7) we know the proportion in each EU country that are in material deprivation according to this measure so we can compare with trial's data.

The MDI score is calculated by scoring 1 if the individual answers "no, I cannot afford it" to the item and then by summing all items (thus the MDI ranges between 0 and 9). A threshold value of 3 of the MDI is used to classify individuals into "material deprivation" and a threshold of 4 is used to classify individuals into "severe material deprivation".

We will analyse the impact of socio-demographics and deprivation level on women's participation to risk stratified breast cancer screening as well as to breast cancer screening in general using multivariate logistic regression analyses.

Frequency : Baseline, +4y

¹ For instance, it is based on the distinction between lack of items (due to choice) and enforced lack of items (people who would like to possess the items but cannot afford them). Thus it excludes lifestyle preferences from the concept of deprivation.

Socio-demographic (SD) variables

Questions SD.1, SD.2 and SD.3 only at baseline

SD.1 In which year were you born?

[drop down menu]

SD.2 In which country were you born?

(Please name the country that your birthplace belonged to at the time of your birth)

[drop down menu]

SD.3 What is the highest diploma that you have obtained?

- | | | |
|-----------------------------------|--------------------------|--------------------------|
| 1. Elementary school | <input type="checkbox"/> | |
| 2. Secondary school | <input type="checkbox"/> | |
| 3. High school | <input type="checkbox"/> | |
| 4. Technical school (not college) | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. University diploma | <input type="checkbox"/> | |
| 6. None | <input type="checkbox"/> | <input type="checkbox"/> |

SD.4 What is your current marital status?

- | | |
|--|--------------------------|
| 1. Married and living together with spouse | <input type="checkbox"/> |
| 2. Registered partnership | <input type="checkbox"/> |
| 3. Married, living separated from spouse | <input type="checkbox"/> |
| 4. Never married | <input type="checkbox"/> |
| 5. Divorced | <input type="checkbox"/> |
| 6. Widowed | <input type="checkbox"/> |

SD.5 What is your current situation?

- | | |
|---------------------------------|--------------------------|
| 1. Retired | <input type="checkbox"/> |
| 2. Employed or self-employed | <input type="checkbox"/> |
| 3. Unemployed | <input type="checkbox"/> |
| 4. Permanently sick or disabled | <input type="checkbox"/> |
| 5. Homemaker | <input type="checkbox"/> |
| 6. Other | <input type="checkbox"/> |

2/ Deprivation index

a) Indicators to build the Townsend index (TI)

The Townsend index is based on four items: 1) unemployment (based on question SD.5), 2) non car ownership (based on question MDI.6), 3) non home ownership (based on question TI.3), 4) overcrowding (based on questions TI.1 and TI.2).

TI.1 Number of people in household

1. One
2. Two
3. Three
4. Four
5. Five
6. Six or more

TI.2 Number of rooms in the house

1. One
2. Two
3. Three
4. Four
5. Five or more

TI.3 Housing tenure

1. Own it

2. Mortgage
3. Rent
4. Other

b) Indicators to build the Material Deprivation Index (MDI)

For each of the following item, please select the answer that best describes your current situation:

MDI.1 I can pay the rent, mortgage or utility bills

Yes No, I cannot afford it No, other reason

MDI.2 I can keep home adequately warm

Yes No, I cannot afford it No, other reason

MDI.3 I can cope with unexpected expenses

Yes No, I cannot afford it No, other reason

MDI.4 I can eat a meal with meat, chicken, fish or vegetarian equivalent every second day

Yes No, I cannot afford it No, other reason

MDI.5 I can have one week annual holiday away from home

Yes No, I cannot afford it No, other reason

MDI.6 I have a personal car

Yes No, I cannot afford it No, other reason

MDI.7 I have a colour television

Yes No, I cannot afford it No, other reason

MDI.8 I have a washing machine

Yes No, I cannot afford it No, other reason

MDI.9 I have a telephone

Yes No, I cannot afford it No, other reason