CLINICAL TRIALS

ESSENTIAL INFORMATION

TITLE: Randomized Comparison Of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70

ACRONYM: MyPeBS (My Personal Breast Screening)

[Note: references refer to the list in master document]
Table of contents
1 Clinical study: MyPEBS-CT ......................................................... 3
  1.1 Identifier ................................................................................. 3
1.2 Study design and endpoints ....................................................... 3
  1.2.1 Study design ........................................................................ 3
  1.2.2 Study objectives ................................................................... 6
  1.2.3 Primary and secondary endpoints .......................................... 7
  1.2.4 Relevant guidance documents .............................................. 7
1.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees ............................................. 8
1.4 Subjects/population(s) .............................................................. 9
  1.4.1 Inclusion criteria ................................................................. 9
  1.4.2 Non inclusion criteria: .......................................................... 9
1.5 Statistic analysis plan(ning) and power calculation ...................... 9
  1.5.1 Randomization ..................................................................... 9
  1.5.2 Stratification ......................................................................... 9
  1.5.3 Required number of women to be included ........................... 10
  1.5.4 Planned statistical analysis ................................................... 10
  1.5.5 Definition of per-protocol .................................................... 11
  1.5.6 Definition of Overdiagnosis ................................................. 11
  1.5.7 Definition and methods for other secondary end points .......... 11
1.6 Cumulative safety and efficacy information .................................. 11
  1.6.1 Cumulative safety information ............................................. 11
  1.6.2 Cumulative efficacy information ......................................... 12
1.7 Conduct ................................................................................... 13
  1.7.1 Schedule for study conduct including timelines for key study milestones ............................................. 13
  1.7.2 Description of recruitment strategy ...................................... 13
  1.7.3 Description and assignment of intervention ......................... 14
  1.7.4 Study management, study monitoring, data and sample management ..................................................... 17
  1.7.5 Sponsor, coordinating centre(s) and committees .................... 21
  1.7.6 Study medication .................................................................. 22
  1.7.7 Clinical centres ..................................................................... 22
1.8 Orphan designation .................................................................... 22
1.9 Unit costs per patient for clinical trials / studies / investigations ....... 22
1 Clinical study: MyPEBS-CT

1.1 Identifier

MyPEBS-CT (My Personal Breast Screening-clinical Trial): A Randomized Comparison Of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70

1.2 Study design and endpoints

1.2.1 Study design

1.2.1.1 Brief description of the rationale:

Breast cancer is the most common cancer and the second leading cause of cancer death among women in Western countries\(^\text{[1,2]}\). Current public health policies generally recommend biennial breast screening using mammography, starting from age 40 or 50, with age as the sole risk factor considered for women to enter screening programs\(^\text{[3-5]}\). Mammographic screening has been associated with a mean 20% reduction in breast cancer-specific mortality in average risk-women\(^\text{[6-11]}\), and reduction in late-stage disease in women older than 50\(^\text{[7]}\). This is not without potential harms. Screening can lead to false-positive recalls, estimated to occur in more than half of women after 10 years of annual screening\(^\text{[12]}\), and many unnecessary biopsies\(^\text{[7-10]}\). 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\(^\text{[8,13]}\). Finally, mammographic screening is also associated with a small lifetime risk of radiation-induced cancer. In a recent publication, annual screening of 100,000 women aged 40 to 74 years was projected to induce 125 breast cancer cases (95% CI, 88 to 178) leading to 16 deaths (CI, 11 to 23)\(^\text{[14]}\). A more personalized screening strategy based on individual risk might therefore improve the balance of benefits and harms and increase the efficiency of screening programs\(^\text{[15,16]}\).

Personalized prevention strategies have been shown to be effective for individuals at very high risk because of inherited mutations that predispose them to breast cancer\(^\text{[17,18]}\). 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 breast cancer. National and international guidelines recommend that these women receive increased screening and other prevention measures, which is associated with some suggested benefits\(^\text{[5,19]}\). However, 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\(^\text{[2]}\). Developing more effective, risk-based screening approaches for this general population requires validated risk-estimation models\(^\text{[20,21]}\) 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\(^\text{[50,51,56]}\).

Breast cancer risk models

Several 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. The most well-known models for the general population without specific risks are the Breast Cancer Risk Assessment Tool (BCRAT/Gail), the Tyrer-Cuzick (IBIS) and the BCSC models\(^\text{[22-24,32]}\).

Over the past 10 years, breast density has been explored and validated as an important breast cancer risk factor\(^\text{[25-28]}\). Density is currently regarded as an indicator that summarizes both a woman’s genetic background and exogenous exposures to hormones or other risk modifiers\(^\text{[29]}\). 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\(^\text{[30-32]}\) compared to 0.58 for models that do not include density\(^\text{[24]}\).

A crucial point is to use models that are internationally validated. 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 French general breast screening populations (after adjustment on national incidence, c-statistic 0.61, E/0 1.005) and can be used as such\(^\text{[35]}\). Furthermore, the BCSC score has been shown to perform well on the UK PROCAS cohort, upon adjustment for national incidence (c-statistic 0.61, E/0 1.1, unpublished data – Evans/Ragusa).
The Tyrer-Cuzick model has been largely described and has particular relevance for women with an important 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) [24,34].

As mentioned, it is crucial as well that the model used has been demonstrated to have clinical usefulness, as defined by Steyerberg et al [77,40]. 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) [55]. 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%) [56]. 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) [55]. In the American cohort of women aged 40-74, 20% only of breast cancers arose in the 41% women with a 5-year risk < 1%.

Genotyping and refinement of breast cancer risk identification

Beside these clinical risk scores, huge international efforts and advances in genome technology have led to the identification of over a hundred common, validated single nucleotide polymorphisms (SNPs) associated with breast cancer risk [52, 56-60].

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 [52, 56-60]. Vachon et al recently found that BI-RADS breast density and a 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 [27]. SNPs incorporated into known risk models allow a refinement of their discrimination potential with an increase of the c-statistics up to 0.69 [52]. They also allow for the identification of women at higher risk of specific breast cancers, such as triple-negative, an aggressive, fast-growing subtype [60-74]. These latter, recently identified polymorphisms are potentially of great interest given the lower value of screening mammography among these subtypes. The Tyrer-Cuzick model 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 [72-74]. A polygenic risk score may be used to refine risk from the Tyrer-Cuzick or similar models in women who are at an elevated risk of breast cancer and considering preventive therapy. [72-74].

Tumor stage II+ 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 [78], in whom all our 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 (EBCTCG ASCO 2016 [79], in press 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 T2 N4-9 (all stage II 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 II 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 I-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 [81] and especially in breast cancer screening trials, such as in the publication by Tabar/Duffy et al in 2015 [80].

**Risk communication**

Communication of high cancer risk to individuals has been largely developed over the past 20 years for use in women bearing a genetic high-risk predisposition to cancer. Information and communication on breast cancer risk and screening risk/benefits in the general population may be a major way to improve awareness and interest in screening, but the channels used and methods have to be carefully chosen [75-76]. Communication of cancer risk as a way to target preventive interventions has recently been extended to the general population, with very positive experiences [81,82, 64-67]. Tools are ready that allow effective communication of risk evaluations, together with prevention proposals, to community individuals.

### 1.2.1.2 Objectives, hypotheses and brief description of study design

My-PEBS is a unique European randomized phase III trial assessing the effectiveness of a risk-based breast cancer screening strategy, based on a clinical risk score and polymorphisms, as compared to the standard of care in terms of detection of high-risk cancers.

**Our overall objective** is to compare the effectiveness of two BCS strategies:

- **Standard strategy**: Current standard of care in participating countries where women are invited to a common schedule of screening mammograms (MMG) performed once every 2-3 years starting from ages 40-50 up to ages 69-74, 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 BC and to an individually-defined plan, for the whole population.

**Our hypotheses** is that risk-based screening will be non-inferior in terms of overall stage II+ BC incidence, superior (decreased incidence of stage II+ BC); equally or more cost-effective; but more acceptable (resulting in a wider coverage and a better compliance) than standard screening.

The primary hypothesis chosen is non-inferiority, for the following reasons: we will be increasing screening among high-risk women but decreasing it in a substantial part of the population, therefore we shall make sure that this decrease is not harmful. The potential very slight increase in stage II+ cancers is low risk population will be compensated by some important benefits for this population -- in this case, fewer false positive and fewer overdiagnoses.

Our hypotheses (see detailed assumptions in 1.6.2) lead us to expect only 46 cancers at 4 years among the near 7300 women for which screening will be decreased, while 329 are expected among around 18000 women for whom screening strategy will be increased. We therefore have a very high probability of non-inferiority in the trial overall, and furthermore, of superiority. Further detailed assumptions are described in 1.6.2.

This study is a pragmatic, international, multicentric randomized controlled trial (RCT) to evaluate the efficacy of risk based screening as compared to standard-of-care screening strategy (according to current national guidelines in each country).

**General design**

In the risk-based arm, risk levels are defined as 5-year risk of **invasive breast cancer**, according to the published literature, with reference to situations of equivalent risk-level, and after agreement and consensus of the whole consortium (dedicated workshop, March 10th, 2017).
Study objectives

**1.2.2 Study objectives**

The primary objective is to show non-inferiority of the stratified screening strategy in terms of incidence of BC of stage II and higher (II+), as compared to standard screening.

Key secondary objective:

The key secondary objective is, only if non-inferiority is shown, to demonstrate the superiority of the risk-based screening arm for reduction of stage II+ BC, over standard screening.

Secondary objectives:

1. To compare the rate of morbidity in terms of false positive findings and benign biopsies between arms
2. To evaluate the global psycho-social impact of each strategy (acceptance, observance, anxiety, distress, satisfaction, decisional regret, etc)
3. To evaluate the costs and cost-effectiveness of each strategy
4. To estimate overdiagnosis and overtreatment rates in risk-based screening as compared to standard screening
5. To compare the rate of interval (detected within 12-24 months of a normal screen) cancers between arms
6. To evaluate superiority of risk-based screening in terms of BC-specific mortality at 10 years among the merged Wisdom and My-PEBS studies
7. To evaluate the added value of tomosynthesis in the detection of stage II+ breast cancers
8. To describe the socio-economic structure of the population included and its representativeness
9. To evaluate the incidence of stage II+ breast cancer in risk-based screening in women aged 40-50 as compared to standard

Additional exploratory objectives:

1. To evaluate the added value of ultra-sound in the detection of stage II+ breast cancers
2. To refine long-term breast cancer risk prediction scores
3. To describe and compare between the two arms, the rate of breast cancers predicted at 10-year metastatic risk >10% using adjuvantOnline® Or Predict™, the rates of cancers requiring chemotherapy
4. To explore the effect of risk-based screening vs standard among subgroups (including countries and age categories)

1.2.3 Primary and secondary endpoints

The primary endpoint is the incidence of stage II or higher breast carcinoma

The secondary endpoints are the following:
1. Rates of false positive recalls and benign biopsies in each arm
2. Socio-psychological assessments at baseline, 1, 4 years: acceptance of the proposed screening strategy, observance, persistence, anxiety, distress, satisfaction, decisional regret, using standard questionnaires
3. Crude costs and comparison of cost-effectiveness and budget impact of each strategy (real costs)
4. Estimates of overdiagnosis and overtreatments rates in each arm
5. Rate of interval cancers in each arm
6. 10-year breast cancer specific survival among the merged Wisdom + My-PEBS companion studies
7. Rate of stage II+ breast cancer detection in women with/without tomosynthesis
8. % of underserved women and other social categories included in the trial
9. Incidence of stage II+ breast cancer in women aged 40-50 versus older

The additional exploratory endpoints are:
1. Screening and early diagnostic impact of Ultrasound (in terms of stage II+ BC)
2. Development of updated European-wide and country specific 5-year risk scores
3. 5-year rate of interval (detected within 12-24 months of a normal screen) cancers, rate of breast cancers predicted at 10-year metastatic risk >10% using AdjuvantOnline® Or Predict™, rates of cancers requiring chemotherapy, in each arm
4. Incidence of stage II+ breast cancers among subgroups

1.2.4 Relevant guidance documents

The global clinical trial will be conducted in accordance with current guidelines ICH-GCP and Methodological guidelines - e.g. statistical principles for clinical trials (CPMP/ICH/363/96).

Breast cancer screening activities and breast density assessments will follow current updated European and national guidelines regarding methods and indications in the standard arm, while they will follow the protocol's descriptions in the exploratory risk-based arm.

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 also 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 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/2018/11/22500/EC+Initiative+on+Breast+Cancer.pdf/a586dbfd83d2-4ee3-a345-9ddf72363fa8

National guidelines

In the standard arm of My-PEBS, breast cancer screening has to comply with the current ongoing national guidelines and procedures:

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


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 My-PEBS
- **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 My-PEBS

### 1.3 Scientific advice / protocol assistance / communication with regulatory / competent authorities / ethics committees

The present clinical trial covers a very hot topic. It was therefore crucial that we had early discussions with health authorities of our countries.

Our large European consortium has conducted several workshops for the construction of this trial, in which some health authorities participated (such as French National Cancer Institute and Santé Publique France).

We have sought scientific advice of the European Commission's Initiative on Breast Cancer. Members of this group have been associated with the construction of the present trial, as well as national representatives of the initiative.

The list of collaborations, discussions, submissions to competent/regulatory authorities at national levels, that are ongoing or planned, is provided below, per country.

<table>
<thead>
<tr>
<th>Country</th>
<th>Authority</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>Local/regional health authorities</td>
<td>All the recruiting centres produced a declaration by the legal representative of the Local Health Authority that all the screening procedures, in both arms, will be covered by the Regional Health Service funds.</td>
</tr>
<tr>
<td></td>
<td>Ministry of Health</td>
<td>The study should be submitted to the Italian Ministry of Health, Health Prevention Direction for approval of the radiologic experimental procedures.</td>
</tr>
<tr>
<td></td>
<td>Privacy protection</td>
<td>The trial procedures will be submitted to the National Authority for Privacy protection (Autorità Garante della Privacy) for approval</td>
</tr>
<tr>
<td></td>
<td>Ethics Committee</td>
<td>Submission of MyPEBS to regional ethics committees is planned as soon as possible in the fall 2017, latest January 2018</td>
</tr>
<tr>
<td>Belgium</td>
<td>Federal Commission for Privacy Protection</td>
<td>Submission of MyPEBS trial to FCPP is planned for June 2017</td>
</tr>
<tr>
<td></td>
<td>Local Ethics Committees (University Hospital for each region involved)</td>
<td>Submission to Ethics Committees is planned as soon as possible in the fall 2017, latest January 2018</td>
</tr>
<tr>
<td></td>
<td>Belgian Cancer Register Foundation</td>
<td>Agreement obtained for support of this trial</td>
</tr>
<tr>
<td>UK</td>
<td>National Ethics Committee</td>
<td>Submission to Ethics Committee (national) is planned as soon as possible in the fall 2017, latest January 2018</td>
</tr>
<tr>
<td></td>
<td>National Breast Screening Programme</td>
<td>Unformal agreement obtained, written agreement pending</td>
</tr>
<tr>
<td>Israel</td>
<td>Assuta University Medical Center IRB</td>
<td>Submission to Ethics Committee (national) is planned as soon as possible in the fall 2017, latest January 2018</td>
</tr>
<tr>
<td></td>
<td>Israel Ministry of Health IRB</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Israel Cancer Association</td>
<td>Agreement will be obtained for support of this trial</td>
</tr>
</tbody>
</table>
1.4 Subjects/population(s)

Women from the general population will be eligible for the study if they fulfill the following criteria:

1.4.1 Inclusion criteria

1. Women
2. Age 40 years to 70 years old (inclusive)
3. Willingness and ability to comply with scheduled visits, laboratory tests, and other trial procedures
4. Written informed consent obtained prior to performing any protocol-related procedures
5. Participant affiliated to a social security system.

1.4.2 Non inclusion criteria:

1. Personal history of prior breast carcinoma, either invasive or ductal carcinoma in situ (DCIS) diagnosis
2. Prior history of atypical breast lesion, lobular carcinoma in situ or chest wall irradiation
3. Known breast cancer very high risk predisposing condition: germline mutation of BRCA1/2, TP53 or equivalent
4. Recent abnormal breast finding under work-up (clinically suspect lesion or BI-RAD 4 or 5 image)
5. Inability to provide signed informed consent
6. Insufficient understanding of any of the available languages
7. Psychiatric or other disorders that are not compatible with compliance to the protocol requirements and follow-up
8. Women who will not be able to be followed-up for 5 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-economic and cultural categories.

Regarding sub-group analyses, these will be conducted in pre-planned stratified sub-groups as defined below, but also as described in the statistical methodology.

1.5 Statistic analysis plan(ning) and power calculation

1.5.1 Randomization

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

1.5.2 Stratification

Randomization will be stratified by country, age (less or more than 50), prior mammogram.
1.5.3 Required number of women to be included

The incidence of stage II or higher breast cancer in My-PEBS standard arm is expected to be 120/100000/year. This number is derived from observation in screening populations of European countries, with integration of women aged 40 to 50 who have a lesser incidence of breast cancer of stage II and higher:

- Incidence of stage II+ breast cancer in women aged 50-69 is 140/100000/year on average in screening populations enriched with non-screening and interval cancers
- We expect 25% of women included to be aged 40-49, for whom incidence of stage II+ is half that of older women
- The expected incidence of stage II+ breast cancers for 100000 women followed up for 1-year in the standard arm of My-PEBS is therefore: (140 x 0.75) + (0.25x0.5x140) = 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 arm and up to 30% of the women in the standard arm. These women will not be included in the per-protocol analysis due to non-compliance.

The primary hypothesis is that the risk-based screening is non-inferior to the standard screening arm in terms of cumulative hazard rate. The cumulative hazard functions of stage II or higher cancers will be compared between the 2 trial 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 $e$ and $c$ standing for experimental and control arm respectively; it corresponds to an increase up to 1.2/1000 stage II cancers of cumulative hazard rate over 4 years in 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 personalized 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 II cancers are required for the non-inferiority assessment using a logrank test. With these hypothesis, we calculated the need for a total of 85000 participants, 42500 in each arm, included over 2.5 years and followed for 4 years.

Each subject will be followed for exactly four years in order to have completely comparable cycles of mammograms between the 2 treatment arms, which will trigger the analysis of the primary and key secondary endpoint. Later updates of the trial analyses will be performed using longer follow-up.

1.5.4 Planned statistical analysis

The primary analysis will compare the cumulative hazard functions of stage II or higher cancers between the two randomized groups of women using a logrank test. The rate of stage II and higher cancers for each arm will be estimated as the number of stage II or higher cancers 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. In an additional sensitivity analysis, we will estimate the average effect of the risk-based screening vs standard screening on stage II incidence as if all participants had complied using causal inference methods.

If non-inferiority of the risk 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 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.

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 treatment arms and estimate hazard ratios adjusted for the stratification factors at a one-sided 0.025 significance level. A multivariate 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.
1.5.5 Definition of per-protocol

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

<table>
<thead>
<tr>
<th>Risk-based arm</th>
<th>Low risk</th>
<th>Average risk</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned images</td>
<td>Mammogram / 4 years</td>
<td>Mammogram / 2 years +/- US according to local practice</td>
<td>Mammogram/year +/- US TS according to local practice</td>
<td>Mammogram + MRI/year +/- US according to local practice</td>
</tr>
<tr>
<td>Per-protocol definition</td>
<td>≤ 1 mammogram over 4 years</td>
<td>≥ 1 mammogram over 4 years</td>
<td>≥ 2 mammograms over 4 years</td>
<td>≥ 2 mammograms over 4 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard arm</th>
<th>(either no mammo or mammo/1-2-3 years according to age and country – will be defined individually at entry)(see 1.7.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned images</td>
<td>No mammogram</td>
</tr>
<tr>
<td>Per-protocol definition</td>
<td>≤ 1 mammogram over 4 years</td>
</tr>
</tbody>
</table>

1.5.6 Definition of Overdiagnosis

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 mode-based estimates of overdiagnosis [82,83]; a microsimulation model will be calibrated to the trial population for overdiagnosis estimates and cost and cost-effectiveness evaluation [84].

1.5.7 Definition and methods for other secondary end points


2. 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

3. Costs and cost-effectiveness will be evaluated as largely described in WP4 of the whole project

4. 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

5. 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.

6. Breast cancer specific survival will be defined according to the DATECAN definition [85]

1.6 Cumulative safety and efficacy information

1.6.1 Cumulative safety information

The study interventions do not differ from routine practice (mammograms, Ultrasound and MRI) and do not present safety or tolerability questions.

Additional safety information are directly linked to the reduction / increase in of the number of exams, biopsies and overdiaognoses and are directly linked with the efficacy (see below)
1.6.2 Cumulative efficacy information

Mammographic screening has been associated with an average 20% reduction in breast cancer-specific mortality in average risk-women \(^{[6-11]}\). The available evidence is derived from 11 randomized trials and their meta-analysis with 13 years of follow-up \(^{[6-11]}\). 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 \(^{[85]}\). 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 (RR 0.98 [95% CI, 0.74 to 1.37]; 4 trials) \(^{[7,85]}\).

As stated before (1.2.1.1), this is not without potential harms. Screening can lead to false-positive recalls, estimated to occur in more than half of women after 10 years of annual screening \(^{[12]}\), and many unnecessary biopsies \(^{[7-10]}\). 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 \(^{[8,13]}\). Finally, mammographic screening is also associated with a small lifetime risk of radiation-induced cancer. In a recent publication, annual screening of 100,000 women aged 40 to 74 years was projected to induce 125 breast cancer cases (95% CI, 88 to 178) leading to 16 deaths (CI, 11 to 23) \(^{[14]}\). A more personalized screening strategy based on individual risk might therefore improve the balance of benefits and harms and increase the efficiency of screening programs \(^{[15,16]}\).

Increasing 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 \(^{[87-90]}\).

Ultrasound has been demonstrated to increase sensitivity and specificity of mammographic screening in dense breast. MRI has been shown to dramatically increase screening sensitivity of mammography in women with high genetic risk condition or a history of chest wall irradiation, and is recommended in these situations by most national and international guidelines \(^{[91-96]}\).

Tomosynthesis with mammography reduces recalls (16/1000), but increases biopsies (1.3/1000) and cancer detection (1.2/1000) \(^{[86]}\). However, definitive evidence of its real benefits is not acquired to make it a standard, nor is technological standardization. Concern exists regarding radiation doses administered; tomosynthesis remains therefore an option, but not a standard of mammographic screening.

Personalized prevention strategies have proven to be effective for individuals at very high risk because of inherited mutations that predispose them to breast cancer \(^{[17,18]}\). 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 breast cancer. National and international guidelines recommend that these women receive increased screening and other prevention measures, which is associated with some suggested benefits \(^{[8,19]}\). However, 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 \(^{[2]}\). Developing more effective, risk-based screening approaches for this general population requires validated risk-estimation models \(^{[20,21]}\) and assessment of the clinical usefulness of such modelsCumulative efficacy is central in MyPEBS, as represented by the co-primary objective and several of the secondary objectives and as fully described .

According to our assumptions (Table below - based on "no screening" before 50 and MMG every 2 years after although there are slight differences in different countries implicated in the trial: 1-yearly MMG in women 45-49 in Italy, and 3-yearly MMG in UK), among 530 women overall expected to develop breast cancer at 4 years in one arm (among 42500 participants), a risk-based strategy will increase the screening intensity in 329 of the women who are expected to develop breast cancer (light green). On the opposite, 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).

We therefore have a very high probability to decrease stage II+ breast cancers and a very low probability of harm in the overall population of the risk based arm.
1.7 Conduct

1.7.1 Schedule for study conduct including timelines for key study milestones

The full protocol of MyPEBS clinical trial will be submitted in the different countries in accordance with the national requirement and according the following calendar:

In France, a submission to the Ethics Committee is sufficient. For Belgium, UK, Italy and Israel the trial has to be submitted to the Ethics Committee and an additional Competent Authority of each country. Preparation of submissions will be underway during spring and summer 2017. Submission to the competent authorities will be done as early as possible after obtaining the grant agreement, at latest on January 2018 so that accrual can start at month 10.

Key study milestones:

After getting the approvals, we expect to have:

- First study subject, First Visit (FPFV): Month 10
- Last study subject, First Visit: Month 39
- Last study subject, Last Visit: Month 87
- End of Study (including follow-up and data analysis): Month 96

1.7.2 Description of recruitment strategy

1.7.2.1 Recruitment per country and per center

We plan to enroll a total of 85,000 participants over 2.5 years. Five countries will accrue women into this clinical trial: UK, Italy, Belgium, Israel and France. The recruitment will be competitive.

The pre-planned accrual per country is:

<table>
<thead>
<tr>
<th>Country</th>
<th>PI</th>
<th>Regions</th>
<th>Planned accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>JB Burrier</td>
<td>Brussel s- Vaanderen (Leuven) - Wallonie</td>
<td>10 000</td>
</tr>
<tr>
<td>Italy</td>
<td>Giorgi Rossi</td>
<td>6 regions, northern Italy</td>
<td>30 000</td>
</tr>
<tr>
<td>UK</td>
<td>F Gilbert</td>
<td>3 areas</td>
<td>10 000</td>
</tr>
<tr>
<td>Israel</td>
<td>M Guindy</td>
<td>Global coverage - Assuta network</td>
<td>15 000</td>
</tr>
<tr>
<td>France</td>
<td>C Balleyguier</td>
<td>15 organised screening structures (15 areas)</td>
<td>20 000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>85 000</strong></td>
</tr>
</tbody>
</table>
According to countries, the recruiting centers will be different: in most countries, centralized screening centers will be the recruiting centers, whereas in France, recruiting centers will be community GPs, Radiologists and gynecologists in participating areas.

The pre-planned accrual per month (after the initiation phase) and per center is very variable according to the country's organization and type of center:

<table>
<thead>
<tr>
<th>Country</th>
<th>Nbr centers</th>
<th>Nbr target women/center</th>
<th>Planned monthly accrual rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>35</td>
<td>286</td>
<td>15/month/center</td>
</tr>
<tr>
<td>Italy</td>
<td>6</td>
<td>5000</td>
<td>180/month/center</td>
</tr>
<tr>
<td>UK</td>
<td>3</td>
<td>3400</td>
<td>120/month/center</td>
</tr>
<tr>
<td>Israel</td>
<td>8</td>
<td>1000-4000 depending of the center</td>
<td>100/month/center</td>
</tr>
<tr>
<td>France</td>
<td>800</td>
<td>25</td>
<td>1/month/investigator</td>
</tr>
<tr>
<td>TOTAL</td>
<td>852</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.7.2.2 Selection and inclusion processes:

They will slightly differ according to country arrangements

Selection:
- All women meeting inclusion criteria in a region participating in the trial will be invited at least once.
- Some women may self-refer to an including center or will be proposed the trial while consulting for a pre-planned screening event or for a regular clinical visit to a GP or radiologist (France).
- Efforts will be made to reach certain targeted populations (underserved, low screening attendance), through the inclusion of regions, areas, and centers covering populations at lower economic situations, populations with high immigration rates, rural regions or other relevant target situations.

Accrual visit:
- Women interested in participating in the trial will have a dedicated visit with a participating physician in a participating center (either GP, radiologist, gynecologist)
- They will get all necessary oral and written information regarding breast cancer screening and the trial
- Women who meet the inclusion criteria and willing to participate will sign a written or online consent form

1.7.3 Description and assignment of intervention

The clinical trial intervention is summarized in the following diagram and is detailed below.
1.7.3.1 Randomisation:
Women will be randomized for either arm immediately during the accrual visit through the use of the online real-time screening module of the trial.

1.7.3.2 Trial conduct if the standard arm
In the standard arm of My-PEBS, women are screened for breast cancer according to the current national guidelines and procedures:

- Bi-yearly or tri-yearly mammogram starting at age 40-50, up to age 69-74 according to countries, +/- Ultrasound (US) and Tomosynthesis (TS) according to breast mammographic density and ongoing guidelines.
- The current national/regional guidelines in use in the including center may vary during the trial. Guidelines and procedures in the standard arm will be updated accordingly.

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 My-PEBS
- **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 My-PEBS

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

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

OS: organized screening, CBE: clinical Breast examination, wn: women
Use of ultrasound and tomosynthesis: will be done in this arm according to current national/regional guidelines in each country
Standard operating procedures regarding all imaging examinations performed in MyPEBS are described in the main text of project (WP3.4). A quality assement chart will be proposed to all participating screening centers.

1.7.3.3 Trial conduct in risk based arm:

Evaluation of 5-year risk in risk-based arm / Risk stratification
Women in the risk-based arm will have their 5-year risk evaluated using risk score (BCSC score adapted to national incidence + Tyrer-Cuzick in case of family history > 1 see below):
• Risk stratification will be done using a validated algorithm, on dedicated risk-evaluation software. This algorithm uses the following variables: age, family history, previous history of benign breast biopsy, breast density, and genotyping results.
  o Clinical and epidemiological characteristics will be retrieved from baseline questionnaires: age, family history of breast cancer (1
\textsuperscript{st} and 2
\textsuperscript{nd} degree relatives), personal history of benign breast disease (with either breast biopsy/FNA and/or surgery)
  o Baseline breast mammographic density will be evaluated using a standard procedure according to national guidelines: radiologist BI-RAD assessment, or validated software. If no baseline breast mammography is available (women under 50y), the maximum risk will be applied.

• Genotyping process
  o During the inclusion visit, women will be given a saliva kit, which will then be sent to one of the three central labs (Israel, France and UK) for DNA extractions and genotyping. The information will be introduced in the risk-evaluation software and the final risk score will be produced and send to the inclusion center.
  o These women will be invited to come back for a second dedicated visit to be explained the risk evaluation result and proposed their personal screening program.

Genotyping in risk-based arm

• DNA will be extracted from saliva samples using standard protocols (DNA Genotek or equivalent). Genotyping will be carried out using the Illumina Global Screening Array, with over 600,000 variants selected to maximise the capacity to capture genetic variability across the genome either directly or through imputation using the 1000 Genomes data. This approach allows the evaluation of variants currently known to be associated with BC risk. Furthermore, it will allow to re-evaluate risk as new variants are validated in the literature by re-analyzing the mature trial data, as opposed to carrying out additional genotyping.

Risk score

The individual breast cancer risk will be estimated using the modified (by inclusion of SNPs) BCSC score and when necessary, Tyrer Cuzick scores including polymorphisms, under a pre-defined algorithm, developed by the consortium. Both scores will be adjusted for national breast cancer incidences and will incorporate genotyping results for all patients.

• The modified BCSC score has been validated in a French cohort (Ragusa et al, Eur J cancer, in press) as well as on the PROCAS (UK) cohort (unpublished data) for the purpose of the preparation of this study. It allows good discrimination and good calibration in the overall population and will be used for the general population
• For women with a strong family history (more than one 1
\textsuperscript{st} degree relative with breast cancer), the Tyrer Cuzick model including breast mammographic density and SNPs results will be preferred, given its higher performances in these populations.

BC risk levels will then be classified into meaningful categories according to available guidelines and published literature\textsuperscript{[32],[19,46]. They have been previously summarized. Screening procedures will be scheduled accordingly, based on the pre-defined screening decision tree (see below).

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. The whole recommendations have been elaborated by the steering committee of the trial.

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Low risk</th>
<th>Average risk</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerical definition</td>
<td>(&lt; 1% ) at 5 years</td>
<td>(1 \leq \leq 1.67% ) at 5 years</td>
<td>(1.67% \leq \leq &lt;6 % ) at 5 years</td>
<td>(\geq 6% ) at 5 years</td>
</tr>
<tr>
<td>Proposed screening program</td>
<td>Mammogram / 4 years - study entry eventually (in accordance with national guidelines) - end of study for all women</td>
<td>Mammogram / 2 years</td>
<td>Mammogram / year</td>
<td>Mammogram + MRI / year</td>
</tr>
<tr>
<td>Additional</td>
<td>High density: US or ABUS/ 2 years</td>
<td>High density: US or ABUS/ year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Use of ultrasound and tomosynthesis: will be done in this arm according to current national/regional guidelines in each country.

Standard operating procedures regarding all imaging examinations performed in MyPEBS are described in the main text of project (WP3.4). A quality assessment chart will be proposed to all participating screening centers.

**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 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. It will include a questionnaire for family history, and if MMG had occurred, the results (breast density evaluation and benign breast biopsy if any).
- At trial level, the re-evaluation will take into account published evidence-based knowledge notably based on SNPs.

**Other measures associated to risk level:**

- **Germline genetic testing:**
  Of note, for the women identified as having a high 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, it has been planned that women of Jewish ancestry will systematically be proposed germline BRCA1/2 testing for the three founder mutations (this will be funded outside of the trial).

- **Breast cancer risk reduction measures**
  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 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.

**1.7.4 Study management, study monitoring, data and sample management**

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

**1.7.4.1 Structure and protection of central web platform and database**

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

It will be developed and hosted by three partners, under the supervision and coordination of UNICANCER (P Arveux, Center Georges François Leclerc, Dijon):

1. UNICANCER/Center Georges François Leclerc, Dijon (modules 1 and 2)
2. Statlife (module 3)
3. an external partner to be defined for modules 4 and 5

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

- Randomization
- Entry of all data (baseline and follow-up) necessary for the CRF
- Filling of all online questionnaires by participants
- Estimation of personal risk in risk-based arm, integrating baseline data and genotyping results
- Automated updates of risk status if additional SNPs or change in clinical variables
• Interactive Participant Portal with secured authentication
• 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
• Email templates used to communicate with participants
• Transmission of participants' personalized programs and invitation dates to screening centers
• For communication purposes, participants IDs (name and email) must be only available for the participants themselves in a protected area; any data leaving this area must be pseudonymized (reversible so that invitation/questionnaire can be sent) with a single anonymous ID per participant.
• Personal data protection must be secured at highest level in all circumstances, all countries and throughout the trial
• Data availability must be guaranteed for all analyses planned in MyPEBS.

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

• Direct collection of breast density assessment upon possibility of link with density software
• 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 pseudonymized)

The web interface for MyPEBS will contain several interconnected modules.

1. Module 1 is the CRF database
   It will be based on server 2 hosted by Centre Georges François Leclerc in Dijon. It will host all CRF data and full genotyping data. All data available will be totally anonymous, participants being identified by a unique code number.

2. Module 2 is the randomization module, developed under the responsibility of Patrick Arveux, as an external module linked to server 1 and server 2

3. Module 3 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. Module 3 will export risk information to modules 1 (CRF), 4 and 5 on server 1 and server 2 respectively. Module 3 will allow automated recalculations of risk in case of new validated snps or new relevant clinical data.

4. Module 4 is the integrated portal for participants with secure authentication.
   It is based on server 2 and is dedicated to participants' secured access to their private account on MyPEBS. It will be developed and hosted by im3D. This will be the only place participants' names and email addresses are entered, and these data will be totally pseudonymized and encrypted for externalization outside of module 4. 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. CRF data will be either directly entered on the CRF or transmitted from server 1 to CRF on server 2.

5. Module 5 is the integrated portal for screening structures and investigators.
   It will be based on server 2 and is dedicated to the interface with the screening centers. It will be partially country-specific. It will be developed and hosted by im3D. It will allow direct entry of data (images, 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.
1.7.4.2 Overall Data collection rules

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

- 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 (economic 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.

<table>
<thead>
<tr>
<th>Type of data</th>
<th>Mode of collection</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline data</td>
<td>Web platform</td>
<td>filled by investigator and women</td>
</tr>
<tr>
<td>Randomization</td>
<td>Web platform</td>
<td></td>
</tr>
<tr>
<td>Initial risk assessment</td>
<td>Web platform</td>
<td>filled by investigator</td>
</tr>
<tr>
<td>Questionnaires</td>
<td>Web platform</td>
<td>filled by participants</td>
</tr>
<tr>
<td>Update of personal participants data</td>
<td>Web platform</td>
<td>filled by participants</td>
</tr>
<tr>
<td>Results of all imaging examinations</td>
<td>Web platform</td>
<td>filled by women + screening centers</td>
</tr>
<tr>
<td>Results of biopsies or surgeries (benign)</td>
<td>Web platform</td>
<td>filled by women + screening centers</td>
</tr>
<tr>
<td>Cancer events</td>
<td>Web platform</td>
<td>women, screening center, national security insurance</td>
</tr>
</tbody>
</table>

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 crossing with national databases (national health insurance databases and national epidemiological and statistical databases) in concerted, pre-planned, anonymous fashion.

Image collection: image collection is not mandatory for the trial but will be organized as much as possible, in some regions/countries.

1.7.4.3 Data management

Data Management will be undertaken by the data management team chaired by Patrick Arveux (P1). The Database will be hosted by the data management centre – Centre Georgaes François Leclerc, Dijon, France (Unicancer). A specific
database will be created, tested and validated before the start of data capture. Database management will be provided by an electronic Case Report Form (eCRF) developed using Clinsight® software. 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 eCRF will be filled in by investigator site, by participant and/or by screening centers. The data will be monitored 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 full database will need to have interrelation with the screening structures and national security insurance. A web platform will be developed to connect these different bases.

For the purpose of long term follow-up and economic 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 a trusted third party according to national guidelines, so that the centralized clinical trial database remains anonymous.

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.

Quality controls, mechanisms to ensure security of data collected

Patient will be identified by a numeric code, the first letter of the last name, the first letter of the first name and the date of birth in case of homonymy.

All women will receive a unique patient 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 case report forms (eCRFs).

In this trial, a minimal data will be collected:

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

During the trial, notification to the women may be sent for data consistency validation, by the Central Data Center (CDC), under the responsibility of Dr Patrick Arveux (Centre Georges François Leclerc, Dijon):

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

Study monitoring plan

The monitoring within MyPEBS will be very limited and mostly automated through the common database and the central web platform.

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
- a light remote monitoring to ensure the authenticity and credibility of data in accordance with the Good Clinical Practice, including:
  - verifying the informed consent (confirmation will be asked to each women in the first questionnaire)
  - verifying that the CRF data is consistent and in agreement with the source documents
- If necessary (too many inconsistencies), an audit of the participating investigational centers

Reporting of specific AE:

Not applicable: As the clinical trial is based on current practices, there is no obligation for any safety and specific AE reporting within MyPEBS-CT.
Sample management:
Saliva kits will be sent to the central lab for DNA extractions and genotyping. DNA extracted from saliva samples will be analyzed and won’t be stored. Indeed, once the genotyping result will be available, the remaining samples will be automatically destroyed. Furthermore, we will be able to re-evaluate risk as new variants could be identified by reanalyzing the mature trial data, as opposed to carrying out additional genotyping.

1.7.5 Sponsor, coordinating centre(s) and committees
MyPEBS 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.

In this trial, organized Breast screening structures will be involved to coordinate women's invitations and data retrieval.

According to countries, the recruiting centers will be different: 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 pseudonimization for transmission to the database. The number of coordinating centers will vary country by country (3 in Belgium, 3 in UK, 5 in Italy, 11 in Israel, 15 in France).

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

- 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 WP3 (Methodology, Statistical analysis, genotyping, imaging, quality insurance, risk evaluation)
- The Steering Committee is composed of and working according to the study related SC Charter, which will be written, approved and signed by all members before any activity.
- All SC members will have to fill and update yearly a conflict of interest statement form, throughout their participation as members of the SC.
- 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 authorising all publications issued from the trial, organisation 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.

Data Monitoring and Ethics Committee
The data monitoring and ethics 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 patient safety and preserve Study integrity;
• Make recommendations at the end of each closed meeting suggesting either to:
  o continue the study according to the protocol and any relevant amendments;
  o discontinue the Study (with provisions for orderly discontinuation in accordance with Good Clinical Practice);
  o 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.

1.7.6 Study medication
This section is not applicable, since no investigational medicinal product is used in the present trial.

1.7.7 Clinical centres
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 (2 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. We will work closely with the network coordinated by Vincent Renard, Chair, CNGE – “Collège National des Généralistes Enseignants” to identify general practitioners who are best specialists in the field and are used to lead clinical trials. Regarding the gynecologists or radiologists participating in the National Screening program, they were already approached and they agreed to participate. When the project will be approved, we will contact them again to select and to finalize a list for each participating area. An on-going study (Riviera – NCT 02997384) by the coordinator demonstrate the feasibility of this approach in France.

1.8 Orphan designation
Not applicable

1.9 Unit costs per patient for clinical trials / studies / investigations
Not used